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SYSTEMATIC REVIEW

Prevalence of Strongyloidiasis in Southeast Asia: A Systematic Review

Mohd Shafik Abd Majid[1], Fadzrul Hafiz Johani[1], Wan Rosmawati Wan Ismail[1], Diyana Mohd Mokhtar[1], Qistina Mohd Ghazali[1], Norfazilah Ahmad[1], Mohammad Saffree Jeffree[2] and Mohd Rohaizat Hassan[1*]

[1]Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia.
[2]Department of Community and Family Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu Sabah Malaysia.

**For reprint and all correspondence: Mohd Rohaizat Hasssan, Department of Community Health, Faculty of Medicine, UKM Medical Centre.*
Email: rohaizat_hassan@yahoo.com

ABSTRACT

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Introduction *Strongyloides stercoralis* is an intestinal helminth that infects humans through contact with soil containing the larvae.

Methods A systematic search was performed for relevant titles, abstract and keywords in database from Cochrane Library, PLOS One, PubMed and several other sources in October 2017 based on PICO strategy. Out of 511 papers that were evaluated for possible inclusion, final assessment for eligibility has yielded a total of 17 papers to be included which were found suitable for analysis covering period from 2012 till 2016.

Results A major challenge of giving an overview of prevalence data for *S. stercoralis* lies in the low sensitivity of diagnostic method used which resulted in very low prevalence in certain countries. Cambodia and Laos presented with high prevalence ranging from 17.4% to 45.9% by using high sensitivity of diagnostic methods. The current prevalence situation of *S. stercoralis* in Southeast Asia still have wide gaps remains due to several reasons.

Conclusions The information we have today only scratches the surface which cannot truly reflect the true burden of *S. stercoralis* in Southeast Asia The main risk factor is personal hygiene practices especially amongst males.

Keywords Southeast Asia - prevalence - review - *Strongyloides stercoralis*.

INTRODUCTION

Strongyloides stercoralis is an intestinal helminth that infects humans through contact with soil containing the larvae. Between 30 and 100 million people are infected worldwide. The prevalence *S. stercoralis* infection ranges between 10% to 40% in tropical and subtropical regions of the world.[1] Infection usually results in asymptomatic chronic disease of the gut, which can remain undetected for decades. However, in patients which is immunocompromised such as receiving long-term corticosteroid therapy, hyper-infection can occur, resulting in high mortality rates (up to 87%).[2]

The life cycle of *S. stercoralis* basically comprised of 2 parts: a free-living cycle outside of the host as rhabditiform larvae and a parasitic life cycle as infective filariform larvae. The free-living cycle of the *S. stercoralis* starts with the deposition of rhabditiform larvae into the soil from infective source. The rhabditiform larvae will develop into the adult male or female worm instead of transforming into the infective filariform larva. Both male and female worm will undergo fertilization and produce rhabditiform larvae and will continue in the free-living cycle. In some cases, it may directly develop into the infective filariform larvae which able to penetrate human skin and thus initiating the infective/parasitic life cycle.[3] Filariform larvae that penetrate the human skin need to reach the intestines to continue the cycle. The filariform larvae penetrate the skin will enter to the blood stream via lymphatic system. In the lungs, the filariform larvae will break through the alveoli and enter the respiratory tract, some may either be coughed out or be swallowed into the alimentary tract and move towards the intestines. In the intestines, the filariform larvae attach themselves to the intestinal epithelial wall and develop to the adult forms. The female worm may undergo self-fertilization (parthenogenesis) to release eggs into the lumen of the intestine which immediately hatch out as rhabditiform larvae. The rhabditiform larvae are passed out through faeces to continue the free-living cycle in the environment or may immediately transform into a filariform larva and penetrate intestinal mucosa/perineal skin resulting in an internal auto-infection. Some of the rhabditiform larvae may move towards the perianal regions and develop into filariform larva and penetrate the skin to cause external autoinfection.[1]

