Tabari Biomedical Student Research Journal

OPEN ACCESS

REVIEW: A Review on the Clinical Symptoms and Treatment Methods of Human Hookworm Infections

Mahdi Shooraj Student Research Committee, Amol School of Paramedical Sciences, Mazandaran University of Medical Sciences, Sari, Iran.

Seif Ali Mahdavi Department of Paramedicine, Amol School of Paramedical Sciences, Mazandaran University of Medical Sciences, Sari, Iran.

ARTICLE INFO

Submitted: 30 Oct 2021
Accepted: 17 Mar 2022
Published: 04 Sep 2022

Keywords:
Clinical symptoms;
Hookworm;
Infection;
Treatment

Correspondence:
Seif Ali Mahdavi, Department of Paramedicine, Amol School of Paramedical Sciences, Mazandaran University of Medical Sciences, Sari, Iran.
Email:
sa.mahdavi@mazums.ac.ir
ORCID: 0000-0003-1522-7796

Citation:
Shooraj M, Mahdavi SA. A Review on the Clinical Symptoms and Treatment Methods of Human Hookworm Infections. Tabari Biomed Stu Res J. 2022;4(3):28-39.

10.18502/tbsrj.v4i3.10515

ABSTRACT

Introduction: Hookworm infection has overwhelmed human beings for ages and there are explanations about helminths in the primary medicinal manuscripts from 1500 BC. Hookworm is one of the immense three Soil-Transmitted Helminths (STH) (Ascaris Lumbricoides, Trichuris Trichiura, and hookworm). The goal of this study is to review the prevailing studies on Hookworm infection, clinical symptoms, prevention and treatment to examine different findings in this dominion.

Material and Methods: In the present investigation, the databases of PubMed, Google Scholar, IranDoc and SID were examined from 2000 to 2021 and related articles were reviewed.

Results: Review of related investigations revealed that nearly, 2 billion individuals are affected with these helminths around the world and the infection encumbrance might approach malaria. Hookworm infection diagnosis relies on fecal trials, either microscopic or molecular. This infection causes intestinal blood loss, which lead to anemia. In this regard, school-aged children and pregnant women are individuals at the highest risk of infections.

Conclusion: Several aspects such as warm and moist environment, polluted water supply, and poor hygiene affect transmission rate. Besides, some risk factors such as agricultural occupation, barefoot walking, exposure to infected soil, poor environmental sanitation, low socioeconomic background, poor personal hygiene, host age, genetics, and nutritional aspects affect both STH transmission and infection. Clinical symptoms of hookworm contagions are frequently non-specific and could be confusing. Thus, attention to the epidemiology, clinical factors, and laboratory results are significant for examination process. Now more than ever, new plans are needed to regulate hookworm and other STH infections.

Introduction

Hookworms are blood-feeding intestinal parasites that usually get transmitted through infested soil (1, 2). Human hookworm disease, a STH infection, denotes chiefly to the iron-deficiency anemia that results from moderate or heavy contagion (3, 4). It is viewed as the most significant mistreated tropical illness and the most significant factor for all human parasitic contagions (3). Besides, it can cause a great problem of morbidity and mortality in developing countries mainly for poor inhabitants. It accounts for approximately 85% of the Neglected Tropical Disease (NTD) problem (5, 6). Presently, hookworm distresses approximately 500 million individuals, with 5.1 billion at risk of infection worldwide (7). They can live for

[DOI: 10.18502/tbsrj.v4i3.10515]

periods in the gastrointestinal tract in spite of immune attack directing hundreds of antigens (8).

Human hookworm infection is generated by two principal nematode parasite species. Necator Americanus or Anclystoma Duodenale, are a main reason of illness and mostly affect poorest individuals in tropical and subtropical areas (1, 2).

Adult parasites which live in the host small intestine, ingest the blood, lead to chronic contagion of the intestinal zone, suck host's blood, break the erythrocytes, and reduce the hemoglobin by attaching to the gut wall and cause anemia in most cases (1, 2, 9). The subsequent anemia can result in stunted development and cognitive shortfalls, intellectual problems in children, abridged work ability in adults, and reduced fertility (9-11).

Methods

In this investigation, related articles were reviewed based on keywords and phrases such as nematode parasites, hookworm infections, Ancylostoma Duodenale and Necator Americanus in PubMed, Google Scholar, IranDoc and SID (Scientific Information Database) databases from 2000 to 2021.

