

Strongyloidiasis

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Abstract

Strongyloidiasis is a neglected tropical disease caused primarily by the roundworm *Strongyloides stercoralis*. Strongyloidiasis is most prevalent in Southeast Asia and the Western Pacific. Although cases have been documented worldwide, global prevalence is largely unknown due to limited surveillance. Infection of the definitive human host occurs via direct skin penetration of the infective filariform larvae. Parasitic females reside in the small intestine and reproduce via parthenogenesis, where eggs hatch inside the host before rhabditiform larvae are excreted in faeces to begin the single generation free-living life cycle. Rhabditiform larvae can also develop directly into infectious filariform larvae in the gut and cause autoinfection. Although many are asymptomatic, infected individuals may report a range of non-specific gastrointestinal, respiratory or skin symptoms. Autoinfection may cause hyperinfection and disseminated strongyloidiasis in immunocompromised individuals, which is often fatal. Diagnosis requires direct examination of larvae in clinical specimens, positive serology or nucleic acid detection. However, there is a lack of standardization of techniques for all diagnostic types. Ivermectin is the treatment of choice. Control and elimination of strongyloidiasis will require a multifaceted, integrated approach, including highly sensitive and standardized diagnostics, active surveillance, health information, education and communication strategies, improved water, sanitation and hygiene, access to efficacious treatment, vaccine development and better integration and acknowledgement in current helminth control programmes.

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Introduction

Strongyloidiasis is an infection caused by a nematode of the genus *Strongyloides* and is often referred to as the most neglected among the neglected tropical diseases (NTDs), having been largely ignored in helminth control programmes due in part to complexities in diagnosis and treatment, and lack of specific funding^{1,2}. The most common species causing strongyloidiasis is *Strongyloides stercoralis*, which has a worldwide distribution^{1,3}. Other species capable of infecting humans are *Strongyloides fuelleborni* in Africa and Asia, and *Strongyloides fuelleborni kellyi* in Papua New Guinea^{4,5}, with *S. fuelleborni* infection recognized as a zoonosis. Infection is most common in tropical and subtropical regions of the world; however, there have been reports of infection in more temperate regions, and there have been imported cases in non-endemic areas^{6–10}. Rather than an NTD, it would be better stated that strongyloidiasis is a disease of disadvantage, marginalization and neglect¹¹. In 2016, most countries where strongyloidiasis was present were in tropical and subtropical zones, and the areas within these countries where strongyloidiasis was endemic had lower socioeconomic status¹¹. Even in high-income countries (HICs), such as the USA and Australia, only in areas of low socioeconomic status is strongyloidiasis endemic¹¹, although imported cases from travellers and immigrants are also a major cohort in those countries⁶. In all species, infection occurs via direct penetration of the skin by infectious larvae¹².

The life cycle of *S. stercoralis* is complex and has many different stages (Fig. 1), with human disease reflecting the complex parasite life cycle. Acute strongyloidiasis occurs early in infection, with symptoms reflecting the initial parasite migration from cutaneous entry to the respiratory and gastrointestinal tracts. Due to its ability to cause autoinfection (infection caused by an agent already inside the body), chronic strongyloidiasis may result in a range of non-specific symptoms, although many individuals are asymptomatic. Severe strongyloidiasis typically occurs in the context of immunocompromise, manifesting as hyperinfection and disseminated disease, which are often fatal. Hyperinfection is characterized by a remarkable proliferation of parasites within the host, potentially causing bacterial sepsis due to perforation of the intestinal lumen, and disseminated disease, where larvae migrate to various organs and tissues outside the usual migration route.

The latest estimates published in 2020 suggest that as many as 600 million individuals worldwide may be infected with *S. stercoralis*³, with Southeast Asia and the Western Pacific having the largest number of infections: 237 million and 133 million infected people, respectively³. Previous estimates from 2006 ranged only between 30 and 100 million infections, which were probably underestimates¹³. Accurate estimations of global infection are affected by diagnostic challenges and, hence, the paucity of quality data. Despite the inclusion of strongyloidiasis as a soil-transmitted helminth (STH) by the World Health Organization (WHO), strongyloidiasis has remained the ‘silent’ STH, with little attention in epidemiological surveys or control programmes, largely due to difficulties and complexities in accurate diagnosis. Similarly, the most widely used treatments in mass drug administration (MDA) targeting STH infection (that is, single-dose albendazole or mebendazole) have no, or only very low, efficacy against *Strongyloides* spp., and thus infection has been largely unchecked¹⁴.

In this Primer, we describe the main features of *Strongyloides* spp. biology and epidemiology, clinical features and disease management, including co-morbidities, diagnostics, treatment and control of strongyloidiasis, while identifying key areas in which improvement is required to achieve control and elimination of this disease.

Epidemiology

The parasites

The most common species infecting humans is *S. stercoralis*, which is found worldwide (Fig. 2). *S. fuelleborni* and *S. f. kellyi* are endemic in Africa and Asia, and Papua New Guinea, respectively.

S. fuelleborni is a zoonotic species, found in non-human primates in both Africa and Asia. Human infections of *S. fuelleborni* in Asia are rare¹⁵; anthroponotic transmission (transmission from human to human; in this case meaning transmission from human faecal contamination to other humans) has not been shown to occur in Asia^{16,17}.

It is hypothesized that *S. f. kellyi* evolved from a local zoonotic host, although the host has not been identified¹⁸. Infection with *S. f. kellyi* has been associated with ‘swollen belly syndrome’ in children in Papua New Guinea, which can be fatal^{5,18}. Transmammary transmission has been identified in human infections of *S. fuelleborni* in Africa¹⁹, and presumed to occur in *S. f. kellyi*, although this has not been proven⁵. It is uncertain whether *S. stercoralis* infection represents a zoonosis in dogs^{20,21} (Box 1).

Global burden of disease

The global burden of disease is difficult to estimate due to the lack of large-scale surveys in many areas; yet, the most recent estimate from 2020 suggests 600 million infections worldwide (Fig. 2). A limitation with estimating global prevalence is bias in the number of studies available for different countries. Most publications on strongyloidiasis come from Thailand and Brazil, while other countries may have very few or no publications, which must stand as proxy for the country-wide prevalence^{3,22,23}. Another limitation is differences in diagnostics used, and lack of standardization of diagnostics, across studies.

A meta-analysis of cross-sectional studies in Africa for the period 2008–2018 revealed a prevalence of 6.8% in rural communities, 6.4% in schools and 0.9% in health institutions²⁴. Prevalence varied widely between studies, even within the same country, as did the diagnostics used. The most common diagnostic used was the formol–ether concentration technique (FECT) – which is not an ideal diagnosis for strongyloidiasis owing to low recovery of larvae, although it was employed in 50 of the 86 studies included in the analysis. The highest prevalence was identified in sub-Saharan countries, specifically Rwanda (17.4%), Ethiopia (10.5–20.7%), Tanzania (13.3–16.6%), Angola (12.2–21.4%), Nigeria (11.0–37.1%), Côte d’Ivoire (21.9–27.1%), Mozambique (48.5%) and Uganda (12.4%), while Egypt had the highest prevalence elsewhere in Africa (15.7%).

Estimated prevalences in different areas of Asia include 6.6% in China, 0.04% in Japan and 6.8% in South Korea³. In a meta-analysis of strongyloidiasis in Southeast Asia, the estimated prevalence was 12.7%, with the highest prevalences identified in Cambodia (24.9%) and Lao People’s Democratic Republic (PDR) (16.5%)²³. Thailand had a country-wide prevalence of 11.3%, with highest burden of disease in Northeast Thailand (22.5%). In Cambodia, the prevalence was universally high across all areas (>20%) with a peak of 33.7% in the Elephant Mountains and Cardamon region. In Lao PDR, prevalence was likewise high in all areas (>14%), but highest (28%) in the Southern region²³. In Timor-Leste, the Philippines and Singapore, only a single study was available to be included in the analysis; and no studies were available for Brunei²³. This highlights gaps in knowledge, particularly given known high prevalence of the other STH in the Philippines and Timor-Leste^{25,26}.

