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Strongyloides stercoralis prevalence in solid-organ and haematopoietic stem cell transplant candidates and recipients: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction *Strongyloides stercoralis* is an intestinal helminth ubiquitous in tropical and subtropical regions worldwide. It persists in the human host for a lifetime as a result of autoinfection and if undetected and untreated, can lead to increased morbidity and high mortality in immunocompromised individuals such as the transplant population. Transplant patients, including solid-organ and haematopoietic stem cell transplants (SOT and HSCT, respectively), are at a high risk of hyperinfection and disseminated strongyloidiasis. Unfortunately screening is often not systematically performed. Prevalence estimates of *Strongyloides* in this high-risk population is not well studied. Through this systematic review, we aim to summarise the descriptive evidence on *Strongyloides* prevalence in SOT and HSCT patients, including diagnostic and screening practices alongside the cases of hyperinfection, disseminated strongyloidiasis and the mortality rate in this population.

Methods and analyses Through the use of various online library databases, we will conduct a systematic review including relevant literature on the prevalence of *Strongyloides* in SOT and HSCT patients as well as studies assessing hyperinfection and disseminated strongyloidiasis in this patient population. The Population, Intervention, Comparison, Outcome and Study Design strategy and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be used to determine a final subset of studies for analysis. Quality assessment for case series and case reports will be determined by a modified quality assessment tool developed by the National Heart, Lung, and Blood Institute (NIH), and the CARE guidelines, respectively. We will provide a narrative synthesis of the findings pertaining to the primary and secondary outcomes of interest (prevalence of *Strongyloides* and mortality rate in transplant population, respectively) alongside the associated 95% CI. Estimates from individual studies will be pooled using a random effects model.

Ethics and dissemination This systematic review does not require formal ethical approval since no primary data will be collected. Findings will be disseminated through a peer-reviewed publication and relevant conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Having searched numerous online databases and with no restriction on dates or languages of publication, we aim to capture the most relevant literature.
⇒ The reported *Strongyloides* prevalence is based on a small number of heterogeneous studies with significant variations in study regions and diagnostic methods used thereby impacting our ability to pool results.
⇒ Studies reporting prevalence of *Strongyloides* in transplant patients are mostly limited to case reports and case series, there by restricting our analyses to these study designs.

INTRODUCTION

Strongyloides stercoralis is an intestinal helminth ubiquitous in tropical and subtropical regions worldwide and infects 10%–40% of the population in these countries.[1–4] The uncertainty in the global burden of strongyloidiasis stems from the challenges associated with the estimation of its prevalence. Recent estimates of the global prevalence of strongyloidiasis suggest 614 (95% CI 313 to 910) million people are infected.[4] The reported prevalence is based on a small number of heterogeneous studies with significant variations in study regions and diagnostic methods used.[5–8] Given the low sensitivity of stool-based parasitological and biomolecular methods, prevalence estimates reported in studies using only stool-based techniques is also likely underestimated.[9 10] Serological testing appears to be more sensitive with sensitivity ranging from 70% to 95%. However, its specificity is of concern because of cross-reactivity with other helminths, especially in endemic countries with high burden of geohelminthiasis.[10]

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Strongyloides is a unique parasite because it persists in the host throughout its life as a result of autoinfection. *Strongyloides* is often asymptomatic or causes mild symptoms that involve the gastrointestinal tract, respiratory tract, or the skin in immunocompetent hosts. In contrast, it can cause life-threatening disseminated disease in people with impaired immunity. People taking corticosteroids, coinfected with human T-cell lymphotropic virus-1, with transplant-related immunosuppression, or with haematological malignancies are at highest risk.[11 12] The mortality rate of disseminated strongyloidiasis can be as high as 85%.[13]

