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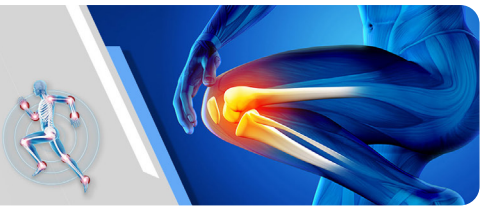
Research Article

JOURNAL OF ORTHOPAEDICS AND SPORTS MEDICINE

ISSN: 2688-5115



Sensitivity of Diagnostic Methods for Detecting *S. stercoralis* Infection and Comparison of the Total Global Number of Strongyloidiasis Cases with Other Recognized NTDs: A Systematic Review

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Abstract

Background: Since 2005, global health policy makers have recognized and designated widespread poverty-related neglected diseases as NTDs (neglected tropical diseases). However, *Strongyloides stercoralis* infection is not included in the list of these recognized NTDs. A systematic review was conducted to estimate the total number of S. stercoralis infections in humans worldwide and compare the result with the prevalence data of other recognized NTDs. In addition, the sensitivity of diagnostic methods that were used for detecting *Strongyloides stercoralis* infection was evaluated.

Methods: An electronic search of the PubMed, WHOLIS, and ISI Web of Science databases was performed for articles published between January 1990 and May 2017. Articles with quantitative data on prevalence, incidence, duration of infection, remission/cure, and mortality in humans were included. After obtaining the raw data from the systematic review, adjustments were made for diagnostic accuracy, selection of the reference population, and adjustments for age and reference year 2017 as a prerequisite for estimating the total number of strongyloidiasis cases in humans worldwide. The estimated number was then compared with other recognized neglected tropical diseases. The sensitivity of diagnostic methods for detecting *Strongyloides stercoralis* infection was also systematically investigated.

Findings: The electronic search included 166 articles to estimate the total number of strongyloidiasis infections. Data analysis yielded 159,542,655 and 260,710,055 strongyloidiasis infections in the best- and worst-case scenarios, respectively. Based on this estimate, the lowest estimated number of infections resulting from this review is between the fourth highest number of Schistosoma and the fifth highest number of foodborne trematodes, while the highest estimate is between the third highest number of hookworms and the fourth highest number of Schistosoma neglected tropical diseases recorded by GBD in terms of global prevalence cases. On the other hand, 47% of the diagnostic techniques identified in this review fall in the low sensitivity range, 45.2% in the medium sensitivity range, and 7.8% in the high sensitivity range.

Conclusions: The global number of human strongyloidiasis infections estimated in this report was higher than estimates for 13 of the 17 recognized Neglected Tropical Diseases (NTDs). In fact, the number of strongyloidiasis infections would have been higher if highly sensitive diagnostic tools had been used. In this context, it is important to note that only less than 10% of the diagnostic instruments used to diagnose the disease were classified as highly sensitive. Therefore, the current information emphasizes that S. stercoralis should not be neglected. Accordingly, the results of this study reflect a friendly appeal to the responsible agency to recognize human strongyloidiasis infection and add it to the list of other neglected tropical diseases.

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Citation: Heron Gezahegn. Sensitivity of Diagnostic Methods for Detecting *S. Stercoralis* Infection and Comparison of the Total Global Number of Strongyloidiasis Cases with Other Recognized NTDs: A Systematic Review. Journal of Orthopedics and Sports Medicine. 5 (2023): 181-187.