Prevalence in countries from the Pacific ranges from 0.3% in Vanuatu, to 15.9% in Fiji, and 19% in the Solomon Islands³. Prevalence in Pacific countries that participate in the Pacific Elimination of Lymphatic Filariasis (PAC-ELF) programme may be lower due to the

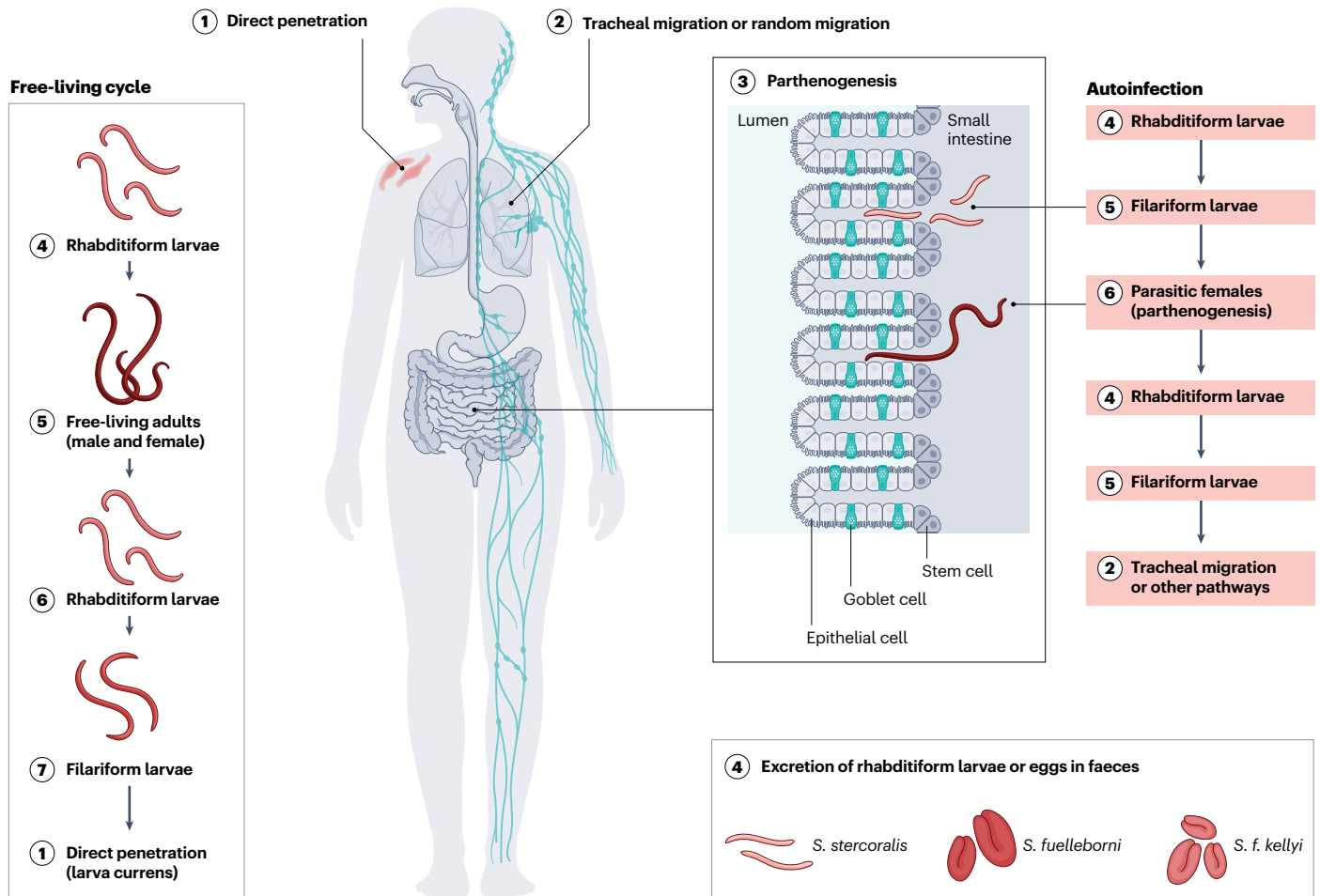


Fig. 1 | Life cycle of *Strongyloides* spp. Filariform larvae (L₃) directly penetrate the skin (1), causing a rash called larva currens. The filariform larvae migrate through venous vessels and lymphatics²¹⁶ to the lungs (2), where the parasite leaves the bloodstream at the alveolar–capillary barrier to enter the air-filled bronchial system. After having ascended into the pharyngeal area, the parasite is swallowed to reach the small intestine⁴¹. Larvae can also migrate to the gut by other, random pathways⁴⁶. In the small intestine (3), the larvae (L₄) mature into parasitic females, which reproduce by parthenogenesis, producing eggs that, in the case of *Strongyloides stercoralis*, hatch into rhabditiform larvae (L₁) in the gut (4), which are then excreted into the environment via the faeces. For *Strongyloides fuelleborni* and *Strongyloides fuelleborni kellyi*, eggs are

released into the environment and quickly hatch into rhabditiform larvae. In the free-living life cycle, once in the environment, the rhabditiform larvae (4) go through several moults becoming free-living adults (5), which reproduce to produce a single generation of rhabditiform larvae (6), which undergo successive moults (L₁, L₂) into infectious filariform larvae (L₃) (7), which then cause infection by direct skin penetration (1). In autoinfection, rhabditiform larvae of *S. stercoralis* (4) can also moult into the infectious filariform larvae (5) within the human host, which can then directly penetrate the host skin causing autoinfection, migrating through the body, and developing into parasitic females producing eggs (6) and continuing the life cycle. Due to this, infections can last decades.

use of ivermectin in an MDA programme. In Australia, the country-wide prevalence is very low (0.01%) but is much higher in the north of the country where the parasite is endemic: 15.5% in the Northern Territory and 10.6% in Queensland, based on seroprevalence data from pathology laboratories (2012–2016)²⁷.

In the Americas, the prevalence is 6.9%; most infections occur in South America, although autochthonous cases also occur in the USA (0.01%)^{3,28}. The highest prevalences in the Americas were identified in Colombia (18.4%), Costa Rica (15.7%), Panama (15.7%) and Nicaragua (15%). In Europe, the prevalence is 2.8%, with the highest prevalence in the Eastern Mediterranean region (5.8%)³, although identified cases may also be as a result of immigration or returning travellers.

Autochthonous cases in the Mediterranean are rarer. Italy, Spain and Portugal have the highest number of autochthonous strongyloidiasis cases in Europe^{29–31}, although this is still relatively low compared with the numbers in countries in Southeast Asia and the Pacific.

Risk factors

Strongyloidiasis is generally considered a disease of the tropics and subtropics, although autochthonous cases have occurred in more temperate regions^{22,27,32,33} (Fig. 2). In Australia and Africa, strongyloidiasis also occurs in dry, desert areas^{6,27}. Infection in drier areas is assumed to occur due to domestic and farm water use, causing moist soil conditions ideal for development of *Strongyloides* spp. larvae. As infection is

