



# CATMAT statement on disseminated strongyloidiasis: Prevention, assessment and management guidelines

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## Abstract

**Background:** *Strongyloides stercoralis* is a parasitic nematode found in humans, with a higher prevalence in tropical and sub-tropical regions worldwide. If untreated, the infection can progress to disseminated strongyloidiasis, a critical illness which may be fatal.

**Objective:** To provide clinical guidance on the prevention, assessment and management of disseminated strongyloidiasis.

**Methods:** A literature review was conducted to evaluate the current evidence and to identify any systematic reviews, case reports, guidelines and peer reviewed and non-peer reviewed medical literature. The Committee to Advise on Tropical Medicine and Travel (CATMAT) assembled a working group to develop this statement, which was then critically reviewed and approved by all CATMAT members.

**Recommendations:** CATMAT recommends that screening for strongyloidiasis should be considered for individuals with epidemiologic risk and/or co-morbidities that place them at risk for *Strongyloides* hyperinfection and dissemination. Those at highest risk of hyperinfection and dissemination are individuals born in a *Strongyloides*-endemic area who undergo iatrogenic immunosuppression or have intercurrent human T-lymphotropic virus (HTLV-1) infection. Diagnosis of strongyloidiasis is based on serologic testing and/or examination of stools and other clinical specimens for larvae. Referral to a tropical medicine specialist with expertise in the management of strongyloidiasis is recommended for suspected and confirmed cases. A diagnosis and treatment algorithm for strongyloidiasis has been developed as a reference tool.

**Conclusion:** Strongyloidiasis is relatively widespread in the global migrant population and screening for the disease should be based on an individual risk assessment. A practical tool for the clinician to use in the prevention, assessment and management of disseminated strongyloidiasis in Canada is now available.

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## Preamble

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to tropical infectious disease and health risks associated with international travel. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practices and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.



## Introduction

Strongyloidiasis is a disease caused by a nematode (i.e., a roundworm), which is present mainly in tropical and sub-tropical regions, but also in temperate climates. Precise data on prevalence are unknown in endemic countries; however, it is estimated that 30-100 million people are infected worldwide (1). Most people who are infected with *Strongyloides* are asymptomatic and unaware of their infection; however, people who are immunosuppressed are at risk of developing the severe form of disseminated strongyloidiasis which, if untreated, can lead to potentially fatal illness (2). Although strongyloidiasis has traditionally been considered a tropical disease, increased worldwide travel and immigration have led to an increased number of cases seeking medical care in Canada.

The objectives of this statement are to:

1. Raise awareness of disseminated strongyloidiasis among clinicians who may encounter these cases (including front-line clinicians such as emergency room physicians, infectious diseases specialists, rheumatologists, dermatologists, gastroenterologists, oncologists, intensivists and transplant teams).
2. Assist clinicians in the prevention, assessment and management of disseminated strongyloidiasis.

## Methods

This statement was created after CATMAT identified a need to inform Canadian clinicians about disseminated strongyloidiasis. A CATMAT working group was assembled and a member was elected to lead the statement development. The available literature was assessed for systematic reviews, guidelines, case reports and peer reviewed and non-peer reviewed medical literature. Based on the evidence compiled as well as expert opinion, a diagnosis and treatment algorithm for strongyloidiasis was designed as a reference tool for clinicians in Canada. The statement was then critically reviewed and approved by all CATMAT members.

## Epidemiology

*Strongyloides stercoralis* is a parasitic nematode of humans, which is found throughout the tropics and subtropics worldwide. High prevalence of infection is found focally in the Caribbean, in West and East Africa and particularly Southeast Asia (3). Data support that anywhere between 10% to 40% of the population in tropical and sub-tropical regions are affected by strongyloidiasis, with rates as high as 60% in countries with ecologies and socioeconomic factors permissive to the transmission of *S. stercoralis* (3). A Canadian study of refugees documented a 77% seroprevalence among refugees from Cambodia and a 12% seroprevalence among refugees from Vietnam (4). Furthermore, strongyloidiasis was the fifth most common diagnosis among 1,321 ill new immigrants presenting for care at a Canadian Travel Medicine Network (CanTravNet) site over a three-year period (5,6). Given that 6.8 million Canadians are foreign born, with approximately 85% emigrating from regions endemic for strongyloidiasis (7), a substantial proportion of

the immigrant and refugee population of Canada is at risk for strongyloidiasis. Asia continues to be the largest source region for immigrants to Canada, with the Philippines, China and India serving as the top single source countries (7). Immigrant populations from Africa, the Caribbean, Central and South America are increasing over time as well (7).

