Soil-transmitted helminth infections in humans: Clinical management and public health control

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ABSTRACT

Over 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, life cycles, pathophysiology, clinical diagnosis and management, and the public health control of soil-transmitted helminths. Recent reviews questioned the impact of population-level deworming; however, it remains beyond doubt that treatment effectively reduces severe consequences of soil-transmitted helminthiasis. We highlight the need for refined diagnostic tools and more effective control options to scale up public-health interventions and to improve clinical detection and management of these infections.

KEY WORDS

Soil-transmitted helminths; *Ascaris lumbricoides*; *Trichuris trichiura*; hookworm; *Necator americanus*; *Ancylostoma duodenale*; *Strongyloides stercoralis*; clinical; global health
INTRODUCTION

Helminthic parasites are among the most common infections in humans. Due to the role of contaminated soil in their transmission cycle, infections with *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*) are, in public health terms, known as soil-transmitted helminthiasis (STH). These parasites affect more than a quarter of the world’s population, and contribute to a substantial burden of human disease and disability. In this seminar we also address an additional soil-transmitted helmith - *Strongyloides stercoralis* - which is an important, but often neglected, cause of severe morbidity. STH primarily affects individuals in communities with limited access to, and use of, water, sanitation, and hygiene (WASH) facilities and is the most widespread among the so-called neglected tropical diseases (NTDs).

The World Health Organization (WHO) and other partners currently support national governments in STH-endemic countries to implement large-scale, periodic anthelmintic treatment (with mebendazole or albendazole) of pre-school-age children, school-age children, and women of reproductive age (except in the first trimester of pregnancy). The primary, and currently most realistic, aim of such mass drug administration (MDA) is to control morbidity due to STH by reducing infection intensity and ultimately prevalence. Mass treatment complements clinical case management by preventing or curtailing chronic, high worm burden infections and associated disease.

This seminar provides an overview of the state-of-the-art clinical diagnosis, management, and follow-up of STH, including a ‘Fast Facts’ clinical summary which can be used on a mobile device, to facilitate case identification and management (Panel 1). Importantly, we aim to bridge the evidence-base for clinical case management with that of public health control to inform and leverage both approaches to morbidity control in endemic and non-endemic countries (Panel 2). Further, we discuss recent reviews that have questioned the health impact of population-level deworming in its current form, and we present the main arguments of the on-going debate that has followed. Panel 3 shows the search strategies we used for this seminar review.

EPIDEMIOLOGY

Infections with soil-transmitted helminths are most common in people living in areas with limited access to adequate sanitation, and in emigrants and visitors returning from such areas. Although most endemic regions are found in low- and middle-income countries, STH also occurs in high-income countries among vulnerable populations who are not reached by public-health measures.

The current geographical distribution of STH is shown in Figure 1A-D. In 2010, the WHO estimated that 875 million children were in need of regular treatment for STH, excluding *S. stercoralis* which is thought to infect up to 100 million people globally. Data from the past decade suggest that disability-adjusted life years (DALYs) associated with STH have declined; however, this reduction has to a large extent been seen in upper-middle income countries, with the disease burden becoming even more concentrated in low- and lower-middle income countries. The DALY estimates have been disputed, with some scientists arguing that the numbers grossly under evaluate the true burden of disease, e.g. by inadequate attribution of iron-deficiency anaemia caused by hookworm infections.

*Ascaris lumbricoides* (roundworm) affects an estimated 804 million people worldwide, most commonly pre-school-age children, school-age children and adolescents in endemic countries. Over the past 25 years, DALYs associated with *Ascaris* have dropped to around 1 million, now a
quarter of the *Ascaris* disease burden in 1990.\textsuperscript{17} Mortality accounts for approximately one-sixth of the current disease burden, whereas most of the severe morbidity averted is thought to be due to a reduction in severe wasting.\textsuperscript{2} Although the vast majority of infections occur in endemic countries, occasionally, zoonotic transmission of *Ascaris suum* occurs in individuals who have been in contact with domestic pigs, even in countries non-endemic for STH.\textsuperscript{18}

*Trichuris trichiura* (whipworm) infects an estimated 477 million individuals, and prevalence and intensity of infection are typically highest in children.\textsuperscript{16, 19, 20} However, data are scarce and suspicion of infection should not be limited by current endemi city maps.\textsuperscript{17} Over the past 10 years, the DALYS due to *Trichuris* have declined to just above 500,000;\textsuperscript{17} The majority of these averted DALYs have been due to lower trichuriasis infestations and fewer cases of mild abdominopelvic problems with a small reduction of more extreme cases, such as severe wasting. In addition, zoonotic transmission to humans can occur with *Trichuris suis*, as for *A. suum*.\textsuperscript{18}

*Ancylostoma duodenale* and *Necator americanus* (hookworm) infect an estimated 472 million people.\textsuperscript{16} In contrast to *A. lumbricoides* and *T. trichiura*, the prevalence and intensity of hookworm infection is highest in adults, although children are also commonly infected.\textsuperscript{21} *Necator americanus* is the most widely distributed hookworm species, found across sub-Saharan Africa, the Americas and Asia, whereas *A. duodenale* is found more focally. Both species may also co-exist in the same area and within the same individuals. The disease burden caused by hookworm is to a large extent due to anaemia, and recent estimates suggest that the burden of disease could be as high as 4,000,000 DALYS, with considerable productivity losses of up to 139 billion US dollars annually worldwide.\textsuperscript{17, 22}

*Strongyloides stercoralis* (threadworm) infects up to 100 million people globally;\textsuperscript{1, 11} however, as with *T. trichiura*, the data are scarce and suspicion of infection should not be limited by endemi city maps.\textsuperscript{4, 11} Although uncommon, dogs, cats and other mammals may serve as reservoir hosts for human *S. stercoralis* infection, even where adequate sanitation exists. Additional risk factors for *S. stercoralis* infection include immunosuppression, certain malignancies, human T-cell lymphotropic virus (HTLV)-1 infection, and alcoholism.\textsuperscript{4, 11} In Central Africa *S. fuelleborni*, a non-human primate *Strongyloides* species, can also infect humans.

**LIFE CYCLES**

*Ascaris lumbricoides* infects humans through faecal-oral transmission (Figure 2A).\textsuperscript{23} After embryonated eggs are swallowed, first-stage (L1) larvae hatch from eggs, moult into second-stage (L2) larvae, penetrate the host intestinal mucosa, and migrate to the vascular system, through the right side of the heart to the pulmonary circulation. Too large to pass through the pulmonary capillaries, the third-stage (L3) larvae migrate across the alveolar wall and traverse along the tracheobronchial tree to the larynx, where they are swallowed and, in the small intestine, moult into fourth-stage (L4) larvae that develop into adult worms. With sexual reproduction, adult female *A. lumbricoides* worms can release thousands of eggs daily that pass into the environment through the stool. Egg production occurs two to three months following ingestion of infective eggs, and adult worms may live for a few years. Eggs can remain viable for several years in warm, moist soil.\textsuperscript{24}

*Trichuris trichiura* is transmitted through a faecal-oral cycle in which infective embryonated eggs typically are ingested via contaminated food or hands, and hatch into larvae that moult in the small intestine. Unlike *A. lumbricoides, Trichuris* does not include a migratory phase outside the intestine (Figure 2B).\textsuperscript{25} The larvae attach to the intestinal villi and develop into adult worms, which reside in the caecum and the ascending colon. Female worms lay thousands of eggs per day, and can survive
for several years. The eggs pass in the stool and embryonate in the soil, where they can survive in
warm, moist conditions for months.\textsuperscript{24, 26}

