Gender Related Differences in Infection Intensity, Prevalence and Risk of Schistosoma Mansoni and Schistosoma Haematobium: A Systematic Review Protocol

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Protocol

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Abstract

Background: The varying extent to which schistosomiasis affects human males and females, depending on context and individual health status is unclear. A key step towards achieving equitable health outcomes and health care delivery is understanding how schistosomiasis is distributed by sex. The purpose of this review is to systematically investigate sex differences in intensity and prevalence of *Schistosoma mansoni* and *S. haematobium* infections.

Methods: The systematic review will be conducted and reported based on the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Ovid-MEDLINE, PubMed, Ovid-PsycINFO, and Web of Science databases were searched for eligible studies published between inception and March 2020. Observational and intervention studies reporting data on the prevalence and/or intensity of schistosomiasis (*S. mansoni/S. haematobium*) distributed by sex in any population group will be included. Hand searches for further relevant publications will also be undertaken. Using a defined criterion, search results have been screened independently and in duplicate by three reviewers, any disputes were resolved by team consensus. Study and population characteristics will be extracted from eligible publications and stored in a structured data extraction sheet in Microsoft Excel. A descriptive synthesis of the results will be undertaken in line with the outcomes of this study.

Discussion: This review aims to provide a current overview of the distribution of the burden of *Schistosoma mansoni* and *S. haematobium* by sex. An understanding of the sex distribution of schistosomiasis will play an important role in designing treatment strategies aimed towards prevention and control.

Systematic review registration: PROSPERO registration number: CRD42020175165

Background

Schistosomiasis, also known as bilharzia, is a neglected tropical disease (NTD) that is currently estimated to infect more than 228 million persons worldwide [1–3]. It is caused by blood flukes of the genus *Schistosoma* and manifests in two main forms: urogenital schistosomiasis (caused by *S. haematobium*) and intestinal schistosomiasis (caused by *S. mansoni, S. japonicum, S. mekongi, S. guineensis and S. intercalatum*). Central to the transmission of both forms of the disease, is human contact with contaminated water bodies. The impact of human sex on exposure, transmission, manifestation and treatment of schistosomiasis is complex and can be influenced by other demographic factors such as age. For example, urogenital schistosomiasis not only manifests differentially between males and females but stigmatisation is often faced by older females due to infertility issues [4]. The Global Burden of Disease study also highlighted differences in disability-adjusted life years by age and sex [5], and previous work has shown a significant difference in the age-infection profile between males and females [6].

Over 90% of people requiring treatment for schistosomiasis live in sub Saharan Africa where the major form of control is through preventive chemotherapy with praziquantel [7]. Although, over the last decade, progress has been made in achieving morbidity control in several countries in this region, more remains to be done [8]. The newly drafted World Health Organization (WHO) NTD roadmap for 2021–2030 outlines achieving elimination as a public health problem for schistosomiasis and aims to attain this by extending treatment to all in need [9]. Recently, emphasis has been placed on gender equity and advocating for expanded treatment beyond school aged children (SAC; 5–14 years old) to often overlooked age groups (pre-SAC and adults) [7, 10–12]. However, little is known about the distribution of prevalence and intensity of schistosomiasis by sex, and what this means for treatment programmes. The output of our review will help in understanding differences in the burden of infection between the sexes, the impact of interventions on the distribution of infection, whilst helping to define who the 'in need' truly are.

This systematic review focuses on infections caused by S. mansoni and S. haematobium. We aim to address these five questions; 1. What is the distribution of infection prevalence and intensity by sex? 2. What sex-specific risk factors contribute to this? 3. How do sex and age interact? 4. What socio-cultural factors contribute to the observed patterns of sex-specific prevalence, intensity and risk? and 5. What effect has mass drug administration had on these sex-specific characteristics of infection? In answering these questions, we aim to qualitatively synthesise all published works that present sex-specific epidemiological data. Understanding the distribution of the prevalence, intensity and risk of schistosomiasis can support programmes to deliver equitable prevention, diagnosis and treatment services.

Methods

Patient and public involvement statement

Patients were not involved in the development of this protocol.

Study design

This systematic review protocol was developed and reported (see checklist) following the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement It has also been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020175165).

Information sources:

The review will be conducted based on the items outlined in the PRISMA statement [13] . The following databases were systematically searched for eligible studies in English: PubMed Central (1800 to March 2020), ovid-Embase (1974 -March 2020), ovid-MEDLINE (1946-March 2020), ovid-PsycINFO (1806 to March 2020) and web of science (1900-March 2020). Automated database searches covered the period

from when the earliest electronic records were available (e.g., 1900 in the case of Web of Science) until March 2020. Electronic searches will be additionally complimented by a manual search of reference lists of eligible articles.

Search strategy

The search terms used included keywords and variants of “schistosomiasis”, “prevalence” and “intensity”. We used Boolean operators “AND” to combine the categories and “OR” to join the terms within each category. The search string used was: Schistosomiasis OR “Schistosoma Mansoni” OR “Schistosoma Haematobium” OR “Urinary Schistosomiasis” OR “Intestinal Schistosomiasis” AND Prevalence OR Burden AND “Infection intensity” OR “intensity of infection”.