Received: March 29, 2023
Accepted: April 05, 2023
Published: April 07, 2023

Gezahegn H., J Ortho Sports Med 2023
DOI:10.26502/josm.511500098

Keywords: Strongyloidiasis; Neglected; Sensitivity; S. stercoralis; Systematic; Comparison

Abbreviations: GBD: Global burden of disease study; WHO: World Health; NTDs: Neglected Tropical Diseases; MeSH: Medical Subject Headings; PubMed: U.S. National Library of Medicine, National Institute of Health; WHOLIS: World Health Organization Library Information System; ISI: Institute for Scientific Information; URL: Uniform Resource Locator; UNSD: United Nations Statistics Division; PCR: Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunosorbent Assays; K-K: Kato – Katz; KAP: Koga Agar Plate; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Introduction

Strongyloides species are slender, cylindrical nematodes with long esophagus and uterus that are intertwined, and because they resemble a twisted thread, they are also called "nematodes" [1]. The adult female worm is nearly transparent, measures 2.2 to 2.5 mm in length, is 50 µm in diameter, and lives in tunnels between enterocytes in the small intestine [2-4]. Although males exist, they play no role in human infections and are readily excreted from the intestine [1,5].

The signs and symptoms of strongyloidiasis infection may be related to the condition of infection as acute or chronic strongyloidiasis [6,7]. The first sign and symptom of patients with acute strongyloidiasis, if noticed at all, is a localized pruritic, erythematous rash at the skin injection site [8,9]. Patients may then develop tracheal irritation and a dry cough as the larvae migrate upward from the lungs through the trachea [10]. After the larvae are ingested into the gastrointestinal tract, patients may develop diarrhea, constipation, abdominal pain, and anorexia [11]. Chronic strongyloidiasis is generally asymptomatic, but gastrointestinal and cutaneous manifestations are most common in patients with clinical disease [12]. In rare cases, patients with chronic strongyloidiasis have complained of arthritis, cardiac arrhythmias, and signs and symptoms associated with chronic malabsorption, duodenal obstruction, nephrotic syndrome, and recurrent asthma [13-15].

Detection of eggs or larvae in host feces is the usual method for diagnosis of strongyloidiasis [16]. However, serology has the disadvantage of cross-reactivity with other helminthic infections, such as ascariasis and slow seroreversion, making it impossible to distinguish between active and expired infections [18,19]. In addition, serology and polymerase chain reaction are diagnostic procedures requiring great expertise and resources [20,21]. Hyperinfection is more easily diagnosed by the detection of filariform larvae because of the high worm burden [22]. Larvae have also been detected in sputum, bronchoalveolar fluid, cerebrospinal fluid, and other fluids or tissues [23]. Eggs and adult worms are rarely detected. Duodenal fluid or biopsy may also be helpful in diagnosis [24]. Peripheral eosinophilia is common in chronic infections but is not a feature of hyperinfection syndrome [25]. However, the diagnostic tools most commonly used in middle- and low-income countries are not very sensitive [4]. This may be due in part to a lack of attention to the disease and its consequences by key stakeholders such as WHO. The objective of the current systematic review was to estimate the total number of S. stercoralis infections in humans worldwide and to compare the result with prevalence data of other recognized NTDs. In addition, the sensitivity of widely used diagnostic methods to detect the infection was evaluated.

Methodology

Systematic review: search strategy

A systematic review was conducted to collect the raw data for this project. An electronic search was conducted on May 23, 2017, in the PubMed, WHOLIS, and ISI Web of Science databases. The keywords used were "Strongyloides" and "strongyloidiasis" combined with the Boolean operator "OR." For searches in the PubMed and WHOLIS databases, the terms were used as Medical Subject Headings (MeSH). Because the ISI Web of Science database does not provide a thesaurus, a simple keyword search was performed there with the "all databases" option. The review included published literature between January 1, 1990, and May 23, 2017. Literature published before 1990 was excluded because the accessibility of older references was often problematic. The systematic review was conducted strictly in accordance with PRISMA guidelines.

Systematic review: extraction of data

All data finally deemed relevant were extracted using a simple Microsoft Excel template. The extracted information included the bibliographic details of the reference, the study location, the study design, the sampling strategy, the study population, the sample size, the period of data collection, the sex and age of the studied population, the diagnostic techniques used to diagnose Strongyloides spp: infections, and the provided quantitative information on key epidemiological parameters.