Results

In the following section, the hookworm epidemiology, pathophysiology, coinfection and comorbidities, hookworm infection initiation, infection features, clinical symptoms, diagnosis techniques, treatment approaches and vaccine development will be discussed thoroughly.

Epidemiology

In 1900s hookworm infection was known as a major reason of anemia and productivity challenge in the southern part of US (12).

Hookworm's recent circulation is limited mostly to low and middle-income nations, with the highest occurrence in sub-Saharan Africa and parts of Asia. Hookworm excessively affects about 2 billion poorest individuals all over the world (3).

Likewise, infection in developing countries result in economic problems due to anemia and it has worsened the poverty and disease. Necator Americanus is the main source of hookworm infections globally, while Ancylostoma Duodenale inclines to be widespread to the Mediterranean area, northern India and China (1).

Currently, Ancylostoma Ceylanicum is regarded as an important basis of zoonotic contagions in some parts of Asia. Although Ancylostoma caninum, a dog hookworm, will not result in blood loss, but it might be the basis of enteritis and ileitis. It worth pointing that, Ancylostoma braziliense is one of the causes of cutaneous larva migration (7, 13).

In this regard, a study conducted by Walana, Kofi Aidoo and Kofi Tay in (2014) revealed that the hookworm infestation was normally high between April and August (2).

Pathophysiology

In human, entrance through the skin is tracked within 10 days by larval migration to the lungs (4). After skin penetration, the third-stage larva make its way to the peripheral vasculature, where it inactively brushed through the bloodstream, firstly to the right side of the heart and later to the pulmonic vasculature (1, 7). During respiratory migration, it may lead to type-1 hypersensitivity response within the alveoli which result in cough and sore throat (1, 4).

It worth noting that when infection with Ancylostoma Duodenale happens via oral track, the initial immigrations of L3 result in a syndrome known as Wakana illness, which is determined by nausea, vomiting, pharyngeal irritation, cough and dyspnea (4). Here the high levels of IgE happens due to migrations of third-stage larvae to the lungs and intestines (14).

The point is that pulmonary hookworm infection is like Löffler's syndrome in the lung. Hardly ever pneumonitis convoys cutaneous larvae migrations. Hookworm pneumonitis may last for more than a month, until the larvae quit the lungs and moves

[DOI: 10.18502/tbsrj.v4i3.10515]

toward the gastrointestinal tract (4, 15). L3 reach the pharynx and enter the gastrointestinal tract (12). Then reach the duodenum, and become L5 immature worm. In this case they can use their cutting plates or teeth for being attached into the host's intestinal mucosa to simplify feeding and avoid being ejected by gut peristalsis (1, 12). Ingestion of blood is aided by metalloproteases and anticoagulant peptides, which reserve the movement of liquid blood via mucosal wound. Though, the procedure through which hemoglobin is distributed in the parasite gut is not completely clear (1).

Worms mature in 4 to 6 weeks into sexually dioecious adult parasites (12). The female produces up to 30000 eggs per day after mating, which are displaced from the host via feces to pass the life cycle (1). It worth mentioning that the procedure of L3 attack takes nearly 6 to 8 weeks for Necator Americanus and perhaps a similar period for Ancylostoma Duodenale (12).

Coinfection and comorbidities

Reviews of associated researches approve that school-aged children and pregnant women are particularly at risk of malaria and hookworm co-infections (16, 17). Hookworm illness is because of intestinal blood loss while malaria-induced anemia is due to haemolysis, splenic sequestration and dyserythropoiesis. Therefore, these infections can produce comorbidities which result in anemia, although, this clinical symptom is formed via various mechanisms (12).

Likewise, co-infections of hookworms and schistosomes are communal in Africa (18). Besides, anemia caused by schistosomiasis is outcome of chronic irritation and blood loss. The point is that triple infection with hookworms, schistosomes and P. falciparum may syndicate to produce a 'perfect storm' of anemia, which is a major issue, particularly in Africa (19).

Hookworm infection initiation

Transmission happens based on multiple elements like warm and moist environment, poor hygiene, and polluted water source (4, 12, 20, 21). A number of risk factors are related with STH transmission. They include barefoot walking, exposure to infected soil, poor environmental hygiene, poor personal sanitation, low socioeconomic background, host age, agricultural occupation, nutritional problems and genetic aspects (1, 3, 22-24). Concerning this issue, children and pregnant women are at the maximum risk (1). In spite of global efforts for managing hookworm and other STH contagions, little development has occurred in this realm. Thus, new strategies are desired to deal with this issue (12).