\textit{Ancylostoma duodenale} and \textit{N. americanus} larvae are free-living in the soil, and infect humans by
attaching to and penetrating the skin, typically through bare feet. The larvae are transported by
lymph and blood to the right side of the heart and the pulmonary circulation (Figure 2C).\textsuperscript{23} In the
pulmonary capillaries, the larvae penetrate the alveolar wall, pass to the larynx and are swallowed.
The larvae moult and develop into mature worms in the small intestine over one to two months, and
can live for several months (\textit{A. duodenale}) or years (\textit{N. americanus}). A female worm releases
thousands of eggs a day that pass in the stool, and after five to ten days, hatch in warm, moist, sandy
soil or in the faeces to produce rhabditiform, L1 larvae. Larvae feed on organic matter, and become
infective after rapid moulting to L2 and L3 larvae that can survive for several weeks.\textsuperscript{24}

In addition to percutaneous infection, \textit{A. duodenale} can also infect humans through ingestion of
larvae, resulting in Wakana syndrome, especially in heavy infections. Hookworms may also remain
dormant in connective tissue or muscle. \textit{Ancylostoma} species that typically infect mammals, such as
dogs and cats, may also infect humans, causing cutaneous larva migrans, a self-limiting skin
infection. Recent data suggest that human infection with zoonotic species can cause pathology
similar to \textit{A. duodenale} and \textit{N. americanus}, and may be more common than previously thought.\textsuperscript{27}

\textit{Strongyloides stercoralis} follows a complex life cycle that may take multiple routes, including a
complete life cycle outside of the human host, in the soil. The life cycle routes of greatest public
health relevance however, are those which involve the human host. Filariform larvae can infect
humans both percutaneously and orally (Figure 2D).\textsuperscript{28} Following penetration of the skin, typically of
the foot, larvae are transported to the right side of the heart and thereafter to the pulmonary
circulation. In the pulmonary capillaries, the larvae penetrate the alveoli, pass to the larynx and are
swallowed to enter the small intestine where they mature to adult worms. Oral infection follows the
same cycle after the larvae penetrate the intestinal mucosa.

The female adult penetrates the gut wall, lodges in the lamina propria of the duodenum and
jejunum and may lay up to 50 eggs a day. The eggs hatch within the gut wall and rhabditiform larvae
migrate in to the lumen and are passed with the stools. The larvae may penetrate the colonic wall or
perianal skin to enter a new cycle, or may disseminate to other organ systems. This aspect of the life
cycle, termed auto-infection, enables chronic infection that may last for several years to decades,
without repeated external exposure.\textsuperscript{29} Larvae (or unhatched eggs) that are expelled in the stool may
survive in moist soil for several weeks, and develop into infective larvae.\textsuperscript{30} \textit{Strongyloides fuelleborni}
which occasionally infects humans, follows the same life cycle.\textsuperscript{31}

\textbf{PATHOPHYSIOLOGY}

\textit{Ascaris lumbricoides} may cause disease in humans through type-1 hypersensitivity reactions to
larval stages (Loeffler syndrome), and by physical obstruction caused by adult worms (Figure 3A).
Pathology is positively related to worm burden, albeit non-linearly.\textsuperscript{25, 31} Common complications in
endemic areas include mechanical small bowel obstruction, volvulus and intussusception, especially
in children.\textsuperscript{32} Adult worms can further invade intestinal orifices, causing complications such as acute
appendicitis, acute cholecystitis, pancreatitis and gastric ascariasis.\textsuperscript{23}

\textit{Ascaris lumbricoides} infection may cause malnutrition, including lactose intolerance and vitamin A
deficiency.\textsuperscript{34, 35} Recent findings suggest that \textit{A. lumbricoides} might alter the normal intestinal
bacterial flora, although *Ascaris* may also have a protective effect against severe enteric infections. Anaemia may result from mucosal bleeding in the upper gastrointestinal tract or through a generalised inflammatory reaction to infection.

Similar to other helminth infections, *A. lumbricoides* induces a predominantly type-2 T helper cell (Th2)-polarised immune response. Increased immunoglobulin (Ig)E titres and eosinophilia are characteristic features of especially acute *Ascaris* infection. Studies have found a combination of host-protective and parasite-evading features, regulated by interleukin (IL)-10 and other cytokines. A shift in the age of peak infection prevalence and host immune response may be seen as partial immunity develops. Further, host genetic factors may play a role in determining the intensity of *Ascaris* infection and disease presentation, including resistance to reinfection. *Ascaris*-induced immunomodulation may affect the host’s response to co-infections, including HIV, tuberculosis, malaria and human papillomavirus (HPV). *Ascaris lumbricoides* infection may also be a risk factor for asthma and atopy, possibly through cross-reaction between parasite, mite and insect epitopes.

*Trichuris trichiura* worms’ whip-shaped form has given this helminth its common name, whipworm. The slender anterior aspect of the worm burrows into the intestinal mucosa (Figure 3B), causing petechial lesions, blotchy mucosal haemorrhage and active mucosal oozing. Although not consistently apparent on endoscopy, *Trichuris* may cause colonic mucosal inflammation, which can potentially be influenced by individual immune regulation and gut microbiota. Morbidity is positively associated with intensity of infection, and trichuriasis can lead to both mucosal and systemic changes in immune response and resistance to reinfection.

Eosinophils are a typical feature of especially acute *T. trichiura* infection, and play a role in local gut pathology. In animal models, *Trichuris* worm expulsion has been associated with intestinal epithelial cell turnover, stimulated by cytokine responses. In contrast to *A. lumbricoides* infection, *T. trichiura* infection is not associated with changes in intestinal bacterial flora, and might even protect against severe diarrhoeal pathogens. Anaemia is a common feature of trichuriasis, and, although often not as pronounced as in hookworm infection, can have severe consequences in vulnerable individuals such as pregnant women.

*Ancylostoma duodenale*, *N. americanus*, i.e. hookworm, derives its name from the hook created by the angle of the head to the rest of the adult worm body. As in *A. lumbricoides* infection, hookworm larvae migrating through pulmonary tissue may cause a type-1 hypersensitivity reaction (Loeffler syndrome). Once established in the small intestine, the adult worm uses its teeth to burrow into the intestinal mucosa and feed on blood (Figure 3C). This damages the mucosal lining and oozing leads to blood loss at the site of burrowing. The associated anaemia is the most characteristic feature of hookworm infection, and is a major cause of anaemia globally, particularly in children and pregnant women.

As with other helminths, hookworm infection is associated with a Th2 polarised immune response, regulated by IL-10 and transforming growth factor (TGF)-β, both systemically and in the local intestinal mucosa. Elevated IgE titres, IL-5 and eosinophilia are features of especially acute hookworm infection, and may play a role in intestinal immune response. However, unlike other soil-transmitted helminth infections, repeated exposure to hookworm infection has not been found to stimulate resistance to reinfection, potentially due to a down-regulation of the immune response.
**Strongyloides stercoralis** larvae migrating through pulmonary tissue may cause a type-1 hypersensitivity reaction, or Loeffler syndrome. The adult worms burrow into the intestinal mucosal wall and cause local inflammation. A Th2-dominated immune response is a pivotal factor in *S. stercoralis* infection, especially in preventing severe morbidity. Eosinophils are a prominent feature of *S. stercoralis* infection, and may provide host protection especially in early-stage infection.

Severe infection, whether restricted to intestinal and pulmonary pathology or disseminated to multiple organ systems, appears to be caused by a defective Th2 response that allows the reproduction of larvae to exceed the number that are effectively controlled by the host’s immune response. Bacterial septicaemia is an independent predictor of shock and mortality in disseminated infection.