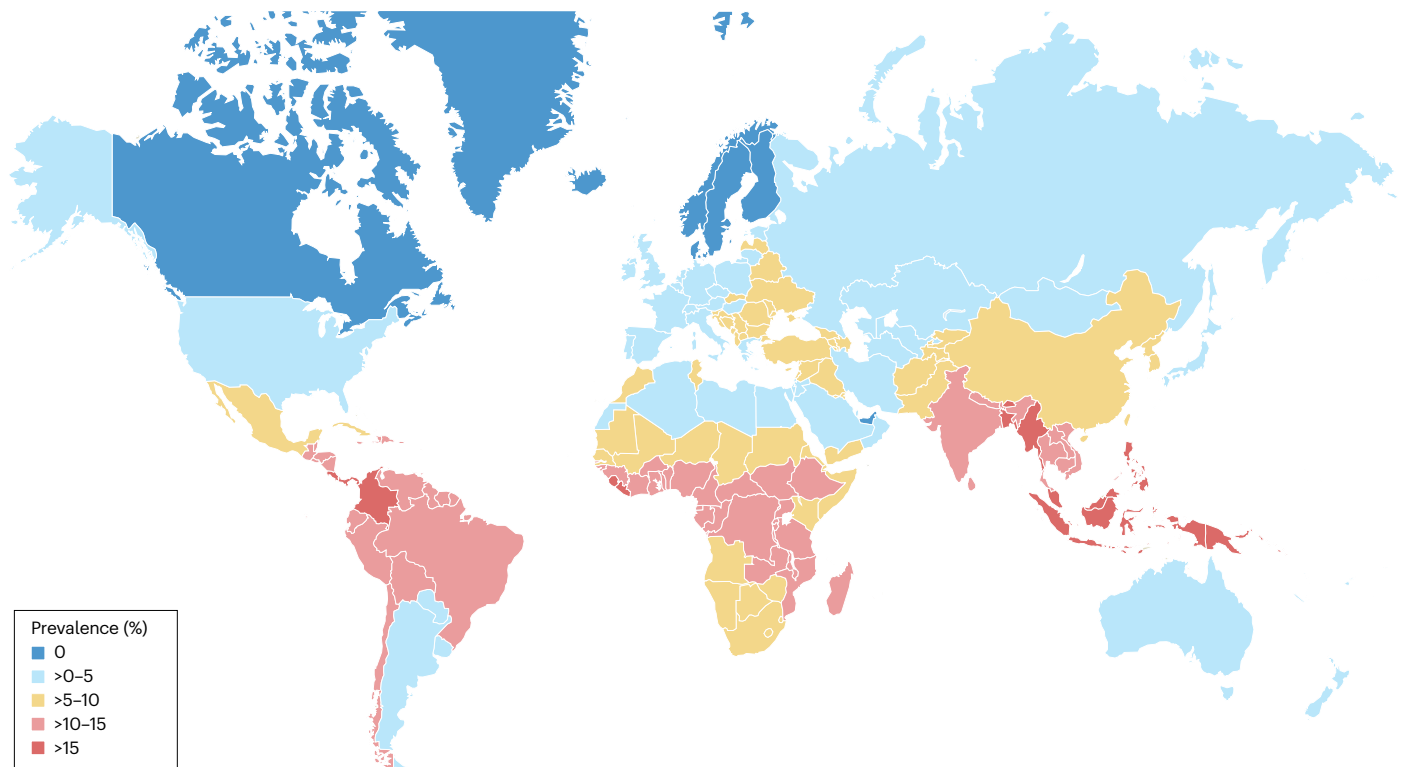


Fig. 2 | Global distribution of *Strongyloides stercoralis* infection. Estimated global prevalence for 2017 based on best-fit estimates from meta-analysis and modelling³. Southeast Asia and the Pacific region have the highest country prevalence (>15%). Reprinted from ref. 3, CC BY 4.0.

caused by direct penetration of infectious filariform larvae present in the soil, walking barefoot is a major risk factor^{12,22,34}. In Malaysia, the risk of infection is higher in those who do not wear shoes (odds ratio (OR) 1.91) than in those who do³⁵. In a Cambodian study, where the risk of infection in men is nearly threefold higher than in women (OR 2.79), farming was primarily in muddy rice fields; therefore, most farmers did not wear shoes while working in the fields³⁶. Fields are more likely to be contaminated due to a lack of latrines near the fields leading to open defaecation, as well as the use of human faeces as fertilizer³⁷. As men are more likely to perform agricultural activities, they are at higher risk of infection than women due to higher exposure to the parasite^{38,39}.

Cases of contaminated fresh fruit and vegetables have also been reported^{40,41}. Open defaecation, which causes contamination of the environment, primarily due to lack of sanitation facilities, and untreated water sources are additional risk factors^{35,36,42}. In Cambodia, the risk of infection was lower in those who had a latrine at home (OR 0.7) while in Malaysia those who practised open defaecation were much more likely to be infected than those who did not (OR 2.81)³⁵. Due to the autoinfective life cycle of the parasite (Fig. 1), infection can also occur person-to-person, although this is rarely reported^{12,43}.

Mechanisms/pathophysiology

Strongyloides stercoralis life cycle

Infection occurs via direct penetration of the skin by infectious L₃ filariform larvae (Fig. 1). *Strongyloides* spp. are attracted to their host by sensing mammal-emitted odorant substances such as urocanic acid⁴⁴. Larval penetration does not require any breaks in the skin, and instead

the larvae use helminth-specific astacin metalloproteinases to help break down tissue and gain entry to the body; these proteins may also be involved in penetrating the gut mucosa⁴⁵.

The migrating larvae enter the circulatory system and are carried to the lungs where they penetrate the alveolar spaces, migrating through the bronchioles to the trachea where they undergo tracheal migration (Fig. 1). Tracheal migration occurs as the larvae move up the trachea, eventually being coughed up and then swallowed, thereby making their way to the small intestine. Larvae may also migrate to the small intestine by random migration⁴⁶. Once in the small intestine the larvae undergo two successive moults to become parasitic females; there are no males in the pathogenic part of the life cycle¹². The female worms are embedded in the submucosa of the small intestine, specifically the duodenum, and reproduce by parthenogenesis, releasing eggs which hatch in the intestine as L₁ rhabditiform larvae (Figs. 1,3d,e). The L₁ rhabditiform larvae may then exit the host in the faeces to begin the free-living life cycle, or may undergo two moults to become infectious L₃ filariform larvae and penetrate the intestine (autoinfection) or skin around the anus and skin of the trunk (contaminative infection) (Fig. 3a), beginning the parasitic life cycle again without ever leaving the host. This ability to reinfect without leaving the body is referred to as autoinfection.

Immunological responses to acute and chronic infection

Acute strongyloidiasis is identified more frequently in individuals from non-endemic areas than in individuals from endemic areas (possibly owing to higher reporting and health resource access in HICs), and

symptoms usually develop 1–4 weeks after infection⁷. There are very few studies that have investigated how the immune response against strongyloidiasis mounts after initial infection; most of the knowledge of immune response has come from animal models^{47,48}, or from individual case studies which generally are only reported in cases of hyperinfection or dissemination when the patient is likely to be immunosuppressed and, therefore, not mounting a ‘normal’ immune response^{49–52} (Box 1). Helminths have immunomodulatory properties that trigger a T helper 2 (T_H2) cell reaction in the host; sperm-coating protein (SCP)-like extracellular proteins (SCP/TAPS (Tpx-1/Ag5/PR-1/Sc7)), identified in a range of parasitic nematodes including hookworms and *Strongyloides* spp., have been identified as important for transition to the parasitic stage, host invasion and immunomodulation⁵³. In animal models of strongyloidiasis using *Strongyloides ratti*, a species that infects rodents and is often used in animal strongyloidiasis models, neutrophils, eosinophils and macrophages were identified in the skin as a direct response to migrating larvae and not as a cell-mediated response⁴⁷. There is rapid production of IgE, IgG1, IgG2 and IgG3 by B cells, whereas parasite-specific IgG4 is produced later in infection as a more specific immune response; its levels are increased in chronic strongyloidiasis⁵⁴. IgG4 can block IgE responses, thereby modulating T_H2 responses⁵⁵.

Eosinophilia can also be high during the chronic phase of infection, but is less likely to be found in hyperinfection due to immune dysregulation common in individuals who develop this state⁴⁷. Eosinophil

larval killing is mediated by major basic protein, and in mouse models with an absence of eosinophils, neutrophils are capable of killing larvae⁴⁷. As with other parasites, complement activation seems to be important in larval killing. In mouse models with *S. ratti*, complement component C3 promotes binding of cells to larvae, and may also cause degranulation of immune cells, promoting larval killing and clearance^{47,56}.

Immune dysregulation and risk factors for developing severe disease

The host’s immune system plays a pivotal role in the control of strongyloidiasis during the autoinfective cycle. The balance between intrainestinal autoinfection and the host’s immune response preventing acceleration of helminth replication and migration to other organs, is severely disturbed in hosts with impaired immune systems (for example, due to advanced age, malignancy and other chronic diseases, immunosuppressive medication or organ transplantation)^{12,57,58}. In turn, this can lead to a rapid replication of *S. stercoralis* larvae (hyperinfection) and disseminated disease. The immune responses in hyperinfection are complicated due to immune dysregulation and the presence of co-morbidities⁵⁹.