In non-endemic countries, foreign born populations account for the majority of cases of strongyloidiasis. A recent systematic review and meta-analysis that summarised prevalence data for strongyloidiasis among migrants originating from endemic countries and migrating to non-endemic countries found that the overall prevalence was 12%.[14] This study was limited by a lack of studies involving migrants from several world regions and the fact that diagnostic methods were often left unreported. Migrants, many of whom are from *Strongyloides* endemic countries, comprise a significant and increasing proportion of the population in most high-income countries such as Canada (21%), Australia (30%), Germany (17%), the UK (14%), Sweden (20%) and the USA(15%).[15] The rise of migration and the increasing use of immunosuppressive therapy in many clinical conditions highlights the need for better data to determine the optimal screening and treatment strategy for *Strongyloides* among immunocompromised migrants.

The prevalence of *Strongyloides* in solid-organ transplant (SOT) and haematopoietic stem cell transplant (HSCT) patients is not well documented. Moreover, *Strongyloides* is not systematically screened in at-risk transplant candidates or transplant recipients which can lead to severe hyperinfection and disseminated strongyloidiasis.[16–24] The numerous clinical manifestations combined with a lack of awareness may impede accurate diagnosis and contribute to the high mortality rate observed. Cases have been reported in kidney, liver, pancreas, intestine, lung SOT and HSCT. A recent study in Austria, a non-endemic country for *Strongyloides,* has demonstrated a seroprevalence of 3% among the kidney transplant recipients.[25] A study from Malaysia, a country with high endemicity, reported a *Strongyloides* prevalence of 4.9% in 288 organ transplant recipients using a stool-based technique (formalin-ether concentration) which likely underestimated the prevalence in this high-risk population.[26]

Given the global burden of strongyloidiasis, increased migration and travel in and from non-endemic countries, increasing recipients of SOT and HSCT as well as high mortality rate of severe strongyloidiasis, it is essential to gather more data on the prevalence of *Strongyloides* in the transplant population to inform more robust prevalence studies and to determine the best screening strategies. Through this systematic review, we aim to consolidate the descriptive evidence specifically on the prevalence of *Strongyloides* infection in the SOT and HSCT in non-endemic/low-endemic and in moderate/high-endemic regions and the methods used to diagnose infections (stool-based methods and serology). As a secondary objective, we also aim to summarise the cases of hyperinfection and disseminated strongyloidiasis in the SOT and HSCT patients and consolidate the mortality rate in that population.

METHODS AND ANALYSIS

Search strategy and study selection

This systematic review will be prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27] The search strategy will be developed with the assistance of a medical librarian and will consist of text words and relevant indexing to identify studies about *S. stercoralis* infection in SOT and HSCT candidates and recipients. The following databases were searched for relevant studies on 27 July 2021: MEDLINE (via Ovid & via PubMed); The Cochrane CENTRAL Register of Controlled Trials & Cochrane Database of Systematic Reviews (via Wiley); Embase (via Ovid); Africa-Wide Information (via EBSCO); Global Health (via Ovid); Global Index Medicus (via WHO); Scopus (via Elsevier), Latin American and Caribbean Health Sciences Literature (LILACS). Clinical trials registries (clinicaltrials.gov, International Clinical Trials Registry Platform) will also be searched. No restrictions on date and language of publication will be applied in effort to optimise the evidence to be captured. The MEDLINE search strategy will be applied to all databases with appropriate modifications (online supplemental appendix 1). In addition, further studies will be identified in Web of Science and Scopus by carrying out citation searches for the reference lists of included studies. The MEDLINE search strategy will be rerun prior to submission to capture studies published in the intervening time interval. The bibliographic software Rayyan will be used for the purposes of citation management (including deduplication) and storage. The implementation of the search strategy will occur prior to the selection of relevant studies and data extraction as per the PRISMA guidelines.[27] Additionally, the Population, Intervention, Comparison, Outcome and Study Design strategy was used to formulate the research question, the inclusion and exclusion criteria and to guide the overall review process (table 1).[28]