**CLINICAL PRESENTATION**

The distribution of soil-transmitted helminth infections is 'over-dispersed', i.e. relatively few heavily-infected individuals harbour the majority of the worms, and this may be due to both exposure and host susceptibility. Although most individuals with low and moderate intensity infections commonly have limited or non-specific symptoms, clinicians should be aware that such infections also can present as acute and chronic cases.

**Ascaris lumbricoides** infection is commonly asymptomatic or may produce mild, non-specific symptoms. In patients who seek health care, symptoms will depend on the phase of the parasite's life cycle and the intensity of infection (Table 1). So-called eosinophilic pneumonia, or Loeffler syndrome, may occur ten to fourteen days after infection and is due to a typically self-limiting inflammatory reaction to *A. lumbricoides* larvae migrating through the pulmonary tissue. Patients present with urticaria, cough, dyspnoea, and haemoptysis, and may have abnormal auscultatory breath sounds. In rare cases, the syndrome may result in pleuritis or pleural effusion.

Infections with adult *Ascaris lumbricoides* may present as acute abdomen, most frequently in children with high worm burdens, including upper gastrointestinal bleeding, small bowel obstruction, intestinal volvulus and intussusception, peritonitis, and gastric ascariasis, even with perforation. Hepatobiliary and pancreatic ascariasis may cause five broad clinical syndromes, including biliary colic, acute cholecystitis, acute pancreatitis, acute cholangitis and hepatic abscess. Hospital-based studies in India have found that *Ascaris* may be the cause of approximately half of cases with biliary disease, a third of pancreatitis cases, and around 15% of liver abscesses and biliary lithiasis. Clinicians in endemic areas must have a high suspicion of *Ascaris* infection, as cases may present as surgical emergencies.

Asthenia, lack of appetite (anorexia), abdominal pain or discomfort, diarrhoea or other altered bowel habits, and weight loss are common symptoms in intestinal ascariasis. Anaemia and/or occult or fresh blood in the stool may be found in cases of mucosal haemorrhage, and patients with intestinal obstruction commonly have findings of abdominal distension, increased bowel sounds and abdominal tenderness by palpation. Jaundice, fever, and/or abdominal tenderness may be found in hepatobiliary and pancreatic ascariasis, depending on the clinical syndrome, as described above.

*Trichuris trichiura* infection is commonly asymptomatic. Loeffler syndrome does not occur as *T. trichiura* does not pass through the lungs. Individuals presenting with symptoms typically complain of asthenia, abdominal pain, and diarrhoea, and can in severe cases present with *Trichuris* dysentery.
syndrome (Table 1). Signs include anaemia, digital clubbing, abdominal tenderness, and, in some
cases, rectal prolapse. These features may be pronounced in high-intensity infection, which can
lead to severe anaemia.

**Ancylostoma duodenale, N. americanus** infections are commonly asymptomatic, and symptoms
depend on stage and intensity of infection (Table 1). Following skin penetration, typically of the feet
or lower leg, so-called “ground itch” may occur – an intense itch at the site of infection with
tortuous, vesicular lesions that follow the trace of the migrating larvae. Although less common than
in ascariasis, eosinophilic pneumonia (Loeffler syndrome) with cough, dyspnoea, and haemoptysis
may occur during larval passage through the lungs. In peroral infection, nausea, vomiting,
pharyngeal irritation, cough, and dyspnoea may occur (Wakana syndrome).

Once the worms are established in the small intestine, symptoms are typically caused by blood loss
and intestinal inflammation, and include asthenia, abdominal pain, and diarrhoea with findings of
pallor, tachycardia, tachypnoea, oedema, abdominal tenderness on palpation, occult blood in the
stool, and occasionally melena. In heavy intensity infections, anaemia may be severe, although
most commonly smaller amounts of blood loss gradually deplete the patient of erythrocytes and
nutrients. In resource-limited settings, this may aggravate the condition of individuals who are
commonly also prone to undernutrition and malaria, such as children and pregnant women. In
contrast to *Ascaris*, the small size of hookworm makes surgical complications uncommon.

**Strongyloides stercoralis** infection is commonly asymptomatic in otherwise healthy individuals.
Migration of larvae through the pulmonary tissue may present as eosinophilic pneumonia (Loeffler
syndrome) with cough, dyspnoea, oedema, and haemoptysis. In hyperinfection (see below),
pulmonary infection can become severe and even fatal. Chronic strongyloidiasis may present with
asthenia, anorexia, nausea, abdominal pain, and diarrhoea, and abdominal tenderness on
examination (Table 1). So-called larva currens is a common feature of chronic infection, and
presents as an urticarial, serpiginous, migratory lesion that typically is found over the abdomen,
torso, buttocks, and/or groin. Lesions typically last for a couple of days and may reoccur weeks to
months later. Rarely, immune-mediated disease may occur, such as reactive arthritis.

Autoinfection will, in immunocompetent hosts, produce a negligible or minimally symptomatic
chronic disease. However, in immunosuppressed individuals, auto-infection can lead to severe
disease, called Strongyloides hyperinfection syndrome (SHS) that can occur decades after the initial
infection. SHS typically presents as intestinal or pulmonary failure. Cutaneous and intestinal
mucosal bleeding may be pronounced, and, if left untreated, SHS has a mortality ratio of close to
100%. Disseminated strongyloidiasis occurs when large numbers of parasites spread beyond the
conventional parasite pathway, and may potentially affect any organ system, including the hepatic,
urogenital, central nervous, musculoskeletal, and cardiovascular organ systems. High-risk individuals
include immunosuppressed patients, i.e. patients on immunosuppressive drugs, especially
corticosteroids and vincristine, and patients with hypogammaglobinaemia, haematologic
malignancies, and HTLV-1 infection.

**DIAGNOSIS**

Individual diagnosis of STH requires knowledge of the geographical distribution of the infections, as
well as the varied, and often overlapping, clinical picture of disease. Returning visitors from endemic
areas typically present with acute, light-intensity infections, whereas individuals living in, and
emigrants from endemic areas are prone to repeated exposure and chronic disease, some with very
high worm burdens.\textsuperscript{89-91} Besides microscopy, which is widely used for stool diagnosis, antibody assays, although yet to be standardised, may in well-resourced settings aid diagnosis of returning travellers with first-time exposure and/or in stool-negative cases.\textsuperscript{92} Also, novel polymerase chain reaction (PCR) assays are being developed for STH, both in clinical case management and for public health purposes; however, the tests have yet to be made broadly available (see Outstanding research).\textsuperscript{93, 94} Co-infections with multiple parasites are a common finding in endemic areas, and may make individual diagnosis challenging.\textsuperscript{95-97} Table 2 indicates the most common differential diagnoses that should be considered.

