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Schistosomiasis infections in South African pregnant women: A review

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Background: Schistosomiasis, a chronic parasitic disease caused by Schistosoma species, has a negative impact on pregnancy outcomes and child development. The disease affects over 230 million people worldwide, and in South Africa an estimated 5.2 million people are thought to be infected. However, there is scant data on the impact of schistosomiasis in pregnancy in South Africa and globally. The aim of this review was to analyse the current knowledge of schistosomiasis in pregnancy, particularly in South Africa, focusing on maternal and neonatal complications linked directly to the disease or its treatment.

Methods: An electronic search of online databases was used to identify and collect relevant research articles related to schistosomiasis in pregnancy, with a focus on South Africa.

Results: Schistosomiasis can cause severe organ damage when left untreated and influences maternal and foetal morbidity and mortality. Although South Africa's first helminth control programme was established in 1997, there is currently no ongoing treatment strategy programme, and little information is available on prevalence rates in pregnant women for the last 20 years. There is also an absence of data from well-controlled clinical trials that focus on the efficacy and safety of treatment during pregnancy, which has led to this vulnerable group being neglected.

Conclusion: This review highlights the dearth of information on the impact of schistosomiasis in pregnant women in South Africa and the need for high-quality evidence-based studies.

Keywords: schistosomiasis; pregnancy; parasites; praziquantel; South Africa.

Background

Schistosomiasis (bilharzia) is a common chronic disease caused by parasitic infection with trematodes of the genus *Schistosoma*. It is one of the most prevalent tropical diseases and is the second most important neglected tropical disease.[1] In 2017, an estimated 220 million people required preventive treatment and about 700 million people were said to be at risk of infection globally.[2] Infections are complicated by socio-demographic factors associated with poverty such as lack of access to clean water and adequate sanitation, as well as co-infections with other helminth infections, malaria, tuberculosis (TB), human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).[3]

The disease is endemic to Africa, Asia, the Middle East and South America.[4] Its prevalence is highest in Africa, with over 90% of those requiring treatment living on the continent.[2] Little progress has been made in reducing disease morbidity in affected regions, despite the public awareness campaigns and policies that are in place.[5] Some countries have even seen an increase in infection levels[6] because of human migration to urban areas. This, coupled with the increased ease of mobility, poses a risk of re-establishing *Schistosoma* species in areas that are non-endemic, or where the disease has been eliminated.[7]

Schistosomiasis is endemic to some regions of South Africa (SA).[8] Research on prevalence has focused largely on children, and treatment strategies aim at eradicating the disease in this vulnerable group.[9] This is not without warrant. Children play the largest role in local disease transmission, and more importantly, the effects of infection have significant immediate and temporal consequences. Without treatment, infection leads to malnutrition and anaemia, retarded growth and poor performance in school.[9,10] Chronic infection is associated with sustained malnutritive disorders that affect their growth and cognitive development[10] and causes chronic inflammation of the organs, which can lead to death in severe cases. Such longstanding infection and reinfection in endemic areas translates

into morbidity in adults.[6] When the body responds to parasites embedded in the tissue, this can lead to collateral damage of the tissue and may translate into urogenital disorders in adulthood.[11]

While research on schistosomiasis in children is critical, other vulnerable groups should also be considered. These children will become adults, half of whom will fall pregnant. Research on the prevalence or treatment in women of reproductive age and during pregnancy is scarce globally, and equally true in SA.[5,12] Studies conducted locally have focused on isolated endemic areas and are largely conducted on school-aged children with virtually none on pregnant women.[13]

Although women of reproductive age are at less risk to infection than their male counterparts, chronic exposure and infection may lead to overt and long-term sequelae during and after pregnancy.[14] Pregnancy naturally increases physiologic demand of most organ systems, and a successful pregnancy outcome is governed by the health status of the mother even prior to pregnancy.[15] Schistosomiasis further affects the uterine environment, besides its contribution to anaemia and malnutrition.[16] Infected women have an increased risk for ectopic pregnancies and higher rate of spontaneous miscarriage.[17] When coupled with poor living conditions, it increases a mother's risk of mortality and is directly related to premature birth, low birth weight and morbidity of infants.[12] This translates into poor growth and development during early childhood, and increased childhood risk for schistosomiasis in endemic areas, thereby compounding the burden.[11]

While most mitigation efforts focus on morbidity control and elimination strategies in children, an awareness and implementation of treatment strategies is of vital importance in pregnant women as well. The World Health Organization (WHO) has proposed prophylactic chemotherapy as a treatment strategy that focuses on reducing disease through regular, targeted treatment of affected populations.[2] At present, praziquantel (PZQ) is the treatment of choice for all schistosome infections, as it is effective and inexpensive and has been used successfully for > 30 years.[18] Treatment is of paramount importance because if infection is left untreated, normal physiological functions such as iron metabolism, physical fitness and cognitive function are impaired, resulting in systemic morbidities such as anaemia, malnutrition as well as impaired development in children.[11,19] Schistosomiasis also occurs alongside other infectious diseases, affecting immunological and physiological relations between the host and co-infecting pathogens.[20] While this may be tolerated in non-pregnant women, successful pregnancy is dependent on adapting the immune system to accommodate a semi-allogeneic foetus, and schistosomiasis alters this dynamic.[21] Thus, better control of schistosomiasis in women of reproductive age and during pregnancy results in better pregnancy outcomes for both mother and child, with additional benefits of control of other diseases.[22]

The objective of this review is to summarise the existing literature on schistosomiasis in pregnant women and to identify research gaps relating to schistosomiasis, particularly in SA.

