

# Imported Strongyloidiasis: Epidemiology, Presentations, and Treatment

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**Abstract** Strongyloidiasis is extremely more frequent in immigrants than in travellers. Clinical presentations do not differ significantly between the two groups, and the most frequent picture is a chronic infection characterized by intermittent, mild, non-specific symptoms. Acute presentation is rare but it has been reported in travellers. Screening of asymptomatic subjects is not generally recommended, while

a presumptive treatment with ivermectin might be justified for all travellers and immigrant patients presenting unexplained eosinophilia and/or compatible symptoms, even in case of negative test results. In fact, delayed diagnosis and treatment has life-threatening consequences in patients with conditions predisposing to development of hyperinfection and dissemination.

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## Introduction

*Strongyloides stercoralis* (*S. stercoralis*, see Fig. 1) is a nematode widely distributed in tropical and subtropical areas, but small foci of low endemicity are also present in temperate climate—countries, like some parts of Southern Europe and USA (Appalachia). Estimates of prevalence indicate that 30 to 100 million people are infected worldwide, but the number is presumably higher because the diagnostic methods traditionally used (stool examination, culture) lack sensitivity [1]. Despite the high burden of the infection, only recently did the WHO add strongyloidiasis to the list of neglected parasitic diseases [1, 2].

Transmitted through direct penetration of human skin put in contact with contaminated soil or sand, this peculiar parasite is characterized by a unique capability to replicate indefinitely inside the host (“auto-infective cycle”), without further exposures to an infected site [3]. Due to this characteristic, the infection can be diagnosed in persons that have been living in non-endemic countries for many years, but acquired the infection decades earlier in endemic countries.

Thus, following the flows of migration and travel, the parasite can be found in patients presenting to health services in Western countries, where the diagnosis might be



**Fig. 1** *Strongyloides stercoralis* adult female

difficult due to the lack of familiarity of physicians with tropical diseases. This was clearly outlined in a study conducted in the USA, where 363 resident physicians were challenged with case presentations of strongyloidiasis and other helminth infections [4]. The results showed limited recognition of *Strongyloides* infection and poor knowledge of helminths in general. In particular, 23% of the US residents participating at the study decided to prescribe empiric corticosteroid therapy in case of eosinophilia, without conducting previous investigations in order to exclude the presence of possible parasites, a procedure that can cause life-threatening consequences in case of strongyloidiasis [5]. The authors conclude that all physicians should at least be aware of the risks of this infection and consider the potential exposure to *Strongyloides* before prescribing immunosuppressive therapies. The need for a better approach to the diagnosis and management of strongyloidiasis in non-endemic countries is also stressed by Nuesch et al. [6], who state that this is probably the imported helminth infection with the highest impact on health.

The aim of this paper is to review, as part of the COHEMI activity (<http://www.cohemi-project.eu/>), the main characteristics of imported cases of strongyloidiasis, including both immigrants and travellers.

## Methods

- Search 1: To collect papers on epidemiology of imported cases we searched MEDLINE using the following search strategy: (strongyloid\* AND (Humans[Mesh] AND “last 10 years”[PDat])) AND ((travel\*) OR (imported) OR (migrant\*) OR (immigrant\*)). The search was conducted on the 20th October 2011. Only papers written in English, French, and Spanish were reviewed. Papers published within the last 5 years were preferentially analyzed, though we extended the analysis to older papers in case of paucity of more recent literature.

- Search 2: To collect papers on hyperinfection syndromes/disseminated cases, we searched MEDLINE using the following search strategy: disease (strongyl\*, anguillulose) AND severity of cases (disseminat\*, hyperinfect\*, severe, death, fatal, mortality) OR disease (strongyl\*, anguillulose) AND associated conditions (tumor\*, cancer, haematolog\*, lymphom\*, leukem\*, leukaem\*, neoplas\*, malignan\*, HTLV\*, HIV, AIDS, hypogammaglobulinemia, rheumat\*, “biological agents”, diabet\*, transplant\*, COPD, steroid\*, glucocorticoid\*, Immunosuppression [MeSH], Immunocompromised Host [MeSH]) and limiting the search to papers published since 2006, related to humans and to the above mentioned languages. Date of search in Pubmed: 20th May 2011.