Table 1 one provides a summary of the studies considered relevant for this review. In our review, we will include all studies that assess the prevalence of *Strongyloides* in SOT and haematopoitic stem cell transplant candidates and recipients. The included studies may be performed on children (less than 18 years of age) and/or adults who are migrants, travellers and residents of *Strongyloides* endemic or non-endemic areas. Diagnosis of *Strongyloides* must be confirmed through either stool-based methods or serology. The primary outcome of interest is the prevalence of strongyloidiasis in SOT and HSCT candidates

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Table 1 Population, Intervention, Comparison, Outcome and Study Design (PICOS) strategy and inclusion and exclusion criteria

PICOS item	Inclusion criteria	Exclusion criteria
Population	Solid-organ and haematopoitic stem cell transplant candidates and recipients tested for strongyloidiasis. Including children (less than 18 years of age) and/or adults who are migrants, travellers and residents of *Strongyloides* endemic and non-endemic areas.	Studies that do not report specifically on *Strongyloides*. Studies reporting on immunocompromised population without reporting specifically on SOT or HSCT candidates or recipients.
Intervention	Diagnosis of *Strongyloides* must be confirmed through either stool-based methods or serology.	Diagnostic methods other than the recognised *Strongyloides* diagnostic methods
Comparator	A comparator is not applicable.	
Outcomes	Prevalence of *Strongyloides* in SOT and HSCT candidates or recipients. Mortality rate of hyperinfection and disseminated strongyloidiasis in in SOT and HSCT candidates or recipients.	Studies that do not report on the prevalence and or on the cases of severe strongyloidiasis will be excluded.
Study Design	Case reports, case-series, observational and interventional studies (if any).	Animal studies

HSCT, haematopoietic stem cell transplant; SOT, solid-organ transplant.

and recipients. A secondary outcome of interest includes mortality rate of the reported cases of hyperinfection and disseminated strongyloidiasis in this population. Finally, we aim to include a variety of study designs in our review, including case reports, case-series, observational and interventional studies, and conference abstracts.

Screening and data extraction

Titles and abstracts of studies retrieved using the predefined search strategies and those from additional sources (eg, clinical trials registries, Web of Science and Scopus) will be screened independently by two review authors (FN and CQ) to identify studies that meet the inclusion criteria. Inclusion of an article will be re-evaluated among the two reviewers if there is a disagreement. If the disagreement persists, an expert reviewer (SB) will make the final decision. Next, the full text of potential eligible studies will be independently assessed by the two review authors (FN and CQ). All articles that meet all the inclusion criteria will be submitted for data extraction by the two review authors who will read the full text articles. Relevant data from the studies that meet the inclusion criteria will be extracted and incorporated into two separate standard data extraction forms by two reviewers (FN and CQ). These two extraction forms will be merged once complete. Extracted data will include: general and methodological study characteristics and more specific variables including, but not limited to: study design, methods, baseline population characteristics (eg, age, sex, ethnicity), SOT (kidney, liver, heart, lung, intestine, pancreas), HSCT (autologous or allogeneic) number of patients, country of origin, severity of infection (asymptomatic, isolated eosinophilia, mild infection, hyperinfection, disseminated disease), method of diagnosis (stool-based method, serology), specific details on treatment regimen, prevalence, treatment response, mortality rate, authors conclusion and any reported biases. In case any data is unclear or unavailable, the corresponding author for the study may be contacted for further clarification. Prior to full extraction, the reviewers (FN and CQ) will perform a pilot data extraction using a small random sample of the included studies. The expert reviewer (SB) will assess the pilot data extraction for quality control and concordance purposes. Cohen's kappa (κ) will be calculated based on the initial pilot data extraction to assess inter-reviewer concordance.