Schistosome life cycle in humans

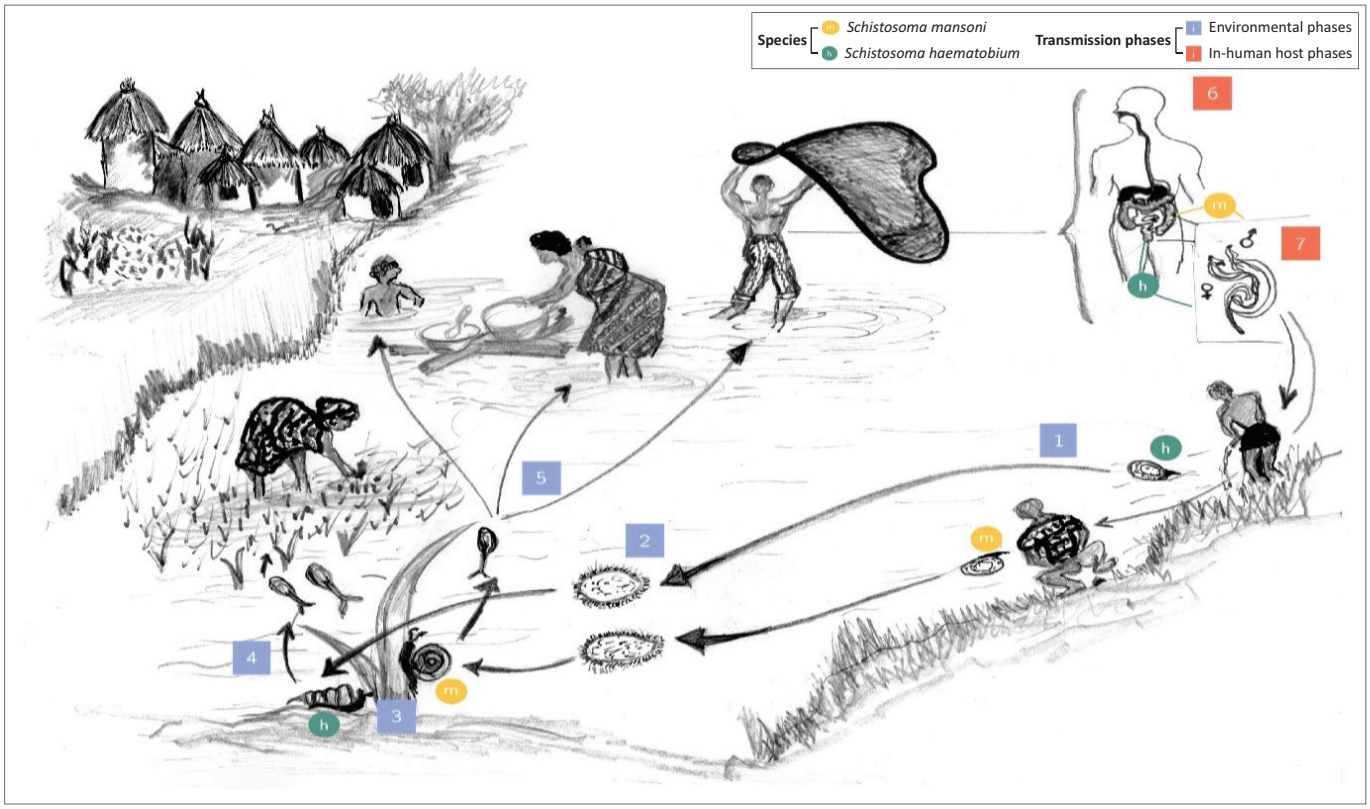
There are three main species of *Schistosoma* that infect humans, *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum*.[23] Of these, *S. haematobium* and *S. mansoni* occur mainly in Africa and the Middle East, whereas only *S. mansoni* is present in South America and *S. japonicum* is localised to Asia.[2,4,11,23] In geographical areas where schistosomes are endemic, infection in humans happens during routine agricultural, domestic, occupational and recreational activities, and are associated with a lack of clean water and inadequate sanitation. Figure 1[24] shows the transmission of *S. haematobium* and *S. mansoni*. Adult schistosomes have an average intra-host lifespan of 5–10 years which allows the parasites to remain in blood vessels producing eggs, developing into chronic infection.[2,11] While the adult schistosomes develop the ability to mask against a host immunogenic response, the eggs of *S. mansoni* and *S. japonicum* or *S. haematobium*, when migrating through intestinal submucosa or the bladder wall, respectively, elicit an inflammatory response that ultimately results in scarring and fibrosis in these organ systems.[2] Eggs released into the bloodstream can also affect other organ systems such as the liver, lungs and the brain.[11]

Review methodology

An electronic search of the following databases was conducted: PubMed/MEDLINE, Google Scholar and Scopus. The search terms included schistosomiasis, bilharzia, pregnancy, pregnant, gestation, women and South Africa. Boolean terms (AND, OR) were used to separate the keywords, and Medical Subject Headings (MESH) terms were included during the search. Websites such as the WHO and governmental websites were searched for policies and guidelines regarding diagnosis and management of anaemia in pregnancy. Relevant studies were identified by searching literature from January 1985 to date. Articles were also searched through the 'Cited by' search as well as citations included in the reference lists of included articles.

The search strategy was piloted to check the appropriateness of selected electronic databases and key words. A PubMed search using MeSH terms 'Schistosomiasis' and 'South Africa' and filtered for studies involving humans returned 495 articles with no restrictions on date of publication. Eligibility criteria for selection of articles included being available in full text and related to schistosomiasis in pregnancy, and involve South African pregnant women.