The possible reason of infection may be due to inappropriate latrine application, inaccessibility of safe water, and lack of hand washing after toilet (25). The findings of related studies at Teda health Center in Ethiopia showed significant connection between barefoot walking and hookworm contagions. It exactly occurs when the infective filariform hatch in the soil and enter human skin (26-28). Additionally, recent study revealed that children who did not wash their hands before meals might be infected with hookworms more than the other children (29).

Likewise, pregnancy is considered as vulnerable time for hookworm infection (30). Some studies highlighted that Iron Deficiency Anemia (IDA) in pregnancy can bring about poor outcomes for both the mother and the baby in resource-limited countries which lead to reduced fertility, maternal morbidity and mortality and reduced child survival (31-34). According to some studies on infant birth outcomes, maternal hookworm infection was associated with low infant birth weight, preterm delivery and infant anemia (35-38).

Furthermore, women of childbearing are also at superior risk of hookworm contagions, which can be deteriorated by mixture of low dietary iron consumption and blood loss either from menstruation or pregnancy (12).

On the other hand, the pediatric physical significances of hookworm contagions comprise reduced pubertal and post-pubertal growth and fitness. Studies in 1920s revealed that moderate and heavy hookworm contagions was associated to abridged

[DOI: 10.18502/tbsrj.v4i3.10515]

intelligence. Similarly, recent investigations have supported the link between hookworm contagion and cognitive challenges in children (39-42).

Infection features

It worth mentioning that the clinical symptoms of hookworm infections are typically non-specific and deceptive. Concerning diagnosis procedure understanding the epidemiology, clinical features, and laboratory decisions are vigorous in this regard (12, 43). Hookworm infection can lead to gastrointestinal blood loss, shortage of energy, discrepancies of protein and zinc. Besides, it can result in malnutrition and anemia in infected person (44). The main clinical indicators of hookworm contagion are the significances of chronic intestinal blood loss (45).

Capillaries and arterioles are broken not only mechanically but also chemically via hydrolytic enzymes (46). Infection with Ancylostoma Duodenale leads to more blood loss in comparison with Necator Americanus; thus, the degree of IDA is determined by the type of nematode (47).

Adult hookworms ingest about 0.001 ml of blood each day, but the quantity of blood loss at the attachment site is greater, such that moderate or heavy Necator Americanus contagions might cause more than 1 ml blood loss per day (48, 49). Heavy hookworm infections can cause immediate protein loss, which leads to hypoalbuminemia and hypoproteinemia which result in anasarca, malnutrition and abdominal distension. In this case, the skin of infected person is yellowish which is mentioned as ‘chlorosis’ in the literature dating back to the third century BC (50).

Regarding this outlook, the blood loss in severe cases might reach up to 9.0 mL per day and happens by two mechanisms. Firstly, through consumption of the parasite, which accounts for a small portion of blood loss. Secondly, the main loss occurs through the attachment site by leakage around it (1). In such cases anemia happens when blood loss surpasses iron and protein consumption and host becomes incapable to recompensate for blood loss, particularly in heavy infections and nutritionally deprived people (4). Moreover, hookworms result in additional blood loss from the damaged gut wall, by changing their feeding sites (2).

The major challenge for anemia is the worm burden. Anemia could happen with a lower worm burden among children. Additionally, individuals with hookworm infections have a wider variety of gut microbiota. This issue encouraged research into the possible use of hookworms to treat immune-mediated gastrointestinal diseases like celiac disease and inflammatory bowel disease (12, 43, 51].

The significant point is that, eosinophilia increases suspicion of hookworm contagion. Systemic and mucosal eosinophilia is observed in hookworm infections (12). Systemic eosinophilia can be apparent within 4 weeks of Necator Americanus infection and it peaks at 6 to 12 weeks as the young adult hookworms reach the small bowel. Besides, flatulence is common in the first 12 weeks and gastrointestinal disturbance is described within the first 3 to15 weeks (52).

In addition, findings of a study conducted on 1,449 adults older than 50 years old in Uganda, revealed that the greatest risk factors for IDA were heavy hookworm load and malaria (45). Heavy hookworm burden in nutritionally deprived adults is adequate to understand IDA with haemoglobin levels of lower than 11 g per dl. On the other hand, in children IDA occurs with lower burden than adults (10). In this regard, the result of a study on 3,600 children from Pemba Island showed that contagion with Necator Americanus resulted in a lower rate of IDA than coinfection with both Necator Americanus and Ancylostoma Duodenale (45). Research findings showed the link between moderate and heavy hookworm burdens and IDA among children and adults (31, 53).