\textbf{Ascaris lumbricoides}. The diagnosis of ascariasis depends on the clinical presentation, and requires identification of parasite eggs, larvae and/or adult worms. In patients presenting with a clinical picture of Loeffler syndrome, chest x-ray may show infiltrates (Figure 4), and bronchoscopy may show evidence of bronchitis. Examination of sputum, bronchoalveolar lavage and/or gastric aspirate may reveal filariform \textit{Ascaris} larvae.\textsuperscript{68} Eosinophilia and increased titres of IgE are associated with acute, larval infections; however, the response is not specific for \textit{Ascaris} and may also occur in other conditions, including other parasite infections and allergies.\textsuperscript{98}

In intestinal infection, light microscopy of stool remains the mainstay of detection and quantification of \textit{A. lumbricoides} eggs (see Figure 2 for size and schematic appearance).\textsuperscript{99-101} Hospital-based laboratories commonly employ concentration techniques with a higher sensitivity for detection of eggs in stool samples, whereas simplified, field-friendly tests, such as Kato-Katz, are used in public health control programmes. Although Kato-Katz egg counts positively correlate with individual worm burden, results are observer-dependent.\textsuperscript{19, 102, 103} Treatment-induced worm expulsion can be used for \textit{A. lumbricoides}, but is cumbersome and resource-consuming, and rarely used as a primary diagnostic. Other reliable and relatively field-friendly stool preparation techniques include McMaster, FLOTAC, and mini-FLOTAC, which concentrate the stool and can be more sensitive than Kato-Katz.\textsuperscript{101}

All techniques are limited by variability of day-to-day egg excretion in stool, as well as focal distribution of eggs within each stool sample, which may provide false negative results, especially in low-intensity infection and post-treatment.\textsuperscript{101-103} In infants, whose stools may be more liquid than other age groups in general, concentration methods were reported to be more sensitive than non-concentration methods.\textsuperscript{104} In early-stage infections, typically seen in returning visitors from endemic areas, parasite eggs may not appear in stool for months after exposure and onset of symptoms. In such cases, clinical alertness is required and attention to travel history and clinical symptoms and signs is essential. An IgG4 enzyme-linked immunosorbent assay (ELISA) assay for detection of \textit{A. lumbricoides} haemoglobin (AsHb) has recently been shown to reflect recent \textit{Ascaris} exposure; however, the test may cross-react with other helminth co-infections\textsuperscript{105}

In patients presenting with acute abdomen, ultrasonography and plain abdominal x-ray are low cost, commonly available techniques that may identify \textit{A. lumbricoides} in the gut, as well as signs of obstruction, i.e. air-fluid levels, dilated bowel loops and thickened bowel wall (Figure 5).\textsuperscript{76, 106-108} Computed tomography (CT), including contrast enhanced CT (CECT) and magnetic resonance imaging (MRI) scans can support the diagnosis, but may not be needed in cases with positive ultrasonography or plain x-ray.\textsuperscript{109} Ultrasoundography remains the diagnostic tool of choice for suspected hepatobiliary and pancreatic ascariasis (Figure 6A),\textsuperscript{76, 81, 110} although its sensitivity may be poor, especially in duodenal ascariasis.\textsuperscript{107} Upper endoscopy may identify \textit{A. lumbricoides} in the duodenum, and endoscopic retrograde cholangiopancreatography (ERCP) can be used to remove worms from the ducts and
duodenum (Figure 6B).\textsuperscript{76,81} Case reports indicate that capsule endoscopy may be an advanced diagnostic tool, especially when small intestine pathology is suspected;\textsuperscript{38,97} however, it is currently not commonly used.

**Trichuris trichiura**. In uncomplicated cases, detection and quantification of parasite eggs by microscopy is sufficient for diagnosis (see Figure 2), with the same limitations as outlined above for *A. lumbricoides*.\textsuperscript{19,103} Colonoscopy may detect *Trichuris* in challenging or severe cases (Figure 7), and biopsies may be needed to confirm diagnosis.\textsuperscript{50,111,117} In patients presenting with *Trichuris* dysentery syndrome, examination and evaluation of anaemia is essential, and microcytic, hypochromic erythrocytes are typical indicators of any associated iron-deficiency anaemia.

**Ancylostoma duodenale, N. americanus**. Patients presenting with Loeffler syndrome, although rare, may be diagnosed with chest x-ray (infiltrates), bronchoscopy (bronchitis), or identification of filiform larvae in sputum or bronchoalveolar lavage.\textsuperscript{68} In intestinal infection, detection and quantification of hookworm eggs in stool is the mainstay of diagnosis (see Figure 2), with the same limitations as described above for *A. lumbricoides*.\textsuperscript{113,114} In addition, the sensitivity of hookworm diagnosis by Kato-Katz technique rapidly declines following sampling, and microscopy should be performed within an hour of slide preparation. Worm expulsion is possible, but rarely used. In well-resourced settings, hookworm may be detected by capsule endoscopy, but is not commonly applied.\textsuperscript{85,115,116} With any hookworm infection, it is essential to determine the extent of blood loss, which typically features microcytic, hypochromic anaemia.

**Strongyloides stercoralis**. In patients presenting with Loeffler syndrome, other than chest x-ray and bronchoscopy findings as described above for *Ascaris* and hookworm infections, *S. stercoralis* larvae may be detected in sputum, bronchoalveolar lavage or by lung biopsy. In intestinal infection, a single wet mount stool preparation may reveal filariform *S. stercoralis* larvae,\textsuperscript{117} although concentration of fresh stool collected on three alternate days may be required for diagnosis. The Baermann method and Koga agar plate culture are among the best techniques to diagnose *S. stercoralis*;\textsuperscript{100} however, they are not commonly in use.\textsuperscript{118} In contrast to other soil-transmitted helminth infections, the Kato-Katz technique is not relevant for diagnosis of *Strongyloides*. A coproantigen test for *S. stercoralis* has been found to be more sensitive than microscopy and the agar plate culture method, and has low cross reactivity with hookworm, *Trichuris* and *Schistosoma mansoni*.\textsuperscript{119} Duodenoscopy with duodenal biopsies can reveal eggs, larvae and/or adult worms, and plain abdominal x-ray, CECT and MRI abdomen may help evaluate gut damage.\textsuperscript{117}

Clinical alertness is vital when patients present with *S. stercoralis* hyperinfection syndrome, as infection may occur decades after the initial infection and can lead to organ failure. History of potential exposure, immunosuppression and a combination of clinical findings and laboratory results are critical for a rapid and accurate diagnosis. One of the hallmarks of hyperinfection is a high *S. stercoralis* worm burden in affected organs, and targeted biopsies may identify *S. stercoralis* adult worms, larvae and/or eggs (Figure 8).\textsuperscript{29} Titres of IgE and eosinophils can be either highly elevated or depleted, depending on host factors and disease progression.\textsuperscript{72} Serological tests for *S. stercoralis* with methods such as ELISA and luciferase immunoprecipitation, have shown promising results,\textsuperscript{120-122} and PCR of blood and/or cerebrospinal fluid (CSF) samples is available in some well-resourced settings.\textsuperscript{123,124}

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**CLINICAL MANAGEMENT AND FOLLOW-UP**
In addition to targeted, disease-specific interventions, health education on the prevention of infection and reinfection has been found effective in reducing disease burden. Individual patients should therefore be provided with relevant information, in particular on adequate sanitation and hygiene facilities and practices, and on the use of footwear to protect against hookworm infection. In endemic areas, patients may be at risk of reinfection, and the WHO recommends regular preventive chemotherapy, especially in children and pregnant women.

**Ascaris lumbricoides.** Albendazole 400 mg or mebendazole 500 mg in a single oral dose, or mebendazole 100 mg twice a day for three days is recommended in uncomplicated, stable patients older than 12 months (Table 3). Alternatively, ivermectin may be given in a single dose of 150-200 µg/kg of body weight. Albendazole might be slightly more efficacious than mebendazole, with a single dose of albendazole curing 85% of infected individuals (95% confidence interval (CI): 73%-96%), and three doses curing 92% (95% CI: 83%-100%).

Patients with intestinal obstruction require intravenous fluids and electrolytes, anthelmintics and, if systemic infection is suspected, antibiotic treatment. In uncomplicated small bowel obstruction, orally swallowed contrast medium may prompt worm expulsion more rapidly than observation. Patients with worms located in the appendix, small intestines, stomach or oesophagus should be given anthelmintic drug therapy in addition to any required surgical or endoscopic intervention.