An initial title screening reduced the number of articles to 76, and from this pool, relevant articles were gleaned for necessary information.



Source: Perez Saez FJ. A field-based modelling framework of the ecohydrology of schistosomiasis [homepage on the Internet]. PhD dissertation. Ecole polytechnique federale de Lausanne; 2018 [cited 2019 June 04]. Available from: http://infoscience.epfl.ch/record/253001

Note: (1) Eggs are excreted into the environment through faeces and urine. (2) Eggs hatch into the first larval stage (miracidia) (3) where they then infect the snail intermediate host. (4) The parasite then matures and reproduces asexually in the intermediate host, producing the second larval stage (cercariae). (5) The cercariae penetrate human skin during prolonged contact with water, resulting in infection. (6) The parasite matures in the human host. (7) The parasite lodges itself in the bladder (h) or intestinal lumen (m) and undergoes sexual reproduction. This results in the release of 300–3000 eggs daily.[24]

FIGURE 1: Overview of the various activities associated with *Schistosoma haematobium* (green circles) and *Schistosoma mansoni* (yellow circles) transmission.

TABLE 1: Estimates of the South African population requiring preventive chemotherapy for schistosomiasis.

Year	SAC population requiring PC for SCH annually	Population requiring PC for SCH annually
2010	2 438 847	5 190 811
2011	2 444 487	5 220 200
2012	2 457 968	5 248 988
2013	2 476 276	5 288 087
2014	2 493 327	5 324 499
2015	2 517 413	5 375 934
2016	2 550 388	5 446 352
2017	2 575 127	5 499 182

Source: World Health Organization. Schistosomiasis: Population requiring preventive chemotherapy and number of people treated in 2010. Releve Epidemiol Hebdomadaire. 2012;87(4):37–44.

PC, preventive chemotherapy; SAC, school age children; SCH, schistosomiasis.

Note: SAC population requiring PC for SCH annually: estimated number of school age children requiring preventive chemotherapy for schistosomiasis annually according to the recommended strategy. Population requiring PC for SCH annually: estimated number of individuals requiring preventive chemotherapy for schistosomiasis annually according to the recommended strategy.

Review findings

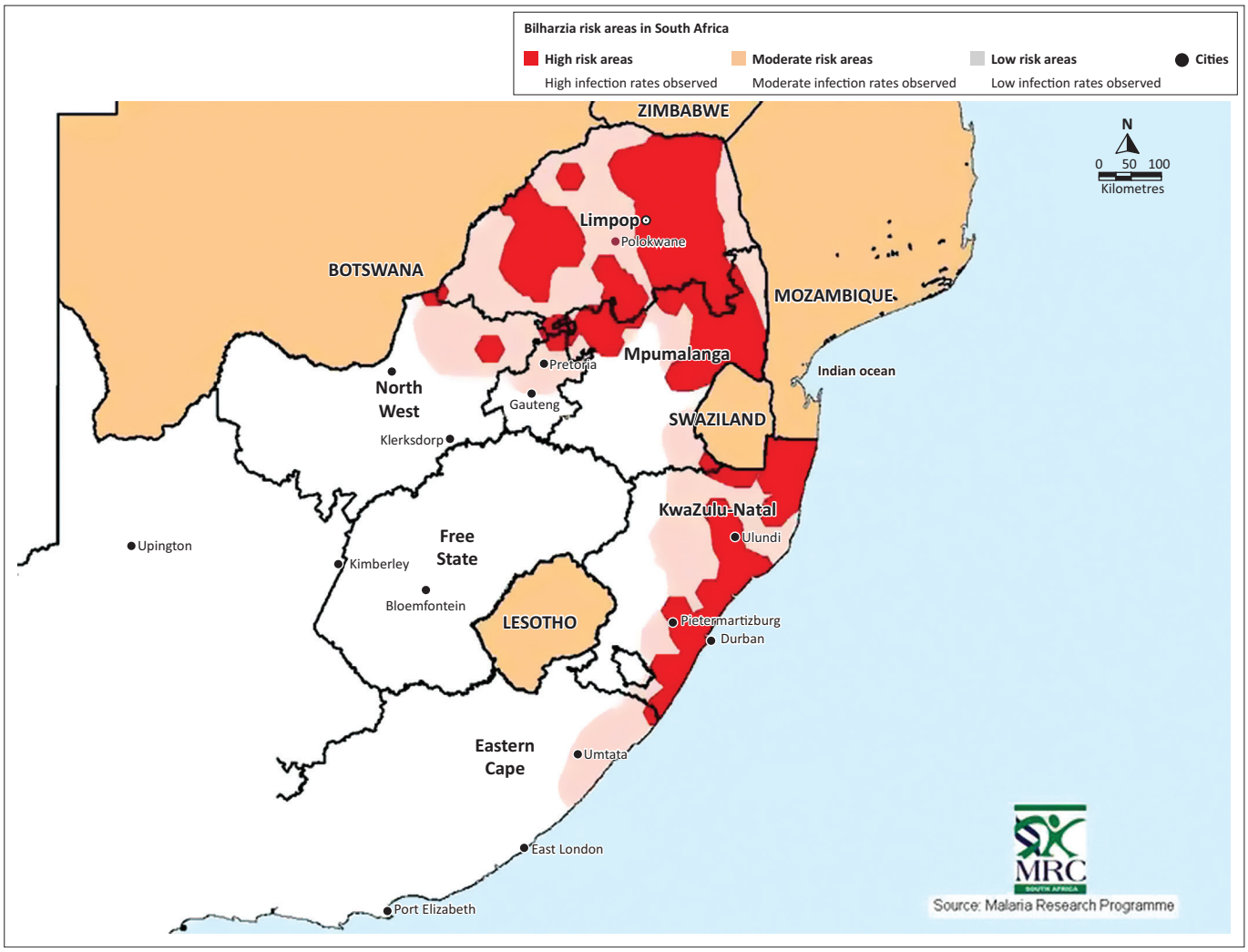
Schistosomiasis in South Africa: Historical data