S. stercoralis infection are mostly asymptomatic in human with intact immune system. However, some signs and symptoms may develop but are non-specific which include gastrointestinal (e.g., abdominal pain, nausea, diarrhea, weight loss), respiratory (e.g., cough (productive and non-productive), hemoptysis, cutaneous (e.g., urticaria) and general malaise.[4] Hyper-infective *S. stercoralis* infection may present as pneumonia, meningitis, septicaemia, paralytic ileus, pulmonary haemorrhage, or other bacterial infections in acute-infection state.[5] Most of the patients with *S. stercoralis* infection do not show distinctive clinical features which makes the diagnosis rather difficult. The risk factors for soil-transmitted helminth infection commonly occurred in rural areas, low-socioeconomic status, poor sanitation, poor availability of clean water and poor personal hygiene.[6]

The laboratory and imaging findings often turn out to be non-specific which requires a high degree of suspicion to diagnose. For mass screening of *S. stercoralis* in the population especially for epidemiological survey, direct stool examination in saline and Lugol's iodine stain were used. However, one sample of stool for direct stool examination is always inadequate, as evidenced by many reports of *S. stercoralis* infection have negative result of stool screening examination. The gold standard to diagnose *S. stercoralis* stated by US CDC is by doing serial stool examination which up to 7 times to get 100% of sensitivity.[7] There are some combination methods to improved sensitivity of stool examination which is Kato-Katz, Baermann and Koga Agar plate culture. Some other method can be used for diagnosis is by serologically which are more preferred due to high sensitivity and ease to conduct. Repeated stool sample examinations are essential to achieve the correct diagnosis, and a negative result does not always indicate the absence of the infection.[4]

Once diagnosed, *S. stercoralis* infection can be eradicated with specific anthelmintic medication; ivermectin is the drug of choice. The recommended treatment for *S. stercoralis* infection has changed with the development of more effective anthelmintic drugs. Thiabendazole was the first moderately effective anthelmintic introduced in the mid-1970s. Albendazole, a benzimidazole like thiabendazole, was recommended as the treatment of choice for *S. stercoralis* infection about the mid-1990s. It was replaced by ivermectin as the first line recommended anthelmintic in the early 2000s.[1] The objective of this systematic review is to determine prevalence of *S. stercoralis* infection in South East Asia region and to identify the risk factors associated with the infection.

METHODS

Search Protocol

This systematic review was based on the PRISMA statement, a tool to summarize accurate, reliable, quality evidence by way of transparent reporting. The search was performed on various databases available in institutional subscription: Cochrane library, PubMed and PLOS One. The search strategy follows the PICO strategy. Key search terms included Strongyloides (Strongyl, Helminth*, Nematod*) and Epidemiology (epidemiol, status, risk factors, prevalen*). The search was restricted to study conducted in South East Asia for the past five years, 2012 to 2016. Literature that is written in English language will be selected. The search was done on 24th October 2017. Unpublished literatures were not searched.

Selection
Articles were reviewed in two stages by two pairs of reviewers. In the first stage, two pairs of reviewers will independently screen part of the titles and abstracts for inclusion of all the potential studies that had been identified as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. As for the second stage, the full-text study reports/publication will be retrieved and another two pairs of reviewers will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. Any disagreement will be solved by the third reviewer.

Data extraction
Data extraction was conducted for the studies which had been accepted after review of the full article by using a standardized form included type of article, study design, country involved, target population, sampling method, sample size, diagnostic method, prevalence and significant risk factor.

Flow of included papers
The electronic search in PLOS One, PubMed and other several additional sources allowed identification of 511 papers that were evaluated for possible inclusion. A total of 56 potential papers related to our review were detected after screening through all the abstracts. Based on the full text of these papers, the assessment for eligibility has yielded a total of 17 papers to be included. A total of 39 papers were rejected due to a couple of reasons. First, a total of 24 papers were rejected because of reporting on *S. stercoralis* other than Southeast Asia and second a total of 15 papers were rejected because of the study is related to *S. stercoralis* however, did not report on the prevalence of infection. (Figure 1).

Study characteristics
We found data about the following countries: Cambodia (7), Laos (2), Malaysia (4), Thailand (4), Vietnam (1) and mixed Southeast Asian countries (1). All studies are original article which mostly are cross-sectional study design and several of other study design.