Laparotomy and manual expression or enterotomy to remove the worms, and resection of any gangrenous tissue may be necessary in persistent cases of small bowel obstruction, volvulus or intussusception despite conservative primary treatment. In unstable cases, anthelmintic treatment should be given once the patient has been stabilised, or under close monitoring, and with supportive treatment where necessary. Acute abdomen caused by *A. lumbricoides* during the second and third trimesters of pregnancy and in puerperium may be treated with benzimidazoles, although laparoscopy may be required to exclude other causes.

Monitoring the effectiveness of treatment is recommended in cases of *A. lumbricoides* requiring surgery and in cases with a high worm burden, and up to three alternate days of stools samples should be examined two weeks post-treatment, unless the clinical condition indicates earlier follow-up.

Empirical data suggest that hepatobiliary ascariasis may be treated with drug therapy alone if conservative treatment is unsuccessful, and with any severe systemic infection, worm extraction and biliary drainage may be done using duodenoscopic basket or ERCP, and nasobiliary catheter. In both cases, treatment and follow-up should be ensured through relevant imaging, e.g. ultrasonography.

**Trichuris trichiura.** A three day regimen of either albendazole 400 mg, mebendazole 500 mg, or mebendazole 100 mg twice daily is recommended for adults and children with *T. trichiura* infection (Table 3). Alternative treatment options are ivermectin 200 µg/kg once daily for three days, or pyrantel pamoate 11 mg/kg base (maximum of 1 g) once daily for three days. Single albendazole and mebendazole treatments have a limited effect, and even three doses of albendazole may cure only 83% (95% CI: 73%-93%). Iron supplementation should be considered in patients with severe or symptomatic anaemia, and supportive treatment is warranted in patients with dysentery. Due to the partial efficacy of anthelmintic drugs on *T. trichiura* infection, cases with high worm load and/or dysentery should be monitored for effectiveness of treatment.

Given the worms’ physical attachment to the colonic mucosal wall, a case study has suggested that colonoscopy could be useful for diagnosis and potentially treatment of severe cases of trichuriasis. However, endoscopy is currently not commonly used for this purpose, and more efficacious and
accessible treatment options are needed for *T. trichiura*. Interestingly, drug combinations of benzimidazoles and ivermectin, and of benzimidazoles and repurposed veterinary drugs such as oxantel pamoate and milbemycin may effectively treat *Trichuris*, and trials are currently being conducted to determine their dosage, indications and effect in human STH. An optimum therapeutic dose range of 15-30 mg/kg oxantel pamoate was recently defined for *T. trichiura* infection in 6-14 year olds.

**Ancylostoma duodenale, N. americanus.** Treatment with albendazole or mebendazole is recommended as described above for uncomplicated *Ascaris* infection (Table 3), although single dose treatment could be insufficient, and three doses of albendazole may be needed to cure 93% (95% CI: 81%-100%). Data on unspecified hookworm infection in south-eastern Asia suggest that a single dose of either drug may have limited efficacy as measured by cure rate. Iron supplementation, additional nutritional support and monitoring of treatment effect should be considered in patients with high worm burden and/or severe anaemia. Phase III trials of tribendimidine, a recently developed broad-spectrum anthelmintic agent, may identify an even more efficacious treatment option against hookworm and other soil-transmitted helminths.

**Strongyloides stercoralis.** Ivermectin 200 µg/kg once daily for two days is recommended for infected asymptomatic and symptomatic individuals (Table 3). Alternatively, albendazole 400 mg may be given twice daily for seven days, or thiabendazole 25 mg/kg/12 h for three days. In *Strongyloides* hyperinfection, ivermectin treatment should continue until stool and/or sputum samples are negative for two 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 where oral treatment is not possible, such as in individuals with severe intestinal morbidity; however, indication and dosage needs to be considered on a case-by-case basis.

Patients treated for *S. stercoralis* infection should be followed up with triple stool examinations two to four weeks post-treatment, and retreatment should be provided if necessary. *Strongyloides* serology may be useful for defining cure six months post-treatment. Patients with SHS require stringent follow-up, including repeat endoscopy, biopsies, and information on preventive measures (see Clinical presentation) to avoid recurrence.

**Drug-associated safety precautions**

Potential side effects of benzimidazoles and ivermectin are mostly mild and self-limiting, although allergic reactions may require specific treatment and follow-up. Benzimidazoles have been shown to be teratogenic in experimental animal studies and are not recommended in the first trimester of pregnancy. However, in individuals with high-intensity infection, treatment with mebendazole in the first trimester may 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. 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 may decrease the efficacy of albendazole and mebendazole, and an outbreak investigation suggested an association between Stevens-Johnson syndrome and co-administration of metronidazole and mebendazole. The quality of generic benzimidazoles is uneven; and many have inadequate efficacy against STH. Contraindications for ivermectin include *Loa loa* infection, with potentially fatal side effects, and infections in children and pregnant or lactating women.
cases of extra-intestinal hookworm and *Strongyloides* infection, anthelmintic drugs can be taken with food in order to increase their bioavailability.

PUBLIC HEALTH CONTROL

Current WHO guidelines recommend MDA of benzimidazoles in areas where *A. lumbricoides*, *T. trichiura* and/or hookworm infection prevalence exceeds 20%; the frequency ranging from one to three times per year depending on STH prevalence.\(^6\)\(^,\)\(^145\) The WHO’s goal for morbidity control for 2020, elimination of STH as a public health problem, is defined as reducing the prevalence of moderate and heavy intensity infections to <1%, based on egg counts.\(^7\) The current school-based deworming platforms have been shown to reduce intensity and, ultimately, prevalence of infection,\(^7\)\(^,\)\(^8\)\(^,\)\(^146\) however, mathematical modelling indicates that additional platforms will be needed to control hookworm, as prevalence and intensity are typically highest in adults.\(^146\)\(^,\)\(^147\) The results of a survey of experts suggest that STH elimination may still be aspirational in most endemic areas and that community-wide treatment and increased access to improved WASH will be needed to further control STH.\(^148\) Recently, reviews conducted by the Cochrane and Campbell Collaborations have questioned the effect of population-level deworming on health outcomes, school performance and cognition in children (see Controversies).\(^149\)\(^-\)\(^151\)

Public health resolutions endorsed by the World Health Assembly (WHA) have mobilised member states to scale up STH control programmes, and have stimulated interest in the global distribution, clinical management, and evidence-based measures to control STH. Both mebendazole and albendazole are currently donated to the WHO free of charge by Johnson & Johnson and GlaxoSmithKline, respectively, for mass treatment of at-risk school-age children. For pre-school-age children, drugs are purchased by governments or other groups and are often co-administered with vitamin A during child health days.\(^152\) Only a single dose is normally administered through mass deworming campaigns, resulting in acceptable reductions in infection intensity but suboptimal cure rates, especially in areas with high burden of *Trichuris* and or hookworm infection. At present, *S. stercoralis* is rarely intentionally targeted by STH control programmes, neither through geographical mapping of infection, mass treatment nor monitoring of treatment effect.\(^11\)