Data analysis

The prevalence data obtained from the systematic review was used as a starting point. Afterward, these raw prevalence data were adjusted for diagnostic accuracy, reference population selection, population growth, and age structure. Then, the total number of infections was calculated and compared with estimates for other NTDs. The total globally estimated number of human strongyloidiasis cases was juxtaposed to estimates for other NTDs to explore the relative importance of strongyloidiasis. Furthermore, the sensitivity of the different diagnostic techniques reported to be used for detecting the Strongyloides spp. infections was determined. Correcting the sensitivity of the diagnostic instruments with

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a correction factor and adjusting the population to 2017 in the respective studies were critical for estimating the global number of human strongyloidiasis cases and comparing the disease with other recognized NTDs.

Ethical consideration

Ethical clearance was not needed.

Findings

Databases search result

The initial electronic search yielded a total of 8441 hits. 2022 and 6419 articles were obtained from PubMed and ISI Web of Science using MeSH term and keywords search strategy, respectively. No study was identified from WHOLIS. A total of 2410 articles were found to be duplicated and excluded through EndNote (1678) and Manual (732) duplicate search strategies. From the 6031 articles without duplicates, 545 were considered potentially relevant based on their title and abstract. Nine papers were additionally identified by searching the bibliographies of included full-texts, personal archives, and recommendations from colleagues and collaborators.

A total of 554 articles were checked for full-text accessibility through EndNote full-text search, URL search, google search, Swiss Tropical and Public Health Institute, and University of Basel library sources. Approximately 97% (n=536) of the total articles checked for full-text accessibility were found, retrieved, and finally assessed based on the inclusion criteria.

After in-depth reading of the entire full-texts available, 166 articles were finally included, containing relevant data for the analysis. The following flow chart diagram illustrates the search strategy and methodology followed in the literature review (Figure 1).

