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

Peter Mark Jourdan (MD, PhD) [1,2], Poppy Helen Louise Lamberton (PhD) [3,4]*, Alan Fenwick (PhD) [1], David G. Addiss (MD) [5]

1 Schistosomiasis Control Initiative, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom

2 DEWORM3, Natural History Museum, Cromwell Rd, London SW7 5BD, United Kingdom

3 Institute of Biodiversity, Animal Health and Comparative Medicine, and Wellcome Centre for Molecular Parasitology, Graham Kerr Building, The University of Glasgow, Glasgow, G12 8QQ, United Kingdom

4 Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom

5 The Task Force for Global Health, 325 Swanton Way, Decatur, GA 30030, United States of America

*Corresponding author: Poppy Lamberton, Institute of Biodiversity, Animal Health and Comparative Medicine, and Wellcome Centre for Molecular Parasitology, Graham Kerr Building, The University of Glasgow, Glasgow, G12 8QQ, United Kingdom; poppy.lamberton@glasgow.ac.uk; telephone: +44 (0) 141 330 2064

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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.[1] 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.[2] In this seminar we also address an additional soil-transmitted helminth - *Strongyloides stercoralis* - which is an important, but often neglected, cause of severe morbidity.[3, 4] STH primarily affects individuals in communities with limited access to, and use of, water, sanitation, and hygiene (WASH) facilities[5] and is the most widespread among the so-called neglected tropical diseases (NTDs).[1]

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).[6] 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.[7] 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.[8-10] 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.[1, 11] 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.[12] 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.[13]

Ascaris lumbricoides (roundworm) infects an estimated 804 million people worldwide, most commonly pre-school-age children, school-age children and adolescents in endemic countries.[14-16] 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.[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.[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.[18]

Trichuris trichiura (whipworm) infects an estimated 477 million individuals, and prevalence and intensity of infection are typically highest in children.[16, 19, 20] However, data are scarce and suspicion of infection should not be limited by current endemicity maps.[17] Over the past 10 years, the DALYs due to *Trichuris* have declined to just above 500,000;[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*.[18]

Ancylostoma duodenale *and* ***Necator americanus*** (hookworm) infect an estimated 472 million people.[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.[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.[17, 22]

Strongyloides stercoralis (threadworm) infects up to 100 million people globally;[1, 11] however, as with *T. trichiura*, the data are scarce and suspicion of infection should not be limited by endemicity maps.[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.[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).[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.[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).[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.[24, 26]

Ancylostoma duodenale and ***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).[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 (*A. duodenale*) or years (*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.[24]

In addition to percutaneous infection, *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. *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 *A. duodenale* and *N. americanus*, and may be more common than previously thought.[27]

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).[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.[29] Larvae (or unhatched eggs) that are expelled in the stool may survive in moist soil for several weeks, and develop into infective larvae.[30] *Strongyloides fuelleborni* which occasionally infects humans, follows the same life cycle.[11]

PATHOPHYSIOLOGY

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.[25, 31] Common complications in endemic areas include mechanical small bowel obstruction, volvulus and intussusception, especially in children.[32] Adult worms can further invade intestinal orifices, causing complications such as acute appendicitis, acute cholecystitis, pancreatitis and gastric ascariasis.[33]

Ascaris lumbricoides infection may cause malnutrition, including lactose intolerance and vitamin A deficiency.[34, 35] Recent findings suggest that *A. lumbricoides* might alter the normal intestinal

bacterial flora,[36] although *Ascaris* may also have a protective effect against severe enteric infections.[37] Anaemia may result from mucosal bleeding in the upper gastrointestinal tract or through a generalised inflammatory reaction to infection.[38]

Similar to other helminth infections, *A. lumbricoides* induces a predominantly type-2 T helper cell (Th2)-polarised immune response.[39, 40] 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.[41, 42] A shift in the age of peak infection prevalence and host immune response may be seen as partial immunity develops.[43] Further, host genetic factors may play a role in determining the intensity of *Ascaris* infection and disease presentation, including resistance to reinfection.[44] *Ascaris*-induced immunomodulation may affect the host's response to co-infections, including HIV, tuberculosis, malaria and human papillomavirus (HPV).[45-48] *Ascaris lumbricoides* infection may also be a risk factor for asthma and atopy, possibly through cross-reaction between parasite, mite and insect epitopes.[40, 49]

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.[50] Although not consistently apparent on endoscopy,[50] *Trichuris* may cause colonic mucosal inflammation,[22, 51, 52] which can potentially be influenced by individual immune regulation and gut microbiota.[53, 54] Morbidity is positively associated with intensity of infection,[55] and trichuriasis can lead to both mucosal and systemic changes in immune response and resistance to reinfection.[56, 57]

Eosinophils are a typical feature of especially acute *T. trichiura* infection, and play a role in local gut pathology.[58] In animal models, *Trichuris* worm expulsion has been associated with intestinal epithelial cell turnover, stimulated by cytokine responses.[59] In contrast to *A. lumbricoides* infection, *T. trichiura* infection is not associated with changes in intestinal bacterial flora,[36] and might even protect against severe diarrhoeal pathogens.[37] 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.[50, 60]

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,[61] and is a major cause of anaemia globally, particularly in children and pregnant women.[62, 63]

As with other helminths, hookworm infection is associated with a Th2 polarised immune response, regulated by IL-10 and transforming growth factor (TGF)-ß, both systemically and in the local intestinal mucosa.[64] Elevated IgE titres, IL-5 and eosinophilia are features of especially acute hookworm infection, and may play a role in intestinal immune response. [65]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.[66, 67]

Strongyloides stercoralis larvae migrating through pulmonary tissue may cause a type-1 hypersensitivity reaction, or Loeffler syndrome.[68] The adult worms burrow into the intestinal mucosal wall and cause local inflammation.[29] A Th2-dominated immune response is a pivotal factor in *S. stercoralis* infection, especially in preventing severe morbidity.[69] Eosinophils are a prominent feature of *S. stercoralis* infection, and may provide host protection especially in early-stage infection.[70]

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.[71] Bacterial septicaemia is an independent predictor of shock and mortality in disseminated infection.[72]

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,[20, 73, 74] and this may be due to both exposure and host susceptibility.[75] 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.[68, 76] 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.[77]

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.[33, 38, 76, 78-80] Hepatobiliary and pancreatic ascariasis may cause five broad clinical syndromes, including biliary colic, acute cholecystitis, acute pancreatitis, acute cholangitis and hepatic abscess.[81] 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.[82-84] 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.[76]

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.[55] These features may be pronounced in high-intensity infection, which can lead to severe anaemia.[50]

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.[68] In peroral infection, nausea, vomiting, pharyngeal irritation, cough, and dyspnoea may occur (Wakana syndrome).[63]

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.[85] In heavy intensity infections, anaemia may be severe, although most commonly smaller amounts of blood loss gradually deplete the patient of erythrocytes and nutrients.[86] 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.[62] 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, wheezing, and haemoptysis.[68] 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).[87] 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.[29] 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.[88]

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.[72] 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.[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.[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).[93, 94] Co-infections with multiple parasites are a common finding in endemic areas, and may make individual diagnosis challenging.[95-97] Table 2 indicates the most common differential diagnoses that should be considered.