Eligibility criteria

A detailed description on population, intervention, comparison, and outcome of the systematic review is outlined in Textbox 1. We will include studies on human schistosomiasis (infection caused by either *S. mansoni* or *S. haematobium*) that document prevalence and/or intensity data distributed by sex. These studies could be observational or intervention studies using cross-sectional or longitudinal designs with no age or geographical restrictions. Studies not written in English, animal studies, quantitative studies not measuring the outcome of interest, studies on human schistosomiasis caused by other *schistosoma* species will be excluded. Also unpublished manuscripts, conference proceedings, reviews, editorials, commentaries, letters to editors and author replies will be excluded.

Population: Human population (no age or geographical restriction) diagnosed with schistosomiasis (*Schistosoma mansoni* or *Schistosoma haematobium*).

Intervention/exposure: Human sex is the exposure of interest for this study which we define as male and female as reported by authors in the search articles.

Comparison: The primary comparison will be schistosomiasis prevalence and/or infection intensity between male and female participants.

Outcome: The primary outcome measures are the male to female ratios of prevalence and/or intensity of infection.

Textbox 1:*Population, intervention, comparison, and outcome (PICO) of systematic review*

Screening and selection procedure

All citations obtained using the search strategy will be imported into Endnote (Endnote X9, Thomson Reuters, San Francisco, CA), and duplicates will be deleted. The remaining unique records will be imported into Microsoft Excel where screening for relevance and eligibility will take place. Three (DA, JC and JT) reviewers will screen the titles, abstracts, figures and tables independently and in duplicates. Any disputes will be resolved by team consensus.

Data extraction

Relevant data will be extracted by three reviewers from eligible publications into a predefined extraction Microsoft Excel sheet developed for this review. Data that will be extracted include:

1. Publication details: title, journal, author(s), year of publication, country and year in which study was carried out
2. Study design: type of study (cross-sectional, longitudinal, cohort, case-control), sampling method, type of drug administration strategy and platform, mass drug administration era, type of *Schistosoma* species, diagnostic method and treatment uptake rate (coverage)
3. Study population demographics: number of individuals in study, population characteristics including age and demographic information
4. Data for outcome measures: male: female ratios of prevalence and intensity of infection at baseline and follow up. Also, if available socio-cultural and economic determinants identified

For cross-sectional studies, we will extract study population demographics and outcome measures of each study area separately if available. For longitudinal studies, we will extract this information at baseline and the first follow up. Data extraction will be done independently, and a small random proportion will be done in duplicates by three reviewers (DA, JC and JT).

Data synthesis

A descriptive synthesis of the results will be undertaken in line with the outcomes of this study. Summary tables of characteristics of the included studies and the male: female prevalence/intensity ratios will be presented. Forest plots will be used to visually assess the extent of heterogeneity between studies. A narrative synthesis will provide a summary of the prevalence and intensity of schistosomiasis according to age, as well as the identified risk factors. Limitations of the studies will be discussed in detail. Implications of the review as well as areas for future research will also be provided.

Where possible, we will also perform subgroup analysis by age group, geographical region and mass drug administration era, in order to assess differences between the strength of association by geography and potential impact of contextual confounders which may vary by geography. This will also be extended to a subgroup analysis across the two *Schistosoma* species if there are enough studies.

Risk of bias assessment for eligible studies

In this review, the methodological quality of studies will not be assessed. This will allow more studies to be included in the review. We will however stratify our results to account for possible selection bias in sampling and include this in the discussion section. The main criteria for inclusion are whether the studies contain data on prevalence and intensity of infection distributed by sex.

Ethics statement

Our review will not require an ethics committee approval or written informed consent because it relies entirely on published data.

Discussion

This protocol describes a systematic review of studies reporting schistosomiasis prevalence and infection data distributed by sex. According to our knowledge, no previous systematic review has specifically addressed this topic. We will summarise the methods used and results of observational studies specifically looking at the male: female ratio of prevalence and intensity as well as identified risk factors. We anticipate facing a challenge of some studies being conducted in a subset of populations i.e. individuals infected with HIV or malaria and not a representative sample of the study area. We do not envisage any amendments to the present protocol. However, should any essential amendments be found to be necessary, they will be reported in the published review. The results will be disseminated in the form of a peer-reviewed journal article.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Raw meta-data extracted for the purposes of this review will be made publicly available with the final published review findings.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JT conceived this project and contributed to the development of the protocol alongside DA. DA developed the search strategies. DA, JT and JC screened the retrieved studies and will extract data from eligible

studies. DA wrote the original protocol draft, and all authors critically reviewed and approved the final version. DA is the guarantor of this protocol.

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Abbreviations

WHO: World Health Organization; NTD: Neglected tropical diseases; SAC: School Aged Children; PRE-SAC: Pre-School Aged Children; PRISMAP: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

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Supplementary Files

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