STRONGYLOIDES (D ABRAHAM, SECTION EDITOR)

The Epidemiology of Human Strongyloidiasis

Rubén O. Cimino · Alejandro Krolewiecki

Abstract An epidemiologic approach for the understanding of the public health relevance of *Strongyloides stercoralis* is currently much needed, due to the renewed interest in the control of soil-transmitted helminthiasis (STH). Despite this fact, the biologic difference of *S. stercoralis* compared to the other STH in terms of life cycle, diagnostic approach and therapeutic options leaves this nematode under uncertainties that hamper the development of control strategies. However, evidence regarding distribution and prevalence allows for the identification of its global distribution, with lack of adequate water and sanitation supplies as the most significant risk factors. The clinical aspects of this infection in immunocompromised populations also highlight its potentially severe morbidity in groups that are at higher risk for complications during infection. The availability of more accurate diagnostic tools appears as a key element for the performance of more reliable surveys, case control studies and even monitoring for the emergence of drug resistance.

R. O. Cimino · A. Krolewiecki (✉)
Instituto de Investigaciones de Enfermedades Tropicales/ CONICET, Universidad Nacional de Salta, Salta, Argentina
e-mail: alekrol@hotmail.com

R. O. Cimino
e-mail: rubencimino@gmail.com

R. O. Cimino · A. Krolewiecki
Cátedra de Química Biológica, Facultad de Ciencias Naturales, Universidad Nacional de Salta, Salta, Argentina

A. Krolewiecki
Ministerio de Salud de la Nación, Buenos Aires, República Argentina

Introduction

Understanding epidemiology as one of the main sources of analytic information that guides rational public health decisions, and that "evidence-based public health" is supported by a solid knowledge base of disease frequency and distribution of the determinants and consequences of disease, and of the safety, efficacy and effectiveness of interventions [1], it is of fundamental practical importance to identify the epidemiologic aspects of the different diseases in order to design interventions with a measurable public health impact. The case of *neglected tropical diseases* (NTDs) and the launching of new coalitions with funds and drug donations that allow the framing of ambitious control, and in some cases, eliminations, is an example of the need for clear and up-to-date information of affected people and all the determinants that need to be considered in the design of these strategies [2, 3]. As programs start their activities, data on the epidemiologic aspects of NTDs are required to target treatment to areas and communities at greatest need and to estimate drug and resource requirements. In addition, as interventions are scaled up, governments and donors require clear information on the impact of these control efforts.

Strongyloides stercoralis is probably among the most significant examples of the need to set a clear agenda of knowledge acquisition in order to brake the vicious circle where the lack of adequate diagnostic and therapeutic tools causes its exclusion from the goals set for the other soil transmitted helminthes (STH). This results in its omission from the list of priorities, despite the lack of knowledge on its clinical, sanitary and epidemiologic implications [4, 5].

The Parasite and the Infection

The parasitic nematodes belonging to the *Strongyloides* group are members of the Rhabditida family of free-living

nematodes. Among the different *Strongyloides* species that have been identified, *S. stercoralis* stands out as the species with the widest distribution and most significant importance as a human pathogen. Originally described in 1876 among French troops in current Vietnam by Louis Normand while evaluating stools from soldiers with diarrhea, it was later that same year that in an autopsy performed by Normand, the adult forms were first described; though he did not realize that were different stages of the same parasite [6, 7]. *Strongyloides fullerborni*, restricted to some parts of Africa and Papua New Guinea, is a parasite of Old World primates that can also infect humans [7, 8].

The distinctively complex life cycle of *S. stercoralis*, compared to other STH of medical importance, makes this species a particularly interesting subject for study and investigation, with the importance placed in the proper identification of features that are shared with the other STH and those features that are both different and of clinical and epidemiologic significance in terms of disease control [5, 9–11]. This alternative switch between parasitic and free-living modes of existence and the rapid evolution into infective forms that allows for reinfection are the most significant, but not the only features that define the biology, the clinical aspects and also the epidemiology of *S. stercoralis* [12].

Strongyloidiasis, the disease caused by infections with *S. stercoralis*, identifies more of an etiologic origin than a particular syndrome, since the infection with this helminth could range from asymptomatic states to diarrheal disease and the hyperinfection state in the extremes of aggressiveness that makes of this infection a life-threatening condition in immune deficient individuals [13–15].

Control strategies against STH and other NTDs, which for the most part have ignored this parasite, require an adequate body of evidence on the epidemiology of this infection and its different clinical presentations; this includes, as in any public health issue, evidence-based and updated data. This package is currently missing and therefore hampering the implementation of control efforts [5].