Glucocorticoid (steroid) treatment is associated with two out of three literature-reported cases of severe strongyloidiasis^{60,61}. While the underlying mechanisms and pathways have yet to be fully elucidated,

Box 1

Research priority areas

Tools and interventions

- Develop, validate and standardize new diagnostics capable of diagnosing at every disease stage
- Develop and validate inexpensive and field-applicable diagnostic assays for use in epidemiological studies and control programmes
- Develop and test current and new drug treatment combinations and dosing schedules
- Develop and evaluate integrated control measures and assess their cost-effectiveness
- Develop and validate environmental tools to detect strongyloidiasis as a proxy for human infection and to identify hotspots of *Strongyloides* spp. infection
- Determine the safety of ivermectin in pregnancy

Transmission

- Undertake genetic studies on animal and human strains to conclusively determine zoonotic status and determine strain interactions and compatibility
- Integrate strongyloidiasis-specific diagnostics, treatment and control into current soil-transmitted helminth control programmes
- Increase public awareness of the risks and effects of strongyloidiasis on individual and community health, and the benefits of disease control
- Determine the effects of environmental changes such as climate change and irrigation projects on the epidemiology and transmission of strongyloidiasis

Disease burden and epidemiology

- Include strongyloidiasis in epidemiological surveys and national helminth control programmes to determine the true burden and prevalence of the disease worldwide
- Determine economic costs and disability-adjusted life-years due to long-term uncomplicated strongyloidiasis and chronic disease
- Mathematically model and perform cost–benefit analysis of prophylaxis or case finding and treatment compared with treatment of hyperinfection and disseminated strongyloidiasis
- Define and determine risk factors associated with development of hyperinfection and disseminated strongyloidiasis

Basic science

- Improve understanding of immunopathology, immunoevasion and interactions with co-morbidities to better understand disease pathways
- Identify vaccine targets
- Test vaccine targets in vitro before testing in animal models of strongyloidiasis (for example, using a model of *Strongyloides ratti* in rodents)
- Undertake clinical and field trials of developed vaccines

Research advocacy

- Advocate for specific funding and research into strongyloidiasis to address these research priority areas
- Advocate for funding, and donations or subsidies of the use of ivermectin in mass drug administration programmes

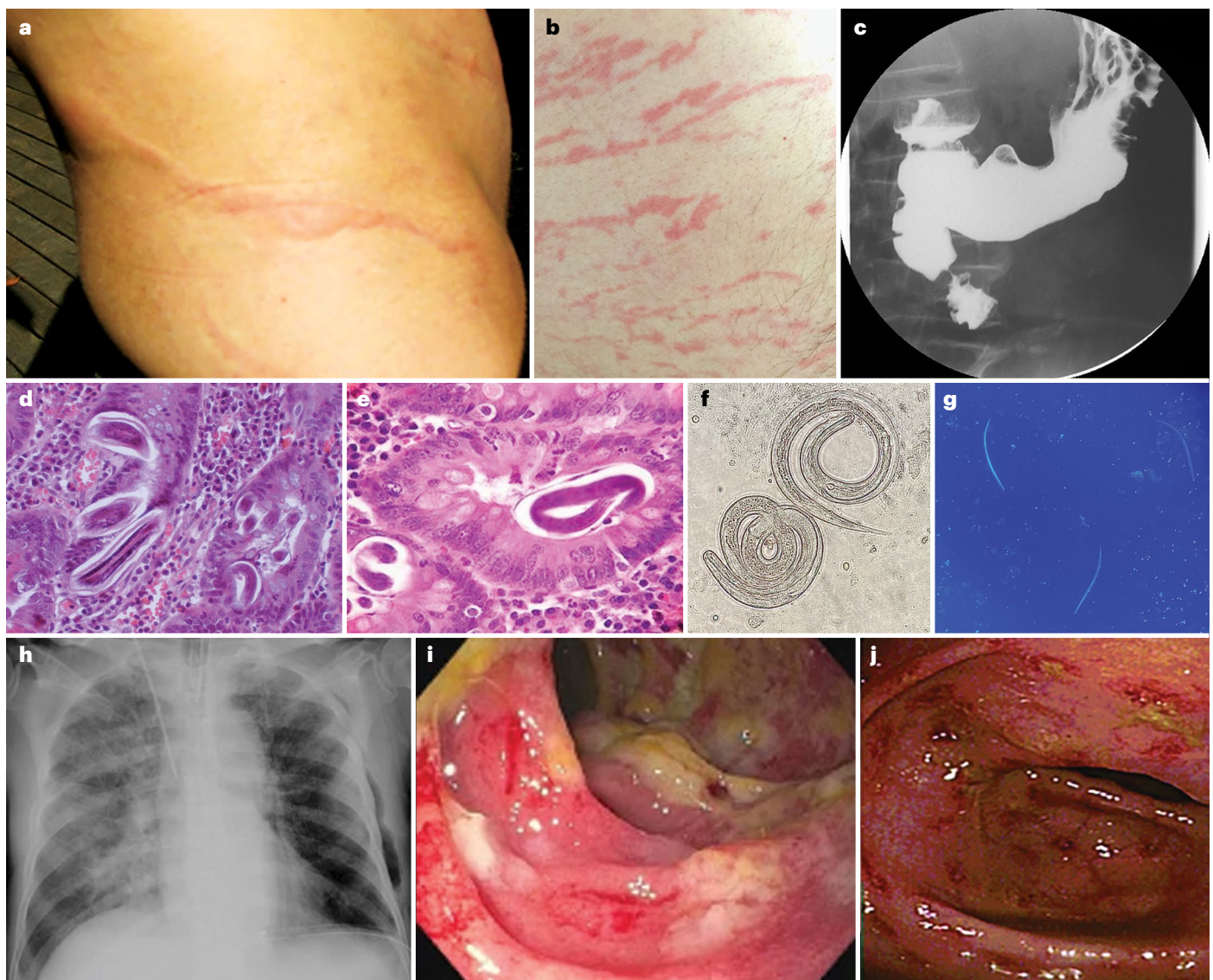


Fig. 3 | Clinical images from patients with *Strongyloides stercoralis* infection.

Larva currents occurring in a patient with uncomplicated strongyloidiasis (panel **a**), and in a patient with hyperinfection (panel **b**); plain radiograph (panel **c**) showing duodenal stricture; larvae of *S. stercoralis* in the gut mucosa (panels **d** and **e**); larvae from bronchoalveolar lavage (panel **f**), and with calcofluor staining (panel **g**); plain radiograph of the chest (panel **h**) showing diffuse ground-glass opacity and consolidation in the lung; images of the

duodenum (panel **i**) showing superficial ulceration, oozing and erythema of the mucosa, and of the descending colon (panel **j**) showing erythema and scattered erosions. Panel **a** reprinted with permission from ref. 202, W. Page. Panel **b** reprinted with permission from ref. 217, OUP. Panels **c–g** images courtesy of H. Sheorey. Panel **h** reprinted from ref. 121, CC BY 4.0. Panel **i** reprinted from ref. 218, Springer Nature Limited. Panel **j** reprinted from ref. 98, Springer Nature Limited.

glucocorticoids impair the clearance of *Strongyloides* spp. by the infected host and directly expedite the helminth's autoinfective life cycle⁶² (Fig. 1). Steroid-induced adverse modifications of the host's immune response to infection are manifold. They include inhibition of histamine release by mast cells, suppression of a T_H2 response with subsequent lower production of IL-4 and IL-5, reduced mucosal immunity due to inhibition of specialized intestinal effector cells (for example, goblet cells), and an upregulation of immunosuppressive effector substances (for example, IL-10). The autoinfective cycle of *Strongyloides* spp. is also accelerated following administration of glucocorticoid

drugs, which might be explained by the observation that the development of infectious L₃ larvae can be regulated by steroid ligands that bind to the parasite's nuclear receptor DAF12 (ref. 63).

Co-morbidities associated with development of hyperinfection and disseminated strongyloidiasis

A distinct association between clinically severe strongyloidiasis and co-infection with HTLV-1, a retrovirus that causes a lifelong infection, has been described⁶⁴. *S. stercoralis* and HTLV-1 coexist in large parts of low-income and middle-income countries (LMICs). It has been reported

that HTLV-1 can modify the host's T cell immune response from a T_H2 reaction, which is required to combat helminths⁶⁵, to a T_H1 -like reaction. This immunological switch may explain the higher rates of hyperinfection and disseminated disease in co-infected individuals⁶⁵. In a recent meta-analysis, HTLV-1 carriers were more likely to be infected with *S. stercoralis* than those negative for HTLV-1 (OR: 3.2)⁶⁶. HTLV-1 infection is associated with an increase in pro-inflammatory cytokines, particularly IFN γ ; however, there are conflicting reports of IFN γ levels in helminth co-infections^{67,68}. In symptomatic HTLV-1 infection, specifically adult T cell leukaemia/lymphoma, there is an increase in regulatory T cells expressing FOXP3 (ref. 69), which produce inhibitory cytokines, which may be a mechanism for the development of hyperinfection through immune suppression. Decreased treatment efficacy of ivermectin against strongyloidiasis in HTLV-1-co-infected individuals has also been observed, and this may have been due to reduced IgE production^{66,70}.

Among HIV-infected individuals, recent systematic reviews identified a global prevalence of ~5% of *S. stercoralis* co-infection⁷¹, with a considerably higher percentage in men than in women⁷². However, co-infection of HIV and strongyloidiasis is not associated with a higher frequency of severe strongyloidiasis^{73,74}.