Schistosomiasis is endemic to SA and poses a challenge to public health. According to the WHO (Table 1)[25] by 2011, an estimated 5.2 million people required prophylactic drug therapy for schistosomiasis in SA.[23]

While some studies on schistosomiasis prevalence rates were undertaken in endemic regions of SA (depicted in Figure 2)[30] in the 1980s and 1990s,[26,27] there is a dearth of information available for the last 20 years.[28] However, in 2012, an increase in disease occurrence was noted in all nine provinces, including the Northern Cape which was previously regarded as a non-transmission region.[29] Schistosomiasis' prevalence rates are reported to be highest in KwaZulu-Natal (KZN), Mpumalanga (MP) and Limpopo (LP) provinces,[8,30] and in 2018, endemic areas included KZN, MP, LP, eastern and northern parts of Gauteng province as well as coastal areas of the Eastern Cape.[31]

Schistosomiasis in pregnancy

Pregnant women, particularly those living in low- and middle-income countries (LMICs), are at increased risk for significant maternal and foetal morbidity and mortality, because of multiple contributing factors.[5,12] Keys amongst these are helminth infections, which are associated with a lower quality of life in women during and after pregnancy, as helminth infections can lead to anaemia, changes in host immune responses, nutritional deficiencies and other more serious complications, such as end organ damage.[15] Altered host immunity during pregnancy increases susceptibility to disease and increases transmission risk for helminth infections,[32] which, in turn, increases the risk of co-infection with other diseases and adversely affects progression of disease, worsening its outcomes.[33] In sub-Saharan Africa, this contributes to the HIV/AIDS and TB epidemics, which increases maternal mortality and the likelihood of poor neonatal outcomes.[34,35,36]



Source: Adapted from: Quayle LM, Appleton CC, Dickens CWS. The impact of river flow regulation and manipulation on the invertebrate hosts of malaria, bilharzia and liver fluke disease. Gezina; 2010.

FIGURE 2: Schistosomiasis risk areas in South Africa.

Schistosomiasis causes an array of adverse outcomes in pregnant women.[33] It interferes with nutrient uptake impairing the nutritional status of the infected mother and causing malnutrition which leads to anaemia as the nutrients that are essential for blood cell formation become reduced or depleted.[32] Chronic schistosomiasis is believed to cause anaemia as a result of effects of pro-inflammatory cytokines produced in response to infection and decreased iron bioavailability because of upregulation of hepcidin in response to a *Schistosoma*-associated cytokine.[37]

Extracorporeal blood loss when eggs are shed through the gut wall (*S. mansoni and S. japonicum*) or through repeat inflammation of the bladder wall and urethra (*S. haematobium*) causes iron deficiency.[11] Socio-economic factors, coupled with subsequent malnutrition because of Schistosoma infection and possible co-infections, lead to iron deficiency anaemia in women of reproductive age and are exacerbated in pregnant women.[38] Anaemia is a major risk factor for preterm labour, low birthweight, stillbirth and maternal death,[12] and there is a positive correlation between anaemia and infection intensity.[39] In heavily infected pregnant women, the morbidity associated with anaemia is more prominent.[5]

Schistosomiasis can cause maternal, placental and foetal infection.[40] Infection with *S. haematobium* is associated with increased pro-inflammatory responses amongst circulating leucocytes[41] which can cause inflammation of the cervix leading to spontaneous miscarriage or of the fallopian tubes resulting in ectopic pregnancy.[17] *Schistosoma mansoni* is associated with elevated concentrations of circulating endotoxins.[42] When found in high concentration in the placenta, these endotoxins have been associated with placental inflammation and preterm labour.[43] *Schistosoma japonicum* is associated with an increase in systemic inflammatory mediators.[44] This causes a pro-inflammatory state in the foetal and maternal compartments and has been associated with low birthweight.[40] These studies make the link between maternal schistosomiasis and adverse birth outcomes evident and highlight the need for treatment of schistosomiasis during pregnancy.

Schistosomiasis also impacts future pregnancies, and *S. haematobium* in non-pregnant women may cause female genital schistosomiasis (FGS).[22] Galappaththi-Arachchige et al. reported that in areas where *S. haematobium* is endemic, FGS is a neglected cause of reproductive

morbidity.[45] Female genital schistosomiasis affects the reproductive tract and is characterised by the presence of schistosome eggs or worms in the epithelium of the urinary bladder, female genital organs or genital mucosa.[8] It is associated with ectopic pregnancies, genital symptoms that are similar to those of sexually transmitted diseases (STDs), infertility and miscarriage, and studies have shown that it may make women more susceptible to HIV.[45]

Despite the many case reports and studies that have shown an association of female genital tract infection with schistosomiasis in pregnant populations,[5,46] there is relatively limited literature that specifically focuses on schistosomiasis and subsequent birth outcomes.[47,48] There has also been no data presented on maternal schistosomiasis in countries that have high paediatric schistosomiasis.[5]