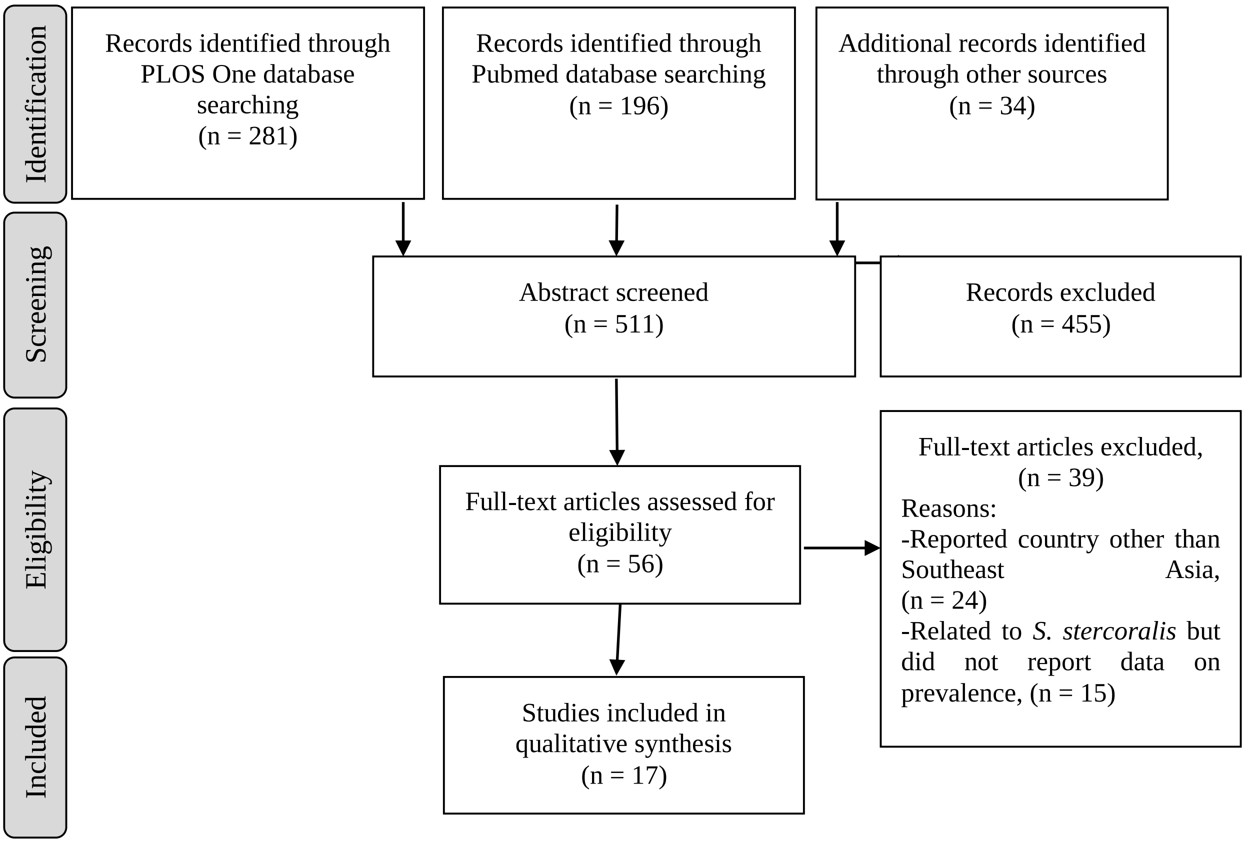

Figure 1 PRISMA flow chart

Diagnostic Methods

Most study are designed to detect intestinal parasite infection, half of it is specifically designed to find prevalence of *S. stercoralis* and some several other study designs have findings on prevalence as part of their study. Most of the diagnostic method used was direct visualization of stool examination which is gold standard. However, most of the studies take one stool sample for direct visualization with additional technique to enhance the detection or sensitivity towards *S. stercoralis* such as Keto Katz, KAP Culture and Baermann method. Only 4 studies use direct stool smear without additional technique or repeated sample which is quite insensitive method for diagnosis. Seven studies were using serological test for the detection of infection such as PCR and ELISA; 4 studies and 5 studies respectively. 4 studies using both direct stool smear and serological test for better yield.