## Incidence of Travel-Related Strongyloidiasis

In literature published since 2005, we found only one paper describing a study specifically designed to investigate the risk of acquiring strongyloidiasis in travellers [7•]. In this prospective study, subjects attending a pre-travel visit at the travel clinic of the Public Health Service of Amsterdam were tested for *Strongyloides* (using an in-house ELISA) before departure and 2 and 6 weeks after return from an endemic country. Among 1178, previously negative people tested, 3 subjects (0.25%) showed seroconversion (incidence rate 6.5 per 1000 persons-month), all returning from Asia. Interestingly, serology performed before the journey was positive in 29 out of 1207 travellers (2.4%); the authors observed that an increasing number of travels to endemic areas leads to a cumulative risk of infection (the same was true for other parasitic infections such as schistosomiasis, filariasis, toxocariasis). Since the incidence rates for all the parasites studied were low, the authors conclude that there is no indication to perform routine screening of returning travellers. The same opinion is shared by Bottieau et al. [8], who remark that screening of asymptomatic, returning travellers would only be justified in case of a stay longer than 3 months in a tropical area. They also suggest that physicians shouldn't rely on eosinophil count and stool examination for screening, as the sensitivity of both is too low; even serology has limited value in detecting recent *S. stercoralis* infections, although some researchers have found serology to be more sensitive in migrants than in travellers [6, 9]; however, the authors did not specify the time elapsed from exposure to serology testing in travellers in their study, and possibly a delayed testing might lead to a higher proportion of positive results.

The approach should be different in subjects with a consistent travel history presenting to physicians with symptoms and/or eosinophilia. In this case, the possibility of helminthic infections should be considered: experts of the British

Infection Society propose a schematic approach based on symptoms/region visited, although it is suggested to perform concentrated stool microscopy and *Strongyloides* serology in all cases, regardless the country visited [10].

### Prevalence of Strongyloidiasis in Immigrants and Refugees

Since 2006, we found three papers reporting the results of cross-sectional surveys [11–13] and one of prospective survey [14], aimed at investigating the prevalence of parasite infections in immigrants and/or refugees from low-middle income countries to countries of low or no endemicity for *S. stercoralis*. Data are summarized in Table 1. Clearly, prevalence data varied according with the diagnostic methods used: serology was found to be much more sensitive than stool microscopy, even in case of people with HIV infection [11], while specificity might be hampered by cross-reactivity with other parasites [13, 15]. We believe that the true prevalence is likely to be between the estimates based on direct methods and those based on serology.

As for the countries of origin of the immigrants, Caruana et al. [13] analyzed only subjects from East Africa and from Cambodia, finding a higher prevalence in the latter group: a positive serology was detected in 82/230 (36%) of Cambodians versus 2/124 (2%) of East Africans. In the paper by Gualdieri et al. [14] subjects tested came from a larger number of countries, but the nationality of the two subjects diagnosed by microscopy (the only method used in this study) is not specified. Hochberg et al. [11] in the US found a high proportion of positive serology (33/128 or 26%) among HIV patients coming from the following countries: Mexico (12 patients), Honduras (4), Ethiopia (3), El Salvador (2), Zambia (2) and one each in Argentina, Congo, Cuba, Grenada, Guatemala, India, Kenya, Niger, Tanzania and Vietnam. However, some areas had insufficient representation for a reliable comparison of the country-related risk. In another study conducted in two Italian hospitals from 2000 to 2009 [16], 15 (11%) of 138 HIV-positive immigrants were infected by *S. stercoralis*. Diagnosis was made with serology (an in-house indirect immunofluorescence antibody test—IFAT) in 11 patients, while 2 had positive stool microscopy and 2 positive stool culture. In this study, all but one positive patient were

Africans (14 positive of 107 tested). The remaining positive subject came from Central/South America. None of the 4 patients from Asia/Oceania tested positive.

Other studies retrospectively analyzed wider aspects of the health profile of asylum seekers or immigrants. The service PRAIDA [17] “Programme régional d’accueil et d’intégration des demandeurs d’asile”, the program for reception and integration of asylum seekers of Montréal, Canada, collected data about the refugees screened from 2000 to 2004; among the 231 patients tested for strongyloidiasis (with EIA), 40 were positive (17.3%). Logistic regression analysis found no association between the continent of origin and the risk of infection. The authors remark that the prevalence found was higher than previous studies based on direct methods; they also argue that false positive results due to cross-reactivity (i.e. with filariae) did not seem to significantly affect their result, given that most subjects with a positive result for strongyloidiasis tested negative for filariasis. Both serology and stool microscopy were performed in African immigrants attending outpatient clinics at the Royal Melbourne Hospital since 2003 to 2006, in a retrospective audit [18]. Of 145 stool samples examined, only 2 (1.4%) were positive for *Strongyloides* larvae by microscopy, while 32 of 179 tested (17.9%) had positive serology. Both patients with positive stool also had a positive serology.