Moreover, moderate and heavy hookworm infections cause hypoalbuminaemia and hypoproteinaemia. In challenging cases, this might lead to kwashiorkor (12). In early twentieth century in China, mixture of chlorosis, anemia, protein losses, and chronic

[DOI: 10.18502/tbsrj.v4i3.10515]

hookworm infection was considered as the 'yellow puffy disease' (54).

Children with a microcytic hypochromic anemia will face stunted growth. This factor is particularly obvious around puberty when diseased youths fail to attain their predictable growth. Intellectual and cognitive problems are likely, but these can be tough to measure (55, 56).

Clinical symptoms

Hookworm infections are frequently asymptomatic. Symptoms are generally associated with the parasite growth and the affected host (1). It happens during skin penetration in the form of a localized erythema (20, 43). Hookworm leads to disease mostly via chronic intestinal blood loss (3). In this regard, light hookworm burden may be asymptomatic but moderate or heavy infection lead to palpitations, exertional dyspnea, fatigue, headache, and epigastric pain (3, 57).

Although mild anemia might be asymptomatic, it can cause tachycardia, weakness, shortness of breath, and poor awareness (58). In addition to anemia, high worm burdens of the two main human hookworm species, Ancylostoma Duodenale and Necator Americanus, can lead to loss of appetite, diarrhea, weight loss and abdominal pain (59, 60). It worth mentioning that during the pulmonary stage infected people would experience cough, sneeze, bronchitis, hemoptysis, and eosinophilic pneumonia (1). The parasite uses broad-spectrum protease inhibitors in response to the host's immune defenses. It assists the parasite to protect itself from proteolytic enzymes. Moreover, it persuades apoptosis of T lymphocytes which result in local immune response (1).

Possibly the most commonly zoonotic hookworm is Ancylostoma braziliense (61). Percutaneous entry of Ancylostoma braziliense L3 does not cause ground itch in humans but can cause cutaneous larva migrants, which is a 1–5 cm tunnels through the epidermis. Cutaneous larva migrants are encountered in military personnel and travelers from tropical locations. In some instances, Ancylostoma braziliense larvae may go to the lungs and lead to pulmonary infiltrates (62), while, in common cases, the infection does not progress beyond cutaneous larva migrants (12).

Diagnosis techniques

Fecal trials, either microscopic or molecular are vital to diagnose hookworm infection (63). Although, stool microscopy is a supportive analysis aid, it has some limitations. It is beneficial in classifying and counting hookworm eggs. Hospital laboratories use egg concentration techniques, besides, simple tests like Kato-Katz techniques are accessible. Such techniques are applied in epidemiological investigations as they offer indirect measure of worm burden (13, 43).

As hookworms are digestive system parasites, the diagnosis process requires investigation of fresh faecal samples. Hookworm eggs, larvae and whole or parts of the parasites can be investigated in this procedure. In fact, faeces must be fixed or frozen within 24 hours of collection, before the eggs hatch into larvae. The important point is that egg production does not happen regularly and can be influenced by the host's nutritional condition.

Also, the constancy of the faeces can definitely affect the number of eggs per gram in faeces, which makes it an untrustworthy for measuring the number of worms in the gut (12).

Microscopic examination methods include Direct Wet Mount Microscopy, Formol-Ether Concentration, Kato-Katz Technique, McMaster and Test Tube Flotation. Furthermore, Capsule endoscopy may display parasites, but it is hardly used to identify infection. Computer-assisted discovery of hookworms on capsule endoscopy imageries is still thought-provoking. The final objective in this realm is to use automatic discovery models for analysis which is more precisely than practiced endoscopists (12, 43, 64).

Treatment approaches

[DOI: 10.18502/tbsrj.v4i3.10515]

The two frequently used benzimidazole-anthelmintic-drugs for Necator Americanus and Ancylostoma Duodenale infections are mebendazole and albendazole. These medicines constrain microtubule polymerization in invertebrates, which kill adult worms. Both Necator Americanus and Ancylostoma Duodenale have parallel vulnerability to benzimidazoles. Though, there are significant differences in therapeutic effectiveness between mebendazole and albendazole. A single 400 mg dose of albendazole is more beneficial than a single 500 mg dose of mebendazole. In this regard, findings of a current research concerning the treatment for hookworm infection showed an overall cure rate of 72% for a single dose of albendazole and 15% for a single dose of mebendazole (65). Likewise, findings of the other study on 1,845 schoolchildren showed an overall cure rate of 87.8% for a single dose of albendazole. It worth noting that this rate varies significantly across different age groups, countries and strength of infection (66).