Several challenges remain towards reaching the WHO targets for 2020. Firstly, although 63% of school-age children and almost half of pre-school-age children in need of treatment are currently being dewormed for *A. lumbricoides*, hookworm, and *T. trichiura*,\(^7\) only 30% and 28% of countries where these children live, respectively, have achieved the 75% treatment coverage target.\(^153\) Secondly, strongyloidiasis is not addressed in the WHO’s STH strategic plan, although its classification as an STH and the sensitivity of *S. stercoralis* to MDA of ivermectin, provided in LF- and onchocerciasis-endemic areas of Africa should make a strong case for targeting it.\(^7\)\(^,\)\(^11\) Thirdly, some 60 million school-age children and at-risk women of reproductive age live in LF-endemic areas that currently benefit from albendazole co-administered through the Global Programme to Eliminate LF.\(^154\) Unfortunately, the success of LF elimination and the scaling back of community-based drug distribution could increase their risk of STH unless other drug delivery platforms are put in place.\(^155\) Trials are being conducted to determine the feasibility of breaking STH transmission in post-LF MDA settings, and the results may inform a new generation of improved public health control programmes.\(^52\) Finally, some population groups are commonly left out of mass treatment programmes targeting STH, for example non-attending school-age children and women of reproductive age, and such at-risk populations require particular attention in both public health control programmes and individual case management.
CONTROVERSIES

In 2015, a Cochrane review of randomised clinical trials concluded that there is no population-level effect of deworming on a range of child health outcomes, including growth and haemoglobin levels. The findings have stirred a heated debate on the effectiveness of mass deworming policies and programmes as they currently stand. Having over the past 15 years synthesised randomised trials of mass deworming, the Cochrane Collaboration argues there is now reasonable evidence of little or no effect of deworming on health outcomes, school performance or cognitive development in children. A review conducted independently by the Campbell Collaboration, which also included data from other experimental trial designs, came to similar conclusions. Based on the findings, the authors suggest that additional policy options be considered to improve child health and nutrition in areas where mass deworming programmes are currently being implemented.

Critics of the Cochrane and Campbell reviews, on the other side, argue that no long-term trials have been conducted to determine the effect of periodic deworming, and that failure to detect diluted, population-level health benefits of mass deworming is an issue of measurement or statistical power and not a lack of benefit of deworming. As such, mass deworming in STH-endemic areas is warranted as the health benefits of treating individuals infected with STH are well established, mass distribution of anthelmintics is safe, and population-level deworming is more cost-effective than testing and treating individuals for infection. In fact, a recent, non-peer reviewed meta-analysis conducted by World Bank and Harvard University health economists reported a significant weight gain in dewormed children, highlighting the differing methods and approaches of health science and economic disciplines in the debate. Yet others have suggested that expanding deworming programmes to include the whole community would more effectively reduce STH prevalence and result in measurable reductions in morbidity in school-age children.

Some authors have invoked the ‘hygiene hypothesis’ to argue that elimination of STH transmission could remove the stimulus needed for maturation of the immune system. Whereas some clinical research is exploring the effects of deliberate low-intensity *T. suis* and *N. americanus* infections on autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and coeliac disease, other data have found a positive association between helminth infections and atopy, contradicting the ‘hygiene hypothesis’. Indeed, a recent review argues that the ‘hygiene hypothesis’ is not valid with regard to helminth infections, and suggests that research should rather prioritise identifying potential helminth-derived therapeutic molecules.

Finally, data suggest that deworming may have beneficial effects on co-infections such as HIV, and further research is needed to determine the impact of anthelmintic treatment on malaria.

OUTSTANDING RESEARCH

One of the principal bottlenecks for adequate individual diagnosis and management, as well as public health control of STH, has been insufficient investment in research and development of diagnostic tools and treatment options. This is especially true for *Strongyloides*, which has been called the most neglected of NTDs. Improved, accessible, and affordable diagnostic tools are needed to facilitate detection of all soil-transmitted helminth infections, particularly where intensity and prevalence are reduced through mass drug treatment.
Currently, mainly microscopic techniques are used to determine the distribution of *Ascaris, Trichuris* and hookworm in endemic areas for public health control. The distribution of all soil-transmitted helminths is 'over-dispersed', i.e. relatively few heavily-infected individuals harbour the majority of the worms, and in order to detect the majority of individuals carrying low-intensity infections, sensitive, field-friendly tools to diagnose and control infection are needed.

At present, no standardised serological antigen tests exist for STH in humans, although such assays exist in veterinary medicine for *T. vulpis* and *T. suis*. Research and development is needed to determine the potential of serological diagnostic tools for STH, including antibody tests for assessment of disease transmission in low-endemic areas, and antigen tests for detection of active infections. Multiplex PCR tests for multiple co-infections, and the use of next-generation sequencing to improve primers for PCR and loop- mediated isothermal amplification (LAMP), show promising results, but require validation as well as adaptation for field-friendly use. Even if DNA amplification methods become field-friendly, challenges to DNA extraction remain, and quality assurance procedures will be essential.

Although commonly observed in veterinary practice, drug resistance to anthelmintics in humans has not yet been documented. Enhanced and continued surveillance, novel drug development and drug-combination investigations are needed to address the inherent concerns of the development of resistance as a consequence of mass distribution programmes. Randomised control trials are currently being conducted to determine the indications and efficacy of tribendimidine, and of combinations of benzimidazoles and ivermectin, oxantel pamoate, and milbemycin, respectively. If these drug combinations are deemed safe and effective their combined use could be endorsed for proactive prevention of drug resistance. Effective vaccines against STH could yield high, long-term impact on the control of STH. The eukaryote nature of parasites makes development of effective vaccines challenging; however, both a hookworm and a 'pan-helminthic' (targeting ascariasis, trichuriasis and hookworm infection) vaccine are currently being developed for human use.

As the global community aims to meet the targets set out in the Sustainable Development Goals (SDGs), further research is needed to identify relevant WASH interventions that may reduce the burden of STH. High quality evidence to inform alternative control strategies, such as community-wide MDA and vaccination programmes in conjunction with WASH interventions, are needed to ensure and optimise control of STH. Finally, increased awareness and knowledge of STH is needed among health care professionals, community health workers, and the general public to improve clinical case detection and management, and public health control.

**CONCLUSIONS**

Soil-transmitted helminth infections, here defined as *A. lumbricoides, A. duodenale, N. americanus, T. Trichiura*, and *S. stercoralis*, are highly prevalent, especially in individuals with limited access to clean water, sanitation, and hygiene. The clinician must consider STH infection in patients with a history of exposure in endemic areas and who present with a range of medical and surgical conditions. Safe and largely effective drugs against *Ascaris*, hookworm, and *Trichuris* are donated free of charge for school-age children in STH-endemic countries; however, the global community has a way to go to achieve the WHO goal for 2020. Increased knowledge of transmission dynamics and infection-associated morbidity, refined diagnostic tools, and more effective treatment strategies are needed to scale up public health control and to improve clinical detection and management of STH.
ACKNOWLEDGEMENTS

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AUTHORS’ CONTRIBUTIONS

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

COMPETING INTEREST STATEMENT

DEWORM3 is funded by the Bill & Melinda Gates Foundation to determine the feasibility of interrupting STH transmission. PL is funded by a European Research Council Starting Grant [680088 SCHISTO_PERSIST], a Wellcome Trust Grant [105614/Z/14/Z], and is a Lord Kelvin Adam Smith Leadership Fellow. The Task Force for Global Health (where DA is employed) receives funding from Johnson & Johnson and GlaxoSmithKline to provide technical and programmatic support to the STH Coalition, a broad coalition of public and private partners engaged in global STH control.

PMJ, PL, AF and DA declare no conflicts of interest.