***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 *Ascaris* larvae.[68] Eosinophilia and increased titres of IgE are associated with acute, larval infections; however, the response is not specific for *Ascaris* and may also occur in other conditions, including other parasite infections and allergies.[98]

In intestinal infection, light microscopy of stool remains the mainstay of detection and quantification of *A. lumbricoides* eggs (see Figure 2 for size and schematic appearance).[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.[19, 102, 103] Treatment-induced worm expulsion can be used for *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.[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.[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.[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 *A. lumbricoides* haemoglobin (AsHb) has recently been shown to reflect recent *Ascaris* exposure; however, the test may cross-react with other helminth co-infections[105]

In patients presenting with acute abdomen, ultrasonography and plain abdominal x-ray are low cost, commonly available techniques that may identify *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).[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.[109]

Ultrasonography remains the diagnostic tool of choice for suspected hepatobiliary and pancreatic ascariasis (Figure 6A),[76, 81, 110] although its sensitivity may be poor, especially in duodenal ascariasis.[107] Upper endoscopy may identify *A. lumbricoides* in the duodenum, and endoscopic retrograde cholangiopancreatography (ERCP) can be used to remove worms from the ducts and

duodenum (Figure 6B).[76, 81] Case reports indicate that capsule endoscopy may be an advanced diagnostic tool, especially when small intestine pathology is suspected;[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*.[19, 103] Colonoscopy may detect *Trichuris* in challenging or severe cases (Figure 7), and biopsies may be needed to confirm diagnosis.[50, 111, 112] 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 filariform larvae in sputum or bronchoalveolar lavage.[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*.[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.[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,[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[100]; however, they are not commonly in use.[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*.[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.[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).[29] Titres of IgE and eosinophils can be either highly elevated or depleted, depending on host factors and disease progression.[72] Serological tests for *S. stercoralis* with methods such as ELISA and luciferase immunoprecipitation, have shown promising results,[120-122] and PCR of blood and/or cerebrospinal fluid (CSF) samples is available in some well-resourced settings.[123, 124]

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.[125] In endemic areas, patients may be at risk of reinfection, and the WHO recommends regular preventive chemotherapy, especially in children and pregnant women.[126]

***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).[127] 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%).[128, 129]

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.[130] 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.[76] 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.[131] 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.[33] 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.[76, 81, 132] 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).[127] 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%).[129] Iron supplementation should be considered in patients with severe or symptomatic anaemia, and supportive treatment is warranted in patients with dysentery.[50, 133] 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.[112] 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.[134] An optimum therapeutic dose range of 15-30 mg/kg oxantel pamoate was recently defined for *T. trichiura* infection in 6-14 year olds.[135]

***Ancylostoma duodenale, N. americanus*.** Treatment with albendazole or mebendazole is recommended as described above for uncomplicated *Ascaris* infection (Table 3),[127] although single dose treatment could be insufficient, and three doses of albendazole may be needed to cure 93% (95% CI: 81%-100%).[128, 129] 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.[136] Iron supplementation, additional nutritional support and monitoring of treatment effect should be considered in patients with high worm burden and/or severe anaemia.[133] 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.[137]

***Strongyloides stercoralis*.** Ivermectin 200 µg/kg once daily for two days is recommended for infected asymptomatic and symptomatic individuals (Table 3).[127] Alternatively, albendazole 400 mg may be given twice daily for seven days, or thiabendazole 25 mg/kg/12 h for three days.[138] 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.[139-141]

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.[117]

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.[127] 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.[54, 142, 143] The quality of generic benzimidazoles is uneven; and many have inadequate efficacy against STH.[144] Contraindications for ivermectin include *Loa loa* infection, with potentially fatal side effects, and infections in children and pregnant or lactating women.[127] In

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*,[1] 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.[149] The findings have stirred a heated debate on the effectiveness of mass deworming policies and programmes as they currently stand.[150, 156] 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.[150] A review conducted independently by the Campbell Collaboration, which also included data from other experimental trial designs, came to similar conclusions.[151, 157] 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.[156] 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.[158] 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.[159]

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.[160, 161] 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, [161]other data have found a positive association between helminth infections and atopy, contradicting the 'hygiene hypothesis'.[162] 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.[163]

Finally, data suggest that deworming may have beneficial effects on co-infections such as HIV,[164, 165] and further research is needed to determine the impact of anthelmintic treatment on malaria.[166, 167]

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.[145] The distribution of all soil-transmitted helminths is 'over-dispersed', i.e. relatively few heavily-infected individuals harbour the majority of the worms.[20, 73, 74, 168] 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*.[169, 170] 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.[92] Multiplex PCR tests for multiple co-infections,[96, 171, 172] 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.[173] 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.[174] 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.[175, 176]

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.[177] 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.

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618

619 AUTHORS' CONTRIBUTIONS

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

623

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632

633 TABLES

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

	A. lumbricoides	***T. trichiura***	**Hookworm**	***S. stercoralis***
At-risk individuals	Children, adults	Children, adults	Adults, children	Adults, children; immunosuppressed patients (SHS)
Medical history	Unremarkable, or history of STH			
Symptoms				
General	Commonly asymptomatic, or mild, non-specific symptoms, asthenia			
Early stage infection	Cough, dyspnoea, haemoptysis, rash	Non-specific	Cough, dyspnoea, haemoptysis, rash; Ground itch - an intense itch, usually of the foot or lower leg	Cough, dyspnoea, rash; may become severe in immunosuppressed patients

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.