Treatment of COVID-19 with corticosteroids and tocilizumab in patients with *S. stercoralis* co-infection has been associated with worsening of pre-existing strongyloidiasis, often leading to hyperinfection⁷⁵⁻⁷⁷. The use of steroids is a major risk factor for the development of hyperinfection and disseminated disease; thus, screening of patients with COVID-19 at risk of infection with *S. stercoralis* should be considered.

Alcohol use disorder (AUD) has been shown to increase susceptibility to infection with *S. stercoralis*, and infected patients with AUD with a high worm burden have reduced IFN γ levels⁷⁸. IFN γ is a pro-inflammatory cytokine, and its reduction leads to reduced cytokine levels and parasite killing. In studies comparing an IgE enzyme-linked immunosorbent assay (ELISA) with coprodiagnostics (analysis of faeces for parasite life cycle stages), patients with AUD were more likely to test negative by IgE ELISA than individuals without AUD, even when larvae were identified in stool samples, suggesting that IgE levels may be downregulated in patients with AUD^{22,79}. IgE is the main immunoglobulin associated with host protection against helminths; thus, reduction in IgE levels in patients with AUD may lead to increased larval load⁸⁰. Patients with AUD are also more likely to be malnourished, and have gastric inflammation, reduced intestinal motility and poor hygiene, the last of which increases the risk of becoming infected^{81,82}.

Diagnosis, screening and prevention

Clinical presentation

Acute strongyloidiasis. Acute infection with *S. stercoralis* reflects initial invasion and migration of L_3 filariform larval that subsequently transit the respiratory system and enter the gastrointestinal tract. Most infections are unrecognized, probably due to the non-specific nature of symptoms and the low initial parasite burden. When recognized and reported, the incubation period of natural infection can be as short as 7–14 days^{7,83}, although human infection studies have suggested that cutaneous lesions appear almost immediately after exposure, followed by a prepatent period of 23–32 days⁸⁴.

Primary cutaneous lesions may cause irritation at the site of penetration. Intradermal filariform larvae seem to migrate rapidly, resulting in a pathognomonic, serpiginous (spreading with an undulating border) urticarial rash known as larva currens (from the Latin, 'running larva') (Fig. 3a), growing in length by up to 10 cm per day⁸⁵. In an experimental

infection, 300 larvae placed onto a forearm led to an immediate pruritic cutaneous eruption that lasted 21 days⁸⁶. Cough and respiratory irritation developed on day 6, lasting for 3 days, with abdominal symptoms and anorexia developing on day 17 and progressing until treatment⁸⁶.

Following initial infection, transpulmonary larval migration may result in transient bronchitis, with signs and symptoms including dry cough, wheeze and shortness of breath. This syndrome of transient eosinophilic pneumonia is known as Loeffler syndrome, which may also be caused by other STHs⁸⁷; however, this is mostly reported to be brief and mild in acute strongyloidiasis⁸⁴. Imaging typically reveals patchy, unilateral or bilateral air space opacities, usually peripherally distributed, and typically without lymphadenopathy or pleural effusion⁸⁸. Acute gastrointestinal strongyloidiasis may cause epigastric discomfort, bloating, abdominal pain, constipation and diarrhoea⁸⁹. Dysentery has also been described⁸⁴. Examination may reveal splenomegaly, while transaminitis has also been reported⁷. Systemic symptoms can include fatigue and fever⁷.

Chronic strongyloidiasis. The clinical symptoms of chronic infection are influenced by the infection intensity and the host's immune response to migrating parasites during the autoinfective cycle (that is, cutaneous, respiratory and gastrointestinal systems). Approximately half of individuals with chronic strongyloidiasis are asymptomatic^{90,91}, although intermittent mild symptoms may lead to under-reporting.

Of those who do report symptoms, gastrointestinal complaints are common, although typically non-specific and mild, and include abdominal pain, altered bowel habit and diarrhoea⁹⁰⁻⁹². In Cambodia, the most common location of abdominal pain is the peri-umbilical and epigastric region⁹³, the latter probably reflecting the duodenal localization of adult parasites. Duodenal obstruction⁹⁴ and protein-losing enteropathy (with symptoms of fluid retention due to hypoalbuminaemia) have also been reported^{95,96}. Recurrent gastrointestinal symptoms may also mimic inflammatory bowel disease⁹⁷⁻⁹⁹ (Fig. 3i,j), which is also paradoxically exacerbated by immunosuppressive therapy^{98,100-102}. Chronic infection has also been associated with growth stunting¹⁰³ and a poor general health status¹⁰⁴.

Cutaneous symptoms are not uncommon^{92,105}, and include pruritus⁹⁰, recurrent urticaria^{106,107} and larva currens^{90,91}. Larva currens in the context of chronic infection is most likely to be reported in the perianal region, buttock, thigh or abdomen, due to larvae emerging during autoinfection and penetrating the local skin⁸⁵ (Fig. 3a). Migration of larvae to more distant cutaneous sites, such as the chest wall, has also been reported¹⁰⁸ (Fig. 3b). Respiratory symptoms are less commonly reported by individuals with chronic strongyloidiasis⁹⁰⁻⁹². Respiratory symptoms may include recurrent cough, dyspnoea and wheeze, which imitate the common symptoms of asthma^{109,110}, and may be paradoxically exacerbated by corticosteroid use^{111,112}.

Severe strongyloidiasis. Unlike chronic strongyloidiasis, in which infection may be asymptomatic or may result in typically mild, chronic symptoms, severe strongyloidiasis is associated with a remarkably acute presentation and is invariably fatal if untreated⁴⁹. This is usually in the context of immunosuppression, most notably due to corticosteroid therapy and HTLV-1 co-infection^{49,60}. Severe strongyloidiasis is categorized as hyperinfection syndrome and disseminated strongyloidiasis, although these conditions probably coexist in most patients experiencing severe disease.

The symptoms of severe strongyloidiasis, therefore, reflect the consequences of exaggerated parasite proliferation and migration.

Due to the large number of filariform larvae penetrating the intestinal lumen, enteric bacterial translocation frequently occurs, resulting in secondary bacterial sepsis. Symptoms of disseminated strongyloidiasis include fever, headache and altered mental status, as enteric bacterial carriage on disseminated larvae may lead to meningitis^{60,113}.

Gastrointestinal symptoms in severe strongyloidiasis again reflect the large burden of luminal infection, with anorexia, nausea, vomiting, abdominal pain, diarrhoea, constipation and ileus reported^{113–115}. Transpulmonary migration during hyperinfection may result in a wide spectrum of cardiorespiratory presentations, such as dyspnoea, cough and haemoptysis, typically due to extensive pneumonia and pulmonary haemorrhage, which is associated with the development of acute respiratory distress syndrome^{116–118}. Plain radiography of the chest may show a diffuse ground glass like opacity and consolidation (Fig. 3h). Pleural effusions may occur due to parasite migration from the lung parenchyma into the pleural space¹¹⁸, while migration from the pleural to the pericardial space may cause pericarditis^{116,119}. Pulmonary abscesses have also been reported, which probably develop as a result of secondary bacterial infection¹¹⁶. Cutaneous signs and symptoms are less commonly reported; however, a pathognomonic rash seen in immunocompromised patients with severe strongyloidiasis is periumbilical purpura^{120,121}. Even among those who receive treatment, case fatality rates of 43–63% have been reported^{49,60,119}, while a mortality rate of 87% has been reported in patients with severe strongyloidiasis and translocated bacterial sepsis^{1,83,122,123}.

Diagnosis

The diagnosis of strongyloidiasis is complicated and lacks both a ‘gold standard’ and standardization of tests, and the best diagnostic varies depending on disease status (see Supplementary Table 1). A target product profile (TPP), which outlines the desired characteristic of a diagnostic for a specific disease, has yet to be developed for strongyloidiasis. In Supplementary Table 1, we compare diagnostics used in STH control programmes and epidemiological surveys, and those specifically employed for strongyloidiasis against some key TPP criteria that have been identified in reference to other parasitic NTDs.

Microscopic/coproparasitological approaches. Stool microscopy and coproparasitological methods detect excreted larvae of *S. stercoralis*, and are particularly useful in revealing which larval output is high in acute strongyloidiasis and in hyperinfection. Concentration techniques, which use various methods to remove faecal debris, reduce sample volume and concentrate any parasites into a smaller volume for easier detection, such as FLOTAC and FECT, have poor sensitivity in *S. stercoralis* infection, with the latter potentially removing larvae through processing^{59,124}. However, a modified FECT¹²⁵ has similar sensitivity to agar plate (AP) copro-culture. The Kato–Katz technique is a mainstay in the diagnosis of STH infection but is not recommended for *S. stercoralis* infection diagnosis^{59,124}.