TABLES

**Table 1. Symptoms and signs of soil-transmitted helminth infections**

<table>
<thead>
<tr>
<th></th>
<th>A. lumbricoides</th>
<th>T. trichiura</th>
<th>Hookworm</th>
<th>S. stercoralis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At-risk individuals</strong></td>
<td>Children, adults</td>
<td>Children, adults</td>
<td>Adults, children</td>
<td>Adults, children; immunosuppressed patients (SHS)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td>Unremarkable, or history of STH</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>General</td>
<td>Commonly asymptomatic, or mild, non-specific symptoms, asthenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early stage infection</td>
<td>Cough, dyspnoea, haemoptysis, rash</td>
<td>Non-specific</td>
<td>Cough, dyspnoea, haemoptysis, rash; Ground itch - an intense itch, usually of the foot or lower leg</td>
<td>Cough, dyspnoea, rash; may become severe in immunosuppressed patients</td>
</tr>
</tbody>
</table>
### Acute, Chronic Established Infection
- Anorexia, abdominal pain and discomfort, diarrhoea and weight loss; in severe cases, acute abdomen with systemic affection, biliary colic
- Anorexia, abdominal pain and diarrhoea, sometimes with dysentery
- Abdominal pain, diarrhoea, dyspnoea
- Anorexia, nausea, abdominal pain and diarrhoea

### Signs
**General**
- Asthenia, anaemia, jaundice, fever if acute cholecystitis or cholangitis, hepatic abscess
- Asthenia, anaemia (may become severe in TDS)
- Pallor, tachypnoea, tachycardia; Ascites and other forms of oedema
- Multi-organ failure in SHS; Petechiae and purpura

**Early Stage Infection**
- Abnormal auscultatory breath sounds
- Non-specific
- Abnormal auscultatory breath sounds
- Abnormal auscultatory breath sounds

**Acute, Chronic Established Infection**
- Occult or fresh blood in stool, abdominal tenderness, including right upper quadrant tenderness, peritonitis
- Digital clubbing, abdominal tenderness (TDS), in some cases, rectal prolapse
- Abdominal tenderness, occult blood in the stool, rarely melena
- Abdominal tenderness; Larva currens - urticarial, serpiginous, migratory lesion over abdomen, torso, buttocks or groin; In SHS, intestinal and pulmonary mucosal bleeding, cutaneous.

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**Table 2. Differential diagnoses of soil-transmitted helminth infections**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Differential diagnoses</th>
<th>Relevant STH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia, anorexia</td>
<td>Other infectious diseases, autoimmune diseases, other causes of anaemia, malignancy, non-specific</td>
<td>All STH, including <em>S. stercoralis</em></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Other causes of anaemia (iron-deficiency anaemia, micronutrient deficiencies hereditary causes)</td>
<td>Hookworm, <em>T. trichiura</em></td>
</tr>
</tbody>
</table>
### Table 3. Anthelmintic treatment of soil-transmitted helminth infections

<table>
<thead>
<tr>
<th></th>
<th>A. lumbricoides</th>
<th>T. trichiura</th>
<th>Hookworm</th>
<th>S. stercoralis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>Albendazole 400 mg</td>
<td>Once daily for three days</td>
<td>Single dose</td>
<td>Ivermectin 200 µg per kg once daily for 2 days</td>
</tr>
<tr>
<td>OR</td>
<td>Mebendazole 500 mg</td>
<td>Single dose</td>
<td>Once daily for three days</td>
<td>Single dose</td>
</tr>
<tr>
<td>OR</td>
<td>Mebendazole 100 mg twice daily for three days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td></td>
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<tr>
<td>Ivermectin in a single dose of 150-200 µg/kg</td>
<td>Ivermectin 200 µg/kg once daily for three days</td>
<td>Albendazole may be given 400 mg twice daily for seven days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Pyrantel pamoate 11 mg/kg base (maximum of 1 g) once daily for 3 days</td>
<td>Thiabendazole 25 mg/kg/12 h for three days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Parenteral ivermectin</td>
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</tr>
</tbody>
</table>

**Relative contraindications**: Adverse reactions to drugs, first trimester of pregnancy, <1 year of age, anti-convulsant drug therapy (albendazole and mebendazole); children, pregnant* and lactating women, Loa loa co-infection (ivermectin, can be fatal);

- STH = soil-transmitted helminthiasis;
- TDS = *Trichuris* dysentery syndrome;
- SHS = *Strongyloides* hyperinfection syndrome

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639 STH = soil-transmitted helminthiasis; TDS = *Trichuris* dysentery syndrome; SHS = *Strongyloides* hyperinfection syndrome

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643 All treatment is oral, except for experimental parenteral treatment in *Strongyloides* hyperinfection syndrome (SHS). Additional treatment options may be approved for treatment in humans, including
combination therapy of benzimidazoles and ivermectin, and of benzimidazoles and oxantel pamoate or milbemycin against in particular *T. trichiura*, and tribendimidine for treatment of hookworm.

Adapted from 127. * In women with high-intensity infection, treatment with mebendazole in the first trimester may 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.

FIGURES

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

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

**Figure 2.** Transmission of *Ascaris lumbricoides* (A), *Trichuris trichiura* (B), hookworm infection (C), and *Strongyloides stercoralis* (D).

*Ascaris lumbricoides* (A). Fertilised eggs get swallowed, release larvae that moult into second-stage (L2) larvae, that in turn penetrate the host intestinal mucosa and migrate to the pulmonary circulation. Third-stage (L3) larvae migrate across the alveolar wall, are swallowed again and moult into fourth-stage (L4) larvae in the small intestine. Adult female *A. lumbricoides* worms can release thousands of eggs daily that pass into the environment and hatch to produce larvae that can survive in the soil for several years.

*Trichuris trichiura* (B). Infective embryonated eggs are ingested and hatch into larvae that moult in the small intestine. The larvae develop into adult worms, and continue to reside in the caecum and the ascending colon. Adult female worms lay several thousand eggs per day, which pass in the stool and survive in the environment for several months.

*Ancylostoma duodenale, Necator americanus* (C). Hookworm larvae infect humans by penetrating bare skin, and are transported to the pulmonary capillaries where they penetrate the alveolar wall, pass to the larynx and are swallowed. The larvae moult and develop into mature worms in the small intestine, and female adult worms release thousands of eggs daily that pass in the stool and hatch in warm, moist, sandy soil or in the faeces to produce rhabditiform, first-stage (L1) larvae. Larvae become infective after rapid moulting to third-stage (L3) larvae that can survive in the environment for weeks.

*Strongyloides stercoralis* (D). Infective filariform larvae may infect humans both percutaneously and orally. Following penetration of the skin, larvae are transported to the pulmonary circulation, penetrate the alveoli, pass to the larynx and swallowed to enter the small intestine where they mature to adult worms. Oral infection follows the same cycle after penetrating the intestinal mucosa. The female adult lodges in the lamina propria of the duodenum and jejunum and may lay up to 50 eggs a day that hatch within the gut wall to become rhabditiform larvae that migrate in to the lumen and are passed with the stools. The larvae may penetrate the colonic wall or perianal skin.
to enter a new cycle, or may disseminate to other organ systems. Larvae (or unhatched eggs) that
get expelled in the stool may survive in moist soil for several weeks, and develop into infective
larvae.

Adapted from www.cdc.gov/parasites.

Figure 3. Endoscopic images of intestinal *Ascaris lumbricoides* and hookworm co-infection (A),
*Trichuris trichiura* (B), and hookworm infection (C).

Note the size of the partially visible *Ascaris* worm in relation to the lumen, as well as multiple blood-
filled hookworms visualised through narrow band imaging (A), the whip-shape part (not visible) of
*Trichuris* burrowed into the mucosa (B), and mucosal bleeding associated with the hookworm
infection (C). With permission by Dr Kunimitsu Inoue.