Risk of bias and quality assessment

Study quality and risk of bias assessment will be performed by the two review authors (FN and CQ) using modified quality assessment tools. The quality assessment tools for case series and observational studies are a modified adaptation of the study quality assessment tool developed by the National Heart, Lung and Blood Institute, National Institutes of Health (NIH).[29] The quality of case reports will be assessed using an adaptation of the CARE guidelines.[30] Any uncertainties will be addressed by the expert reviewer (SB).

Descriptive and statistical analysis

A narrative synthesis will be carried out for all studies included in our review. The primary outcome of interest, the prevalence of strongyloidiasis in SOT and HSCT candidates or recipients will be reported along with an estimated 95% CI. The prevalence of *Strongyloides* will be stratified by type of sample; stool or serum sample. If possible, the prevalence will be further stratified by age (ie, ≤18 years old vs general population), region of origin, study setting, host country, and decade of publication. The second outcome of interest which consists of the mortality rate of severe strongyloidiasis will be reported alongside appropriate 95% CI. Prevalence and mortality rate of severe strongyloidiasis will be presented in the form of proportions (with associated precision) for case reports and case series and in the form of effect sizes (OR, HR, relative risk) for interventional/observational

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studies. Outcomes reported for SOT and HSCT as well as outcomes from endemic and non-endemic regions among articles with the same study design will be pooled using a random effects model.

Through our comprehensive systematic review, we aim to fill the evidence gap and increase the body of knowledge on the prevalence of *Strongyloides* in SOT and HSCT and the mortality rate of severe strongyloidiasis in this population by including all of the relevant literature. Not only will this review compile the available evidence, it will also shed light on the need for further, high-quality prevalence studies of strongyloidiasis in the transplant population.

Amendments

In the case of any amendments to the present protocol, specific details and justifications will be provided through PROSPERO prior to the publication of this review.

Patient and public involvement

Patients nor the public were involved in the design, conduct, reporting or dissemination plans of our research.

Ethics and dissemination

This systematic review does not require formal ethical approval since no primary data will be collected. Findings will be disseminated through a peer-reviewed publication and relevant conferences.