Transmission

The most salient aspect of a review of the literature with regard to the epidemiologic characteristics of *S. stercoralis*, unfortunately, is the scarcity of information regarding the distribution, prevalence, and burden of disease. The roots of this deficiency are, for the most part, the same that are shared by all the diseases that despite their biologic and clinical differences belong to the group of NTDs; these are the historic lack of investments and efforts for control by the governments and industry, and the uniform link to poverty and inequality suffered by those affected by these diseases [16].

The life cycle of *S. stercoralis* defines its distribution, as explained above, through the elimination of larvae and not eggs. It also defines a critical transmission characteristic, which is the auto-infective stage, where the filariform larval stage is reached before leaving the human environment, whether intraluminal in the gut or cutaneous in the perianal region, allowing autoinfection and the perpetuation of infection to its chronic stages for periods of as long as 75 years [17]. Currently, with a renewed interest on the use of transmission dynamics modeling as a source of information for STH control strategies, the classification between microparasites and macroparasites in the classic works by Anderson & May for the study of population dynamics [18] requires a particularly cautious approach in the case of *S. stercoralis*, which unlike the other STH and despite having the characteristics of a macroparasite for the most part, also features a distinctive ability for direct multiplication at large scale within the host. This characteristic also has therapeutic implications in terms of the requirement for curative treatments rather than the much-accepted regimens against STH, which aim for lowering the worm burden.

The approach to the identification of the determinants for the transmission of *S. stercoralis* to the human host can also be inferred from studies carried out on human volunteers, before the potential lethality of this parasite was known, which showed the ability of the filariform larvae to penetrate the human skin [19•]. As per the risk of infection through drinking water, the inability of the larvae to swim, an issue that can be verified in the Baermann diagnostic method, leaves the larvae to settle in the bottom of the water source. This issue suggests that WASH (water, sanitation and hygiene) efforts should impact the prevalence and distribution of *Strongyloides* through the sanitation component to a higher degree than the water component. Sexual transmission and inter-human transmission through close contact, despite being feasible, do not pose significant transmission routes [7, 20].

S. stercoralis infections are unusual in countries where fecal contamination of soil is rare and the exposure to third-stage larvae by the general population is not present due to sanitation improvements. A recent study in a cohort of children aged 8–18 years old from rural villages of Cambodia showed that children who reported having shoes and defecating in toilets were less likely to be infected with *S. stercoralis* than those who did not possess shoes and used unimproved latrines [21•].

Diagnosis

S. stercoralis has some particularities that make it harder to diagnose, compared to other STH; central to this situation are the diagnostic difficulties posed by this parasite, which is systematically missed by the diagnostic methods recommended by the World Health Organization for the diagnosis of STH, like Kato Katz and secondarily McMaster, since these

methods are based on the detection of eggs, a stage that is very rarely, if ever, found aside from in hyperinfective states of infection [5]. This issue, added to the requirement of multiple serial samples in order to properly call an individual non-infected, renders most surveys useless to estimate prevalence and distribution, unless alternative methods specific for the detection of larvae in stools are performed. These limitations in diagnosis cancel the possibilities of determining the risk factors and infection determinants through case control studies, since it is not possible to rule out infections in individuals from endemic areas with stool analyses that are negative for *S. stercoralis*.

In contrast to other STH such as *Necator americanus*, *Ancylostoma duodenale*, *Trichuris trichura* and *Ascaris lumbricoides,* the diagnosis of strongyloidiasis is primarily based on the detection of the filariform larvae (L3) by microscopic examinations of stool samples. Nowadays, the standard parasitological diagnostic methods for detecting *S. stercoralis* infections are Baermann and Agar plate culture methods, or, if possible, a combination of these methods [22, 23]. These are techniques with higher sensitivity, but are not considered as "Gold Standard" for the diagnosis of the strongyloidiasis. Direct fecal smear examination, formol-ether concentration and Harada-Mori are other parasitologic methods that are available, all with sub-optimal sensitivity, which is lowered further when performed on a single specimen per patient due to the fluctuating nature of larva elimination in stool [24–26].

Several immunological tests, such as ELISA, western blot, immunofluorescence and luciferase immunoprecipitation system (LIPS), have also been described for the diagnosis of strongyloidiasis [27–29]. These assays show variable sensitivity and specificity, depending on the antigen used (crude extract or recombinant antigens) and population tested [27, 30]. Currently, there is a need to improve the tools available for the diagnosis of this parasite, and for this, it will be very important to incorporate new technologies (i.e., LIPS or multiplex assays), as well as the search for new recombinant antigens (i.e., phage display technology) [29, 31, 32]. In order to be useful for the understanding of the epidemiology of strongyloidiasis and its clinical circumstances, there is a need for a better understanding of the accuracy and dynamics of antibody decay in response to curative antiparasitary regimens [27]. Polymerase chain reaction (PCR) has been developed and used for the detection of DNA from *Strongyloides* and other helminths in fecal samples. Recently, the evaluation of conventional PCR and real-time PCR has proved to be a sensitive and specific method for the diagnosis of *S. stercoralis* [33–36].