Strongyloidiasis in the different Southeast Asia countries

Among 19 articles selected, seven were conducted in Cambodia.[8-14] All studies were cross-sectional study design with wide range of target population. In Cambodia the lowest proportion of infected individuals was found among children in four schools in semi-rural area Province of Kandal south of Phnom Penh in Cambodia.[14] The study found 17.4% of 218 asymptomatic children were infected with *S. stercoralis* by using real-time PCR method. On the other hand, a cross sectional study was conducted among women of child bearing age between 15 to 39 years across Cambodia shows seroprevalence of 45.9% by using serological test.[8] The prevalence of *S. stercoralis* infection among rural village in northern Cambodia shows 44.7% with by using direct microscopy as diagnostic method.[9]

In Thailand there were 3 studies with two cross-sectional and one case-control with the range of prevalence of 1.44% up to 9.5%.[15-17] In Malaysia based on one retrospective cohort and three cross-sectional studies showed prevalence of *S. stercoralis* infection range between 0.08% to 11% seroprevalence across different target population.[16-19] Meanwhile in Laos, based on two cross-sectional articles among population age 2 years and more showed prevalence of 41%.[20,21] One retrospective study in Vietnam that almost 43,000 of blood samples in Medic Medical Center Laboratory, Ho Chi Minh were test serologically for *S. stercoralis* infections showed seroprevalence of 7.4%. [22] Significant risk factors associated with *S. stercoralis* infections are summarized in Table 1.

Table 1 Prevalence and significant factors associated with Strongyloides Stercoralis infection in South East Asia

No	Title	Author	Country	Study Design	Target population	Sampling method	Sample size	Diagnostic method	Prevalence (%)	Significant factor
1	Integration of Multiplex Bead Assays for Parasitic Diseases into a National, Population-Based Serosurvey of Women 15-39 Years of Age in Cambodia.	Priest et al.(2016)[8]	Cambodia	Cross-sectional	women of child-bearing age (15–39 years) throughout Cambodia.	Multi-stage cluster	2150	Serology (Recombinant parasite antigen)	45.9%	1. Urban (X^2 ,0.44; p, 0.003)
2	High Prevalence and Spatial Distribution of Strongyloides stercoralis in Rural Cambodia	Khieu et al.(2014)[9]	Cambodia	Cross-sectional	60 rural villages of PreahVihear province, Northern Cambodia	Random	2396	1. Light microscopy (Kato-Katz thick smear)- eggs 2. Combined Koga agar plate (KAP) culture and Baermann method- larvae	44.7%	1. Male gender (mOR: 1.7; 95% CI: 1.4–2.0;P,0.001) 2. Reported taking anthelminthic drugs (mOR: 0.7; 95% CI: 0.6–0.8; P,0.001) 3. Defecated in latrines significantly less infected (mOR: 0.6; 95% CI: 0.4–0.8; P = 0.001) 4. Risk significantly decreased with increasing rainfall (mOR: 0.8; 95% CI: 0.7–0.9; P=0.004) and soil organic carbon content (mOR: 0.6; 95% CI: 0.5–0.9; P = 0.003) 5. The land cover class corresponding to croplands associated with increased risk for infection (mOR: 1.7, 95%CI:1.2–2.4; P = 0.004).
3	Diagnosis, Treatment and Risk Factors of Strongyloides stercoralis in Schoolchildren in Cambodia	Khieu et al.(2013)[10]	Cambodia	Cross-sectional	Four primary school in semi-urban villages in Saang District, Kandal Province, Phnom Penh, Cambodia	Random	458	KAP culture, Kato -Katz thick smear, Baermann technique	24.4%	1. Defecate usually in the toilet (RR 2.2 , 1.5 - 3.3) 2. Child washed hand after defecation (RR 2.2 , 1.6 - 3.1) 3. Child has shoes (RR 2.3, 1.7 - 3.1) 4. Toilet at home (RR 4.7, 2.4 - 9.0) 5. Gender (female) (RR 1.3, 0.9-1.8).
4	Prevalence and risk factors of acquiring Strongyloides stercoralis infection among patients attending a tertiary hospital in Thailand	Jongwutiwes et al. (2014)[15]	Thailand	Case-control	adult patients attending Siriraj Hospital (tertiary hospital in Thailand)	Cases are positive sample from 6022 sample, control from random negative sample.	Ratio case to control 1:2 149 case, 300 control	1. Direct microscopy 2. Modified Koga agar culture	2.47% (149 patients had S. stercoralis larvae positive from 6022 samples from patient in the hospital)	1. Male gender (OR:2.79; 95% CI:1.78–4.27) 2. HIV infection (OR:3.23; 95% CI 1.43–7.29) 3. Eosinophilia (OR: 1.81; 95% CI 1.33–2.47)
5	Epidemiology of Strongyloides stercoralis on Mekong islands in southern Laos.	Vonghachack et al. (2015)[21]	Laos	Cross sectional	All household members aged 2 years or older in Donlong, Donthan and Donlieng island located in the Mekong	Random	729	1. Baermann techniques 2. Kato-Katz techniques	41.0%	Male (OR: 1.97; 95% CI1:45-2.67)

