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Review Article

Human *Strongyloides stercoralis* infection

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KEYWORDS
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Abstract *Strongyloides stercoralis* is an important soil-transmitted helminth occurring world-wide and affecting 30—100 million people. Because many cases are asymptomatic and sensitive diagnostic methods are lacking, *S. stercoralis* infection is frequently underdiagnosed. The increasing incidence of autoimmune and wasting diseases and increased use of immunosuppressive agents, as well as the increased use of immunosuppressants and cytotoxic drugs, have increased *S. stercoralis* infection and their mortality. This review provides information about *S. stercoralis* epidemiology, life cycle, aetiology, pathology, comorbidities, immunology, vaccines, diagnosis, treatment, prevention, control and makes some recommendations for future prevention and control of this important parasite.

Introduction

Strongyloides stercoralis (*S. stercoralis*), a soil-transmitted nematode, occurs worldwide and causes higher infection rates in the tropics and subtropics where there are favourable ecological conditions, low sanitary standards, and poor hygiene.[1] It is prevalent in sub-Saharan Africa, southeast Asia, the southeastern United States, southern

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Europe, Latin America, South America, Bangladesh, and the West Indies.[2—5] Despite strongyloidiasis worldwide occurrence, global prevalence is largely unknown due to limited surveillance.[6,7] However, efforts to update this outdated estimation are underway. Buonfrate et al. have provided new estimates of *S. stercoralis* prevalence globally, indicating that the worldwide prevalence of strongyloidiasis may reach up to 613.9 million individuals.[8,9] Furthermore, an analysis of studies has shown that an equation based on hookworm prevalence can serve as a useful proxy for estimating the global burden of *S. stercoralis* in most, but not all, epidemiological environments.[10] *S. stercoralis* is an important soil-transmitted nematode, a cause of severe morbidity and mortality, but has often been neglected.[11]

The World Health Organisation (WHO) points out that with lack of appropriate therapy, strongyloidiasis cannot be resolved and may persist for life.[12] Furthermore, the infection may be severe and even life-threatening in patients with immunodeficiency.[13] In this review, we provide an overview of the most recent data on strongyloidiasis, including epidemiology, life cycle, aetiology and pathology, comorbidities, immunology and vaccines, diagnosis, treatment, prevention, and control.

Epidemiology

S. stercoralis is highly prevalent in people living in or coming from areas with high humidity, inadequate water, low sanitary standards, and poor hygiene.[11,14] Transmission mainly occurs in the tropics and subtropics, as well as in countries with temperate climates.[15] *S. stercoralis* infection is common not only in low-income and middle-income countries but also in high-income countries (Fig. 1, Table 1).[16] It is estimated that Southeast Asia and the Pacific region have the highest national prevalence (>15%).[7,8,17] *S. stercoralis* infection is associated with malnourishment and stunting in children.[18,19] Numerous studies indicated that the prevalence of strongyloidiasis tends to be greater in adults compared to children, paralleling the distribution observed in hookworm infections.[8,19—21] It can be seen that the global burden of disease is substantial.[22] Because many cases are asymptomatic and sensitive diagnostic methods are lacking, strongyloidiasis is frequently underdiagnosed.[23] The incidence of *S. stercoralis* infection is associated with autoimmune diseases and wasting disease, including systemic lupus erythematosus (SLE), inflammatory bowel disease, autoimmune encephalomyelitis, malignant tumors, leukemia, tuberculosis, diabetes, congenital immunodeficiency, and human T-lymphotropic virus type 1 (HTLV-1).[19,24,25] Eosinophils induce the adaptive immune response by acting as antigen-presenting cells, thus inducing the T-helper 2 response with the consequent production of cytokines and specific antibodies (both IgM and IgG) against worms.[19] HTLV-1 decreases the type 2 response, therefore reduces immunity to helminth infections.[26] In addition, the use of immunosuppressive agents and cytotoxic drugs increase the risk of *S. stercoralis* infection as does the increasing incidence of organ transplantation.[27—32] *S. stercoralis* infection can also alter the gut microbiota,[33] and is often found in areas where chronic kidney disease (CKD) is common.[34] Soil-transmitted helminths (STHs) are on the WHO list of 17 neglected tropical diseases. *S. stercoralis*, as a species of STHs, has unique characteristics: it necessitates distinct diagnostic approaches from other soil-transmitted helminth infections, leading to frequent under-identification. Additionally, the parasite is not sensitive to albendazole or mebendazole, rendering it unaffected by large-scale preventive treatment campaigns aimed at other soil-transmitted helminthiases.