In Canada, approximately 2.5-million individuals are estimated to have simple intestinal strongyloidiasis, assuming a source country prevalence of 40% (3). This estimate excludes travel-acquired strongyloidiasis, which is expected to account for a minority of cases in Canada. However, it is important to recognize that even short-term travel to highly endemic areas may be associated with acquisition of strongyloidiasis (8,9,10).

It is difficult to estimate the proportion of Canadian immigrants and refugees who are at risk of developing disseminated strongyloidiasis, such as individuals who require iatrogenic immunosuppression or have HTLV1 co-infection.

## Pathogenesis

Strongyloidiasis is acquired when infectious larvae, found in sand or soil, penetrate intact human skin and after an obligatory tissue migration phase, mature into adults in the small bowel. Unlike other parasitic helminths, *Strongyloides* has an indefinite lifespan in the human host and due to an autoinfection cycle whereby infective stage larvae re-penetrate host skin or bowel, clinical disease is a lifelong risk unless treated.

## Clinical features

*Strongyloides* infection may cause a spectrum of illness ranging from asymptomatic eosinophilia to gastrointestinal symptoms to accelerated autoinfection (or "hyperinfection syndrome") to fulminant and fatal disseminated disease. Immune suppression such as that which occurs in the setting of prolonged corticosteroid therapy, HTLV-1 infection, or hematologic malignancy, is a risk factor for disseminated strongyloidiasis (11,12,13,14), an entity documented to carry a mortality rate in excess of 85% (15,16). The exact mechanisms for immunologic control of this infection are unclear.

## Diagnosis and screening

The Canadian Consortium on Refugee and Immigrant Health (CCRIH) has recently recommended *Strongyloides* screening only for refugees from Southeast Asia and Sub-Saharan Africa (17). Broader based screening was not recommended as there are little data on the prevalence of strongyloidiasis in immigrant populations and serologic screening is not easily or rapidly available in many parts of Canada. It has been our collective clinical experience, however, that strongyloidiasis is widespread in the global migrant population and screening should be based on a risk assessment, taking into account the risk of exposure to *Strongyloides*, the risk of disseminated disease and the presenting clinical syndrome (including asymptomatic persons who are planned to undergo iatrogenic immune suppression). This is supported by a case series in Toronto that documented ten cases of disseminated strongyloidiasis over



a seven-month period, all of which occurred in immigrants to Canada, originating from Southeast Asia, the Caribbean, South America or Italy (11). Collectively, members of CATMAT have contributed to the care of patients with strongyloidiasis arising from travel to or residence in the Mediterranean, all parts of Africa, the Caribbean and Latin America, South Asia including the Indian subcontinent and the very high risk Southeast Asia. Thus, we recommend careful consideration of epidemiologic risk as outlined below in order to inform screening decisions.

Due to the low sensitivity of stool examination for ova and parasites (O&P) arising from low larval burden and intermittent shedding in the stool, serologic testing is the diagnostic method of choice in the patient suspected to have simple intestinal strongyloidiasis.

It is important to note that sensitivity of serology may be reduced in the patient with immunosuppression, especially due to HTLV-1 infection or hematologic malignancy and associated chemotherapy (18,19). These individuals are also at risk of developing disseminated strongyloidiasis and screening should generally involve both serologic and stool testing as outlined below. A stool O&P sample that is positive for *Strongyloides* larvae should prompt screening for HTLV-1 infection and referral to a specialist in tropical medicine with expertise in the management of strongyloidiasis. Physician members of the Canadian Malaria Network are available to provide advice in such cases (20).

## Treatment

The drug of choice for treatment of simple intestinal and asymptomatic strongyloidiasis is ivermectin (15,21) given in two doses. Persons born or with prolonged residence in nations of the rainforest area of central Africa (e.g., Cameroon, Equatorial Guinea, Gabon, Central African Republic, Congo and the Democratic Republic of the Congo, as well as southern areas of Nigeria, Chad, South Sudan and northern Angola) should have high microfilaremic loiasis excluded prior to administration of ivermectin. This should be done by daytime blood film examination for microfilaria of *Loa loa*.

For *Strongyloides* hyperinfection or dissemination syndrome, CATMAT recommends dual-therapy with ivermectin and albendazole as outlined below, which is based on case report data (11,22,23,24,25), expert opinion and the clinical experience of CATMAT members. Clinical specimens, including sputum and stool, should be rechecked periodically during the course of treatment of *Strongyloides* hyperinfection or dissemination to ensure clearance of larvae.