AP and the Baermann technique have high sensitivity compared to other copro-based diagnostics, such as the Harada–Mori filter paper technique, and PCR assays, although sensitivity is low compared with immunodiagnostics^{12,24,126}. These techniques rely on viable larvae and, therefore, the use of fresh, unfixed stool. There is poor standardization with these methods – indeed AP can refer to a whole suite of different methodologies – which can limit meaningful comparisons between published studies (see Supplementary Table 1). Hookworm and strongyloidiasis are often present in the same areas, and thus culturing methods will also result in viable hookworm larvae being present, which will then need to be distinguished (Fig. 4).

Microscopy can also be utilized in the evaluation of sputum samples and duodenal aspirates, which have high larval content in hyperinfection¹²⁷ (Fig. 3f,g). Diagnosis of *S. fuelleborni* and *S. f. kellyi* infection relies on identification of eggs in the faeces¹⁵, although eggs hatch rapidly and rhabditiform larvae may be present. *S. fuelleborni* eggs are passed individually, while *S. f. kellyi* are often passed in strings⁵.

Serology and immunodiagnostics. There are several serological tests, including both in-house and commercially available tests for *S. stercoralis* detection, utilizing crude *S. stercoralis*, *Strongyloides venezuelensis* or *S. ratti* extracts or more sensitive *S. stercoralis* recombinant antigen (NIE)¹²⁸ (see Supplementary Table 1). Most immunodiagnostics are



Fig. 4 | Differentiating between hookworm and *Strongyloides stercoralis* larvae based on morphology. **a**, Rhabditiform larvae of *Strongyloides* show a short buccal cavity (blue arrow) and a bulb oesophagus (black arrow), and a prominent genital primordium (red arrow). **b**, By contrast, rhabditiform larvae of hookworm show a long buccal cavity (blue arrow). **c**, In filariform larvae of *Strongyloides*, the oesophagus–intestine junction (white arrow) is halfway down

the larval body. **d**, By contrast, in hookworm filariform larvae, the junction (white arrow) is roughly one-third of the way down the larval body. Filariform larvae of *Strongyloides* also possess a notched tail while those of hookworm have a pointed tail. Images in panels **a** and **c** adapted with permission from ref. 219, CDC. Images in panels **b** and **d** adapted with permission from ref. 220, CDC.

based on IgG detection, although there are also IgM based diagnostics, and a commercially available IgG–IgM combination diagnostic. Sensitivity and specificity vary depending on other reference tests utilized. Immunodiagnostics identify more positives than copro-based diagnostics; however, while high sensitivity can be exhibited by serological diagnostics, cross-reactivity can be observed with other helminths depending on the antigen used^{129,130}. Circulating antibodies persist for some months after successful treatment and thus positive serology may not indicate active infection. Antibody titre levels do drop rapidly after successful treatment, and re-testing after 6 months should determine the success of treatment^{131–134}. This may be more useful in non-endemic areas where the rate of re-infection is low.

Serological diagnostics lend themselves to point-of-care diagnostics, which are of particular utility in LMICs¹²⁴. SsRapid, a rapid diagnostic test (RDT), utilizing NIE has been developed, and has shown high sensitivity and specificity in laboratory set-ups¹³⁵, and in a field-based trial in Ecuador conducted in 2021–2022 (refs. 136–139). The RDT had a higher sensitivity in that study than copro-PCR, the Bordier and Strongy Detect ELISAs and the Baermann technique, although specificity (93.6%) was lower for the RDT than all other tests except the Strongy Detect ELISA (91.7%)¹³⁶; the RDT builds on a previous lateral flow dipstick^{137,138}. Similarly, ELISA of dried blood spots has also shown comparable sensitivity and specificity to analysis of conventional serum samples¹⁴⁰.

Urine-based ELISAs have also been developed but have generally performed less well than serum-based ELISAs. However, more recent studies have shown results comparable to those of serum-based ELISAs^{141,142}. Urine is a non-invasive clinical sample and may be easier to obtain from patients and therefore may have greater uptake and utility for control programmes and surveys. There are fewer antigen detection tests for strongyloidiasis: a single serum-based antigen detection ELISA (SsAg-ELISA) and a stool-based antigen detection ELISA (copro-ELISA)^{143,144}. The copro-ELISA utilizes *S. ratti* excretory–secretory (E–S) antigens and shows low cross-reactivity with other helminth E–S products¹⁴³. The SsAg-ELISA similarly shows no cross-reactivity with other helminths¹⁴⁴.

Molecular-based techniques. There are a range of different laboratory developed PCR assays^{145–147} and loop-mediated isothermal amplification assays (LAMP)¹⁴⁸. In general, PCR is considered to be sensitive and specific, and while it maintains specificity for *Strongyloides* detection, it is not as sensitive as other copro-based diagnostics, such as the Baermann technique, or serological tests^{149,150}. As with other diagnostics, there is a lack of standardization of methods, including sample collection and preservation, and DNA extraction methods, and sensitivity varies depending on reference tests used to calculate sensitivity and specificity^{17,149–152}. Few molecular assays have been validated clinically or in population-based studies for strongyloidiasis. The WHO also recommends standardization of DNA extraction methods¹²⁴. Most assays are based on DNA extracted from stool samples. Urine-based PCR has also been explored; however, sensitivity is low^{153,154}. A major limitation of DNA-based methods employed in resource limited settings is the cost, and the requirements for thermocyclers and highly trained laboratory personnel.

Limitation for current diagnostics. The lack of standardization for any diagnostic for strongyloidiasis, and the lack of validation across the many in-house molecular-based and immuno-based diagnostics, is a major limitation for current diagnostics, which makes meaningful comparison of diagnostic performance across studies virtually impossible (Box 1).

Copro-diagnostics are most useful when larval output is high, during acute strongyloidiasis and in hyperinfection, while serological diagnostics are particularly useful in chronic strongyloidiasis; however, serology can give false-negative results in acute or early infections in which an immune response has not been mounted and in hyperinfection due to reduced antibody production in immunosuppressed patients despite heavy infection^{131,155} (see Supplementary Table 1). According to the US Centers for Disease Control and Prevention (CDC), serial stool examination is the gold standard for *S. stercoralis* detection, but that it may require as many as seven stool samples to reach 100% sensitivity^{12,59}.

In view of these shortcomings, a combination of diagnostics that include a serological test with a copro-diagnostic has been proposed to more accurately detect *Strongyloides* infection^{136,156}. It is particularly pertinent for clinicians to be aware of the limitations of available diagnostics, as missed infection can have potentially severe consequences. A recent cross-sectional study in Ecuador compared five different diagnostics and assessed the sensitivity and specificity of each diagnostic separately, and as combinations of immunodiagnostics (SsRapid RDT, Bordier ELISA and Strongy Detect ELISA) with copro-diagnostics (stool PCR and the Baermann technique)¹³⁶. Both sensitivity and specificity were increased when two diagnostics were employed.

Peripheral eosinophilia. Individuals with or without symptoms of chronic strongyloidiasis may be referred for investigation of unexplained eosinophilia (defined as an elevated eosinophil count in peripheral blood above 500/ μ l). Eosinophilia is common in helminth-infected individuals, and occurs in up to 50–75% of people infected with *S. stercoralis*⁹⁰, although co-infections are common and may overestimate rates of eosinophilia⁹⁰. In migrants and travellers returning from endemic settings with otherwise unexplained eosinophilia, diagnostic work-up for strongyloidiasis is indicated, even if other symptoms are lacking^{157,158}. In patients with eosinophilia at the time of diagnosis, eosinophil counts usually decrease within 4–6 weeks after treatment, and may be used to monitor treatment response¹⁵⁹. Not all *Strongyloides*-infected individuals present with eosinophilia, and a normal eosinophil count never excludes strongyloidiasis^{92,160}. Eosinophilia is often absent in *Strongyloides* hyperinfection and disseminated disease, and might be a predictor of a worse outcome in such patients¹⁶¹.