Colley et al. reported that globally, *S. haematobium*, *S. mansoni* and *S. japonicum* infected an estimated 40 million women of childbearing age.[11] Global estimates by the WHO have also shown that annually, over 10 million women in Africa contract schistosomiasis during pregnancy.[23] Despite the high prevalence of this important condition, there are still gaps in the knowledge on the specific morbidity and outcomes of the disease on pregnant women and their offspring.[12]

Maternal schistosomiasis in South Africa

Despite the large risk they present to both mother and child, very limited epidemiological data on schistosomiasis are available for the reproductive phase of life in SA. Most interventions and research conducted in SA focus on school children,[9] justified by the highest incidence and intensity of infection amongst this 6–20-year-old group and the reported effects on their growth, physical development and school performance.[49] Pregnant women who are exposed to the same environment are not given priority, because of concerns of treatment during gestation and lactation.[50] This lack of research impacts on effective and timeous management of the disease, resulting in these mothers becoming infection reservoirs and making reinfection inevitable.[6] Higher rates of teenage pregnancy conflate incidence rates with socio-economic factors and increase the impact of schistosomiasis on women of reproductive age, which is left largely untreated or ignored. This is evident in South African studies on women of childbearing age in rural areas. A study by Kleppa et al. reported a 20% prevalence rate of urogenital schistosomiasis in high school students above 16 years of age.[51] In addition, Galappaththi-Arachchige et al. have reported 19.7% and 17.3% prevalence rates in women of childbearing age.[45,52]

There is little evidence of the effects of schistosomiasis in pregnant women in SA. A recent study showed a prevalence of *S. haematobium* of at least 17% in sexually active schoolgirls aged 16–22 in a rural endemic area of KZN.[52] The study compared various diagnostic test sensitivities for detecting active and past exposure. Notable urogenital lesions were present in the study population which could possibly be misdiagnosed as a sexually transmitted infection. These lesions cause genital itching, bleeding and dyspareunia and may lead to infertility, and continue to manifest even though ovum laying worms are no longer present and likely to affect reproductive health.[48]

Current needs

Schistosomiasis can be treated, and snail reduction has shown to benefit endemic populations.[53] Early and effective treatment can benefit pregnant women.[54] However, the lack of data from well-controlled clinical trials that focus on the efficacy and safety of PZQ during pregnancy, compounded by previous recommendations that treatment should be avoided during pregnancy and lactation, has led to pregnant women being excluded from treatment.[54] When left untreated, schistosomiasis infection results in significant morbidity and mortality. No high-quality epidemiological studies that have assessed the impact of schistosomiasis on pregnancy have been undertaken to date, particularly in SA.[12]

Present strategies to reduce schistosomiasis

Currently, PZQ is the only drug recommended for the regular treatment of schistosomiasis,[19] and when taken at a dose of 40 mg/kg,[55] adult schistosomes are eradicated. Although the cost makes mass treatment programmes effective, at only ± R7.00 per treatment course per person,[56] such programmes are not being implemented and the disease remains endemic in at least five of the nine provinces.[32] This is partially because of poor education and information dissemination amongst populations at risk of infection, the lack of resources that would support PZQ distribution and delivery of the drug to areas where it is needed.[19] The Medicines Control Council and the National Department of Health have also only approved brand name drugs (such as Bayer's Biltricide®) for treatment, while having stringent regulation in place that makes manufacturing generic PZQ a costly and time-consuming process, thereby making treatment unaffordable in afflicted districts.[57]

Implications

The lack of sufficient, well-controlled studies on the use of PZQ in pregnant and lactating women has deterred many countries (including SA) from using this drug during pregnancy.[9,58] As a result, implementing treatment strategies has been inconsistent[32] despite WHO recommendations that, in endemic areas, pregnant and lactating women be treated with PZQ[59] and that anti-helminth treatment be incorporated into antenatal care after the first trimester of pregnancy.[60] This is despite there being no severe adverse incidents reported in non-interventional studies where pregnant women were treated or accidentally exposed to PZQ.[58] These reports include a Sudanese study in which 88 women were exposed to PZQ (37

during the first trimester of their pregnancy). None of the pregnancies resulted in stillbirths or miscarriages, and there were no congenital abnormalities.[61] Praziquantel was found to have no significant effect on birth weight, congenital anomalies, maternal anaemia or perinatal mortality in a randomised, double-blind, placebo-controlled trial that recruited 2507 pregnant women to investigate the benefits of anthelminthic use during pregnancy.[62] Thus, there certainly may be a place for the treatment of schistosomiasis in the second and third trimesters of pregnancy. In addition, healthcare professionals should investigate for schistosomiasis in pregnant women presenting with haematuria, and persistent or recurrent urinary tract infections, especially in HIV-positive women.[58] To effectively control schistosomiasis, early detection of the disease is required to ensure optimum efficiency of both control and treatment programmes.[19,29] In sub-Saharan Africa, the incidence of infection ranges from 2.5% to 63.5% in maternal schistosomiasis, and this will gradually increase with time if the recommended interventions and preventative measures are not implemented.[5]

Conclusion

Schistosomiasis is a public health concern in SA with approximately a tenth of the population at risk. There is significant evidence implicating schistosomiasis directly in maternal and foetal morbidity and mortality, and indirectly by causing nutrient deficiencies leading to anaemia and malnutrition or by association with other co-morbidities such as HIV and TB. However, very little data exist on schistosomiasis amongst pregnant women in SA. Research on the distribution and prevalence of schistosomiasis, as well as frequent and consistent surveillance and intervention programmes that target all population groups, especially pregnant women, will contribute significantly to controlling this disease.[29,55]

High-quality evidence-based studies assessing the impact of schistosomiasis on pregnancy are urgently required to support global intervention and treatment programmes in pregnant and lactating women and their babies.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

M.D.B. contributed doing the literature search on schistosomiasis and initiating the first draft. She was also responsible for finalising all corrections and modifications suggested by the other contributors. This study is part of her master's degree. V.D. contributed by reading the draft review, and suggesting modification and corrections. He is the supervisor of the principal author's master's degrees. J.M. contributed by directing the literature search, reading the drafts and making modifications where appropriate.