In order to prevent the development of disseminated strongyloidiasis, patients at risk for treatment failure or complications, such as those with HTLV-1 or *Loa loa* co-infection, should be referred to a tropical medicine specialist with expertise in the management of such infections. There is no evidence to support that a "test and treat" strategy is superior or more cost-effective compared to empiric administration of ivermectin to at risk individuals about to undergo immune suppression (26). As access to ivermectin is limited in Canada, CATMAT recommends that empiric treatment be reserved for individuals whose planned immune suppression cannot await

diagnostic testing, as outlined in Step 3 of the diagnosis and treatment algorithm below.

Any patient with disseminated strongyloidiasis should also receive empiric treatment with broad-spectrum antibiotics to cover polymicrobial sepsis, a common complication of the hyperinfection syndrome. Both albendazole and ivermectin are pregnancy category C agents. In a pregnant person with *Strongyloides* hyperinfection or dissemination, the benefits of treatment likely outweigh the risks due to the life threatening nature of disseminated strongyloidiasis. Ivermectin and albendazole are only available in Canada through the Special Access Programme of Health Canada (27). Applications to the program typically have a one week turnaround time, although emergency use, same-day requests may be made by telephone.

## Infection control issues

Patients with disseminated strongyloidiasis should be managed in contact precautions due to the risk of infectious filariform larvae being shed in effluents such as stool, urine, sputum and endotracheal aspirates. Most of these patients are critically unwell and require intensive nursing and medical care, thus precautions to prevent nosocomial transmission to health care workers is important. However, it must be noted that nosocomial transmission is a theoretical risk that has not been well documented in the literature (28,29).

Contact precautions are also recommended for laboratory workers, due to the potential risk of encountering infectious filariform larvae, particularly in cultures of stool or sputum that have been sent to the laboratory to exclude bacterial infection. Agar plates of specimens from patients with disseminated strongyloidiasis should be handled with gloves and sealed with Parafilm® tape. Filariform larvae of other nematode helminths are susceptible to 70% ethanol for 10 minutes, 0.5% Dettol® for 20 minutes and chlorinated hydrocarbons (tetrachloroethylene) (30). Filariform larvae can also be inactivated by water heated above 80°C (30). Household contacts of patients with disseminated strongyloidiasis or *Strongyloides* hyperinfection syndrome should be screened for strongyloidiasis serologically and by stool examination in order to identify person to person transmission.

## Diagnosis and treatment algorithm for strongyloidiasis – Steps 1-4

Note to reader: All steps are to be completed sequentially, as Step 3 requires input from Steps 1 and 2.



## Step 1: Define risk category for disseminated strongyloidiasis based on epidemiologic and clinical factors

Epidemiologic risk category for <i>Strongyloides</i> exposure/Infection	Clinical risk factors for disseminated <i>Strongyloides</i>	
	<ul style="list-style-type: none"> <li>HTLV-1<sup>1</sup> infection</li> <li>Glucocorticoid<sup>2</sup> therapy</li> <li>Immunomodulatory agent<sup>3</sup></li> <li>Hematologic malignancy</li> </ul>	<ul style="list-style-type: none"> <li>No known defects in cell-mediated immunity</li> </ul>
Birth or residence or long-term travel <sup>4</sup> in Southeast Asia, Oceania, Sub-Saharan Africa, South America, Caribbean	High	Moderate
Birth or residence or long-term travel <sup>4</sup> in Mediterranean countries, Middle East, North Africa, Indian sub-continent, Asia	Moderate	Low
Birth or residence or long-term travel <sup>4</sup> in Australia, North America <sup>5</sup> or Western Europe	Very low	Very low

<sup>1</sup> HTLV-1 = Human T-lymphotropic virus

<sup>2</sup> Equivalent to 20 mg/day of prednisone for  $\geq 2$  weeks.

<sup>3</sup> Includes: alkylating agents, antimetabolites, immunosuppressive or immunomodulatory agents used in the management of solid-organ transplant and multiple sclerosis, tumor necrosis factor (TNF), Interleukin 1 (IL-1) and adhesion blocking agents, lymphocyte depleting agents.

<sup>4</sup> Defined as cumulative six-month exposure in rural or beach areas, or contact of skin with sand or soil in a risk area even during shorter-term travel (8,9,10). If significant re-exposure accumulates, consider re-screening if initially negative.

<sup>5</sup> Areas of North America that may be higher than low risk include Florida, Kentucky and Virginia. Aboriginal Australians are at elevated risk of strongyloidiasis.