Epidemiological Determinants

Strongyloidiasis caused by *S. stercoralis* has been estimated to affect 30–100 million people worldwide [4, 22]. These numbers are, however, just estimates that need better evidence and updates. This threadworm intestinal parasite that infects dogs, cats and primates including humans is endemic in tropical and subtropical regions with poor sanitation conditions and where climatic conditions are warm and humid, such as Central and South America, sub-Saharan Africa, and South and Southeast Asia [37•].

In a recent study aimed at the description of the global distribution of strongyloidiasis through a literature search of surveys and reports, including hospital records, on all types of populations from around the world, the conclusions suggest that *S. stercoralis* infections affect between 10 % and 40 % of the population in many tropical and subtropical countries. This information is taken mainly from community-based studies. Brazil and Thailand provided the greatest amount of epidemiological information from community-based studies, while Australia and United States were the main sources of information from hospital-based reports and immigrant and refugees surveys [37•]. The application of methods with poor sensitivity is a problem that leads to underestimation of the prevalence; of 194 community surveys, only 9 % included techniques with relatively high sensitivity to detect *S. stercoralis* [23, 37•]. In Table 1, we summarize the prevalence in different endemic countries, understanding that these studies do not represent the overall prevalence in the whole country, but rather in communities where the socio-economic conditions support the persistence and proliferation of this parasite. In each of these studies, the diagnostic method used was Baermann and/or Agar plate.

The reports with the highest prevalence are from Argentina and Cambodia (>40 %). In Argentina, data about the prevalence of *S. stercoralis* is scarce and limited to few areas, mainly in the northwest, but significant for the presence of surveys with prevalences of over 80 % in school children and

Table 1 Reports of prevalence of endemic countries in tropical and subtropical regions

Country	Province	Prevalence[1] (%)	Seroprevalence (%)	Reference
Argentina	Salta	50.5	-	[54]
Argentina	Misiones	29.0	-	[39]
Australia	Doomadgee QueenIsland	27.5	-	[41]
Cambodia	Kandal	24.8	-	[55]
Cambodia	PreahVihear	24.3	-	[56]
Cambodia	Takeo	21.0	-	[57]
Cambodia	PreahVihear	44.7	-	[58]
China	Yunnan	16.3	-	[59]
Peru	Tambopata	22.0	-	[60]
Peru	Iquito	8.7	72[2]	[61]

[1] Determined using Baermann and/or Agar culture methods
[2] Crude antigen ELISA

community-based surveys including children and adults [30, 38]. In northern Argentina, particularly in the region of the Yungas rainforest and the Chaco region, different reports indicate prevalence rates of over 20 % [39]. In a recent study in Salta (unpublished data), examination of stool samples including several parasitological methods (concentration-sedimentation, Agar plate, Harada-Mori and Baermann) showed that 16 % of the populations were infected, while an enzyme-linked immunosorbent assay for detecting *S. stercoralis* antibody (NIE-ELISA) revealed a prevalence of 31 % in the same population. These surveys, performed mainly by academic centers with activities in that region, probably represent a marker of similar levels of infection prevalence across a wider territory, including the whole Chaco region where ecological and socio-economic conditions allow the transmission of *S. stercoralis* and other STH.

Developed countries like Japan, Australia, Western Europe and United States currently have prevalence levels of *S. stercoralis* that are low and mostly restricted to immigrants from endemic countries [37•, 40]. In Japan, it is only endemic in the Okinawa island area, where it has for a long time been identified at high levels in association with HTLV-1 infections; there, the prevalence in community surveys was 18.7 % and 13.6 % in hospital investigations. The cases reported are mostly among the older population [37•]. In Australia, data about the prevalence of *S. stecoralis* infection derives from studies on refugees and immigrants, with prevalence estimates of 25 %, and also from aboriginal communities in the northern territories [37•, 41, 42]. In the United States, the prevalence estimate of the infection rates among refugees and immigrants, mainly from Southeast Asia, was found to be up to 40 % [37•]; in Canada, a similar finding was obtained in a seroepidemiology study of refugees from Southeast Asia, with Cambodians being distinctively affected [43].