Since serology has been used to test immigrants, a high prevalence of strongyloidiasis has been observed [11, 12, 17, 18]. Although the need for immigrant screening should not be overstated, the potential severity of the disease warrants a proper diagnosis and possibly a presumptive treatment in some subgroups of migrants at high risk of developing severe infection [19]. For instance, transplant candidates should be extensively screened for infectious/parasitic diseases that could reactivate after transplant, and in case of immigrant patients it is mandatory to extend the screening to infections that are endemic in their countries of origin. Fitzpatrick et al. [20••] describe the results of the extended screening program proposed for Hispanic kidney transplant candidates. For strongyloidiasis, of 75 patients tested with serology, 5 (6.7%) were positive: they were all asymptomatic, and only one had eosinophilia; these findings confirm the need for screening all patients at high risk of developing the life-threatening stages of strongyloidiasis, irrespectively of the presence of clinical symptoms/signs or eosinophilia.

**Table 1** Prevalence of strongyloidiasis in immigrants and/or refugees

Paper	Country	Population	Diagnostic method	Positive/tested subjects. N (%)
Gualdieri 2011	Italy	Immigrants	Microscopy	2/514 (0.4)
Hochberg 2011	USA	Immigrants HIV+	Microscopy and serology	Microscopy:0/128; serology:33/128(26)
Posey 2007	USA	Refugees	Serology	214/462 Sudanese (46);23/100 Somali Bantu (23)
Caruana 2006	Australia	Immigrants and refugees	Microscopy and serology	Microscopy:10/321; serology:84/354

## Clinical Presentation

In most cases, strongyloidiasis is a chronic asymptomatic infection, frequently associated with eosinophilia as the unique finding that could raise suspicion. When symptoms occur, they are usually mild and non-specific, and involve the gastrointestinal tract (abdominal pain, diarrhea), the respiratory tract (cough, dyspnea) and the skin (pruritus, rash) [10, 21]. Another, rarer manifestation is an itchy, serpiginous rash that develops as the result of subcutaneous larval migration: *larva currens*. It is mostly observed around the trunk, upper legs and buttocks and it moves quickly (around 5–15 cm/h), lasting for some hours to a few days [10, 22].

Acute strongyloidiasis is rarely reported, but it should be considered in tourists returning from highly endemic countries with compatible symptoms and signs: within a few days from exposure, a Loeffler's syndrome usually occurs, along with skin signs (urticaria, itch). Experimental human infections demonstrated that a local reaction at the site of entry may appear and may last up to several weeks [5]. A recent paper [23•] described a case of acute strongyloidiasis in a couple of tourists returning to Italy from Southeast Asia where in addition to the classical Loeffler's syndrome, a transient splenomegaly and increased serum AST and ALT were recorded.

Severe, potentially fatal clinical syndromes occur especially in immunosuppressed patients, who can experience hyperinfection (HI) or dissemination (DS). As it has been outlined above, corticosteroid therapy is the most frequent trigger of both [24]. Other conditions commonly associated to HI/DS are malignancies (particularly lymphomas), organ transplantation, HTLV-1 infection. Malnutrition, alcohol abuse and diabetes have also been associated with the severe forms of strongyloidiasis [5, 24]. Hyperinfection is usually defined as an increased larval load, causing severe symptoms [25]; the larvae in this case remain confined to the respiratory and gastrointestinal tracts. Sometimes during HI, gram-negative sepsis and meningitis develop because *Strongyloides* larvae can carry enteric bacteria through the bowel mucosa into the host's circulation [15]. On the other hand, in DS larvae are found virtually in any organs [5]. The mortality associated to these two syndromes is significant: for HI it is estimated to be around 15%, while it is exceedingly high (87%) in case of dissemination [24]. Unfortunately, just like in case of chronic infection, symptoms in HI/DS are nonspecific; moreover, eosinophilia is often absent, therefore diagnosis is often delayed. However, in contrast with the low sensitivity of direct methods in case of chronic strongyloidiasis, in hyperinfection and dissemination the larval output is so accelerated and increased that diagnosis is easily done with direct examination of the clinical samples (stool, sputum, and other) [25].

The results of the MEDLINE search 2 defined above, permitted to identify 290 papers. We reviewed the full text of the papers and selected the cases of hyperinfection syndromes/disseminated strongyloidiasis diagnosed in low-endemicity countries in patients with previous stays in endemic countries. We identified 37 papers accounting for 41 case reports. None of the cases were related to travel, while 36 cases were diagnosed in immigrants. A total of 15 of the 36 patients (41.7%) were Hispanic (originating from Spanish-speaking countries in Central America, South America or the Caribbeans) [26–39]. An interesting finding concerns 5 cases occurring in transplant recipients who did not have a history of possible exposure to *S. stercoralis*, but who received the transplanted organ from Hispanic donors [40–45]. One of the patients developed intercurrent cytomegalovirus sepsis and died [45]. Strongyloidiasis was retrospectively confirmed in 4 of those donors [40, 41, 43–45], and subsequent investigations were conducted on all the patients who had received organs from the same infected donors. This procedure led to the diagnosis of strongyloidiasis in a kidney recipient, who had already developed hyperinfection but was successfully treated [41].