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

637

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

Clinical features	Differential diagnoses	Relevant STH
Asthenia, anorexia	Other infectious diseases, autoimmune diseases, other causes of anaemia, malignancy, non-specific	All STH, including *S. stercoralis*
Anaemia	Other causes of anaemia (iron-deficiency anaemia, micronutrient deficiencies hereditary causes)	Hookworm, *T. trichiura*

Loeffler syndrome	Pneumonia, asthma, other causes of dyspnoea	*A. lumbricoides*, hookworm, *S. stercoralis*
Abdominal discomfort, diarrhoea	Other gastrointestinal infections, inflammatory bowel disease, malignancies, non-specific	All STH, including *S. stercoralis*
Acute abdomen	Other causes of acute abdomen, including intestinal obstruction, pancreatitis, cholecystitis, intestinal perforation	*A. lumbricoides*, *S. stercoralis*
Trichuris dysentery syndrome	Other causes of dysentery, gastrointestinal infections	*T. trichiura*
Strongyloides hyperinfection syndrome	Other causes of disseminated infection, sepsis, multi-organ failure	*S. stercoralis*

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

641

642 **Table 3. Anthelmintic treatment of soil-transmitted helminth infections**

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

643 All treatment is oral, except for experimental parenteral treatment in *Strongyloides* hyperinfection
644 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*.[2] Data for *S. stercoralis* are especially scarce and may be associated with strong publication bias, estimates from data by Schär *et al*.[4] 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 Medicine; 44(3): 377-389. http://www.amjmed.com/ Copyright 1968, with permission from 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 Review of the Literature. Medicine; 94(16): e655. http://journals.lww.com/md-journal/ Copyright 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 sonolucent 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*. *Ascaris*-induced acute pancreatitis. The British Journal of Surgery; 79(12): 1335-1338. https://www.bjs.co.uk/ Copyright 1992, with permission from John Wiley and Sons.)

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). Gastrointestinal Endoscopy; 71(1): 200-204. http://www.giejournal.org/ Copyright 2010, with 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 ascariasis manifesting as biliary colic, acute cholecystitis, acute pancreatitis, acute cholangitis, and hepatic abscess;
- ***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

Feature or factor	Clinical diagnosis and management	Public health control
Diagnosis	Individual	Community-level (e.g. in selected schools)
Diagnostic criteria	Parasitological	Residence in an area with STH prevalence >20%
Treatment approach	Single 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	Deceased worm burden; reduction in transmission
Ancillary treatment	Based on clinical signs and symptoms	Typically, only if included in mass treatment (e.g. vitamin A supplementation)
Follow-up	Parasitological test of cure; improvement in associated health conditions	Not usually done
Health education (sanitation and hygiene)	Recommended	Recommended

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.

REFERENCES

1. WHO. Investing to overcome the global impact of neglected tropical diseases. Third WHO report on neglected tropical diseases. 2015.
2. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasites & vectors* 2014; **7**: 37.
3. Krolewiecki AJ, Lammie P, Jacobson J, et al. A public health response against *Strongyloides stercoralis*: time to look at soil-transmitted helminthiasis in full. *PLoS neglected tropical diseases* 2013; **7**(5): e2165.
4. Schar F, Trostdorf U, Giardina F, et al. *Strongyloides stercoralis*: Global distribution and risk factors. *PLoS neglected tropical diseases* 2013; **7**(7): e2288.
5. Strunz EC, Addiss DG, Stocks ME, Ogden S, Utzinger J, Freeman MC. Water, sanitation, hygiene, and soil-transmitted helminth infection: a systematic review and meta-analysis. *PLoS Med* 2014; **11**(3): e1001620.
6. WHO. Accelerating work to overcome the global impact of neglected tropical diseases. A roadmap for implementation. 2012.
7. WHO. Soil-transmitted helminths: Eliminating soil-transmitted helminthiases as a public health problem in children. Progress report 2001-2010 and strategic plan 2011-2020. Available: [http://whqlibdoc.who.int/publications/2012/9789241503129_eng.pdf], accessed: 26 October 2016. Geneva: World Health Organization, 2012.
8. Hotez PJ, Alvarado M, Basanez MG, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS neglected tropical diseases* 2014; **8**(7): e2865.
9. Davies J, Majumdar SS, Forbes RT, Smith P, Currie BJ, Baird RW. Hookworm in the Northern Territory: down but not out. *Med J Aust* 2013; **198**(5): 278-81.
10. Starr MC, Montgomery SP. Soil-transmitted helminthiasis in the United States: a systematic review--1940-2010. *The American journal of tropical medicine and hygiene* 2011; **85**(4): 680-4.
11. Olsen A, van Lieshout L, Marti H, et al. Strongyloidiasis--the most neglected of the neglected tropical diseases? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009; **103**(10): 967-72.
12. Stolk WA, Kulik MC, le Rutte EA, et al. Between-country inequalities in the neglected tropical disease burden in 1990 and 2010, with projections for 2020. *PLoS neglected tropical diseases* 2016; **10**(5): e0004560.
13. King CH, Bertino AM. Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. *PLoS neglected tropical diseases* 2008; **2**(3): e209.
14. Elkins DB, Haswell-Elkins M, Anderson RM. The epidemiology and control of intestinal helminths in the Pulicat Lake region of Southern India. I. Study design and pre- and post-treatment observations on *Ascaris lumbricoides* infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1986; **80**(5): 774-92.
15. Greenland K, Dixon R, Khan SA, et al. The epidemiology of soil-transmitted helminths in Bihar State, India. *PLoS neglected tropical diseases* 2015; **9**(5): e0003790.
16. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
17. de Vlas SJ, Stolk WA, le Rutte EA, et al. Concerted efforts to control or eliminate neglected tropical diseases: How much health will be gained? *PLoS neglected tropical diseases* 2016; **10**(2): e0004386.
18. Nejsum P, Betson M, Bendall RP, Thamsborg SM, Stothard JR. Assessing the zoonotic potential of *Ascaris suum* and *Trichuris suis*: looking to the future from an analysis of the past. *J Helminthol* 2012; **86**(2): 148-55.