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REFERENCES

1 Puthiyakunnon S, Boddu S, Li Y, *et al*. Strongyloidiasis--an insight into its global prevalence and management. *PLoS Negl Trop Dis* 2014;8:e3018.
2 Bisoffi Z, Buonfrate D, Montresor A, *et al*. Strongyloides stercoralis: a plea for action. *PLoS Negl Trop Dis* 2013;7:e2214.
3 Schär F, Trostdorf U, Giardina F, *et al*. Strongyloides stercoralis: global distribution and risk factors. *PLoS Negl Trop Dis* 2013;7:e2288.
4 Buonfrate D, Bisanzio D, Giorli G, *et al*. The Global Prevalence of *Strongyloides stercoralis* Infection. *Pathogens* 2020;9. doi:10.3390/pathogens9060468. [Epub ahead of print: 13 06 2020].
5 Yori PP, Kosek M, Gilman RH, *et al*. Seroepidemiology of strongyloidiasis in the Peruvian Amazon. *Am J Trop Med Hyg* 2006;74:97–102.
6 Roldán WH, Espinoza YA, Huapaya PE, *et al*. Frequency of human toxocariasis in a rural population from Cajamarca, Peru determined by DOT-ELISA test. *Rev Inst Med Trop Sao Paulo* 2009;51:67–71.
7 Rodríguez J, Calderón J. [Intestinal parasitosis in pre-school children from Tarapoto]. *Rev Gastroenterol Peru* 1991;11:153–60.
8 Cabada MM, Lopez M, Arque E, *et al*. Prevalence of soil-transmitted helminths after mass albendazole administration in an Indigenous community of the Manu jungle in Peru. *Pathog Glob Health* 2014;108:200–5.
9 Buonfrate D, Requena-Mendez A, Angheben A, *et al*. Accuracy of molecular biology techniques for the diagnosis of Strongyloides stercoralis infection-A systematic review and meta-analysis. *PLoS Negl Trop Dis* 2018;12:e0006229.
10 Requena-Méndez A, Chiodini P, Bisoffi Z, *et al*. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. *PLoS Negl Trop Dis* 2013;7:e2002.
11 Buonfrate D, Requena-Mendez A, Angheben A, *et al*. Severe strongyloidiasis: a systematic review of case reports. *BMC Infect Dis* 2013;13:78.
12 Nutman TB. Human infection with Strongyloides stercoralis and other related Strongyloides species. *Parasitology* 2017;144:263–73.
13 Boggild AK, Libman M, Greenaway C, *et al*. Committee to advise on tropical M, travel. CATMAT statement on disseminated strongyloidiasis: prevention, assessment and management guidelines. *Can Commun Dis Rep* 2016;42:12–19.
14 Asundi A, Beliavsky A, Liu XJ, *et al*. Prevalence of strongyloidiasis and schistosomiasis among migrants: a systematic review and meta-analysis. *Lancet Glob Health* 2019;7:e236–48.
15 United Nations. World migration report, 2020. Available: https://www.un.org/sites/un2.un.org/files/wmr_2020.pdf [Accessed 16 Nov 2020].
16 Soman R, Vaideeswar P, Shah H, *et al*. A 34-year-old renal transplant recipient with high-grade fever and progressive shortness of breath. *J Postgrad Med* 2002;48:191–6.
17 Dulley FL, Costa S, Cosentino R, *et al*. Strongyloides stercoralis Hyperinfection after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2009;43:741–2.
18 Vilela EG, Clemente WT, Mira RRL, *et al*. Strongyloides stercoralis Hyperinfection syndrome after liver transplantation: case report and literature review. *Transpl Infect Dis* 2009;11:132–6.
19 Mizuno S, Iida T, Zendejas I, *et al*. Strongyloides hyperinfection syndrome following simultaneous heart and kidney transplantation. *Transpl Int* 2009;22:251–3.
20 El Masry HZ, O'Donnell J. Fatal stongyloides Hyperinfection in heart transplantation. *J Heart Lung Transplant* 2005;24:1980–3.
21 Gupta S, Jain A, Fanning TV, *et al*. An unusual cause of alveolar hemorrhage post hematopoietic stem cell transplantation: a case report. *BMC Cancer* 2006;6:87.
22 Patel G, Arvelakis A, Sauter BV, *et al*. Strongyloides hyperinfection syndrome after intestinal transplantation. *Transpl Infect Dis* 2008;10:137–41.
23 Weiser JA, Scully BE, Bulman WA, *et al*. Periumbilical parasitic thumbprint purpura: Strongyloides hyperinfection syndrome acquired from a cadaveric renal transplant. *Transpl Infect Dis* 2011;13:58–62.
24 Martinez-Perez A, Roure Díez S, Belhassen-Garcia M, *et al*. Management of severe strongyloidiasis attended at reference centers in Spain. *PLoS Negl Trop Dis* 2018;12:e0006272.

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25 Winnicki W, Eder M, Mazal P, *et al*. Prevalence of Strongyloides stercoralis infection and Hyperinfection syndrome among renal allograft recipients in central Europe. *Sci Rep* 2018;8:15406.
26 Hassan N-A, Lim YAL, Mahmud R, *et al*. Microsporidia infection among various groups of the immunocompromised patients. *Trop Biomed* 2018;35:521–30.
27 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
28 The Cochrane Collaboration. Chapter 5: Defining the review question and deveoloping criteria for including studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook of systematic reviews. version 5.0.1*, 2008.
29 National Heart, Lung, and Blood Institute. Study quality assessment tools, 2019. Available: https://www. nhlbi. nih. gov/health-topics/study-quality-assessment-tools [Accessed 20 Jul 2021].
30 Gagnier JJ, Kienle G, Altman DG, *et al*. The CARE guidelines: consensus-based clinical case reporting Guideline development. *J Med Case Rep* 2013;7:223.

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