Ethical consideration

This article followed all ethical standards for carrying out research without direct contact with human or animal subjects.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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References

1. Sharma VK. Hypnotherapy in clinical cancer care and benefits. J Health Res Rev. 2017;4(3):26–32. https://doi.org/10.4103/jhrr.jhrr
2. World Health Organization. Schistosomiasis fact sheet [homepage on the Internet]. 2018 [cited 2019 Feb 5]. Available from: http://www.who.int/mediacentre/factsheets/fs115/en/
3. Bourke CD. Human cytokine responses during natural and experimental exposure to parasitic helminth infection [homepage on the Internet]. PhD dissertation. The University of Enidburgh; 2011 [cited 2019 Apr 15]. Available from: https://www.researchgate.net/publication/292450227_Human_cytokine_responses_during_natural_and_experimental_exposure_to_parasitic_helminth_infection
4. Gray DJ, Ross AG, Li YS, McManus DP. Diagnosis and management of schistosomiasis. Br Med J. 2011;342(7807):1–12. https://doi.org/10.1136/bmj.d2651
5. Salawu OT, Odaibo AB. Maternal schistosomiasis: A growing concern in sub-Saharan Africa. Pathog Glob Health. 2014;108(6), 263–270. https://doi.org/10.1179/2047773214Y.0000000150
6. Schur N, Hu¨rlimann E, Garba A, Traore´ M, Ndir O, Ratard R. Geostatistical model-based estimates of schistosomiasis prevalence among individuals aged <20 years in West Africa. PLoS Negl Trop Dis. 2011;5(6):e1194. https://doi.org/10.1371/journal.pntd.0001194
7. Utzinger J, Becker SL, Van Lieshout L, Van Dam GJ, Knopp S. New diagnostic tools in schistosomiasis. Clin Microbiol Inf. 2015;21(6):529–542. https://doi.org/10.1016/j.cmi.2015.03.014
8. Magaisa K, Taylor M, Kjetland EF, Naidoo PJ. A review of the control of schistosomiasis in South Africa. S Afr J Sci. 2015;111(11):1–6. https://doi.org/10.17159/sajs.2015/20140427
9. Freer JB, Bourke CD, Durhuus GH, Kjetland EF, Prendergast AJ. Schistosomiasis in the first 1000 days. Lancet Infect Dis. 2017;3099(17):1–11. https://doi.org/10.1016/S1473-3099(17)30490-5
10. Stecher CW, Sacko M, Madsen H, et al. Anemia and growth retardation associated with *Schistosoma haematobium* infection in Mali: A possible subtle impact of a neglected tropical disease. Trans R S Trop Med Hyg. 2017;111(4):144–153. https://doi.org/10.1093/trstmh/trx037
11. Colley DG, Bustinduy AL, Secor WE, King CH, Human schistosomiasis. Lancet. 2014;383(9936):2253–2264. https://doi.org/10.1016/S0140-6736(13)61949-2
12. Mombo-Ngoma G, Honkpehedji J, Basra A, et al. Urogenital schistosomiasis during pregnancy is associated with low birth weight delivery: Analysis of a prospective cohort of pregnant women and their offspring in Gabon. Int J Parasitol. 2017;47(1):69–74. https://doi.org/10.1016/j.ijpara.2016.11.001
13. Sacolo H, Chimbari M, Kalinda C. Knowledge, attitudes and practices on schistosomiasis in sub-Saharan Africa: A systematic review. BMC Inf Dis. 2018;18(1):46. https://doi.org/10.1186/s12879-017-2923-6