19. Bundy DA, Cooper ES, Thompson DE, Didier JM, Anderson RM, Simmons I. Predisposition to *Trichuris trichiura* infection in humans. *Epidemiol Infect* 1987; **98**(1): 65-71.
20. Bundy DA, Thompson DE, Golden MH, Cooper ES, Anderson RM, Harland PS. Population distribution of *Trichuris trichiura* in a community of Jamaican children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1985; **79**(2): 232-7.
21. Bradley M, Chandiwana SK, Bundy DA, Medley GF. The epidemiology and population biology of *Necator americanus* infection in a rural community in Zimbabwe. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992; **86**(1): 73-6.
22. Bartsch SM, Hotez PJ, Asti L, et al. The global economic and health burden of human hookworm infection. *PLoS neglected tropical diseases* 2016; **10**(9): e0004922.
23. Brooker SJ BD. Soil-transmitted Helminths (Geohelminths). In: Farrar J HP, Junghanss T, Kang G, Lalloo DG et al., ed. Manson's Tropical Diseases 23rd ed: Elsevier Saunders; 2014: 766-76.
24. Holland CV. Gastrointestinal nematodes - *Ascaris* , hookworm, *Trichuris* , and *Enterobius*. In: Cox FEG, Wakelin D, Gillespie SH, Despommier DD, eds. Topley & Wilson's Microbiology and Microbal Infections London: Hodder Arnold; 2005: 713-36.
25. Bundy DA, Chan MS, Medley GF, Jamison D, Savioli L. Global epidemiology of infectious diseases: Intestinal nematode infections. Geneva: World Health Organization; 2004.
26. Burden DJ, Whitehead A, Green EA, McFadzean JA, Beer RJ. The treatment of soil infested with the human whipworm, *Trichuris trichiura*. *The Journal of hygiene* 1976; **77**(3): 377-82.
27. Traub RJ. *Ancylostoma ceylanicum*, a re-emerging but neglected parasitic zoonosis. *Int J Parasitol* 2013; **43**(12-13): 1009-15.
28. Albarqi MM, Stoltzfus JD, Pilgrim AA, et al. Regulation of life cycle checkpoints and developmental activation of infective larvae in *Strongyloides stercoralis* by dafachronic acid. *PLoS pathogens* 2016; **12**(1): e1005358.
29. Toledo R, Munoz-Antoli C, Esteban JG. Strongyloidiasis with emphasis on human infections and its different clinical forms. *Advances in parasitology* 2015; **88**: 165-241.
30. Baek BK, Islam MK, Matsuda K. Viability of eggs, filariform larvae and adults of *Strongyloides venezuelensis* (Nematoda: Strongyloidea) maintained in vitro. *Korean J Parasitol* 1998; **36**(2): 99-107.
31. de Silva NR, Guyatt HL, Bundy DA. Worm burden in intestinal obstruction caused by *Ascaris lumbricoides*. *Trop Med Int Health* 1997b; **2**(2): 189-90.
32. Baba AA, Ahmad SM, Sheikh KA. Intestinal ascariasis: the commonest cause of bowel obstruction in children at a tertiary care center in Kashmir. *Pediatric surgery international* 2009; **25**(12): 1099-102.
33. Das AK. Hepatic and biliary ascariasis. *J Glob Infect Dis* 2014; **6**(2): 65-72.
34. Carrera E, Nesheim MC, Crompton DW. Lactose maldigestion in *Ascaris*-infected preschool children. *Am J Clin Nutr* 1984; **39**(2): 255-64.
35. Strunz EC, Suchdev PS, Addiss DG. Soil-transmitted helminthiasis and vitamin A deficiency: Two problems, one policy. *Trends Parasitol* 2016; **32**(1): 10-8.
36. Cooper P, Walker AW, Reyes J, et al. Patent human infections with the whipworm, *Trichuris trichiura*, are not associated with alterations in the faecal microbiota. *PloS one* 2013; **8**(10): e76573.
37. Cooper PJ, Sandoval C, Chico ME, Griffin GE. Geohelminth infections protect against severe inflammatory diarrhoea in children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2003; **97**(5): 519-21.
38. Wang P, Li RZ, Huang ZY, Tang CW. Report on 16 cases of small intestine ascariasis diagnosed by capsule endoscopy. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 2013; **31**(3): 242-3.
39. Cooper PJ, Chico ME, Sandoval C, et al. Human infection with *Ascaris lumbricoides* is associated with a polarized cytokine response. *J Infect Dis* 2000; **182**(4): 1207-13.
40. Fitzsimmons CM, Falcone FH, Dunne DW. Helminth allergens, parasite-specific IgE, and its potective role in human immunity. *Front Immunol* 2014; **5**: 61.

41. Sanchez AL, Mahoney DL, Gabrie JA. Interleukin-10 and soil-transmitted helminth infections in Honduran children. *BMC Res Notes* 2015; **8**: 55.
42. Figueiredo CA, Barreto ML, Rodrigues LC, et al. Chronic intestinal helminth infections are associated with immune hyporesponsiveness and induction of a regulatory network. *Infect Immun* 2010; **78**(7): 3160-7.
43. Blackwell AD, Gurven MD, Sugiyama LS, et al. Evidence for a peak shift in a humoral response to helminths: age profiles of IgE in the Shuar of Ecuador, the Tsimane of Bolivia, and the U.S. NHANES. *PLoS neglected tropical diseases* 2011; **5**(6): e1218.
44. Williams-Blangero S, Criscione CD, VandeBerg JL, et al. Host genetics and population structure effects on parasitic disease. *Philos Trans R Soc Lond B Biol Sci* 2012; **367**(1590): 887-94.
45. Ndibazza J, Mpairwe H, Webb EL, et al. Impact of anthelminthic treatment in pregnancy and childhood on immunisations, infections and eczema in childhood: a randomised controlled trial. *PloS one* 2012; **7**(12): e50325.
46. Mkhize-Kwitshana ZL, Taylor M, Jooste P, Mabaso ML, Walzl G. The influence of different helminth infection phenotypes on immune responses against HIV in co-infected adults in South Africa. *BMC Infect Dis* 2011; **11**: 273.
47. Van der Zalm MM, van Soelen N, Mandalakas AM, et al. The effect of deworming on tests of tuberculosis infection in children with recent tuberculosis exposure - A randomized controlled trial. *Pediatr Infect Dis J* 2016.
48. Gravitt PE, Marks M, Kosek M, et al. Soil-transmitted helminth infections are associated with an increase in human papillomavirus prevalence and a T-helper type 2 cytokine signature in cervical fluids. *J Infect Dis* 2016; **213**(5): 723-30.
49. Hawlader MD, Ma E, Noguchi E, et al. *Ascaris lumbricoides* infection as a risk factor for asthma and atopy in rural Bangladeshi children. *Trop Med Health* 2014; **42**(2): 77-85.
50. 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). *Gastrointestinal endoscopy* 2010; **71**(1): 200-4.
51. Cooper ES, Spencer J, Whyte-Alleng CA, et al. Immediate hypersensitivity in colon of children with chronic Trichuris trichiura dysentery. *Lancet* 1991; **338**(8775): 1104-7.
52. Dige A, Rasmussen TK, Nejsum P, et al. Mucosal and systemic immune modulation by *Trichuris trichiura* in a self-infected individual. *Parasite immunology* 2017; **39**(1).
53. MacDonald TT, Spencer J, Murch SH, et al. Immunoepidemiology of intestinal helminthic infections. 3. Mucosal macrophages and cytokine production in the colon of children with Trichuris trichiura dysentery. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; **88**(3): 265-8.
54. Broadhurst MJ, Ardeshir A, Kanwar B, et al. Therapeutic helminth infection of macaques with idiopathic chronic diarrhea alters the inflammatory signature and mucosal microbiota of the colon. *PLoS pathogens* 2012; **8**(11): e1003000.
55. Cooper ES, Bundy DA. *Trichuris* is not trivial. *Parasitol Today* 1988; **4**(11): 301-6.
56. Bundy DA, Cooper ES, Thompson DE, Didier JM, Simmons I. Effect of age and initial infection intensity on the rate of reinfection with *Trichuris trichiura* after treatment. *Parasitology* 1988; **97 (Pt 3)**: 469-76.
57. Bundy DA, Lillywhite JE, Didier JM, Simmons I, Bianco AE. Age-dependency of infection status and serum antibody levels in human whipworm (*Trichuris trichiura*) infection. *Parasite immunology* 1991; **13**(6): 629-38.
58. Wright VJ, Ame SM, Haji HS, et al. Early exposure of infants to GI nematodes induces Th2 dominant immune responses which are unaffected by periodic anthelminthic treatment. *PLoS neglected tropical diseases* 2009; **3**(5): e433.
59. Cliffe LJ, Humphreys NE, Lane TE, Potten CS, Booth C, Grencis RK. Accelerated intestinal epithelial cell turnover: a new mechanism of parasite expulsion. *Science* 2005; **308**(5727): 1463-5.