					River in Khong district, Champasack province, southern Laos.					
6	Determining intestinal parasitic infections (IPIs) in inmates from Kajang Prison, Selangor, Malaysia for improved prison management.	Angal et al. (2015)[17]	Malaysia	Cross-sectional	Inmates from Kajang Prison, Selangor, Malaysia	Convenient	294	ELISA Kit (IgG antibodies)	8.8%	No significant factors
7	Detection of Strongyloides stercoralis infection among cancer patients in a major hospital in Kelantan, Malaysia	Zueter et al. (2014)[18]	Malaysia	Cross-sectional	cancer patients undergoing chemotherapy with or without steroid treatment between December 2010 and August 2011	not mentioned	192 cancer pt (stool, serum)	1. microscopic examination 2. PCR 3. ELISA	1. 0.5% among cancer pt (stool microscopy) 2. 1.5% among cancer pt (PCR) 3. 4.2% among cancer pt (IgG ELISA), 3.1% (IgG4 ELISA), 0% (IgE ELISA).	No significant factors
8	Review of patients with Strongyloides stercoralis infestation in a tertiary teaching hospital, Kelantan.	Azira et al. (2013)[16]	Malaysia	Cohort (Retrospective)	Records of patients with positive *S. stercoralis* larvae from January 2000 to December 2012.		15155 of total stool samples	Single direct stool micoscopial examination	0.08%	No significant factors
9	The prevalence and diversity of intestinal parasitic infections in humans and domestic animas in a rural Cambodia village.	Schär et al. (2014)[11]	Cambodia	Cross-sectional	Dong village, Rovieng district, PreahVihear province, Cambodia	Simple random sampling of a village household	218	Stool Sample, Direct smear (Koga-agar and Baermann method)	24.30%	Age > 30 (OR: 2.02, 95% CI: 1.03 – 3.97
10	Prevalence and risk factors of Strongyloides stercoralis in Takeo Province, Cambodia.	Khieu et al. (2014)[12]	Cambodia	Cross sectional	60 villages of Takeo Province, Cambodia	Random	2861	1. Koga-agar plate culture 2. Baermann 3. Kato-Katz	21.0%	1. Males (OR: 1.7; 95% CI: 1.4 – 2.0; P < 0.001) 2. Had latrine less frequently infected (OR: 0.7; 95% CI: 0.4 – 0.8;P =0.003).
11	A Cross-Sectional Survey of Intestinal Helminthiases in Rural Communities of Nakhon Ratchasima Province, Thailand.	Kaewpitoon et al. (2015)[23]	Thailand	Cross-sectional	Villagers in Wang Sai sub-district of Pak Chong district (May 2012) and the Tanod sub-district (July 2013) of Mueang Nakhon Ratchasima, Thailand.	Random	209	Kato's Thick Smear technique (Stool Specimen)	1.44%	No significant factors
12	Strongyloides stercoralis infection and re-infection in a cohort of children in Cambodia.	Khieu et al. (2014)[13]	Cambodia	Cross-sectional	484 children from four primary schools in semi-rural villages in Kandal province	Convenient	302	Direct smear (Koga-agar and Baermann method)	22.50%	Male (OR: 3, P<0.001) Child defecate in toilet (OR: 0.3, P<0.001), Child has shoes (OR: 0.4, P=0.031) Have toilet at home (OR: 0.3, P<0.001).