14. McClure EM, Meshnick SR, Mungai P, et al. The association of parasitic infections in pregnancy and maternal and fetal anemia: A cohort study in Coastal Kenya. PLoS Negl Trop Dis. 2014;8(2):e2724. https://doi.org/10.1371/journal.pntd.0002724
15. Blackwell AD. Helminth infection during pregnancy: Insights from evolutionary ecology. Int J Women's Health. 2016;8(1):651–661. https://doi.org/10.2147/IJWH.S103529
16. Friedman JF, Mital P, Kanzaria HK, Olds GR, Kurtis JD. Schistosomiasis and pregnancy. Trends Parasitol. 2007;23(4):159–164. https://doi.org/10.1016/j.pt.2007.02.006
17. Laxman VV, Adamson B, Mahmood T. Recurrent ectopic pregnancy due to *Schistosoma hematobium*. J Obstet Gynaecol. 2008;28(4):461–462. https://doi.org/10.1080/01443610802164896
18. Tweyongyere R, Naniima P, Mawa PA, et al. Effect of maternal *Schistosoma mansoni* infection and Praziquantel treatment during pregnancy on *Schistosoma mansoni* infection and immune responsiveness among offspring at age five years. PLoS Negl Trop Dis. 2013;7(10):e2501. https://doi.org/10.1371/journal.pntd.0002501
19. Siqueira LP, Fontes DAF, Aguilera CSB, et al. Schistosomiasis: Drugs used and treatment strategies. Acta Tropica. 2017;176(1):179–187. https://doi.org/10.1016/j.actatropica.2017.08.002
20. Mabbott NA. The influence of parasite infections on host immunity to co-infection with other pathogens. Front Immunol. 2018;9(1):2579. https://doi.org/10.3389/fimmu.2018.02579
21. Nash S, Mentzer AJ, Lule SA, et al. The impact of prenatal exposure to parasitic infections and to anthelminthic treatment on antibody responses to routine immunisations given in infancy: Secondary analysis of a randomised controlled trial. PLoS Negl Trop Dis. 2017;11(2):1–13, https://doi.org/10.1371/journal.pntd.0005213
22. Le L, Hsieh MH. Diagnosing urogenital schistosomiasis: Dealing with diminishing returns. Trends Parasitol. 2017;33(5):378–387. https://doi.org/10.1016/j.pt.2016.12.009
23. World Health Organization. 'Schistosomiasis progress report 2001–2011 and strategic plan 2012–2020', Geneva, 2013. p. 80.
24. Perez Saez FJ. A field-based modelling framework of the ecohydrology of schistosomiasis [homepage on the Internet]. PhD dissertation. Ecole polytechnique federale de Lausanne; 2018 [cited 2019 June 04]. Available from: http://infoscience.epfl.ch/record/253001
25. World Health Organization. Schistosomiasis: Population requiring preventive chemotherapy and number of people treated in 2010. Releve Epidemiol Hebdomadaire. 2012;87(4):37–44.
26. Pitchford R. Temperature and schistosome distribution in South Africa. S Afr J Sci. 1981;1(77):252–261.
27. Schutte C, Van Deventer J, Lamprecht T. A cross-sectional study of the prevalence and intensity of infection with *Schistosoma haematobium* in students of northern KwaZulu-Natal. Am J Trop Med Hygiene. 1981;30(2):364–372. https://doi.org/10.4269/ajtmh.1981.30.364
28. Banhela N, Taylor M, Gift Zulu S, Sund Strabo L, Floerecke Kjetland E, Gunnar Gundersen S. Environmental factors influencing the distribution and prevalence of *Schistosoma haematobium* in school attenders of ILembe and uThungulu Health Districts, KwaZulu-Natal Province, South Africa. S Afr J Inf Dis. 2017;32(4):132–137. https://doi.org/10.1080/23120053.2017.1335974
29. Mkhize-Kwitshana ZL, Mabaso MHL. Status of medical parasitology in South Africa: New challenges and missed opportunities. Trends Parasitol. 2012;28(6):217–219. https://doi.org/10.1016/j.pt.2012.03.005
30. Quayle LM, Appleton CC, Dickens CWS. The impact of river flow regulation and manipulation on the invertebrate hosts of malaria, bilharzia and liver fluke disease. Gezina: Water Research Commission; 2010.
31. National Institute for Communicable Diseases (NICD). Schistosomiasis (Bilharzia) frequently asked questions [homepage on the Internet]. 2018 [cited 2019 July 30]. Available from: https://www.nicd.ac.za/wp-content/uploads/2017/03/Schistoosomiasis-Bilharzia_20181104_Final.pdf
32. Tsoka-Gwegweni J, Ntombela N. A double load to carry: Parasites and pregnancy. S Afr J Epidemiol Inf. 2014;29(2):52–55. https://doi.org/10.1080/23120053.2014.11441569
33. Hotez PJ, Brindley PJ, Bethony JM, King, CH, Pearce EJ, Jacobson J. Helminth infections: The great neglected tropical diseases. J Clin Invest. 2008;118(4):1311–1321. https://doi.org/10.1172/JCI34261.tion
34. Ivan E, Crowther NJ, Mutimura E, et al. Effect of deworming on disease progression markers in HIV-1-infected pregnant women on antiretroviral therapy: A longitudinal observational study from Rwanda. Clin Inf Dis. 2015;60(1):135–142. https://doi.org/10.1093/cid/ciu715
35. Resende Co T, Hirsch CS, Toossi Z, Dietze R, Ribeiro-Rodrigues R. Intestinal helminth co-infection has a negative impact on both anti-Mycobacterium tuberculosis immunity and clinical response to tuberculosis therapy. Clin Exp Immunol. 2007;147(1):45–52. https://doi.org/10.1111/j.1365-2249.2006.03247.x
36. Simon GG. Impacts of neglected tropical disease on incidence and progression of HIV/AIDS, tuberculosis, and malaria: Scientific links. Int J Infect Dis. 2016;42(1):54–57. https://doi.org/10.1016/j.ijid.2015.11.006
37. Ganz T. The role of hepcidin in iron sequestration during infections and in the pathogenesis of anemia of chronic disease. IMAJ. 2002;4(11):1043–1045.
38. Murenjekwa W, Makasi R, Ntozini R, et al. Determinants of urogenital schistosomiasis among pregnant women and its association with pregnancy outcomes, neonatal deaths, and child growth. J Infect Dis. 2019:1–12. https://doi.org/10.1093/infdis/jiz664