60. Gyorkos TW, Gilbert NL, Larocque R, Casapia M. *Trichuris* and hookworm infections associated with anaemia during pregnancy. *Trop Med Int Health* 2011; **16**(4): 531-7.
61. Glinz D, Hurrell RF, Righetti AA, et al. In Ivorian school-age children, infection with hookworm does not reduce dietary iron absorption or systemic iron utilization, whereas afebrile *Plasmodium falciparum* infection reduces iron absorption by half. *Am J Clin Nutr* 2015; **101**(3): 462-70.
62. Brooker S, Hotez PJ, Bundy DA. Hookworm-related anaemia among pregnant women: a systematic review. *PLoS neglected tropical diseases* 2008; **2**(9): e291.
63. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. Hookworm infection. *The New England journal of medicine* 2004; **351**(8): 799-807.
64. Gaze S, McSorley HJ, Daveson J, et al. Characterising the mucosal and systemic immune responses to experimental human hookworm infection. *PLoS pathogens* 2012; **8**(2): e1002520.
65. Fujiwara RT, Cancado GG, Freitas PA, et al. *Necator americanus* infection: a possible cause of altered dendritic cell differentiation and eosinophil profile in chronically infected individuals. *PLoS neglected tropical diseases* 2009; **3**(3): e399.
66. Loukas A, Constant SL, Bethony JM. Immunobiology of hookworm infection. *FEMS Immunol Med Microbiol* 2005; **43**(2): 115-24.
67. Geiger SM, Caldas IR, Mc Glone BE, et al. Stage-specific immune responses in human *Necator americanus* infection. *Parasite immunology* 2007; **29**(7): 347-58.
68. Akuthota P, Weller PF. Eosinophilic pneumonias. *Clin Microbiol Rev* 2012b; **25**(4): 649-60.
69. Iriemenam NC, Sanyaolu AO, Oyibo WA, Fagbenro-Beyioku AF. *Strongyloides stercoralis* and the immune response. *Parasitol Int* 2010; **59**(1): 9-14.
70. O'Connell AE, Hess JA, Santiago GA, et al. Major basic protein from eosinophils and myeloperoxidase from neutrophils are required for protective immunity to *Strongyloides stercoralis* in mice. *Infect Immun* 2011; **79**(7): 2770-8.
71. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the Immunocompromised Population. *Clin Microbiol Rev* 2004; **17**(1): 208-17.
72. Geri G, Rabbat A, Mayaux J, et al. *Strongyloides stercoralis* hyperinfection syndrome: a case series and a review of the literature. *Infection* 2015; **43**(6): 691-8.
73. Croll NA, Anderson RM, Gyorkos TW, Ghadirian E. The population biology and control of *Ascaris lumbricoides* in a rural community in Iran. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1982; **76**(2): 187-97.
74. Schad GA, Anderson RM. Predisposition to hookworm infection in humans. *Science* 1985; **228**(4707): 1537-40.
75. Hotez PJ, Bundy DAP, Beegle K, et al. Helminth infections: Soil-transmitted helminth infections and schistosomiasis. In: Jamison DT, Breman JG, Measham AR, et al., eds. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC); 2006.
76. Khuroo MS. Ascariasis. *Gastroenterology clinics of North America* 1996; **25**(3): 553-77.
77. Lal C, Huggins JT, Sahn SA. Parasitic diseases of the pleura. *Am J Med Sci* 2013; **345**(5): 385-9.
78. de Silva NR, Guyatt HL, Bundy DA. Morbidity and mortality due to *Ascaris*-induced intestinal obstruction. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997a; **91**(1): 31-6.
79. Sotto Mayor J, Esperanca S. Images in clinical medicine. Gastric *Ascaris* infection. *The New England journal of medicine* 2015; **373**(15): e18.
80. Khuroo NS, Khuroo MS, Khuroo MS. Gastric ascariasis presenting as unique dyspeptic symptoms in an endemic area. *The American journal of gastroenterology* 2010; **105**(7): 1675-7.
81. Khuroo MS, Zargar SA, Mahajan R. Hepatobiliary and pancreatic ascariasis in India. *Lancet* 1990; **335**(8704): 1503-6.
82. Khuroo MS, Zargar SA. Biliary ascariasis. A common cause of biliary and pancreatic disease in an endemic area. *Gastroenterology* 1985; **88**(2): 418-23.
83. Khuroo MS, Zargar SA, Yattoo GN, et al. Ascaris-induced acute pancreatitis. *The British journal of surgery* 1992; **79**(12): 1335-8.