Figure 4. Eosinophilic pneumonia (Loeffler syndrome).

Posteroanterior chest x-ray of 35-year-old male presenting with fever, tachypnoea, and eosinophilia,
showing bilateral, peripheral mottled infiltrates. *Ascaris* larvae were identified in sputum and gastric
aspirate samples. (Reprinted from Gelpi AP, Mustafa A. *Ascaris* pneumonia. The American Journal of
Elsevier.)

Figure 5. *Ascaris*-induced intestinal obstruction.

A. Plain abdominal x-ray of 3-year-old female with *Ascaris*-induced intestinal obstruction showing
air-fluid levels, dilated bowel loops and multiple worm structures, and B. Ileum enterotomy with
extraction of causative bolus of *Ascaris* worms. (Reprinted from Andrade AM, Perez Y, Lopez C et al.
Intestinal Obstruction in a 3-Year-Old Girl by *Ascaris lumbricoides* Infestation: Case Report and
2015, with permission from Wolters Kluwer.)

Figure 6. Biliary and pancreatic ascariasis.

A. Abdominal ultrasonography showing the dilated common bile duct containing a thick, long, non-
shadowing echogenic strip with a central sonoluent tube (arrow), representing the digestive tract of
*Ascaris*, and B. Endoscopic retrograde cholangiopancreatography in *Ascaris*-induced pancreatitis
showing the pancreatic duct containing a filling defect in distal part (arrows) and the common bile
duct containing multiple *Ascaris* worms. (Reprinted from Khuroo MS, Zargar SA, Yattoo GN et al.

Figure 7. *Trichuris* dysentery syndrome.

Colonoscopy of 15-year-old female with *Trichuris* dysentery syndrome showing massive infestation
of *Trichuris* worms (posterior segments visible), petechial lesions, mucosal haemorrhages and
oedema. (Reprinted from Khuroo MS, Khuroo MS, Khuroo NS. *Trichuris* dysentery syndrome: a
common cause of chronic iron deficiency anemia in adults in an endemic area (with videos).
permission from Elsevier.)

Figure 8. *Strongyloides* hyperinfection syndrome.
Human T-cell lymphotrophic virus (HTLV)-1 positive 62-year-old female with acute respiratory distress syndrome following high-dose corticosteroids during chemotherapy for cervical cancer. Bronchoscopy (A) showed diffuse intrabronchial haemorrhage, and microscopy of Papanicolaou stain of bronchoalveolar lavage fluid (B) revealed multiple filariform S. stercoralis larvae (left image x20, right image x400). (From Kinjo T, Nabeya D, Nakamura H et al. Acute Respiratory Distress Syndrome due to Strongyloides stercoralis Infection in a Patient with Cervical Cancer. Internal Medicine; 54(1): 83-87. http://www.naika.or.jp/imonline/) Awaiting response from permission request)
Panel 1:

**FAST FACTS**

**Soil-transmitted helminths** infect humans through faecal-oral transmission or skin penetration. These infections are among the most common diseases in the world, and are caused by the parasites *Ascaris lumbricoides, Trichuris trichiura, hookworm (Ancylostoma duodenale and Necator americanus)* and *Strongyloides stercoralis*.

The main risk factors for STH include living in or returning from areas with limited access to adequate sanitation and hygiene.

**Clinical presentation.** Most individuals are asymptomatic or experience mild symptoms. So-called eosinophilic pneumonia, or Loeffler syndrome, may occur 10–14 days after infection with *A. lumbricoides*, hookworm or *S. stercoralis*. It presents as a usually self-limiting urticaria, cough, dyspnoea, and haemoptysis with abnormal auscultatory breath sounds. Common to all soil-transmitted helminth infections are asthenia, lack of appetite (anorexia), abdominal pain, diarrhoea or other altered bowel habits and weight loss. Species-specific features in severe cases include:

- **Ascaris lumbricoides** - Acute abdomen due to upper gastrointestinal bleeding, small bowel obstruction, intestinal volvulus and intussusception, peritonitis, and hepatobiliary and pancreatic ascarisis manifesting as biliary colic, acute cholecystitis, acute pancreatitis, acute cholangitis, and hepatic abscesses;
- **Trichuris trichiura** - A syndrome of anaemia, digital clubbing, abdominal tenderness and, in some cases, rectal prolapse (*Trichuris* dysentery syndrome);
- **Hookworm** - Anaemia, sometimes severe, with pallor, tachypnoea, tachycardia and protein deficiency;
- **Strongyloides stercoralis** - *Strongyloides* hyperinfection syndrome manifests as severe intestinal and pulmonary inflammation in immunosuppressed (especially corticosteroid-induced) patients. Disseminated *Strongyloides* can affect any organ system, including the central nervous, musculoskeletal, cardiovascular, hepatic and urogenital organs.

**Diagnosis.** Detection and quantification of *A. lumbricoides*, hookworm and *T. trichiura* eggs and of *S. stercoralis* larvae in stool by microscopy remains the mainstay of diagnosis, despite low sensitivity, and at least three stool samples on alternate days may be required to identify the cause of infection. In early-stage infections, parasite eggs or larvae may not appear in stool, and antibody assays and polymerase chain reaction (PCR) may aid diagnosis.

Ultrasonography, plain abdominal x-ray, computed tomography (CT), including contrast enhanced CT, and magnetic resonance imaging (MRI) scans may identify infections and/or determine the extent of gut pathology. Gastroduodenoscopy, colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) may serve as both diagnostic and therapeutic tools, and duodenal biopsies may identify *S. stercoralis* eggs, larvae and/or adult worms.

**Treatment and follow-up.** *A. lumbricoides, T. trichiura* and hookworm infections may be treated effectively with albendazole or mebendazole, although repeated treatment might be necessary for cure, particularly for *T. trichiura*. *S. stercoralis* infection may be treated with ivermectin, albendazole or thiabendazole. Alternative drugs and drug combinations are currently being trialled for treatment of STH. Follow-up of severe infection is required, including treatment of anaemia if relevant.
Reinfection is frequent in endemic areas, and periodic re-treatment with an anthelmintic drug is warranted, in addition to relevant sanitary and hygienic health education.

Panel 2. Features of clinical versus public health control of STH

<table>
<thead>
<tr>
<th>Feature or factor</th>
<th>Clinical diagnosis and management</th>
<th>Public health control</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>Individual</td>
<td>Community-level (e.g. in selected schools)</td>
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<tr>
<td>Diagnostic criteria</td>
<td>Parasitological</td>
<td>Residence in an area with STH prevalence &gt;20%</td>
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<tr>
<td>Treatment approach</td>
<td>Single or multiple-dose</td>
<td>Single-dose periodic mass treatment</td>
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<tr>
<td>Threshold for treatment</td>
<td>Travel history, symptoms and signs, positive laboratory test</td>
<td>Estimated prevalence of infection in target population</td>
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<tr>
<td>Treatment objective</td>
<td>Parasitological cure</td>
<td>Deceased worm burden; reduction in transmission</td>
</tr>
<tr>
<td>Ancillary treatment</td>
<td>Based on clinical signs and symptoms</td>
<td>Typically, only if included in mass treatment (e.g. vitamin A supplementation)</td>
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<tr>
<td>Follow-up</td>
<td>Parasitological test of cure; improvement in associated health conditions</td>
<td>Not usually done</td>
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<tr>
<td>Health education (sanitation and hygiene)</td>
<td>Recommended</td>
<td>Recommended</td>
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Panel 3. 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 in the past five years especially. Furthermore, 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.
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953 53. Trichuris trichiura with chronic Trichuris trichiura dysentery. 
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