Prevention

Public health measures. Strongyloidiasis is the most neglected of all the NTDs with the WHO clearly stating that “no public health strategy has been developed to control strongyloidiasis”, and “no public health strategies for controlling the disease are active at the global level”³⁴. Despite this, *S. stercoralis* has been recognized as a public health problem and an evidence-based comprehensive public health strategy is urgently required. Strongyloidiasis is generally grouped with the STHs (*Ascaris lumbricoides*, *Trichuris trichiura* and hookworm) even though it is not included in STH control programmes (primarily due to a different drug and diagnostics required for strongyloidiasis); however, the recommendations for STH control should be a starting point for a strongyloidiasis control strategy (Box 1). Ivermectin as a single oral dose can reduce infection levels and morbidity as part of a community-based MDA programme; and preventive measures such as water, sanitation and hygiene (WASH) along with health promotion can augment MDA, preventing transmission and re-infection. We posit that a multicomponent integrated approach is required for the sustainable control and potential elimination of strongyloidiasis. Such a programme would combine ivermectin MDA, WASH, community

engagement, potentially animal management (if *S. stercoralis* infection is indeed a zoonosis), and precise surveillance (Box 1).

Ivermectin was previously expensive, which was a barrier to its use for strongyloidiasis MDA unless the medication was donated or heavily subsidized (Box 1); however, an affordable generic version of ivermectin is now available. The WHO is currently developing guidelines for the control of strongyloidiasis to provide guidance to endemic countries on methods for achieving public health control of strongyloidiasis¹⁶². The existing infrastructure for STH drug distribution already facilitates distribution of >400 million albendazole or mebendazole tablets to children each year¹⁶³. Of note, ivermectin is used as preventive chemotherapy in control programmes targeting scabies, onchocerciasis and/or lymphatic filariasis^{164,165}, and has been shown to have an effect on strongyloidiasis where it is co-endemic¹⁶⁶. Ivermectin has been donated as part of the Pacific Programme to Eliminate Lymphatic Filariasis (PacELF), and over >1,800 million tablets for onchocerciasis control have been donated as part of the Mectizan Donation Program^{167,168}. Similarly, preventive measures, including health education and WASH, in STH control programmes, particularly against hookworm, such as the wearing of shoes, will probably have an effect – unfortunately, no data exist on this.

Health education and community-based interventions. While health education for STH, particularly hookworm, is likely to positively affect strongyloidiasis, there is limited specific health education available; and what there is largely stems from Northern Australia. A health promotion flip chart was developed with the Miwatj Health Aboriginal Corporation for East Arnhem Land, Australia, which tells the ‘*Strongyloides* story’. The flip chart was developed to help explain the transmission of strongyloidiasis, its importance to health, and risk factors for infection to community members (*Strongyloides* Australia). A second flip chart was designed by the Aboriginal Resource Development Services, which tells about both *strongyloidiasis* and *scabies*, which is also available in the local Yolgnu language. Health information, education and communication are important aspects of integrated control. For strongyloidiasis, this should encompass not only those who may become infected, but also health professionals for diagnosis and correct treatment strategies (Box 1).

Vaccines. There are no vaccines currently available for any human helminth species. The successful identification and development of a vaccine candidate against strongyloidiasis is hampered by the myriad immune-modulating characteristics of the parasite and by the occurrence of several stages (that is, L₁, L₂ and L₃ larvae and adult worms) with stage-specific antigen expression in the infected host. It is also unclear whether, and how, partial protective immunity might develop after natural infection compared with a possible vaccine-induced immune response. In studies of vaccine development for other STHs, vaccine effectiveness was assessed in terms of rising cytokine and/or specific IgG4 production or a documented decrease in infection intensity¹⁶⁹. Some experimental studies used immune-reactive antigens obtained from the glandular oesophagus of *S. stercoralis* or heat shock protein 60 from the closely related *S. ratti* as antigen vaccine candidates in mice, but the specific immunological responses remain poorly understood¹⁶⁹. Hence, it is unlikely that a *Strongyloides*-specific vaccine candidate will enter into clinical trials over the next 3–5 years.

Screening

Screening is performed in HICs and rarely in LMICs, including those endemic for strongyloidiasis. In many HICs, such as Australia, Canada

and the USA, screening is recommended for refugees entering the country^{8–10}; Australia and the USA are also endemic and have autochthonous transmission^{6,27,28}. In the Northern Territory of Australia, which has the highest rates of autochthonous strongyloidiasis in the country, treatment with ivermectin is recommended regardless of serology results prior to immunosuppression^{170,171} due to the consequences of missed diagnosis and the high pre-test probability of infection. In other non-endemic countries, screening is also recommended prior to immunosuppression due to the risk from migrants with unrecognized strongyloidiasis¹⁷².

The lack of a gold-standard diagnostic hampers screening, including issues around false-negative results, depending on the test used and the disease status of the patient, as well as lengthy testing times if using culture techniques (see Supplementary Table 1). An algorithm has been developed as a diagnostic flow chart for use in immunosuppressed patients¹⁷³. The flow chart incorporates epidemiological exposure risk and current immunosuppression status to help determine if the patient is at risk of strongyloidiasis, and then suggesting diagnostics to use¹⁷³. In patients at high risk waiting for immunosuppression or currently immunosuppressed then a combination of serology and copro-based diagnostics are suggested¹⁷³.

The only exception to no active control programmes for strongyloidiasis is a ‘test and treat’ strategy implemented in East Arnhem Land, Australia, by the Miwatj Health Aboriginal Corporation, whereby community members are tested for strongyloidiasis as part of routine health assessments and those found positive treated with ivermectin¹⁷⁰. Prevalence in endemic communities has been reduced utilizing this strategy. This strategy is not implemented in other communities beyond those associated with the Miwatj region.

Management

Current and future drugs

Since the 1990s, the macrocyclic lactone ivermectin has been the first-line treatment for strongyloidiasis¹⁷⁴. Ivermectin acts on glutamate-gated chloride ion channels triggering an increase in the permeability of the cell membrane in invertebrates which results in the influx of chloride ions and hyperpolarization leading to paralysis and death of the worm¹⁷⁴. Ivermectin has good efficacy and safety profiles and outperforms the benzimidazoles albendazole and thiabendazole that serve as alternative treatments¹⁷⁵. In two randomized controlled trials, a single oral dose of ivermectin resulted in cure rates of 86–95%^{176–178}. Multiple doses of ivermectin showed the same efficacy as single dose regimens but were associated with more adverse events¹⁷⁶. It is considered that oral ivermectin in children weighing <15 kg is safe¹⁷⁹. Hence, the current contraindication against treating children under 5 years old might be reconsidered considering the efforts to develop an ivermectin formulation suitable for use in children. Pharmacometric modelling has indicated that a higher dose might be required in children than in adults because of higher clearance¹⁸⁰. To overcome the challenge of a weight-based administration in resource-constrained settings, the use of a ‘tablet pole’, which uses height rather than weight to estimate dosage has also been assessed, as it would facilitate MDA in LMICs¹⁸¹. The use of ivermectin is currently contraindicated in pregnant women¹⁸² and research into safety in pregnant women is urgently required. Albendazole is the only alternative medication currently available, which should be avoided in the first trimester of pregnancy¹⁸² and is inferior to ivermectin in terms of efficacy¹⁴.

Current treatment guidelines are available from organizations such as the CDC¹⁸². Targeted treatment using diagnostic testing is

the ideal approach to slow the development of resistance to ivermectin; however, ivermectin MDA could also form the foundation of a community-level strongyloidiasis control programme that also incorporates preventive measures as discussed below. Presumptive treatment may be required before imminent administration of immunosuppression in individuals at risk of strongyloidiasis⁶¹.

Moxidectin, a compound from the same family as ivermectin with small structural differences, was registered in 2018 for the treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged ≥ 12 years, and is now being evaluated for use in treating strongyloidiasis¹⁸³. Moxidectin is considerably more lipophilic and displays a longer half-life in plasma and broader distribution compared with ivermectin^{174,184,185}. Studies of the use of moxidectin in children are underway to extend the indication to children aged 4–11 years and to obtain additional data to inform the WHO and the ministries of health in endemic countries on moxidectin use in treatment programmes¹⁸⁶. A dose-ranging phase IIa study evaluating moxidectin in adults infected with *S. stercoralis* revealed cure rates of 83–88%¹⁸⁴. Moxidectin was well tolerated at all doses. Phase IIb studies comparing the efficacy of moxidectin and ivermectin side-by-side were completed in Cambodia and Lao PDR in 2022 (refs. 187,188). A population pharmacokinetic study demonstrated equivalent exposures after fixed-dose and weight-dependent dosing, which supports the use of a weight-independent dosing, which in turn would enable MDA campaigns¹⁸⁹. To further increase cure rates, which is a key factor to mitigate autoinfection, repeated dosing (for example, a two-dose regimen with moxidectin 3 weeks apart) should be considered, which needs to go hand-in-hand with safety investigations¹⁸⁵.