Although three successive daily doses of either drug approve egg reduction rates and better treatment, it is less suitable for mass treatment movements. Instead, a 3-day routine of 100 mg twice daily, mebendazole, is appropriate for stable uncomplicated cases. Similarly, pyrantel pamoate 11 mg/kg (up to a maximum of 1 g) orally daily for three days could be an accessible option (12).

Thus, the efficiencies of benzimidazole drugs in treatment can be flexible. Astonishingly high rates of single dose drug failure are reported for both mebendazole and albendazole (67, 68). In such cases the observed failures of mebendazole or albendazole in treatment of human hookworm infections are not clear. Frequent use of mebendazole in the same societies has been linked with diminishing efficacy over time. Although it recommends the advent of drug resistance, this hypothesis is still debatable (69). Besides, resistance to benzimidazoles is observed in intestinal nematodes contaminating livestock which is connected to mutations in the β-tubulin gene in the parasite genome (70). Consequently, it merits to investigate albendazole and mebendazole failure in treatment of hookworm and other STH contagions (71).

There have been doubts about the use of these drugs in children younger than 1 year old and in pregnant women. Currently, a study of nearly 800 women who were treated with albendazole during the second and third trimesters showed no opposing effects (72). WHO highlighted that albendazole and mebendazole are practically safe in children older than 1-year-old. However, no formal studies were conducted on children younger than 2 years old, both drugs have been extensively used to treat entire communities regardless of the individuals' age range (73, 74).

Definitely, anthelmintic drugs are extensively applied and their treatment effectiveness differs based on the age groups, geographical distribution and harshness of infection. Findings of a recent study showed that the efficacy of single dose oral albendazole, mebendazole, and pyrantel pamoate against hookworm infections was 72%, 15%, and 31% (65). It worth noting that both mebendazole and albendazole are safe with some side effects such as dizziness, headache, and abdominal upset (12, 75). Due to absenteeism of a defensive immune response, reinfection can occur within 4 to 6 months in high transmission areas (76).

Control actions for hookworm and STHs infections includes shoe wearing plans, water sanitation, hygiene and preventive chemotherapy movements (9). WASH programs try to interrupt hookworm transmission through some mechanisms. Firstly, via health education, application of latrines and treatment of human waste to decrease ground defecation behavior. These interferences can stop fecal eggs from reaching the soil. Secondly, via access to clean water and promotion of hand washing (77).

Although hookworm infection has been eradicated via economic growth in Japan, South Korea, United States and western European countries, the illness burden

[DOI: 10.18502/tbsrj.v4i3.10515]

remained high in low-income and middle-income countries (78).

Pyrantel pamoate and levamisole are the alternative drugs but none of them is as effective as albendazole. Both of these drugs affect the function of nicotinic acetylcholine receptors on the body muscles of hookworms, which leads to depolarization of muscle cells and spastic paralysis which cause exclusion of the worm from the gastrointestinal tract (79). Asynthetic derivative of amidantel is Tribendimidine which act as a nicotinic acetylcholine receptor agonist. It is considered as a highly active treatment against hookworm infection in animals and human beings (80). It was initially presented in the 1980s in China, where it was listed for human use in 2004, but no other country has accepted it yet (81).

The use of accessible drugs and the growth of new ones are significant issue. They are significant investments towards economic development and enhanced sanitation in endemic and resource-limited regions. Though, merely drugs cannot remove hookworm infection, particularly due to the inconsistency of mebendazole and albendazole efficiencies (12). Although multiple medicines are offered for treatment of hookworm infections, prevention is a vital step to deal with these problems (5, 6, 12).

Vaccine development

A human hookworm vaccine would signify a leap to global eradication. Much investigation is needed for biomedical experts, public health workers and clinicians to wipe out hookworm infection from countries (12).

Other approaches to this global health risk include application of a new human hookworm vaccine under development either alone or mutually directed with a new malaria vaccine, which might result in noteworthy benefit precisely for pregnant women (78).