995 84. Khuroo MS, Khuroo NS, Khuroo MS. Biliary ascariasis in the etiology of recurrent pyogenic
996 cholangitis in an endemic area. *Int J Hepatobil Pancr Dis* 2015; **5**: 22-0.
997 85. Ghoshal UC, Venkitaramanan A, Verma A, Misra A, Saraswat VA. Hookworm infestation is
998 not an uncommon cause of obscure occult and overt gastrointestinal bleeding in an endemic area: A
999 study using capsule endoscopy. *Indian J Gastroenterol* 2015; **34**(6): 463-7.
1000 86. Roche M, Perez-Gimenez ME, Layrisse M, Di Prisco ME. Study of urinary and fecal excretion
1001 of radioactive chromium Cr51 in man; its use in the measurement of intestinal blood loss associated
1002 with hookworm infection. *J Clin Invest* 1957; **36**(7): 1183-92.
1003 87. Concha R, Harrington W, Jr., Rogers AI. Intestinal strongyloidiasis: recognition, management,
1004 and determinants of outcome. *J Clin Gastroenterol* 2005; **39**(3): 203-11.
1005 88. Forzy G, Dhondt JL, Leloire O, Shayeb J, Vincent G. Reactive arthritis and *Strongyloides*. *JAMA*
1006 1988; **259**(17): 2546-7.
1007 89. Einsiedel L, Spelman D. *Strongyloides stercoralis*: risks posed to immigrant patients in an
1008 Australian tertiary referral centre. *Intern Med J* 2006; **36**(10): 632-7.
1009 90. Barnett ED, Weld LH, McCarthy AE, et al. Spectrum of illness in international migrants seen
1010 at GeoSentinel clinics in 1997-2009, part 1: US-bound migrants evaluated by comprehensive
1011 protocol-based health assessment. *Clin Infect Dis* 2013; **56**(7): 913-24.
1012 91. McCarthy AE, Weld LH, Barnett ED, et al. Spectrum of illness in international migrants seen
1013 at GeoSentinel clinics in 1997-2009, part 2: migrants resettled internationally and evaluated for
1014 specific health concerns. *Clin Infect Dis* 2013; **56**(7): 925-33.
1015 92. Lamberton PH, Jourdan PM. Human Ascariasis: Diagnostics update. *Curr Trop Med Rep* 2015;
1016 **2**(4): 189-200.
1017 93. Staudacher O, Heimer J, Steiner F, et al. Soil-transmitted helminths in southern highland
1018 Rwanda: associated factors and effectiveness of school-based preventive chemotherapy. *Trop Med*
1019 *Int Health* 2014; **19**(7): 812-24.
1020 94. Mejia R, Vicuna Y, Broncano N, et al. A novel, multi-parallel, real-time polymerase chain
1021 reaction approach for eight gastrointestinal parasites provides improved diagnostic capabilities to
1022 resource-limited at-risk populations. *The American journal of tropical medicine and hygiene* 2013;
1023 **88**(6): 1041-7.
1024 95. Bisanzio D, Mutuku F, Bustinduy AL, et al. Cross-sectional study of the burden of vector-
1025 borne and soil-transmitted polyparasitism in rural communities of Coast Province, Kenya. *PLoS*
1026 *neglected tropical diseases* 2014; **8**(7): e2992.
1027 96. Gordon CA, McManus DP, Acosta LP, et al. Multiplex real-time PCR monitoring of intestinal
1028 helminths in humans reveals widespread polyparasitism in Northern Samar, the Philippines. *Int J*
1029 *Parasitol* 2015; **45**(7): 477-83.
1030 97. Inoue K, Ozaka S, Okamoto K, et al. Multiple infections with helminths--whipworm,
1031 hookworm, and roundworm. *Endoscopy* 2014; **46 Suppl 1 UCTN**: E117-8.
1032 98. Akuthota P, Weller PF. Eosinophils and disease pathogenesis. *Semin Hematol* 2012a; **49**(2):
1033 113-9.
1034 99. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique
1035 in Schistosomiasis *mansoni*. *Rev Inst Med Trop Sao Paulo* 1972; **14**(6): 397-400.
1036 100. Knopp S, Mgeni AF, Khamis IS, et al. Diagnosis of soil-transmitted helminths in the era of
1037 preventive chemotherapy: effect of multiple stool sampling and use of different diagnostic
1038 techniques. *PLoS neglected tropical diseases* 2008; **2**(11): e331.
1039 101. Nikolay B, Brooker SJ, Pullan RL. Sensitivity of diagnostic tests for human soil-transmitted
1040 helminth infections: a meta-analysis in the absence of a true gold standard. *Int J Parasitol* 2014;
1041 **44**(11): 765-74.
1042 102. Sinniah B. Daily egg production of *Ascaris lumbricoides*: the distribution of eggs in the faeces
1043 and the variability of egg counts. *Parasitology* 1982; **84**(1): 167-75.

103. Speich B, Ali SM, Ame SM, Albonico M, Utzinger J, Keiser J. Quality control in the diagnosis of *Trichuris trichiura* and *Ascaris lumbricoides* using the Kato-Katz technique: experience from three randomised controlled trials. *Parasites & vectors* 2015; **8**: 82.
104. Goodman D, Haji HJ, Bickle QD, et al. A comparison of methods for detecting the eggs of *Ascaris*, *Trichuris*, and hookworm in infant stool, and the epidemiology of infection in Zanzibari infants. *The American journal of tropical medicine and hygiene* 2007; **76**(4): 725-31.
105. Vlaminck J, Supali T, Geldhof P, Hokke CH, Fischer PU, Weil GJ. Community rates of IgG4 antibodies to *Ascaris* haemoglobin reflect changes in community egg loads following mass drug administration. *PLoS neglected tropical diseases* 2016; **10**(3): e0004532.
106. Aydin R, Bekci T, Bilgici MC, Polat AV. Sonographic diagnosis of ascariasis causing small bowel obstruction. *J Clin Ultrasound* 2014; **42**(4): 227-9.
107. Das CJ, Kumar J, Debnath J, Chaudhry A. Imaging of ascariasis. *Australas Radiol* 2007; **51**(6): 500-6.
108. Ramareddy RS, Alladi A, Siddapa OS, Deepti V, Akthar T, Mamata B. Surgical complications of *Ascaris lumbricoides* in children. *Journal of Indian Association of Pediatric Surgeons* 2012; **17**(3): 116-9.
109. Nag HH, Ji R. Ascariasis presenting as acute abdomen-a case report. *The Indian journal of surgery* 2013; **75**(Suppl 1): 128-30.
110. Khuroo MS, Zargar SA, Mahajan R, Bhat RL, Javid G. Sonographic appearances in biliary ascariasis. *Gastroenterology* 1987; **93**(2): 267-72.
111. Tokmak N, Koc Z, Ulusan S, Koltas IS, Bal N. Computed tomographic findings of trichuriasis. *World journal of gastroenterology* 2006; **12**(26): 4270-2.
112. Wang DD, Wang XL, Wang XL, Wang S, An CL. Trichuriasis diagnosed by colonoscopy: case report and review of the literature spanning 22 years in mainland China. *Int J Infect Dis* 2013; **17**(11): e1073-5.
113. Anderson RM, Schad GA. Hookworm burdens and faecal egg counts: an analysis of the biological basis of variation. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1985; **79**(6): 812-25.
114. Krauth SJ, Coulibaly JT, Knopp S, Traore M, N'Goran EK, Utzinger J. An in-depth analysis of a piece of shit: distribution of *Schistosoma mansoni* and hookworm eggs in human stool. *PLoS neglected tropical diseases* 2012; **6**(12): e1969.
115. Pickard L, Rattehalli D, Iqbal T. Iron deficiency anemia: buried evidence. *Gastroenterology* 2013; **144**(1): e11-2.
116. Wu X, Chen H, Gan T, Chen J, Ngo CW, Peng Q. Automatic hookworm detection in wireless capsule endoscopy images. *IEEE Trans Med Imaging* 2016.
117. Khuroo MS. Hyperinfection strongyloidiasis in renal transplant recipients. *BMJ case reports* 2014; **2014**.
118. Requena-Mendez A, Chiodini P, Bisoffi Z, Buonfrate D, Gotuzzo E, Munoz J. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. *PLoS neglected tropical diseases* 2013; **7**(1): e2002.
119. Sykes AM, McCarthy JS. A coproantigen diagnostic test for *Strongyloides* infection. *PLoS neglected tropical diseases* 2011; **5**(2): e955.
120. Bisoffi Z, Buonfrate D, Sequi M, et al. Diagnostic accuracy of five serologic tests for *Strongyloides stercoralis* infection. *PLoS neglected tropical diseases* 2014; **8**(1): e2640.
121. Buonfrate D, Formenti F, Perandin F, Bisoffi Z. Novel approaches to the diagnosis of *Strongyloides stercoralis* infection. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2015; **21**(6): 543-52.
122. Rascoe LN, Price C, Shin SH, McAuliffe I, Priest JW, Handali S. Development of Ss-NIE-1 recombinant antigen based assays for immunodiagnosis of strongyloidiasis. *PLoS neglected tropical diseases* 2015; **9**(4): e0003694.