Unique cases of ivermectin use. In patients with hyperinfection and disseminated strongyloidiasis, parenteral ivermectin treatment has been used, using a veterinary formulation not licensed for use in humans^{14,190}. This is usually only performed due to reduced intestinal absorption which limits uptake of orally or rectally administered ivermectin tablets. Ivermectin toxicity has been reported in a small number of patients in whom ivermectin was given subcutaneously. Neurological symptoms have been described; however, these may also be attributable to the disseminated strongyloidiasis instead^{14,191}. Ivermectin is generally blocked from crossing the blood–brain barrier by P-glycoprotein, a protein pump^{14,192}. Thus, mutations in this pump may lead to neurotoxicity.

Management of severe disease

In the setting of severe strongyloidiasis in immunocompromised individuals, immunosuppression should be reduced or ceased, if feasible. Intensive care may be required in patients with respiratory failure, septic shock, bacterial meningitis or other organ dysfunction. In patients with suspected bacterial infection (for example, sepsis and meningitis), antimicrobial therapy should be commenced following the collection of blood cultures, with empirical therapy broadly targeting enteric bacteria¹⁹³. Anthelmintic treatment with ivermectin is administered enterally, orally or via nasogastric tube¹⁹³. In a number of patients unable to tolerate or absorb enteral therapy (for example, due to small-intestinal obstruction or paralytic ileus), subcutaneous treatment using an unlicensed veterinary formulation has been used^{194–196}, generally administered either daily or every alternate day, and continued until enteral therapy is feasible. Rectal instillation of ivermectin has also been reported¹⁹⁷, although systemic absorption is poor when using a suppository preparation¹⁹⁸. In patients with persistent

severe strongyloidiasis despite ivermectin monotherapy, the addition of albendazole (given concurrently with ivermectin) has also been described¹⁹⁹. Moxidectin has not yet been used for individual management in such patients. Ivermectin in patients who recover from severe strongyloidiasis is generally continued daily until symptoms have resolved and larvae have been absent on examination of stool/sputum for at least 2 weeks (that is, one autoinfection cycle)¹⁹³.

Monitoring after treatment

In patients with larvae detectable in stool prior to treatment, guidelines recommend that repeat stool examination should be performed 2–4 weeks after therapy; if larvae remain visible, re-treatment is required, although intermittent shedding of larvae makes this an unreliable measure of treatment success¹³⁰. In those who report persisting symptoms despite treatment, even if stool examination is unrevealing, a repeat course of therapy may be warranted, and additional investigations for an alternative cause may be indicated. In patients who fail treatment without an apparent cause, HTLV-1 infection should be excluded. In those with eosinophilia prior to treatment, eosinophilia may persist for months²⁰⁰, although eosinophilia ≥ 1 year after treatment, without an alternative aetiology, may also warrant re-treatment^{12,193}. In people who are IgG seropositive at the time of diagnosis, repeated testing 6–12 months after treatment has been recommended, with seroreversion suggestive of treatment success^{133,134}. In patients who were initially diagnosed using PCR, the role of monitoring stool PCR remains unclear^{159,201}.

Quality of life

There are currently no global burden of disease estimates for strongyloidiasis. The latest global estimate of disease burden report put the disability-adjusted life-years (DALYs) due to STH (excluding strongyloidiasis, which is not mentioned) at 25.5 DALYs per 100,000 in 2019.

As a chronic infection strongyloidiasis can be referred to as asymptomatic; however, that may not be true. Instead symptoms are often intermittent, wide ranging and general in nature, and thus may not be recognized²⁰². Abdominal pain, diarrhoea and urticaria are the most commonly observed symptoms in chronic infections, although these are not reported in all patients¹⁰⁶. While there are limited data available on the morbidity and quality of life in patients with chronic strongyloidiasis, long-term diarrhoea can be associated with dehydration and nutritional deficiencies, as well as irritation and inflammation of the colon and rectum.

Growth stunting in children was found in a study in Cambodia, with odds ratios of 2.5 in those with a heavy infection (one or more larvae per gram of faeces) and 1.35 in those with a light infection (less than one larva per gram of faeces)¹⁰³. While only physical growth was examined, stunting can also be associated with diminished mental ability and learning capacity, a pernicious syndrome that has knock-on effects leading to poor school performance and reduced earnings in adulthood, as well as a stronger likelihood of developing chronic diseases later in life^{203,204}. Strongyloidiasis is a disease of poverty¹¹, and growth and mental stunting in children caused by the parasite perpetuates the cycle of poverty.

Outlook

The WHO roadmap for NTDs 2021–2030 set several specific targets for STH, including controlling morbidity due to strongyloidiasis^{205,206}. Emphasis was put on the development of guidelines for preventive

chemotherapy, prioritization of control efforts, advocacy and funding, capacity strengthening, and awareness building and diagnosis. To add to the WHO list of areas that need work, we would also add the need for specific guidelines and standardization of diagnostics, and guidelines for disease management, which currently vary from one country to another.

Strongyloidiasis has been referred to as the most neglected of the NTDs¹. This observation is borne out by the general lack of accurate diagnostic tools and control programmes specifically targeting strongyloidiasis. While included in the STH group of helminths when national surveys are performed, strongyloidiasis is not identified, and in MDA campaigns, ivermectin, the drug of choice against *Strongyloides* is not used²⁰⁷. Insensitive diagnostics, such as the Kato–Katz thick smear and FECT techniques, are performed, and drugs such as albendazole and mebendazole, which have poor efficacy against strongyloidiasis, are used²⁰⁸. Thus, the main problem facing strongyloidiasis is a lack of recognition. Without inclusion in national surveys, the true burden of disease will not be known, and without correct treatment the disease goes unnoticed and uncontrolled.

Diagnostics

There is an urgent need for new diagnostics that are inexpensive, rapid and field-friendly (Box 1). Any new diagnostic test should be capable of detecting strongyloidiasis at all stages of the disease; however, it may be that a two-step diagnostic process will be required, with an initial population screening test that has high sensitivity, followed by a more specific test for confirmation.

In addition, there is a need for specific strongyloidiasis guidelines that include validation and standardization of available diagnostics. The WHO is developing new guidelines around strongyloidiasis, which will hopefully lead to standardization and greater uptake in national control programmes¹⁶².

New drugs and treatment

In settings with other STHs, co-administration with albendazole is recommended, which would be highly beneficial against *T. trichiura* infections²⁰⁹. However, in areas where *Loa loa* is co-endemic, ivermectin is contraindicated as sudden death of the worms can result in severe adverse events²¹⁰. The development of drug resistance due to widespread MDA is a threat, with resistance against ivermectin already noted in helminths of veterinary importance, such as *Parascaris equorum*, *Haemonchus contortus* and *Cyathostomum* spp.^{211,212}. Thus, the development of new drugs that are safe and highly efficacious against strongyloidiasis is important. An ideal drug, or drug combination, would also have activity against other STH infections.

A future drug that could be of interest for the treatment of strongyloidiasis is the cyclo-octadepsipeptide emodepside, which targets latrophilin-like receptors and calcium-dependent voltage-gated potassium slowpoke (SLO-1) channels in the parasite²¹³. At present, emodepside is being developed against onchocerciasis and STH infection. In view of high cure rates against *T. trichiura* and hookworm infections at a single dose²¹⁴, a phase IIa dose-ranging study with emodepside has been launched in patients with strongyloidiasis in Lao PDR^{214,215}.

Control and prevention

Strongyloidiasis and other STHs, particularly hookworm, share common risk factors. Many prevention strategies implemented to reduce the burden of STH infection, including health information, education, communication, promoting shoe wearing, and providing WASH

infrastructure, will also affect the incidence of strongyloidiasis. Vaccine development should be a major focus to advance the prevention of strongyloidiasis, and the vaccination of immunosuppressed individuals in endemic areas may be useful to prevent severe disease, although vaccine efficacy in this group will remain a challenge. Thus, new approaches should be explored to achieve protection in those most at risk of poor outcomes (Box 1).

There is a pressing need to enhance global surveillance and develop a control strategy for strongyloidiasis. Integrating *Strongyloides* spp. into existing STH and intestinal schistosomiasis control programmes could be a way forward given similarities in transmission (that is, hookworm) and prevention strategies (for example, provision of sanitation and hygiene education). Research is needed to develop and validate novel diagnostics, treatments and prophylactics for strongyloidiasis. Integrated, cross-sectoral control approaches are warranted to have a lasting impact on strongyloidiasis on the road towards elimination on this important, yet severely neglected NTD.

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