Life cycle

S. stercoralis belongs to the genus Strongyloides, family Strongyloididae, order Rhabditida. The life cycle of *S. stercoralis* is more complex than that of other nematodes,

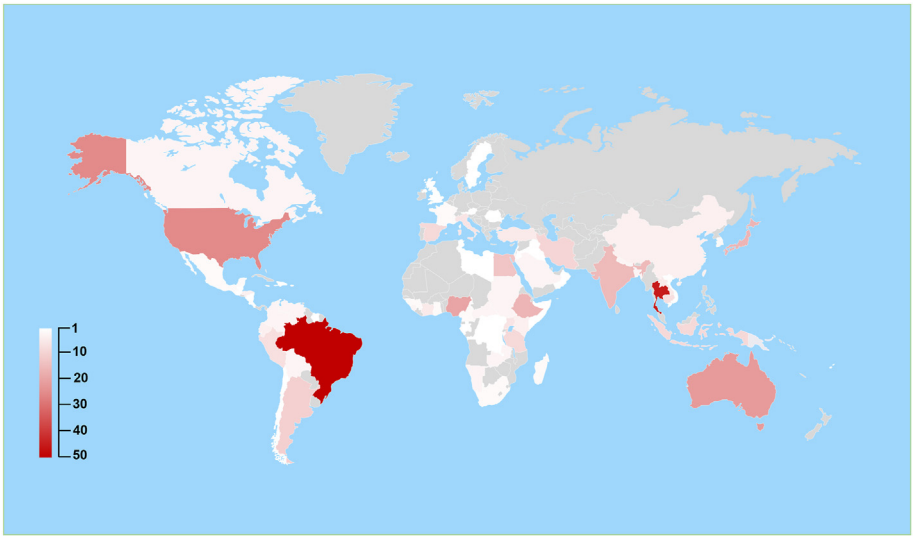

Figure 1. Number of surveys for prevalence calculation per country from January 1989 to June 2021. Adapted from Fabian Schär and colleagues.[1] A scheme showing the number of retrieved documents for each step in the search strategy was shown in the supplementary files (Additional file 1).

Table 1 Number of surveys for prevalence calculation per country from January 1989 to June 2021. Adapted from Fabian Schär and colleagues.[1] A scheme showing the number of retrieved documents for each step in the search strategy was shown in the supplementary files (Additional file 1).

	Number of surveys		Number of surveys
Argentina	10	Japan	15
Australia	20	Jordan	1
Austria	1	Kenya	4
Bangladesh	3	Kuwait	1
		Lao People's Democratic	
Belize	1	Republic	5
Bolivia	3	Libya	1
Brazil	49	Madagascar	2
Burundi	2	Martinique	2
Cambodia	7	Mexico	2
Cameroon	2	Mozambique	1
Canada	3	Namibia	3
Central African			
Republic	3	Nepal	3
China	4	Nicaragua	1
Colombia	3	Nigeria	18
Costa Rica	1	Palestinian Territories	1
Côte d'Ivoire	5	Oman	1
DR of the Congo	1	Papua New Guinea	1
Dominica	1	Peru	7
Ecuador	4	Puerto Rico	2
Egypt	12	Republic of Korea	2
Ethiopia	15	Romania	1
Fiji	1	Saint Lucia	1
France	2	Saudi Arabia	3

Gabon	1	Sierra Leone	3
Ghana	2	South Africa	2
Grenada	1	Spain	8
Guadeloupe	2	Sudan	3
Guatemala	1	Suriname	1
Guinea	2	Sweden	1
Guinea-Bissau	2	Thailand	44
Haiti	1	Tunisia	1
Honduras	4	Turkey	5
India	14	Uganda	6
Indonesia	8	UK	1
Iran	9	UR of Tanzania	8
Iraq	1	US of America	23
Israel	3	Venezuela	3
Italy	6	Viet Nam	1
Jamaica	3	Zambia	3
		Chile	1

including both a free-living and a parasitic cycle (Fig. 2).[35] During the free-living cycle, the rhabditiform larvae are shed in the stool or hatched from eggs of adult female worms laid in warm, moist environment. They can moult into filariform larvae (infective stage) or following four moults, develop into free-living male and female adult worms. Sexual reproduction occurs exclusively in the free-living cycle. Rhabditiform larvae develop into filariform larvae, which then infect human, a process known as direct development. This second generation of filariform larvae cannot mature into free-living adults and must find a new host to continue the life cycle.[7,36,37] Some studies indicated that *S. stercoralis* locates human hosts via thermal cues through unknown neural mechanisms, such as the heat-sensing neuron AFD, which senses ambient temperature and regulates temperature-dependent behavior.[38—40] Besides, a study showed that chemosensation drives host seeking and activation in skin-penetrating nematodes, such as the olfactory preferences.[41] During the parasitic cycle, the third-stage infective larvae (filariform larvae) infect humans by penetrating intact skin (typically on the feet when people walk barefoot), then enter the circulation, are transported to the pulmonary capillaries, penetrate the alveoli, migrate up the tracheobronchial tree, pass to the larynx, and finally are swallowed to enter the small intestine.[11] The pulmonary route is just one of the several possible pathways and is most clinically relevant but perhaps not the predominant one.[42,43]

In the small intestine, larvae mature into adult females after undergoing two moults[44]; only parasitic females are detectable in humans, and subsequent reproduction occurs asexually. The parasitic females may live up to 5 years, continuing asexual reproduction.[3] The parthenogenetic females penetrate the gut wall, embed in the duodenal mucosa and jejunal lamina propria, and lay dozens of embryonated eggs daily.[11,45] Eggs hatch in situ, releasing the first-stage larvae (rhabditiform larvae) in the gut wall.[46] The rhabditiform larvae migrate into the lumen, and most of larvae are passed out in faeces (video) and develop into filariform larvae or into free-living male and female adult worms. Alternatively, a small number may develop into the filariform stage within the gastrointestinal tract and penetrate the colonic wall or perianal skin to initiate a new cycle without leaving the host, resulting in autoinfection and the maintenance of parasitism. Autoinfection can result in chronic infection lasting for several decades, up to 75 years after initial exposure.[47] Autoinfection usually occurs in patients with impaired cell-mediated immunity, leading to hyperinfection syndrome and disseminated strongyloidiasis.[3,48]