Conclusion

Definitely, the capability of hookworms to evade the immune system may hold the key to the control of modern day immune and metabolic illnesses. It is regarded as the most important NTD. Besides, human hookworm infection is one of the most universal illnesses for people who live in extreme poverty. Due to hookworm's particular effect on agricultural worker output especially in north of Iran, its prevention requires to be better arranged by the finance ministers, and global leaders who wish to present or develop interventions that endorse people's health and empowerment. The review of related studies revealed the association between occurrence and transmission is not determined and it depends on the grade of organism aggregation in societies.

Thus, informing people to avoid specific behaviors such as barefoot walking, exposure to infected soil, poor personal hygiene and poor environmental sanitation, can control and even prevent infection prevalence in their living zone.

Acknowledgments

The present study has been approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC. 1400.238). The authors of the article express their gratitude to the Vice-Chancellor of Research and Technology and Student Research Committee of Mazandaran University of Medical Sciences for supporting this project.

Conflicts of interest

Authors declare no conflict of interests.

Authors' contributions

All authors have intellectually committed to the study design and process. The final manuscript was revised and accepted by all authors.

Funding

The funding was provided by Mazandaran University of Medical Sciences.

References

[DOI: 10.18502/tbsrj.v4i3.10515]

1. Ghodeif AO, Jain H. Hookworm. InStatPearls [Internet] 2021 Jan 27. StatPearls Publishing.
2. Zeleke AJ, Addisu A, Derso A, Tegegne Y, Birhanie M, Sisay T, et al. Evaluation of Hookworm Diagnosis Techniques from Patients in Debre Elias and Sanja Districts of the Amhara Region, Ethiopia. Journal of parasitology research. 2021;2021.
3. Hotez PJ. Forgotten people, forgotten diseases: the neglected tropical diseases and their impact on global health and development. John Wiley & Sons; 2021.
4. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. Hookworm infection. New England Journal of Medicine. 2004;351(8):799-807.
5. Wei KY, Yan Q, Tang B, Yang SM, Zhang PB, Deng MM, et al. Hookworm infection: a neglected cause of overt obscure gastrointestinal bleeding. The Korean journal of parasitology. 2017;55(4):391.
6. Periago MV, Bethony JM. Hookworm virulence factors: making the most of the host. Microbes and infection. 2012;14(15):1451-64.
7. Albonico M, Savioli L. Hookworm: a neglected resurgent infection.
8. Tang YT, Gao X, Rosa BA, Abubucker S, Hallsworth-Pepin K, Martin J, et al. Genome of the human hookworm Necator americanus. Nature genetics. 2014;46(3):261-9.
9. Haldeman MS, Nolan MS, Ng'habi KR. Human hookworm infection: Is effective control possible? A review of hookworm control efforts and future directions. Acta tropica. 2020;201:105214.
10. Olsen A, Magnussen P, Ouma JH, Andreassen J, Friis H. The contribution of hookworm and other parasitic infections to haemoglobin and iron status among children and adults in western Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998;92(6):643-9.
11. Koukounari A, Estambale BB, Njagi JK, Cundill B, Ajanga A, Crudder C, et al. Relationships between anaemia and parasitic infections in Kenyan schoolchildren: a Bayesian hierarchical modelling approach. International journal for parasitology. 2008;38(14):1663-71.
12. Loukas A, Hotez PJ, Diemert D, Yazdanbakhsh M, McCarthy JS, Correa-Oliveira R, et al. Hookworm infection. Nature Reviews Disease Primers. 2016;2(1):1-8.
13. Brooker S, Bethony J, Hotez PJ. Human hookworm infection in the 21st century. Advances in parasitology. 2004;58:197.
14. Maxwell C, Hussain R, Nutman TB, Poindexter RW, Little MD, Schad GA, et al. The clinical and immunologic responses of normal human volunteers to low dose hookworm (Necator americanus) infection. The American journal of tropical medicine and hygiene. 1987;37(1):126-34.
15. Feldmeier H, Schuster A. Mini review: hookworm-related cutaneous larva migrans. European journal of clinical microbiology & infectious diseases. 2012;31(6):915-8.
16. Brooker S, Akhwale W, Pullan R, Estambale B, Clarke SE, Snow RW, et al. Epidemiology of plasmodium-helminth co-infection in Africa: populations at risk, potential impact on anemia, and prospects for combining control. The American journal of tropical medicine and hygiene. 2007;77(6_Suppl):88-98.
17. Brooker S, Clements AC, Hotez PJ, Hay SI, Tatem AJ, Bundy DA, et al. The co-distribution of Plasmodium falciparum and hookworm among African schoolchildren. Malaria journal. 2006;5(1):1-8.
18. Raso G, Vounatsou P, Singer BH, Eliézer KN, Tanner M, Utzinger J. An integrated approach for risk profiling and spatial prediction of Schistosoma mansoni–hookworm coinfection. Proceedings of the National Academy of Sciences. 2006;103(18):6934-9.
19. Hotez PJ, Molyneux DH. Tropical Anemia: One of Africa's Great Killers and a Rationale for.
20. Parija SC, Chidambaram M, Mandal J. Epidemiology and clinical features of soil-transmitted helminths. Tropical parasitology. 2017;7(2):81.