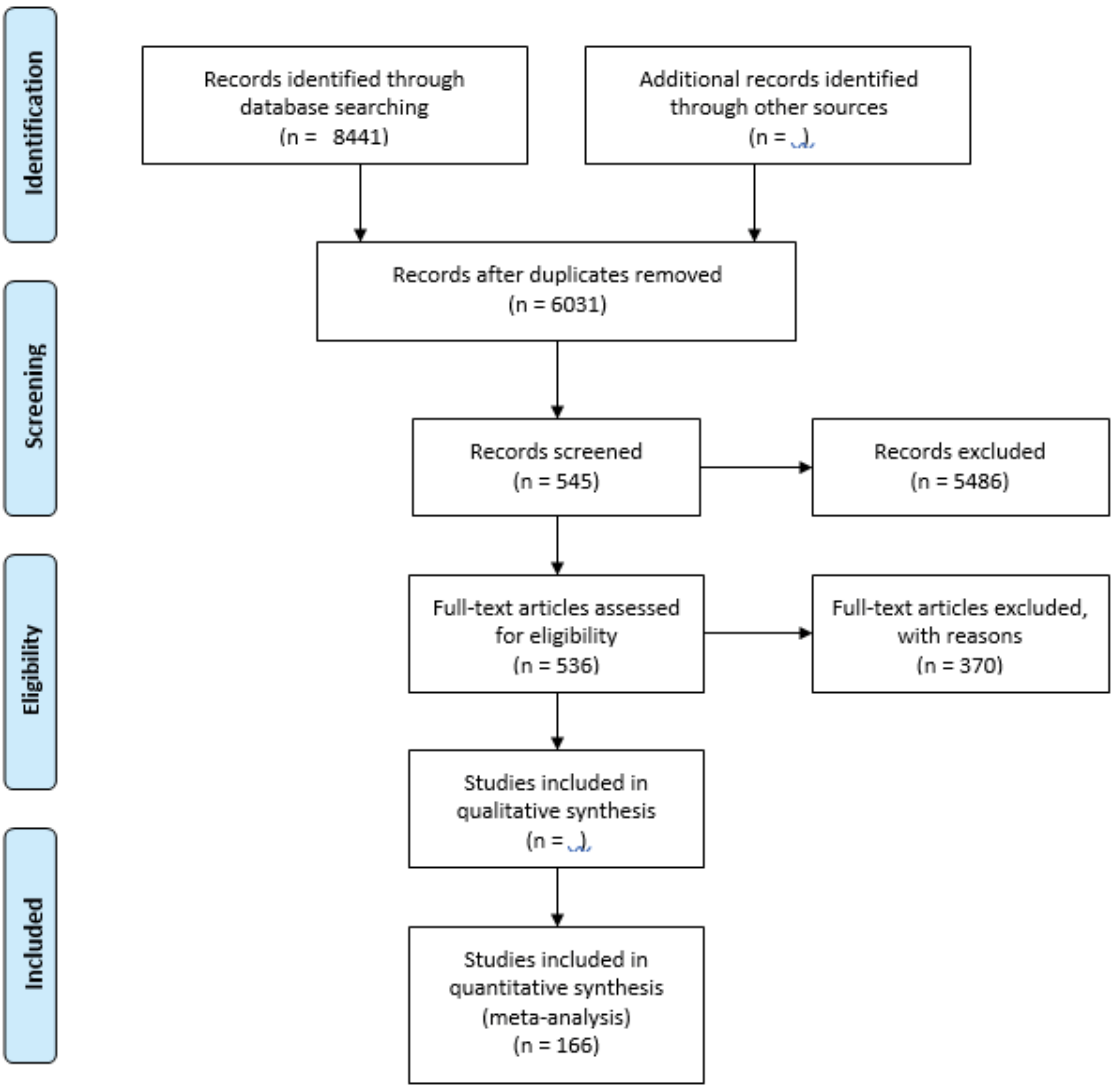

Figure 1: PRISMA flow diagram illustrating the systematic review process.

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Characteristics in terms of the kind of diagnostic tools used

Out of the 166 articles reviewed in this study, 75.3% (n=125) used a single diagnostic tool, whereas 19.9% (n=33) and 4.8% (n=8) used two and three diagnostic tools, respectively. Twenty-eight different types and modified diagnostic tools were reported. Formol ether concentration techniques FECT was used 53 (22.1%) times, which made it the most utilized diagnostic tool, followed by 39 (16.3%), 38 (15.8%), 26 (10.8%), 20 (8.3%), 11 (4.6%), 5 (2.1%), direct microscopic, kato – katz K-K, Bearmann, koga agar plate KAP, polymerase chain reaction PCR, enzyme-linked immunosorbent assay ELISA diagnostic methods respectively. Other diagnostic techniques were used 48 (20%) times. According to the sensitivity classification considered, 78 (47%) studies used diagnostic methods with low sensitivity, 75 (45.2%) with moderate sensitivity, and 13 (7.8%) with high sensitivity.

Total number of infections globally

The total number of the infected population globally was calculated based on the methodology developed and for a best and worst-case scenario. Accordingly, a minimum and maximum number of infected was produced. Based on the reviewed literature and the respective assumptions and methodology, in the best scenario, 159,542,655 people were estimated to be infected with S. stercoralis, and in the worst scenario, 260,710,055 people globally.