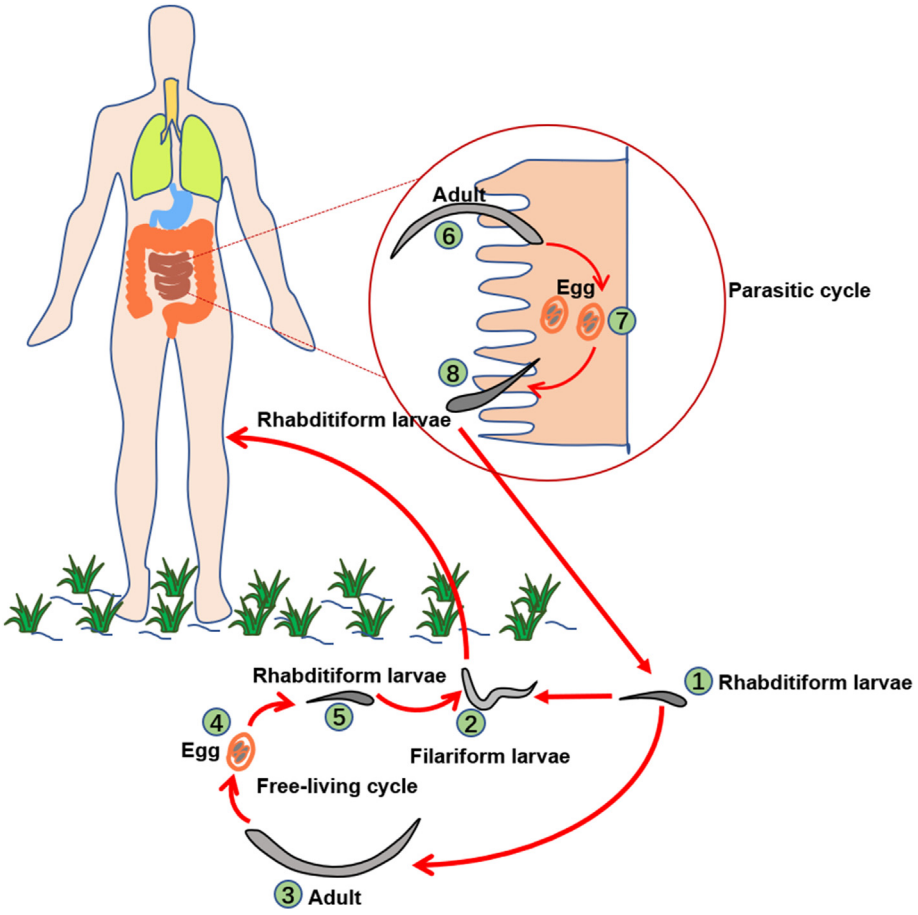

Figure 2. The life cycle of *Strongyloides stercoralis*. (1) In the free-living cycle, the rhabditiform larvae are shed in the stool or hatched from eggs of adult female worms laid in a warm, moist environment; (2) Rhabditiform larvae moult into filariform larvae (infective stage); (3) Rhabditiform develop into free-living male and female adult worms after moulting four times; (4) Sexual reproduction in the free-living cycle and lay eggs; (5) Rhabditiform larvae are hatched from eggs and development into filariform larvae that then infect humans; (6) In the parasitic cycle, filariform larvae infect humans, larvae mature into adult females after moulting twice in the small intestine; (7) The parthenogenetic females penetrate the gut wall, embed in the duodenal mucosa and jejunal lamina propria, and lay embryonated eggs daily; (8) Eggs hatch in situ, releasing the first-stage larvae (rhabditiform larvae) in the gut wall.

Aetiology and pathology

The larvae and adults of *S. stercoralis* are pathogenic, but the severity of disease in humans is closely correlated with health conditions, immunologic status, and worm burden.[49] Healthy individuals are usually asymptomatic, chronic infected, or mildly symptomatic.[50] In contrast, immune-compromised patients, such as those with systemic lupus erythematosus (SLE), malignant tumours, leukaemia, tuberculosis, diabetes, and HTLV-1 infection, may have disseminated hyperinfection characterised by *S. stercoralis* mass migration. Common symptoms include fever, headache and altered mental status.[51] *S. stercoralis* invades lungs, liver, kidneys, and brain and can lead to severe organ failure and death.[49]