13	A cross-sectional study on intestinal parasitic infections in rural communities, northeast Thailand.	Boonjaraspinyo et al. (2013)[24]	Thailand	Cross-sectional	19 villages through which the Shi and Pong Rivers flow in KhonKaen Province, northeastern Thailand, from March to August 2013.	not mentioned	253	light microscopy	9.50%	Not specific to *S.stercoralis*
14	Evaluation of real-time PCR for Strongyloides stercoralis and hookworm as diagnostic tool in asymptomatic schoolchildren in Cambodia.	Schär et al. (2013)[14]	Cambodia	Cross-sectional	Children from four school in semi-rural province of Kandal, south of Phnom Penh in Cambodia	Random	218	Real-time PCR in comparison with gold standard Baermann/Koga Agar	17.4%	No Risk Factor studied because this is a diagnostic test study
15	First molecular identification and report of genetic diversity of Strongyloides stercoralis, a current major soil-transmitted helminth in humans from Lao People's Democratic Republic.	Laymanivong et al. (2016)[20]	Lao	Cross-sectional	> 5y/o pop in three provinces spanning northern, central, and southern regions of the country	not mentioned	327	1. Agar plate culture 2. Kato-Katz 3. DNA extraction 4. Phylogenetic analysis	41.0%	positive correlation of S. stercoralis only with hookworm infection ($p < 0.001$)
16	Seroprevalence of fascioliasis, toxocariasis, strongyloidiasis and cysticercosis in blood samples diagnosed in Medic Medical Center Laboratory, Ho Chi Minh City, Vietnam in 2012.	Nguyen T et al. (2012)[22]	Vietnam	Cohort (Retrospective)	retrospective study was performed on diagnostic results of Fasciola spp., Toxocara spp., Strongyloidesstercoralis and Taeniasolium IgG ELISA tests from Medic Medical Center laboratory, HCMC, Vietnam in the year 2012.		42,920	IgG ELISA (DRG Instruments GmbH, Springfield, USA)	Seroprevalence 7.4 %	1. males (RR: 1.292; 95 % CI: 1.21–1.38) 2) 2. lower risk in age group of ≤ 60 year-old (RR: 0.635; 95 % CI: 0.57–0.71).
17	Epidemiological Characteristics of Strongyloidiasis in Inhabitants of Indigenous Communities in Borneo Island, Malaysia.	Ngui et al. (2016)[19]	Malaysia	Cross-sectional	Inhabitants of longhouse indigenous communities in Pakan town of Sarawak	Convenient	236	1. Stool microscopy 2. Serological ELISA test 3. Stool nested PCR if (2) positive	1. Prevalence by stool microscopy is negative 2. Seroprevalence 11% (26/236)	Seroprevalence significantly: 1. higher in males than in females (20.7% vs 2.4%, P =0.018) 2. higher in adults than in children (11.8% vs 4.0%; P =0.041) 3. increased with age (P =0.039)

DISCUSSION

In general, it is not possible to define a reliable prevalence estimate for Southeast Asia. The use of different diagnostic methods leads to a very heterogeneous picture of reported prevalence rates. In general, *S. stercoralis* is likely to be underreported. Four of the studies focusing on other soil-transmitted helminths which apply diagnostic methods that are inappropriate to detect *S. stercoralis.* Cases of *S. stercoralis* infection are therefore found "accidentally", via sub-optimal diagnostic methods. Information on risk factors associated with *S. stercoralis* infection is even rarer, since the parasite is often not the main focus of the studies conducted. Age (older age) and sex (male) are the best documented risk factors. Furthermore, studies conducted among possible risk groups or among hospital-based individuals makes it difficult to compare them to studies conducted among the general population.

The studies from Thailand provide good example to show the problem of inadequately estimating infection rates.[15,23,24] More in-depth knowledge were needed about age- or sex-related infection rates as the risk factors for *S. stercoralis* in general is even more uncommon. In other SEA countries, the situation is even direr, as the number of studies reporting *S. stercoralis* infection rates are much fewer compared to Thailand. This lack of reports makes it difficult to draw a clear picture of the geographical distribution.

There are severe underreported cases, especially in areas where there is a lack of proper sanitation, behavioral and economic factors that may suggest high transmission rate of *S. stercoralis*. We could not identify any study in such country such as Indonesia which is one of the most populous countries in the world with almost 240 million inhabitants. Furthermore, in Vietnam, we only managed to find one published report while none was found from Myanmar. In general, we argue that the absence of information might be because of a real lack of research or due to publication/language biases.