Comparison of the global estimate of strongyloidiasis cases with other NTDs

The estimated number of human strongyloidiasis cases in both scenarios revealed that *Strongyloides stercoralis* infection affects much more people than most of the recognized neglected diseases globally (Figure 2). Only the estimates for Ascariasis, trichuriasis, and hookworm infection are estimated to be higher than the worst-case scenario

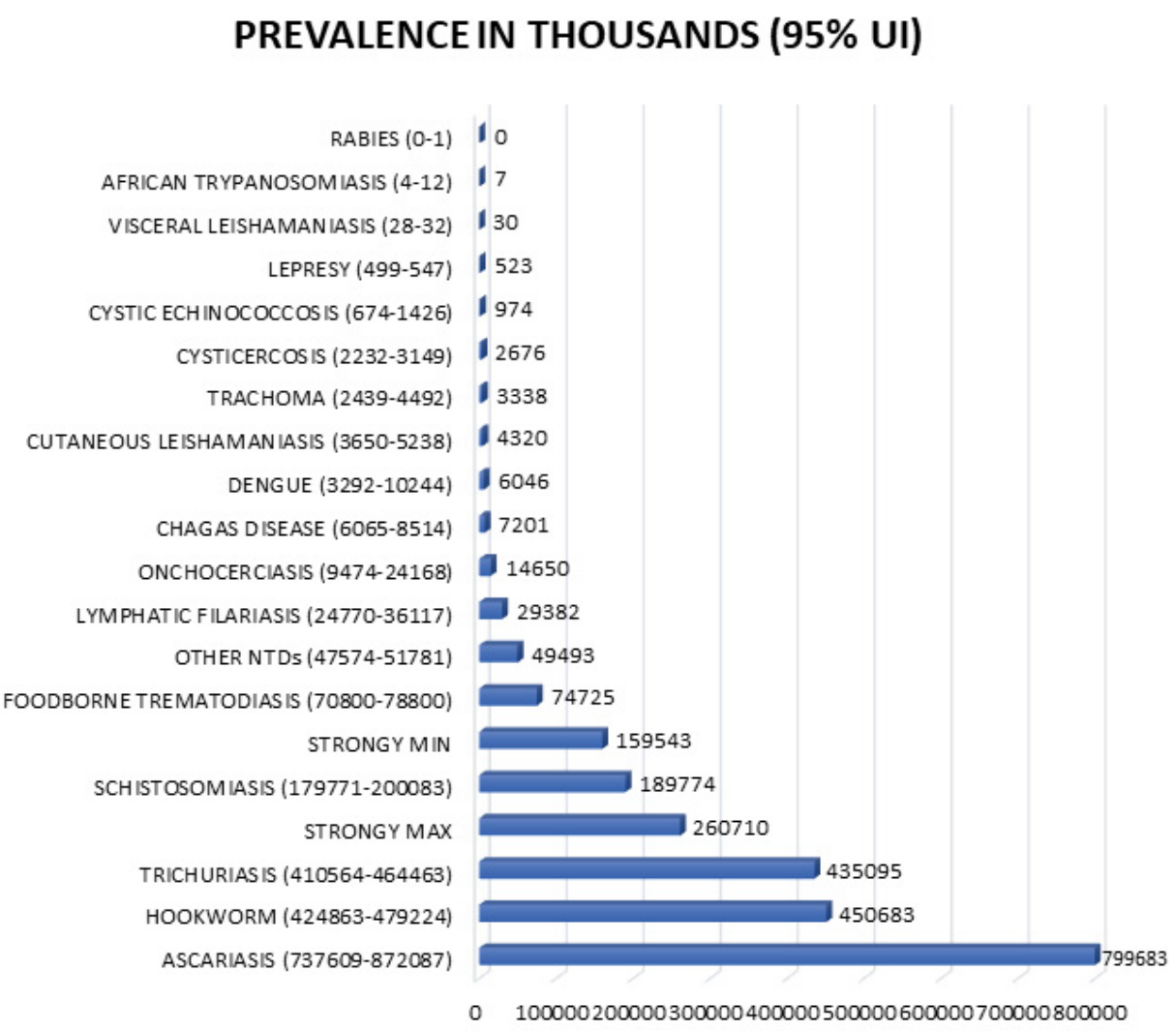

Figure 2: Describes comparison of strongyloidiasis prevalence cases with other Neglected Tropical Diseases recognized by GBD 2016.