In acute infection, *S. stercoralis* larvae might cause Loeffler's syndrome (a type-1 hypersensitivity reaction).[52] Female adult worms live in the intestine, lay eggs, and release first-stage larvae, thereby causing local inflammation.[53] Gastrointestinal (GI) symptoms begin about 2 weeks after infection and include diarrhoea, constipation, anorexia, nausea, vomiting, abdominal pain, fever, anaemia and malaise.[16,49] Filariform larvae migrate into the pulmonary tract, causing point bleeding and inflammatory cell infiltration with cough, dyspnoea, haemoptysis, and wheezing.[52] In chronic infection, more than 50% of patients are asymptomatic, while others may show diarrhoea, nausea, intermittent vomiting, constipation, borborygmus, and abdominal discomfort.[16] In addition, pruritus ani and dermatologic manifestations (urticaria and larval rashes) are also common, usually on the abdomen, torso, groin, and buttocks.[53,54] Chronic strongyloidiasis infection has been associated with recurrent asthma and nephrotic syndrome in some cases.[55–58] Strongyloides hyperinfection syndrome occurs when patients chronically infected with *S. stercoralis* become immunosuppressed, or when immunosuppressed patients develop acute strongyloidiasis.[59] Increased larval burden may be accompanied by obstruction, ileus, gastrointestinal bleeding, and enterobrosis.[60–62] The clinical symptoms are summarised from

four studies in endemic areas and five studies in non-endemic settings (Fig. 3).[63]

Larva currens is a rare and pathognomonic cutaneous sign of strongyloidiasis, but is poorly described due to its unpredictable and fleeting occurrence.[64,65] Generally, hyperinfection is caused by autoinfection, which results in multiplication and migration of infective larvae in immunocompromised patients. The migration of larvae through the bowel wall or intestinal ulcers lead to bacterial sepsis or other bacterial infections. Parasitologically, the distinction between autoinfection and hyperinfection is primarily quantitative and not strictly defined. Development or exacerbation of gastrointestinal and pulmonary symptoms are observed, and the hallmark of hyperinfection is a large number of infective larvae detected in extraintestinal regions, especially in the lungs and sputum.[16] Hyperinfection occurs mainly in patients who are immunocompromised or immunodeficient, although some studies also described hyperinfection in immunocompetent patients.[66] Clinical manifestations of the hyperinfection syndrome, including malabsorption syndrome, paralytic ileus, ulcerative enteritis, gastrointestinal bleeding, pulmonary hemorrhage, pneumonia, and meningitis, may exacerbate the complexity of the disease.[16,67–74] Eosinophilia is commonly seen in immunocompetent patients with strongyloidiasis and might provide some protection (especially in early-stage infection).[75] However, in immunosuppressed patients, eosinophilia may be absent, and they may have a worse prognosis than patients with peripheral eosinophilia.[5,16] Disseminated infection involves widespread dissemination of larvae to organs outside the parasite's ordinary life cycle, including liver, heart, kidney, central nervous system, and endocrine organs.[76] Hyperinfection with disseminated infection is associated with corticosteroid administration and HTLV-1 infection, granulocyte function, Th2-dominated immune responses, and mucosal immunity are disrupted.[77,78] Hyperinfection and disseminated infection usually result in high mortality, ranging from 70% to 85%,[79,80] indicating the importance of early diagnosis and therapy to improve patient outcomes.[81]

Comorbidities

Hyperinfection and disseminated infection often occur following autoimmune and wasting diseases. The comorbidities reported in 127 immunocompromised patients with strongyloidiasis are summarised (Fig. 4).[82] Some immunosuppressive agents, such as steroids, are commonly used to treat autoimmune diseases, thereby increasing the risk of opportunistic infection with *S. stercoralis*.[83–85] Corticosteroids are widely used in SLE, IBD, allergic disorders, and autoimmune encephalomyelitis, and their usage is associated with hyperinfection,[86] often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.[87] In addition, corticosteroids administered for COVID-19,[88–92] lymphoma,[93] rheumatoid arthritis,[94] leprosy,[93] polymyositis,[56] corneal ulcer,[95] Bell's palsy,[96] and haematologic malignancies,[97] can result in hyperinfection. One possible explanation is that corticosteroids suppress eosinophilia and lymphocyte activation. It has have suggested that corticosteroids stimulate *S. stercoralis* virulence by activation of nematode ecdysteroid receptors,[16] whereas an

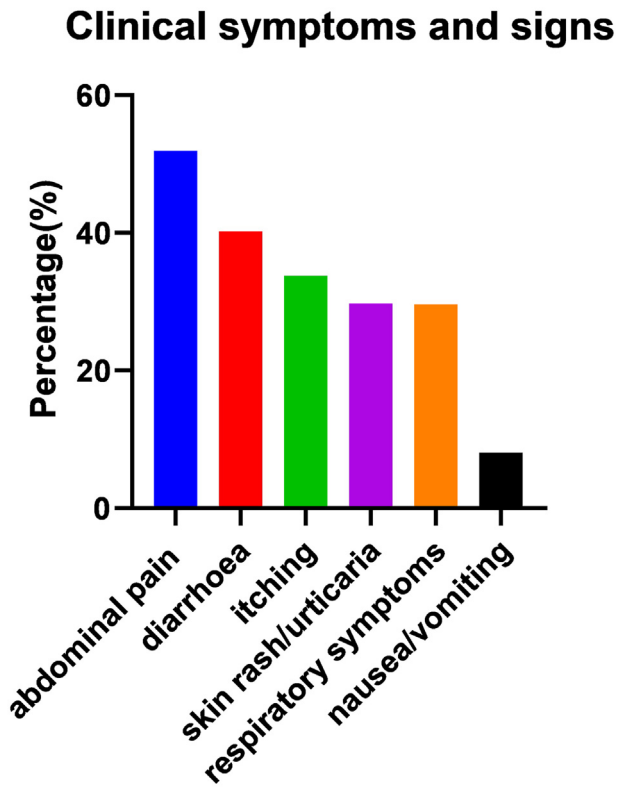

Figure 3. Summary of the clinical symptoms reported from four studies in endemic areas and five studies in non-endemic settings. Data from Dora Buonfrate and colleagues.[63]