The current strategy of the World Health Organization (WHO) for the control of the morbidity caused by STH has preventive chemotherapy as the mainstay [44]; however, neither of the drugs used for this effort, albendazole and mebendazole, has significant activity against *S. stercoralis* at single doses. Adding ivermectin would be the complement to the benzimidazol drugs if activity against *S. stercoralis* for a wider anti-STH regimen was to be attained. The mass distribution of ivermectin had its benefits, but re-infection is possible; in a 2-year follow-up in children treated for *S. stercoralis* infection, 31 % were re-infected, while 20 % of the healthy children were infected during follow-up [21•].

Risk Groups

The epidemiology of hyperinfection syndromes in strongyloidiasis, which occur due to the amplification of the auto-infective path, is mostly secondary to the presence of immunosuppressive conditions due to drugs or health conditions, with the added effect of corticosteroids in the enhanced fecundity of the parthenogenetic adult females of *S. stercoralis* in the gastrointestinal tract [14]. These groups of health conditions with impaired immune responses include lymphomas, alcoholism, HTLV-1 infections and corticosteroids as the most widely used among a longer list of immunosuppressive drugs. It should be noted, however, that these conditions have not been linked to an increased risk of infection, but rather to the development of severe clinical forms of the disease [37•]. HIV infection, despite initial impressions, does not predispose to hyperinfection, and strongyloidiasis is therefore not in the list of opportunistic infections related to this retroviral infection [37•]. Among the impoverished populations of the world, where the sanitary conditions favor the exposure to all STH, malnutrition among children is the most common condition affecting adequate immune responses, and therefore is a risk factor most frequently seen related to severe strongyloidiasis. Malnutrition is also probably related to the occurrence of these clinical forms among alcoholics, since despite studies demonstrating a higher prevalence of *S. stercoralis* in alcoholics than controls, animal studies have shown that chronic alcohol consumption does not affect specific immune responses against *S. stercoralis* in mice kept with diets that were adequate regarding caloric and micronutrient components [45, 46].

Strongyloides fuelleborni

Among the other species of *Strongyloides*, *S. fuelleborni* is the only other potentially significant human pathogen; this species infects principally non-human primates. The infection has been found in humans in Africa and Papua New Guinea [4]. In a recent study in wild Japanese macaques (*Macaca fuscata*), *S. fuelleborni* was detected among other helminths (*Trichuris trichiura* and *Oesophagostoma maculeatum*) [47]. In mountain gorillas (*Gorilla beringei*) from Bwindi Impenetrable National Park (BINP), Uganda, the presence of *S. fuelleborni* was also detected [48]. This parasitic infection is zoonotic and rare in humans, with the first cases of infection with *S. fuelleborni* reported in Zambia [8]. In regions where there is frequent contact between humans and non-human primates, this zoonotic nematode poses a potential health issue to local people.

Antihelmintic Resistance in *S. stercoralis*

The emergence of antihelmintic drug resistance is a major problem for animal and human health. To date, there is no evidence of anthelmintic resistance in humans among STH,

but this absence of evidence should be interpreted with caution as large-scale deworming programs are deployed, coverage is increased and a larger group of people receives repeated cycles of drugs at not uniformly curative regimens [49•, 50]. The case for *S. stercoralis* falls within this situation, and there is no information on resistance that might alter response to therapy and the epidemiologic aspects related to the response to intervention programs.

Current guidelines for the control of STH recommend mass drug administration (MDA) once a year when STH prevalence is ≥20 % but less than 50 %, and twice a year when the prevalence is >50 % [49•, 51]. The benzimidazole drugs, albendazole and mebendazole, are commonly used for MDA, while ivermectin is recommended for strongyloidiasis, lymphatic filariasis and onchocerciasis [5, 52]; however, its use in MDA programs is currently limited to onchocerciasis, with other indications not covered by drug donations therefore used only for individual case management [53]. The MDA programs reduce the incidence and intensity of infections; however, this strategy could trigger the development of anthelmintic resistance [49•].

Many studies have demonstrated that the frequent use of anthelmintic drugs (up to eight times per year) in veterinary nematodes has led to the development of resistance. In humans, the frequency of treatment is low (once or twice per year) and the coverage is far from the 100 % achieved in veterinary nematodes; therefore, the selection pressure is less than for parasites in animals and development of anthelmintic resistance in STH will be slow and less likely to occur [49•].

Conclusion

The epidemiology of *S. stercoralis* has distinctive features that require careful consideration for the management of affected communities and individuals. The lack of accurate diagnostic and monitoring tools is a significant obstacle for a more complete understanding of its dynamics, risk factors and response to interventions. These issues should trigger renewed efforts and creativity in epidemiologic research in order to find ways to tackle this NTD.

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