123. Nadir E, Grossman T, Ciobotaro P, et al. Real-time PCR for *Strongyloides stercoralis*-associated meningitis. *Diagn Microbiol Infect Dis* 2016; **84**(3): 197-9.
124. Repetto SA, Ruybal P, Solana ME, et al. Comparison between PCR and larvae visualization methods for diagnosis of *Strongyloides stercoralis* out of endemic area: A proposed algorithm. *Acta Trop* 2016; **157**: 169-77.
125. Gyorkos TW, Maheu-Giroux M, Blouin B, Casapia M. Impact of health education on soil-transmitted helminth infections in schoolchildren of the Peruvian Amazon: a cluster-randomized controlled trial. *PLoS neglected tropical diseases* 2013; **7**(9): e2397.
126. Jia TW, Melville S, Utzinger J, King CH, Zhou XN. Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis. *PLoS neglected tropical diseases* 2012; **6**(5): e1621.
127. Letter TM. Treatment guidelines from the medical letter: Drugs for parasitic infections. 2013.
128. Levecke B, Montresor A, Albonico M, et al. Assessment of anthelmintic efficacy of mebendazole in school children in six countries where soil-transmitted helminths are endemic. *PLoS neglected tropical diseases* 2014; **8**(10): e3204.
129. Adegnika AA, Zinsou JF, Issifou S, et al. Randomized, controlled, assessor-blind clinical trial to assess the efficacy of single- versus repeated-dose albendazole to treat *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm infection. *Antimicrob Agents Chemother* 2014; **58**(5): 2535-40.
130. Hamid R, Bhat N, Baba A, et al. Use of gastrografin in the management of worm-induced small bowel obstruction in children. *Pediatric surgery international* 2015; **31**(12): 1171-6.
131. Gupta A, Rathore AM, Manaktala U. Ascariasis presenting as acute abdomen during pregnancy and puerperium. *Southeast Asian J Trop Med Public Health* 2013; **44**(2): 150-3.
132. Khuroo MS, Zargar SA, Yattoo GN, et al. Worm extraction and biliary drainage in hepatobiliary and pancreatic ascariasis. *Gastrointestinal endoscopy* 1993; **39**(5): 680-5.
133. International Nutritional Anemia Consultative Group (INACG), World Health Organization (WHO), United Nations Childrens Fund (UNICEF) 1998 Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Editors: Stoltzfus, R.J. and Dreyfuss, M.L.
134. Speich B, Ame SM, Ali SM, et al. Oxantel pamoate-albendazole for *Trichuris trichiura* infection. *The New England journal of medicine* 2014; **370**(7): 610-20.
135. Moser W, Ali SM, Ame SM, et al. Effi cacy and safety of oxantel pamoate in school-aged children infected with *Trichuris trichiura* on Pemba Island, Tanzania: a parallel, randomised, controlled, dose-ranging study. *The Lancet Infectious diseases* 2016; **16**: 53-69.
136. Soukhathammavong PA, Sayasone S, Phongluxa K, et al. Low efficacy of single-dose albendazole and mebendazole against hookworm and effect on concomitant helminth infection in Lao PDR. *PLoS neglected tropical diseases* 2012; **6**(1): e1417.
137. Bergquist R. Tribendimidine: great expectations. *The Lancet Infectious diseases* 2016; **16**(10): 1089-91.
138. Igual-Adell R, Oltra-Alcaraz C, Soler-Company E, Sanchez-Sanchez P, Matogo-Oyana J, Rodriguez-Calabuig D. Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother* 2004; **5**(12): 2615-9.
139. Marty FM, Lowry CM, Rodriguez M, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis* 2005; **41**(1): e5-8.
140. Lichtenberger P, Rosa-Cunha I, Morris M, et al. Hyperinfection strongyloidiasis in a liver transplant recipient treated with parenteral ivermectin. *Transpl Infect Dis* 2009; **11**(2): 137-42.
141. Donadello K, Cristallini S, Taccone FS, et al. Strongyloides disseminated infection successfully treated with parenteral ivermectin: case report with drug concentration measurements and review of the literature. *International journal of antimicrobial agents* 2013; **42**(6): 580-3.
142. Pawluk SA, Roels CA, Wilby KJ, Ensom MH. A review of pharmacokinetic drug-drug interactions with the anthelmintic medications albendazole and mebendazole. *Clin Pharmacokinet* 2015; **54**(4): 371-83.