## Studies Comparing Strongyloidiasis in Travellers versus Immigrants

In a retrospective study of 33 imported cases in Spain, González et al. [21] reviewed clinical, epidemiological and biochemical characteristics of immigrants (23 patients) and travellers (10) diagnosed with strongyloidiasis at the Hospital Clinic (University of Barcelona) in a 3-year time. A high proportion of the travellers had visited Sub-Saharan Africa (40%), while the immigrants mostly came from South America (69.6%). About half of the patients had a chronic, asymptomatic infection (the diagnostic work-up was usually carried out to investigate eosinophilia in these cases). No significant differences in clinical presentations were found between immigrants and travellers. The levels of eosinophil count were also compared between the two groups, and >the range of variation was similar (with eosinophilia frequently lacking in severe disease). An analogous retrospective analysis was conducted on 31 patients (12 travellers and 19 immigrants) diagnosed with strongyloidiasis in two referral centres in Switzerland from 1998 to 2002 [15]. In contrast to the Spanish study, only 16% of the patients were asymptomatic, while the others underwent the diagnostic work up because of nonspecific symptoms: immigrants had less frequently abdominal symptoms (47% vs 75% in travellers) but more frequently respiratory symptoms (25% vs 8%). Neither study found statistically significant differences in clinical presentations between immigrants and travellers.



## Treatment

Currently, ivermectin is the best therapeutic option for strongyloidiasis. The most recent trials comparing albendazole and ivermectin confirm the superiority of the latter in terms of efficacy: in particular, Nontasut et al. [46] treated 33 patients with albendazole 400 mg for 5 days and 78 patients with ivermectin 0.2 mg/Kg single dose, finding cure rates of 78.8% vs 98.7%, respectively. Supputtamongkol et al. [47] compared single and double doses (given 2 weeks apart) of ivermectin with high dose albendazole (800 mg daily for 7 days); the parasitological cure rates were 96.8% and 93.1% in the single dose and in the double doses regimens of ivermectin, respectively, and 63.3% in the albendazole group. It was not possible to demonstrate a difference in efficacy between the two ivermectin groups. However, some experts empirically recommend repeated doses, arguing that the “classical” single dose [48, 49] is often insufficient to eradicate the infection, especially in immunocompromised subjects [25].

In another study [50] ivermectin was compared to thiabendazole, finding no difference in efficacy but better tolerability with ivermectin. This is the only study conducted so far in which the treatment efficacy was evaluated not only with direct methods but also with serology (an in-house IFAT), and was found to be much lower than in any previous trial (below 70% for both drugs). Given the low sensitivity of diagnostic methods, the authors suggest that the treatment efficacy could have been overestimated in previous trials, as negative stool cultures/examinations after treatment are too insensitive to prove eradication of the infection. Other groups evaluated serology in monitoring the response to therapy, though not in randomized controlled trials; in particular, Biggs et al. [51] showed its usefulness in immigrants and refugees.

On the other hand, particularly in case of refugees who could be difficult to follow up, some guidelines consider presumptive treatment before their resettlement to be more cost-effective than screening [12].

Further research is needed to determine the optimal dose schedule of ivermectin (unquestionably the best available drug) to cure strongyloidiasis. Future trials should take into consideration the accuracy of the currently available diagnostic tools for trial inclusion and cure monitoring.

## Conclusions

The increase in travel and migration facilitate the spread of pathogens and diseases all around the world. Strongyloidiasis, widely distributed in large parts of Asia, Africa and South America, has become an emerging global infection that has migrated from developing regions to industrialized

areas [24]. Clinicians should be aware of this infection as well as the conditions exposing patients to the risk of hyperinfection and dissemination.

Travellers are at relatively low risk of acquiring strongyloidiasis, therefore routine screening in the absence of symptoms is probably of no value. On the other hand, it is important to investigate eosinophilia in subjects that have visited endemic countries. It is less easy to define common guidelines for the management of asymptomatic immigrants and in particular refugees: in the latter group a presumptive treatment could also be worthwhile if a high prevalence of strongyloidiasis has been demonstrated previously. Doubtlessly, clinicians must be even more careful with patients needing chemotherapy, corticosteroids or presenting any condition exposing to the risk of hyperinfection or dissemination, and a presumptive treatment with ivermectin would be justified for all traveller and immigrant patients presenting unexplained eosinophilia and/or compatible symptoms, even in the setting of negative test results.

Important knowledge gaps still remain regarding the optimal management of this peculiar parasitic infection. In particular, more research is needed to find the optimal tool, or combination of tools, for individual diagnosis, prevalence studies and monitoring of treatment efficacy.

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