[DOI: 10.18502/tbsrj.v4i3.10515]

21. Jiraanankul V, Aphijirawat W, Mungthin M, Khositnithikul R, Rangsin R, Traub RJ, et al. Incidence and risk factors of hookworm infection in a rural community of central Thailand. The American journal of tropical medicine and hygiene. 2011;84(4): 594.
22. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. The lancet. 2006;367(9521):1521-32.
23. De Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L. Soil-transmitted helminth infections: updating the global picture. Trends in parasitology. 2003;19(12):547-51.
24. Mabaso ML, Appleton CC, Hughes JC, Gouws E. The effect of soil type and climate on hookworm (Necator americanus) distribution in KwaZulu-Natal, South Africa. Tropical Medicine & International Health. 2003;8(8):722-7.
25. Shiferaw MB, Mengistu AD. Helminthiasis: hookworm infection remains a public health problem in Dera District, South Gondar, Ethiopia. PLoS One. 2015;10(12): e0144588.
26. Abate A, Kibret B, Bekalu E, Abera S, Teklu T, Yalew A, et al. Cross-sectional study on the prevalence of intestinal parasites and associated risk factors in Teda Health Centre, Northwest Ethiopia. International Scholarly Research Notices. 2013;2013.
27. Alemu A, Atnafu A, Addis Z, Shiferaw Y, Teklu T, Mathewos B, et al. Soil transmitted helminths and Schistosoma mansoni infections among school children in Zarima town, northwest Ethiopia. BMC infectious diseases. 2011;11(1):1-7.
28. Ziegelbauer K, Speich B, Mäusezahl D, Bos R, Keiser J, Utzinger J. Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis. PLoS medicine. 2012;9(1): 1001162.
29. Punsawad C, Phasuk N, Bunratsami S, Thongtup K, Viriyavejakul P, Palipoch S, et al. Prevalence of intestinal parasitic infections and associated risk factors for hookworm infections among primary schoolchildren in rural areas of Nakhon Si Thammarat, southern Thailand. BMC Public Health. 2018;18(1):1-7.
30. Kassebaum NJ, GBD 2013 Anemia Collaborators. The global burden of anemia. Hematology/oncology clinics of North America. 2016;30(2):247-308.
31. Brooker S, Hotez PJ, Bundy DA. Hookworm-related anaemia among pregnant women: a systematic review. PLoS neglected tropical diseases. 2008;2(9):e291.
32. Hotez P, Whitham M. Helminth infections: a new global women's health agenda. Obstetrics & Gynecology. 2014;123 (1):155-60.
33. Blackwell AD, Tamayo MA, Beheim B, Trumble BC, Stieglitz J, Hooper PL, et al. Helminth infection, fecundity, and age of first pregnancy in women. Science. 2015;350 (6263):970-2.
34. Christian P, Khatry SK, West Jr KP. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. The Lancet. 2004;364(9438):981-3.
35. Yatich NJ, Jolly PE, Funkhouser E, Agbenyega T, Rayner JC, Ehiri JE, et al. The effect of malaria and intestinal helminth coinfection on birth outcomes in Kumasi, Ghana. The American journal of tropical medicine and hygiene. 2010;82(1):28.
36. Ojurongbe O, Okorie PN, Opatokun RL, Ojurongbe TA, Mabayoje VO, Olowe OA, et al. Prevalence and associated factors of Plasmodium falciparum and soil transmitted helminth infections among pregnant women in Osun state, Nigeria. African health sciences. 2018;18(3):542-51.
37. Fairley JK, Bisanzio D, King CH, Kitron U, Mungai P, Muchiri E, et al. Birthweight in offspring of mothers with high prevalence of helminth and malaria infection in coastal Kenya. The American journal of tropical medicine and hygiene. 2013; 88(1):48.
38. McClure EM, Meshnick SR, Mungai P, Malhotra I, King CL, Goldenberg RL, et al. The association of parasitic infections in pregnancy and maternal and fetal anemia: a cohort study in coastal Kenya. PLoS