39. Koukounari A, Gabrielli AF, Toure S, et al. *Schistosoma haematobium* infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. J Infect Dis. 2007;196(5):659–669. https://doi.org/10.1086/520515
40. Kurtis JD, Higashi A, Wu H-W, et al. Maternal schistosomiasis japonica is associated with maternal, placental, and fetal inflammation. Infect Immun. 2011;79(3):1254–1261. https://doi.org/10.1128/IAI.01072-10
41. Bourke CD, Nausch N, Rujeni N, et al. Integrated analysis of innate, Th1, Th2, Th17, and regulatory cytokines identifies changes in immune polarisation following treatment of human schistosomiasis. J Infect Dis. 2013;208(1):159–169. https://doi.org/10.1093/infdis/jis524
42. Seto EYW, Sousa-Figueiredo JC, Betson M, Byalero C, Kabatereine NB, Stothard JR. Patterns of intestinal schistosomiasis among mothers and young children from Lake Albert, Uganda: Water contact and social networks inferred from wearable global positioning system dataloggers. Geospat Health. 2013;7(1):1–13. https://doi.org/10.4081/gh.2012.99
43. Schmiedel Y, Mombo-Ngoma G, Labuda LA, et al. CD4+CD25hiFOXp3+ regulatory T cells and cytokine responses in human schistosomiasis before and after treatment with praziquantel. PLoS Negl Trop Dis. 2015;9(8):1–14. https://doi.org/10.1371/journal.pntd.0003995
44. Qunhua L, Jiawen Z, Bozhao L, et al. Investigation of association between female genital tract diseases and Schistosomiasis japonica infection. Acta Tropica. 2000;77(2):179–183. https://doi.org/10.1016/S0001-706X(00)00129-7
45. Galappaththi-Arachchige HN, Zulu SG, Kleppa E, et al. Reproductive health problems in rural South African young women : Risk behaviour and risk factors. Reprod Health. 2018;15(1):138. https://doi.org/10.1186/s12978-018-0581-9
46. Gadoth A, Mvumbi G, Hoff N, et al. Urogenital schistosomiasis and sexually transmitted coinfections among pregnant women in a schistosome-endemic region of the Democratic Republic of Congo. Am J Trop Med Hyg. 2019;101(4):828–836. https://doi.org/10.4269/ajtmh.19-0024
47. Bustinduy AL, Stothard JR, Friedman JF. Paediatric and maternal schistosomiasis: Shifting the paradigms. Br Med Bull. 2017;123(1):115–125. https://doi.org/10.1093/bmb/ldx028
48. Hotez PJ, Harrison W, Fenwick A, et al. Female genital schistosomiasis and HIV/AIDS: Reversing the neglect of girls and women. PLoS Negl Trop Dis. 2019;13(4);e0007025. https://doi.org/10.1371/journal.pntd.0007025
49. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: A systematic analysis of population-representative data. Lancet Glob Health. 2013;1(1):e16–e25. https://doi.org/10.1016/S2214-109X(13)70001-9
50. Adenowo AF, Oyinloye BE, Ogunyinka BI, Kappo AP. Impact of human schistosomiasis in sub-Saharan Africa. Brazilian J Infect Dis. 2015;19(2):196–205. https://doi.org/10.1016/j.bjid.2014.11.004
51. Kleppa E, Klinge KF, Galaphaththi-Arachchige H-N, et al. *Schistosoma haematobium* infection and CD4 + T-cell levels: A cross-sectional study of young South African women. PLoS One. 2015;10(3):e0119326. https://doi.org/10.1371/journal.pone.0119326
52. Galappaththi-Arachchige HN, Holmen S, Koukounari A, et al. Evaluating diagnostic indicators of urogenital *Schistosoma haematobium* infection in young women: A cross sectional study in rural South Africa. PLoS One. 2018;13(2):e0191459. https://doi.org/10.1371/journal.pone.0191459
53. Lo NC, Gurarie D, Yoon N, et al. Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis. Proc Natl Acad Sci USA. 2018;115(4):E584–E591. https://doi.org/10.1073/pnas.1708729114
54. Olveda RM, Acosta LP, Tallo V, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: A phase 2, randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2016;16(2):199–208. https://doi.org/10.1016/S1473-3099(15)00345-X
55. Doenhoff MJ, Pica-Mattoccia L. Praziquantel for the treatment of schistosomiasis: Its use for control in areas with endemic disease and prospects for drug resistance. Expert Rev Anti-Infect Therapy. 2006;4(2):199–210. https://doi.org/10.1586/14787210.4.2.199
56. World Health Organization. Strategy: Control and preventive chemotherapy [homepage on the Internet]. Geneva: WHO; 2014 [cited 2018 Jan 19]. Available from: http://www.who.int/schistosomiasis/strategy/en/
57. Berge ST, Kabatereine N, Gundersen SG, et al. Generic praziquantel in South Africa: The necessity for policy change to provide cheap, safe and effcacious schistosomiasis drugs for the poor, rural population. *S Afr J Epidemiol Infect.* 2011;26(1):22–25. https://doi.org/10.1080/10158782.2011.11441415
58. Friedman JF, Olveda RM, Mirochnick MH, Bustinduy AL, Elliott AM. Praziquantel for the treatment of schistosomiasis during human pregnancy. Bull World Health Organization. 2018;96(1):59–65. https://doi.org/10.2471/BLT.17.198879
59. World Health Organistation. Report of the WHO informal consultation on schistosomiasis control. Geneva: World Health Organization; 1998.
60. World Health Organization. Preventive chemotherapy in human helminthiasis: Coordinated use of anthelminthic drugs in control interventions: A manual for health professionals and programme managers. Geneva: World Health Organization; 2006.
61. Adam I, El Elwasila T, Homeida M. Is praziquantel therapy safe during pregnancy? Trans Royal Soc Trop Med Hygiene. 2004;98(9):540–543. https://doi.org/10.1016/j.trstmh.2004.01.001
62. Ndibazza J, Muhangi L, Akishule D, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: A randomized controlled trial. Clin Infect Dis. 2010;50(4):531–540. https://doi.org/10.1086/649924