## Step 2: Define suspected clinical syndrome

Suspected clinical syndrome	Appropriate diagnostic test	Appropriate diagnostic specimen
Asymptomatic $\pm$ eosinophilia (This would include asymptomatic individuals undergoing planned immune suppression.) (Very low risk)	<ul style="list-style-type: none"> <li>Serology</li> <li>Stool ova and parasites (O&amp;P) examination</li> </ul>	<ul style="list-style-type: none"> <li>Serum</li> <li>SAF<sup>4</sup>-preserved stool specimen</li> </ul>
Simple intestinal strongyloidiasis <sup>1</sup> (Low risk)	<ul style="list-style-type: none"> <li>Serology</li> <li>Stool O&amp;P examination</li> </ul>	<ul style="list-style-type: none"> <li>Serum</li> <li>SAF-preserved stool specimen</li> </ul>
Mild hyperinfection syndrome <sup>2</sup> (Moderate risk)	<ul style="list-style-type: none"> <li>Serology</li> <li>Stool O&amp;P examination</li> <li>Sputum O&amp;P examination</li> <li>Agar plate culture</li> </ul>	<ul style="list-style-type: none"> <li>Serum</li> <li>SAF-preserved stool specimen</li> <li>Fresh sputum in sterile container</li> <li>Fresh stool/sputum for agar plate culture</li> </ul>
Disseminated strongyloidiasis <sup>3</sup> (High risk)	<ul style="list-style-type: none"> <li>Serology</li> <li>Stool O&amp;P examination</li> <li>Sputum O&amp;P examination</li> <li>Urine O&amp;P examination</li> <li>CSF<sup>5</sup> O&amp;P examination</li> <li>Tissue O&amp;P examination</li> <li>Agar plate culture</li> </ul>	<ul style="list-style-type: none"> <li>Serum</li> <li>SAF-preserved stool specimen</li> <li>Fresh sputum in sterile container</li> <li>Urine in sterile container</li> <li>CSF in sterile container</li> <li>Tissue, paraffin-embedded or unprocessed</li> <li>Any fresh specimen as above for agar plate culture</li> </ul>

<sup>1</sup> Characterized by weight loss, abdominal discomfort and loose stools, with or without eosinophilia.

<sup>2</sup> Symptoms of intestinal strongyloidiasis plus respiratory symptoms (cough, wheezing, dyspnea) with or without immunosuppression. (corticosteroids, HTLV-1 infection, malignancy, non-steroidal immunomodulating agents) and absence of signs of systemic toxicity or sepsis; all persons shedding larvae of *Strongyloides* should be screened for intercurrent HTLV-1 infection.

<sup>3</sup> Severe clinical syndrome characterized by Gram-negative or polymicrobial sepsis and/or meningitis, with evidence of end-organ failure, including acute renal failure, acute respiratory distress, impaired consciousness, coma.

<sup>4</sup> SAF = Sodium acetate-acetic acid-formalin

<sup>5</sup> CSF = Cerebrospinal fluid



**Step 3: Suggested diagnostic and empiric management approach based on identified risk category (Step 1) and clinical syndrome (Step 2)**

Risk category (as per Step 1)	Suspected clinical syndrome (as per Step 2)			
	Asymptomatic ± eosinophilia <sup>1</sup>	Simple intestinal strongyloidiasis	Mild hyperinfection syndrome	Disseminated strongyloidiasis
High	Send appropriate specimens for diagnostic testing <sup>2</sup> (Moderate risk)	Empiric treatment while awaiting diagnostic testing (High risk)	Empiric treatment while awaiting diagnostic testing (High risk)	Empiric treatment while awaiting diagnostic testing (High risk)
Moderate	Send appropriate specimens for diagnostic testing (Moderate risk)	Send appropriate specimens for diagnostic testing (Moderate risk)	Empiric treatment while awaiting diagnostic testing (High risk)	Empiric treatment while awaiting diagnostic testing (High risk)
Low	Send appropriate specimens for diagnostic testing (Low risk)	Send appropriate specimens for diagnostic testing (Low risk)	Send appropriate specimens for diagnostic testing (Low risk)	Send appropriate specimens for diagnostic testing (Low risk)
Very low	Screening not recommended. Consider alternate diagnosis (Very low risk)	Screening not recommended. Consider alternate diagnosis (Very low risk)	Send appropriate specimens for diagnostic testing (Very low risk)	Send appropriate specimens for diagnostic testing (Very low risk)

<sup>1</sup> This includes asymptomatic individuals undergoing planned immune suppression.

<sup>2</sup> In the rare circumstance where the patient is deemed high risk for strongyloidiasis and immunosuppression cannot await definitive diagnostic testing, we recommend empiric treatment with two doses of ivermectin as outlined in Step 4 below.