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DOI:10.26502/josm.511500098

estimates for strongyloidiasis. When considering the best-case scenario for human strongyloidiasis, schistosomiasis is the only additional NTD with a higher number of infected.

Discussion

Strongyloidiasis is a harmful gastrointestinal disease caused mainly by infection with *Strongyloides stercoralis*. *Strongyloides stercoralis* is soil-transmitted helminthiasis that is common worldwide [26]. The infection affects a significant number of populations living in extreme poverty [27]. However, at the present time, *Strongyloides stercoralis* infection is not recognized by WHO and is included in the category of NTDs [28]. On the contrary, the estimated global total number of Strongyloidiasis cases (min = 159,542,655 and max = 260,710,055) in both scenarios indicates that more people are affected by *Strongyloides stercoralis* infections than by many of the 17 recognized neglected tropical diseases. These data support the argument that Strongyloidiasis is truly undermined, considering that it is not yet recognized like other NTDs. According to the Global Burden of Disease Study (GBD) 2016, ascariasis is the leading helminthic disease among the 17 neglected diseases recognized by GBD, with a prevalence of 799,683,000 cases, followed by trichuriasis, hookworm, Schistosoma, and foodborne trematode infections with 435,095,000; 450,683,000; 189,774,000; and 74,725,000 prevalence cases, respectively. Therefore, the minimum estimated number of infections resulting from this review is between the fourth-ranked Schistosoma and fifth-ranked foodborne trematode, while the maximum estimate is between the third-ranked hookworm and fourth-ranked Schistosoma, which are recorded by the GBD as neglected tropical diseases in terms of the number of prevalent cases worldwide [28].

On the other hand, identifying larvae by microscopic stool examination is usually considered a definitive diagnosis of strongyloidiasis [28-30]. However, low parasite load and irregular larvae output in the majority of subclinical infections makes it difficult [12]. As a result, the true prevalence of S. stercoralis infection is often underestimated [1]. In order to overcome the situation of underestimation of the disease, advanced diagnostic tools with high sensitivity should be applied whenever possible [29]. In this systematic review, a number of diagnostic tools were identified. The diagnostic tools used were classified into three sensitivity classes based on information gathered by another systematic review [29]. Of the diagnostic techniques identified in this review, 43.7% fall in the low, 44.9% in the medium, and 7.8% in the high sensitivity divisions. Ether concentration technique and direct microscopy were the majority, followed by Kato – Katz and agar plate culture methods. Only a few serological and molecular diagnostic tools were used. Serological tests have demonstrated high sensitivity though the extent of specificity remains a concern in other diagnostic techniques in diagnosing strongyloidiasis. The issue of specificity in the diagnosis of strongyloidiasis can be overcome by combining different diagnostic methods [26]. In the presented estimation of the total number of infected, diagnostic tools have employed a sensitivity correction factor to address the problem of low sensitivity [29].

Conclusion

Strongyloidiasis is a major health problem in many parts of the world. Nevertheless, little attention has been paid to the disease. The fact that the disease is not yet recognized as a neglected tropical disease and the low sensitivity of the main diagnostic tools used to detect the disease can certainly support this argument. The results of this study suggest that *Strongyloides stercoralis* infection should no longer be overlooked. In addition, highly sensitive diagnostic tools must be used to diagnose the disease and determine the true burden of the disease worldwide. Therefore, the disease should be recognized by the World Health Organization as a neglected tropical disease and included in Category A of the list of neglected tropical diseases to better facilitate access to highly sensitive diagnostic tools, provide more funding for research, and expand treatment options globally..

Acknowledgement

I want to thank Dr. Thomas Fuest and Prof. Peter Odermatt for their excellent supervision throughout the research work. Without their sound scientific support, this work would not have been accomplished. My thanks also go to Dr. Dora Buonfrate for her contribution during the data extraction phase of the project.

Conflict of Interest

The author declares no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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