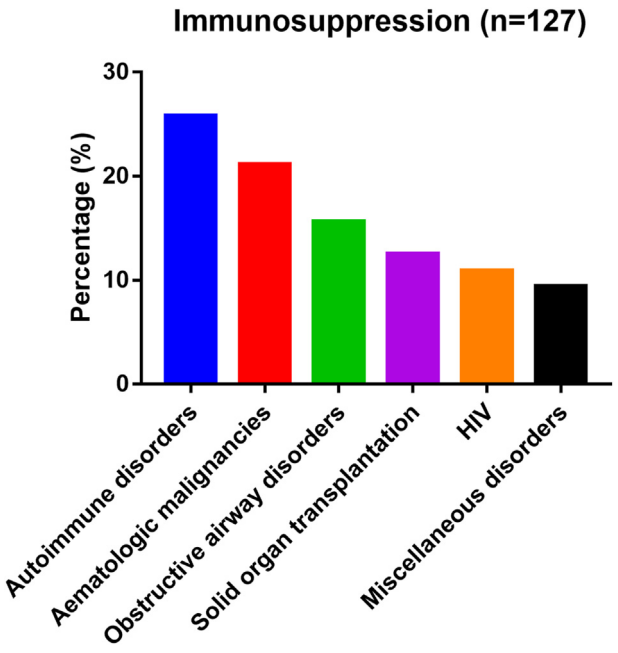

Figure 4. Summarises of the comorbidities reported in 127 immunocompromised patients with strongyloidiasis. Data from Guillaume Geri and and colleagues.[82]

Table 2 Vaccine candidates tested in the mice model against *Strongyloides stercoralis* infection.

	Antigen description	Worm reduction rat
DOC-Ag vaccine[126]	Deoxycholic soluble proteins from *S. stercoralis* L3i	83%
IgG vaccine[123]	Human IgG—specific antigens	76%
DNA vaccine[124]	Sseat-6 gene	35%
Recombinant protein vaccine[125]	Ss-IR	80%
Recombinant protein vaccine[127]	srHSP60	Partial protection with reduction in worm burden and in the larval output

impaired T-cell-mediated immune response seems to facilitate dissemination of *S. stercoralis*.[87]

A result showed a significant increase in antibody responses in individuals coinfected with *Plasmodium falciparum* and helminths in comparison with individuals infected with only one of these parasites, and suggest that this increase is due to a more permissive immune environment to infection in the host.[98] *S. stercoralis* and HTLV-1 are both endemic in regions such as South America, Japan, and Jamaica.[99] Infection with HTLV-1 is associated with increased prevalence of *S. stercoralis* infection and the hyperinfection syndrome.[100—102] *S. stercoralis* appears to accelerate the natural course of HTLV-1 infection.[26] The period of latency prior to leukemogenesis was shortened after HTLV-1 co-infection with *S. stercoralis*.[103] Administration of immunosuppressive therapies in patients with HTLV-1/*S. stercoralis* co-infection may trigger potentially fatal dissemination.[104] Interestingly, *S. stercoralis* coinfection may modulate the intracerebral inflammatory response to *Mycobacterium tuberculosis* and improve tuberculous meningitis (TBM) clinical outcomes.[105] *S. stercoralis* and HIV have been reported to coexist, and *S. stercoralis* hyperinfection was once considered as an opportunistic AIDS-defining illness.[106,107] However, *S. stercoralis* hyperinfection is not common in patients with advanced HIV disease.[108] Several patients with HIV/*S. stercoralis* co-infection had previously received steroids. Therefore, the link between HIV and *S. stercoralis* remains inconclusive, leading to the removal of disseminated strongyloidiasis from the World Health Organisation and U.S. Centers for Disease Control lists of HIV-signature infections in 1987.[109] *S. stercoralis* hyperinfection has also been reported with hypogammaglobulinemia.[110] Cancer has been associated with hyperinfection following the administration of immunosuppressive chemotherapy.[60,111] Many cases of hyperinfection occurring after organ transplantation have been associated with increased glucocorticoid doses administered in response to rejection.