143. Chen KT, Twu SJ, Chang HJ, Lin RS. Outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with mebendazole and metronidazole use among Filipino laborers in Taiwan. *American journal of public health* 2003; **93**(3): 489-92.
144. Suleman S, Zeleke G, Deti H, et al. Quality of medicines commonly used in the treatment of soil transmitted helminths and giardia in ethiopia: a nationwide survey. *PLoS neglected tropical diseases* 2014; **8**(12): e3345.
145. WHO. Helminth control in school-age children. A guide for managers of control programmes. Geneva: World Health Organization, 2011.
146. Truscott JE, Turner HC, Anderson RM. What impact will the achievement of the current World Health Organisation targets for anthelmintic treatment coverage in children have on the intensity of soil transmitted helminth infections? *Parasites & vectors* 2015; **8**: 551.
147. Turner HC, Truscott JE, Bettis AA, et al. An economic evaluation of expanding hookworm control strategies to target the whole community. *Parasites & vectors* 2015; **8**: 570.
148. Keenan JD, Hotez PJ, Amza A, et al. Elimination and eradication of neglected tropical diseases with mass drug administrations: a survey of experts. *PLoS neglected tropical diseases* 2013; **7**(12): e2562.
149. Taylor-Robinson DC, Maayan N, Soares-Weiser K, Donegan S, Garner P. Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance. *The Cochrane database of systematic reviews* 2015; **7**: CD000371.
150. Tovey D, Littell JH, Grimshaw JM. The end of the wormwars? *The Cochrane database of systematic reviews* 2016; **9**: ED000116.
151. Welch VA, Ghogomu E, Hossain A, et al. Mass deworming to improve developmental health and wellbeing of children in low-income and middle-income countries: a systematic review and network meta-analysis. *The Lancet Global Health* 2017; **5**(1): e40-e50.
152. Kumapley RS, Kupka R, Dalmiya N. The role of child health days in the attainment of global deworming coverage targets among preschool-age children. *PLoS neglected tropical diseases* 2015; **9**(11): e0004206.
153. WHO. Summary of global update on preventive chemotherapy implementation in 2015. *Weekly Epidemiological Record* 2016; **39**: 456-60.
154. Ottesen EA, Hooper PJ, Bradley M, Biswas G. The Global Programme to Eliminate Lymphatic Filariasis: Health impact after 8 years. Washington DC: National Academies Press; 2011.
155. Mupfasoni D, Montresor A, Mikhailov A, King J. The impact of lymphatic filariasis mass drug administration scaling down on soil-transmitted helminth control in school-age children. Present situation and expected impact from 2016 to 2020. *PLoS neglected tropical diseases* 2016; **10**(12): e0005202.
156. Andrews JR, Bogoch, II, Utzinger J. The benefits of mass deworming on health outcomes: new evidence synthesis, the debate persists. *The Lancet Global Health* 2017; **5**(1): e4-e5.
157. Taylor-Robinson D, Garner P. Campbell replication confirms little or no effect of community deworming. *The Lancet Global Health* 2017; **5**(1): e2-e3.
158. Croke K, Hicks JH, Hsu E, Kremer M, Miguel E. Does mass deworming affect child nutrition? Meta-analysis, cost-effectiveness, and statistical power. *NBER Working Paper No 22382* 2016.
159. Clarke NE, Clements AC, Doi SA, et al. Differential effect of mass deworming and targeted deworming for soil-transmitted helminth control in children: a systematic review and meta-analysis. *Lancet* 2016.
160. Nampijja M, Webb EL, Kaweesa J, et al. The Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA): study protocol for a randomised controlled trial. *Trials* 2015; **16**: 187.
161. Wammes LJ, Mpairwe H, Elliott AM, Yazdanbakhsh M. Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. *The Lancet Infectious diseases* 2014; **14**(11): 1150-62.

162. Webb EL, Nampijja M, Kaweesa J, et al. Helminths are positively associated with atopy and wheeze in Ugandan fishing communities: results from a cross-sectional survey. *Allergy* 2016; **71**(8): 1156-69.
163. Briggs N, Weatherhead J, Sastry KJ, Hotez PJ. The Hygiene Hypothesis and its inconvenient truths about helminth infections. *PLoS neglected tropical diseases* 2016; **10**(9): e0004944.
164. Walson JL, Herrin BR, John-Stewart G. Deworming helminth co-infected individuals for delaying HIV disease progression. *The Cochrane database of systematic reviews* 2009; (3): CD006419.
165. Means AR, Burns P, Sinclair D, Walson JL. Antihelminthics in helminth-endemic areas: effects on HIV disease progression. *The Cochrane database of systematic reviews* 2016; **4**: CD006419.
166. Kinung'hi SM, Magnussen P, Kishamawe C, Todd J, Vennervald BJ. The impact of anthelmintic treatment intervention on malaria infection and anaemia in school and preschool children in Magu district, Tanzania: an open label randomised intervention trial. *BMC Infect Dis* 2015; **15**: 136.
167. Efunshile AM, Olawale T, Stensvold CR, Kurtzhals JA, Konig B. Epidemiological study of the association between malaria and helminth infections in Nigeria. *The American journal of tropical medicine and hygiene* 2015; **92**(3): 578-82.
168. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press; 1991.
169. Hill DE, Romanowski RD, Urban JF. A *Trichuris* specific diagnostic antigen from culture fluids of *Trichuris suis* adult worms. *Veterinary Parasitology* 1997; **68**: 91-102.
170. Elsemore DA, Geng J, Flynn L, Cruthers L, Lucio-Forster A, Bowman DD. Enzyme-linked immunosorbent assay for coproantigen detection of *Trichuris vulpis* in dogs. *Journal of Veterinary Diagnostic Investigation* 2014; **26**(3): 404-11.
171. Liu J, Gratz J, Amour C, et al. A laboratory-developed TaqMan Array Card for simultaneous detection of 19 enteropathogens. *J Clin Microbiol* 2013; **51**(2): 472-80.
172. Easton AV, Oliveira RG, O'Connell EM, et al. Multi-parallel qPCR provides increased sensitivity and diagnostic breadth for gastrointestinal parasites of humans: field-based inferences on the impact of mass deworming. *Parasites & vectors* 2016; **9**(1): 38.
173. Pilotte N, Papaiakovou M, Grant JR, et al. Improved PCR-based detection of soil transmitted helminth infections using a next-generation sequencing approach to asay design. *PLoS neglected tropical diseases* 2016; **10**(3): e0004578.
174. Geary TG. Are new anthelmintics needed to eliminate human helminthiases? *Curr Opin Infect Dis* 2012; **25**(6): 709-17.
175. Hotez PJ, Bottazzi ME, Strych U. New vaccines for the world's poorest people. *Annu Rev Med* 2016; **67**: 405-17.
176. Zhan B, Beaumier CM, Briggs N, et al. Advancing a multivalent 'Pan-anthelmintic' vaccine against soil-transmitted nematode infections. *Expert Review of Vaccines* 2014; **13**(3): 321-31.
177. WHO. Water, Sanitation & Hygiene for Accelerating and Sustaining Progress on Neglected Tropical Diseases. A global strategy 2015-2020. Geneva: World Health Organization, 2015.