The sample size of individual studies reviewed ranging from 192 to 42,920, are liable to heterogeneity of the studies resulting in large prevalence disparities. The different composition of the study population accounts for different prevalence. Other factors such socioeconomic status and sanitary conditions and practices are also likely to contribute to the differences observed. More data is required for almost all countries and for various socio-economic/cultural settings. Large-scale surveys that sample the general population, and use highly sensitive combination methods over three consecutive days would help to narrow this gap.

The lack of information about the prevalence of *S. stercoralis* also makes it challenging to estimate the true disease burden and the attributable morbidity caused by strongyloidiasis. It is known that hyper-infection and disseminated strongyloidiasis can have a severe outcome, yet no data about the frequency in high risk populations is available except one study done among cancer patients in a tertiary hospital in Malaysia.[18]

Laboratory Method

A major challenge of giving an overview of prevalence data for *S. stercoralis* lies in the low comparability of the studies reporting infection rates in term of diagnostic method used. Studies in countries that only use direct smear with single light microscopic examination resulted in very low prevalence with 0.0 to 0.5 percent, 1.44 to 9.5 percent for Malaysia and Thailand respectively. This technique has low sensitivity and may give negative results in those with low intestinal worm load and larvae output in the stool which are occurring in most uncomplicated cases. This may explain why the 'true' prevalence is often underestimated.

Cambodia and Laos show the highest prevalence of *S. stercoralis* infection. The main reason for such high prevalence is likely to be due to the more rigorous diagnostic approach employed in the studies (number of stool specimen, multiple diagnostic methods), compared to the other countries, where a single method to examine a single fecal sample was used. 71.4 percent of studies in Cambodia[8-14] and 100 percent of studies from Laos[20-21] used the combination method of Kato- Katz, Baermann and Koga Agar plate culture yielding higher prevalence of *S. stercoralis* ranging from 21.0 to 44.7 percent and 41 percent respectively.

The prevalence of *S. stercoralis* infection measured via serological test in Malaysia were found to be higher than microscopic examination ranging from 4.2 to 11 percent and 0 to 0.5 percent respectively.[16-19] The difference is most likely due to the low sensitivity of microscopic examination as previously explained. Serological test is recommended for non-endemic areas due to its practicality of not relying on fresh stools, and easy to be used in average-equipped laboratories. The low prevalence from studies done in Malaysia is not enough to conclude that Malaysia is not an endemic area for *S. stercoralis* infection. More studies using combination method of Kato- Katz, Baermann and Koga Agar plate culture are needed. Relying on serological result only is not accurate because even though the sensitivity is up to 95 percent, it has specificity concern in which, cross reaction with other infection with nematodes will give false-positive results.[25,26]

The striking risk factor in this review is being male with odds ratio ranging from 1.29 up to

3 across 7 studies. The most probable reason might be due to the level of hygiene habit practices by this group. Added with the role of males to work and spent most of time out of home. Some protective factor found is defecating in toilet with odds ratio 0.3 which is better than defecate in latrines with odds ratio 0.6 – 0.7. This is due to the nature of toilet build that is usually with proper sewage plumbing compared to latrines. Some other protective factors are wearing shoes and washing hand after defecates.

CONCLUSIONS

In determining the current prevalence situation of *S. stercoralis* in Southeast Asia, many gaps remain. The information we have today only scratches the surface. In most countries in the region, the existence of *S. stercoralis* has been shown. Most often this is the only certainty, as detailed information about infections intensities, geographical differences and burden of disease remain undiscovered. Summarising the existing data for the region, *S. stercoralis* is likely to have a much higher burden than what is currently indicated by published study results. Large-scale community-based studies that apply high sensitivity diagnostic methods are needed in order to draw a clearer picture. The main risk factor is personal hygiene practices especially amongst males. To reduce the burden of *S. stercoralis*, we suggest to educate on personal hygiene especially among males and provide proper toilet to the public. We recommend studies that focus on other soil-transmitted helminths should specifically include and test for *S. stercoralis.* Further research efforts are needed to draw a more conclusive picture of the prevalence situation of *S. stercoralis* in Southeast Asia.

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