Immunology and vaccines

Neutrophils, macrophages, and eosinophils are recruited by *S. stercoralis*.[44] Cell contact is required for killing *S. stercoralis* larvae, and elimination of neutrophils and eosinophils results in an increase in parasite survival.[75] Neutrophils can independently kill *S. stercoralis* larvae, dependent on the neutrophil-specific granular protein myeloperoxidase (MPO).[75,112] Molecules extracted from *S. stercoralis* can directly recruit neutrophils through CXCR2, MIP-2, and KC. Eosinophils have a direct role in killing *S. stercoralis* larvae.[63] The capacity of mice to control the larvae of *Strongyloides ratti* was reduced after a reduction in eosinophils.[112] Mouse eosinophils' killing of *S. stercoralis* larvae was dependent on the granular protein major basic protein (MBP).[75] Both neutrophils and eosinophils can be directly recruited to the parasite without the need for other host cell assistance. Chemoattractants derived from the larvae and host species stimulate similar receptors and second messenger signals to induce eosinophil chemotaxis.[44] Eosinophils also act as antigen presenting cell (APC), inducing parasite-specific Th2 responses and antibody responses in *S. stercoralis* infection.[113,114] This may explain why patients with no eosinophil elevation tend to have a poorer prognosis. Complement activation is required for protection from larval *S. stercoralis*. Complement component C3 was detected on the surface of the larvae in vitro.[115] *S. stercoralis* larvae activated complement in vitro by the classical and alternative pathways and promoted the adherence of neutrophils and monocytes to the surface of larvae.[116] Autoinfective larvae are associated with chronic infections and hyperinfection, and immunity generated with infective larvae cannot kill the autoinfective larvae.[117] This may explain why infections persist in human hosts for decades but in most cases cause only minor pathological effects except in immunosuppressed individuals. Consistent with Th2 responses, which are the hallmark of many helminth infections, CD4+ T-helper type-2 cell (Th2) activity is required to protect against *S. stercoralis*.[118] Depletion of the type-2 cytokines IL-4 or IL-5 in immunised mice impaired larval killing.[118] In addition, B cells and IgM are required for adaptive immunity to protect against *S. stercoralis*.[119] High concentrations of IgA, IgG1, and IgM have been measured in sera of mice immunised with *S. stercoralis*.[120]

Studies have been performed to identify antigens that would induce protective immunity and thereby be components of a vaccine against *S. stercoralis*. However, all vaccine candidates are in the preclinical phase,[121] with some of showing promising results in the mice model (Table 2). Vaccine strategies have used antigenic preparations solubilised in deoxycholate (DOC-Ag), human IgG-specific antigens, recombinant proteins, and DNA. Most vaccines used to control *Strongyloides* spp. infection included DOC-Ag and DOC-Ag proteins in aluminium hydroxide adjuvant to induce protective immunity.[122] One study showed that

human IgG could reduce the survival of larvae in mice.[123] For DNA vaccines, genes were cloned into plasmids and mice were immunised intradermally; Na + -K + ATPase (Sseat-6) was the only plasmid that induced a limited level of protective immunity, reducing larval survival by 35%.[124] Recombinant antigen proteins tested for efficacy as a vaccine against *S. stercoralis* showed that the recombinant antigen Ss-IR decreased larval survival by approximately 80%.[125] Given the differences in immune response and resistance to reinfection between rodents and humans, more research is needed to develop an effective human vaccine against *S. stercoralis*.

Diagnosis

The detection of *S. stercoralis* larvae is the gold standard for diagnosis of *S. stercoralis* infection (Fig. 5). The metabolic alteration in stool samples is explored as potential markers, which indicates involvement of microbiota remodeling, parasite constitution, and host response during *S. stercoralis* infection.[128] Numerous techniques are utilized to detect *S. stercoralis* larvae in stool, including direct smears, Baermann concentration, formalin-ethyl acetate concentration, Harada-Mori filter paper culture, Koga agar plate culture, TF-Test and Coproplus. Direct faecal smear is often performed in hospitals. However, a disadvantage of direct smear is low sensitivity, especially for detection of low-intensity infection. This is probably the reason why the global prevalence has been consistently underestimated. The Baermann method, Harada-Mori filter paper culture, and Koga agar plate culture are much more sensitive than single-stool smears,[129,130] but they are rarely used as standard procedures in clinical laboratories. Studies have improved and optimized the detection methods of Koga agar plate culture and Baermann techniques, which greatly improved the sensitivity of detection.[131—133] However, research has shown that Baermann technique and Koga agar plate culture are currently the most feasible and implementable standard methods for diagnosing *S. stercoralis* at a hospital setting such as Mahosot Hospital and provincial and district hospitals in low and middle income countries in Southeast Asia.[134] Formalin-ether acetate increases the concentration of larvae, but dead individual larvae are more difficult to detect. TF-Test and Coproplus methods presented low sensitivity for *S. stercoralis* infection diagnosis; therefore, they should be used in parasitological diagnosis only when associated with other more effective methods of helminth identification.[135]

Studies have reported that duodenal biopsies can reveal eggs, larvae, and adult worms.[136] However, this invasive method is time-consuming and is typically recommended in the case of immunocompromised patients suspected of having a severe infection. The string test enjoyed a brief period of popularity, but now it is used infrequently.[74]

Clinical alertness is essential in cases of hyperinfection, and detection of *S. stercoralis* larvae is usually easier because large numbers of worms are involved in disseminated infections.[11,46] The larvae can be detected in sputum, bronchoalveolar lavage fluid, bronchial washings and brushings, and lung biopsies. Chest x-ray, CT, and MRI are usually used to aid detection and demonstrate reticulonodular shadowing throughout lung fields and pulmonary infiltrates.[137]