### Step 4: Treat strongyloidiasis according to clinical syndrome and diagnostic results

Clinical syndrome	Diagnostic confirmation	Adult management	Pediatric management
Asymptomatic ± eosinophilia (including asymptomatic individuals undergoing planned immune suppression) (Very low risk)	<ul style="list-style-type: none"> <li>• Serology</li> <li>• Stool ova and parasites (O&amp;P) examination for larvae</li> </ul>	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup>	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup>
Simple intestinal strongyloidiasis <sup>2</sup> (Low risk)	<ul style="list-style-type: none"> <li>• Serology</li> <li>• Stool O&amp;P examination for larvae</li> </ul>	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup>	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup>
Mild hyperinfection syndrome <sup>3</sup> (Moderate risk)	<ul style="list-style-type: none"> <li>• Serology</li> <li>• Stool O&amp;P</li> <li>• Sputum O&amp;P examination for larvae</li> </ul>	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup> PLUS Albendazole 400 mg po BID x 7 days OR, Monotherapy: Ivermectin 200 µg/kg/day po once daily x 7 days	Ivermectin 200 µg/kg/day po once daily x 2 doses on day 1 and 2, or 14-days apart <sup>1</sup> PLUS Albendazole 400 mg po BID x 7 days OR, Monotherapy: Ivermectin 200 µg/kg/day po once daily x 7 days
Disseminated strongyloidiasis <sup>4,5</sup> (High risk)	<ul style="list-style-type: none"> <li>• Serology</li> <li>• Stool O&amp;P examination for larvae</li> <li>• Sputum O&amp;P examination for larvae</li> <li>• Urine, cerebrospinal fluid (CSF) or other body fluid or tissue examination for larvae.</li> </ul>	Ivermectin 200 µg/kg/day po or sc <sup>6</sup> once daily PLUS Albendazole 400 mg po BID until cessation of larval shedding and clinical improvement	Ivermectin 200 µg/kg/day po or sc <sup>6</sup> once daily PLUS Albendazole 400 mg po BID until cessation of larval shedding and clinical improvement

<sup>1</sup> A 14-day dosing interval is preferred due to the risk of prepatent infection arising from autoinfection (15).

<sup>2</sup> Characterized by weight loss, abdominal discomfort and loose stools, with or without eosinophilia.

<sup>3</sup> Symptoms of intestinal strongyloidiasis plus respiratory symptoms (cough, wheezing, dyspnea) with or without immunosuppression (corticosteroids, HTLV-1 infection, malignancy, non-steroidal immunomodulating agents) and absence of signs of systemic toxicity or sepsis; all persons shedding larvae of *Strongyloides* should be screened for intercurrent HTLV-1 infection.

<sup>4</sup> Severe clinical syndrome characterized by Gram-negative or polymicrobial sepsis and/or meningitis, with evidence of end-organ failure, including acute renal failure, acute respiratory distress, impaired consciousness, coma.

<sup>5</sup> Patients with disseminated strongyloidiasis should also receive empiric coverage of polymicrobial sepsis with broad-spectrum antibiotics.

<sup>6</sup> Available only as a veterinary formulation; use in humans is off-label and not Health Canada approved (25,31,32,33)



## Conclusion

Strongyloidiasis is relatively widespread in the global migrant population. Screening for the disease should be based on an individual risk assessment, taking into account the risk of exposure to *Strongyloides*, the risk of disseminated disease and the presenting clinical syndrome (which may include asymptomatic persons who are planned to undergo iatrogenic immune suppression). This statement summarizes the available relevant information on strongyloidiasis and provides a practical tool for the clinician to use in the prevention, assessment and management of disseminated strongyloidiasis in Canada.

## Key points

- Screening for strongyloidiasis should be considered for individuals with epidemiologic risk and/or comorbidities that place them at risk for *Strongyloides* hyperinfection and dissemination. Those at highest risk of hyperinfection and dissemination are individuals born in a *Strongyloides*-endemic area who undergo iatrogenic immunosuppression, or have intercurrent HTLV-1 infection.
- Diagnosis of strongyloidiasis rests on serologic testing and/or examination of stools and other clinical specimens for larvae. Serology is generally highly sensitive, while stool examination is highly specific.
- Performance characteristics of diagnostic tests may be altered by immune suppression and coinfections such as HTLV-1, in that stool examination sensitivity may improve, while sensitivity of serology may decline.
- Referral to a tropical medicine specialist with expertise in the management of strongyloidiasis is recommended for any patient with suspected or confirmed disseminated strongyloidiasis and for patients with both *Strongyloides* and HTLV-1 or Loa loa infections.

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## Conflict of interest

None.

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