Immunodiagnostic assays, including skin testing with larval extracts, indirect immunofluorescence analysis, gelatin particle agglutination, and radio-allergo-sorbent testing for specific IgE, are used to test for *S. stercoralis* but with limited success.[138—140] Serodiagnosis by ELISA using crude antigens has shown high sensitivity and specificity.[141,142] However, ELISA tests that detect antibodies cannot distinguish between past and current infection. Furthermore, it is difficult to know whether low-level autoinfection is continuing. This may because antibody levels remain detectable for years after anti-*S. stercoralis* treatment.[143,144] The antibody test also shows cross-reactivity with other helminth infections, such as *filariasis*, acute schistosomiasis, and *Ascaris lumbricoides* infection.[145,146] At present, some studies have improved ELISA tests. One study highlights the potential of IgE-ELISA using larval lysate to diagnose strongyloidiasis, particularly in probable early infections.[147] The detection of immune complexes involving circulating NIE antigens bound to *Strongyloides*-specific IgG antibodies can help distinguish early and chronic infections.[148] Besides, the concentration of urine samples prior to analysis by ELISA improved the sensitivity for diagnosis and is potentially useful in the diagnosis of strongyloidiasis in immunocompromised individuals or in low-prevalence areas.[149,150] At present, without sophisticated instruments and highly trained staff, an immunochromatographic test (ICT) kit for rapid serodiagnosis of human strongyloidiasis is easy to use at the point-of-care and a result can be obtained in 15 min, which can be used in public-health settings.[151] PCR diagnosis has

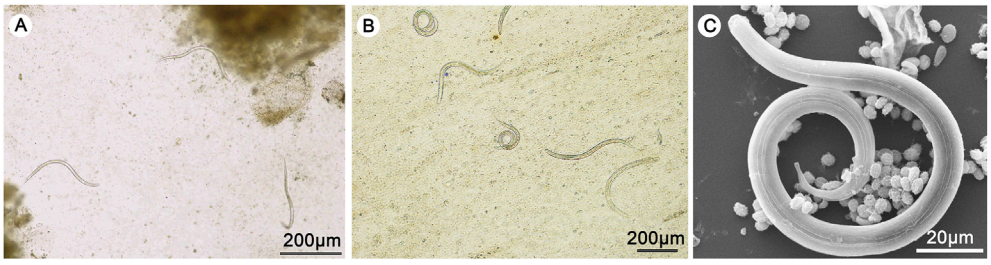

Figure 5. Larvae of *Strongyloides stercoralis*. (A) Microscopic examination of stool shows the rhabditiform larvae of *Strongyloides stercoralis*. (B) Microscopic examination of sputum shows the flariform larvae of *Strongyloides stercoralis*. (C) The flariform larvae of *Strongyloides stercoralis* in sputum were detected by scanning electron microscopy.

performed well in the diagnosis of *S. stercoralis* infection, distinguishing *S. stercoralis* from other nematodes.[24,152,153] A novel duplex LAMP method is available for simultaneous real-time detection of *Schistosoma mansoni* and *Strongyloides* spp.[154] A novel detection method (the droplet digital polymerase chain reaction, ddPCR) exhibited high sensitivity and specificity for detection of *S. stercoralis* in stool samples. This technique may help to improve diagnosis, particularly in cases with light infection.[155] Besides, nucleic acid amplification tests (NAATs) are increasingly being used as diagnostic tools for soil-transmitted helminthiasis, strongyloidiasis and schistosomiasis. In the public health field, NAATs are being explored as diagnostic tools to assess the distribution of prevalence and infection intensity at the population level in endemic areas(Table 3).[156]

Treatment

Traditionally, treatment of strongyloidiasis has been based on thiabendazole (25 mg/kg/12 h for 3 consecutive days). However, side effects (asthenia, epigastralgia, and disorientation) were common and the parasites could not be eradicated in up to 30% of cases.[173] Ivermectin has shown fewer side effects and is more effective than thiabendazole in treating strongyloidiasis. The efficacy of ivermectin depends on the treatment schedule and infection status. For chronic uncomplicated strongyloidiasis, ivermectin 200 μg/kg once daily for 2 days is recommended and can be highly efficacious.[174] One study showed that after treatment with ivermectin 200 μg/kg for 2 consecutive days, 100% of patients met the criteria for cure; among those treated with ivermectin 200 μg/kg on a single day, only 77% met the criteria for cure.[173] However, there are studies illustrating comparable efficacy (>93%) for both regimens.[59] In addition, a multicentre, open-label, phase 3, randomised controlled superiority trial showed that Multiple doses of ivermectin did not show higher efficacy and was tolerated less than a single dose.[175] Therefore, selecting the most appropriate drug administration strategy according to the local context is imperative. Albendazole has been used widely to treat intestinal parasites since 1982 and is considered as an alternative therapy.[176] The recommended schedule is an oral dose of 400 mg given twice daily for 7 days. Ivermectin results in more cures than does albendazole.[176] Combination treatment with both albendazole and ivermectin would improve the efficiency of mass drug administration targeting *S stercoralis*.[177] Recently a study has shown that moxidectin, a Food and Drug Administration (FDA)-approved medication for the treatment of human onchocerciasis, may be a safe and efficacious alternative to ivermectin for the treatment of *S. stercoralis* infection.[178–181]

In immunocompromised or strongyloides hyperinfection syndrome patients, additional doses or drug combinations may be necessary.[182] Ivermectin treatment should continue until stool or sputum samples are negative for 2 weeks in disseminated disease.[11] If possible, immunosuppressants should be considered for reduction or discount, and nutritional support, hydration, analgesics, and antibiotics should be provided.[11] In patients with severe hyperinfection who were unable to take anthelminthics or ileus and small-bowel obstruction that may prevent enteral absorption, veterinary subcutaneous and enema formulations of ivermectin have been used.[183–187] Patients should undergo triple stool examinations within 2–4 weeks after treatment, and *strongyloides* serology at 6 months post treatment might be useful for ascertaining a cure.[11]

Prevention and control

Although the lethality of hyperinfection and research studies have increased attention to *S. stercoralis* infection, systematic action plans still lag behind. Implementation of control programmes for *Strongyloides stercoralis* infection is a target within the World Health Organization Roadmap to 2030.[188] Enhancing information, education, and communication will be essential to improve the public's understanding of strongyloidiasis and its prevention, treatment, and control. Education emphasising personal hygiene in endemic areas should be given to patients, persons at risk, and the general population.[189] In rural and remote communities in tropical regions, access to clean sanitation, water, and footwear has been fundamental to preventing strongyloidiasis.[190,191] Testing for strongyloidiasis is important in patients from endemic areas, rural and remote communities, and those who are immunocompromised.[192,193] For at-risk children and adults, working to eradicate or reduce *S. stercoralis* infection with early detection and immediate treatment is necessary. Contact isolation should be used in hospitalized patients with hyperinfection, and all family members should be examined for *S. stercoralis* infection.[16,189] Patients undergoing

Table 3 Techniques for the detection of *Strongyloides stercoralis*.

Techniques	Sensitivity (%)	Specificity (%)
Direct smear[157]	21	100
Baermann concentration[158]	47.1	78.4
Formol-ether concentration[157]	48	100
Harada-Mori filter paper culture[159]	28.5	100
Agar plate culture[157]	89	100
ELISA (antigens)[140,142,152,160–164]	73–97.8	82.6–100
ICT kit[151]	93.3	83.7
PCR (18s rRNA, ITS, cytochrome *c* oxidase)[165–170]	61–100	100
LAMP[171,172]	Limit of detection<10 copies	100

transplantation or taking immunosuppressive agents should be screened for *S. stercoralis* infection.[194,195] In addition, strongyloidosis in patients with eosinophilia should also be considered.[196]

In some studies, delayed diagnosis, inadequate knowledge, lack of communication, and lack of follow up by health professionals were described as significant problems.[71,197—199] Health professionals should be required to have detailed information and education regarding strongyloidiasis. It is important to recognize that *S. stercoralis* infection can potentially exist for years with nonspecific symptoms and signs. Lack of awareness of chronic infections in patients increases risk for infection in the patients' community and decreases the awareness of health professionals and community of the need to eradicate the infestation within community.[193] Therefore, experts should establish prevalence thresholds to define *S. stercoralis* as a public health problem and propose control strategies, including mass treatment regimens.[200,201] In addition, networking is crucial among the researchers interested in *S. stercoralis* to improve coordination and optimize resources. Moreover, it is important to establish testing and treatment initiatives within communities. *S. stercoralis* and strongyloidiasis reporting protocols can be established between health care systems and communities.[73,202] Prevalence studies of STHs should also target *S. stercoralis*, and it is important to develop more sensitive and specific diagnostic methods. Donors and funding agencies should not ignore *S. stercoralis*.[200] For countries/areas with a high prevalence, ivermectin should be made available for mass treatment.[200] However, implementation of such measures is hindered by emphasis on human immunodeficiency virus (HIV), malaria, tuberculosis, other neglected diseases, and war.[190]

Conclusions

Infection with *S. stercoralis* is highly prevalent in the tropics and subtropics, especially in rural, remote communities with poor sanitation and hygiene. The clinician must consider *S. stercoralis* infection in patients who are immunocompromised, using cytotoxic drugs, having wasting diseases and organ transplants. Health professionals, financial commitment, and policies are needed to strengthen management of *S. stercoralis*. Over the past decade, increasing efforts have been allocated to vaccine research, effective treatment strategies, and refined diagnostics. Other measures should be included to advance diagnosis and therapy. New control strategies, including enhancing information, education, communication, patient management, epidemiological surveillance, environmental modification, better sanitation and clean water, and building through intersectoral collaboration should be formulated and implemented.

Search strategy and selection criteria

Literature searches were done by using PubMed (http://www.ncbi.nlm.nih.gov), WHO (http://www.who.int/en), and ScienceDirect (http://www.sciencedirect.com) predominantly. Search terms included "*Strongyloides stercoralis*", "*Strongyloides stercoralis* infection", "*Strongyloides stercoralis* and epidemiology", "*Strongyloides stercoralis* and aetiology", "*Strongyloides stercoralis* and pathology", "*Strongyloides stercoralis* and immunology", "*Strongyloides stercoralis* and vaccines", "*Strongyloides stercoralis* and diagnosis", "*Strongyloides stercoralis* and treatment", "*Strongyloides stercoralis* and prevention", and "*Strongyloides stercoralis* and control". Titles and abstracts were reviewed. The full texts of these articles were read to verify their relevance.

CRediT authorship contribution statement

Ruibing Yang: Writing — original draft, Investigation, Data curation, Conceptualization. **Meiyining Xu:** Supervision, Project administration, Data curation. **Lichao zhang:** Writing — review & editing, Visualization, Validation. **Yao Liao:** Supervision, Investigation. **Yuheng Liu:** Data curation. **Xiaoyan Deng:** Writing — review & editing, Conceptualization. **Lifu Wang:** Writing — review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.07.010.