[DOI: 10.18502/tbsrj.v4i3.10515]

neglected tropical diseases. 2014;8(2):2724.
39. Hotez PJ, Ferris MT. The antipoverty vaccines. Vaccine. 2006;24(31-32):5787-99.
40. Smillie WG, Augustine DL. Hookworm infestation: the effect of varying intensities on the physical condition of school children. American Journal of Diseases of Children. 1926;31(2):151-68.
41. Smillie WG, Spencer CR. Mental retardation in school children infested with hookworms. Journal of Educational Psychology. 1926;17(5):314.
42. Sakti H, Nokes C, Subagio Hertanto W, Hendratno S, Hall A, Bundy DA. Evidence for an association between hookworm infection and cognitive function in Indonesian school children. Tropical Medicine & International Health. 1999;4(5): 322-34.
43. Jourdan PM, Lamberton PH, Fenwick A, Addiss DG. Soil-transmitted helminth infections. The Lancet. 2018;391(10117): 252-65.
44. Skolnik RL, Ahmed A. Ending the neglect of neglected tropical diseases. Population Reference Bureau; 2010.
45. Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. Nutrition reviews. 1997;55(6):223-32.
46. Skolnik RL, Ahmed A. Ending the neglect of neglected tropical diseases. Population Reference Bureau; 2010.
47. Albonjco M, Stoltzfus RJ, Savioli L, Tielsch JM, Chwaya HM, Ercole E, Cancrini G. Epidemiological evidence for a differential effect of hookworm species, Ancylostoma duodenale or Necator americanus, on iron status of children. International Journal of Epidemiology. 1998; 27(3):530-7.
48. Layrisse M, Linares J, Roche M, Ojeda A, Carstens A, Dugarte I. Excess hemolysis in subjects with severe iron deficiency anemia associated and nonassociated with hookworm infection. Blood. 1965;25(1):73-91.
49. Crompton DW. The public health importance of hookworm disease. Parasitology. 2000;121(S1):S39-50.
50. Hoeppli R. Parasites and parasitic infections in early medicine and science. Parasites and Parasitic Infections in Early Medicine and Science. 1959.
51. Pearson MS, Tribolet L, Cantacessi C, Periago MV, Valerio MA, Jariwala AR, et al. Molecular mechanisms of hookworm disease: stealth, virulence, and vaccines. Journal of allergy and clinical immunology. 2012;130(1):13-21.
52. Daveson AJ, Jones DM, Gaze S, McSorley H, Clouston A, Pascoe A, et al. Effect of hookworm infection on wheat challenge in celiac disease–a randomised double-blinded placebo controlled trial. PloS one. 2011;6(3):17366.
53. Smith JL, Brooker S. Impact of hookworm infection and deworming on anaemia in non-pregnant populations: a systematic review. Tropical medicine & international health. 2010;15(7):776-95.
54. Hotez PJ. China's hookworms. The China Quarterly. 2002;172:1029-41.
55. Dickson R, Awasthi S, Williamson P, Demellweek C, Garner P. Effects of treatment for intestinal helminth infection on growth and cognitive performance in children: systematic review of randomised trials. Bmj. 2000;320(7251):1697-701.
56. Jardim-Botelho A, Raff S, DeÁvila Rodrigues R, Hoffman HJ, Diemert DJ, Corrêa-Oliveira R, et al. Hookworm, Ascaris lumbricoides infection and polyparasitism associated with poor cognitive performance in Brazilian schoolchildren. Tropical Medicine & International Health. 2008;13(8): 994-1004.
57. Paniker CJ. Textbook of medical parasitology. Jaypee Brothers Medical Publishers (P) Ltd; 2007.
58. Ness TE, Agrawal V, Bedard K, Ouellette L, Erickson TA, Hotez P, et al. Maternal Hookworm Infection and Its Effects on Maternal Health: A Systematic Review and Meta-Analysis. The American Journal of Tropical Medicine and Hygiene. 2020;103 (5):1958-68.
59. Majid MF, Kang SJ, Hotez PJ. Resolving" worm wars": An extended comparison review of findings from key

[DOI: 10.18502/tbsrj.v4i3.10515]

economics and epidemiological studies. PLoS neglected tropical diseases. 2019;13 (3):0006940.
60. Lenk EJ, Redekop WK, Luyendijk M, Rijnsburger AJ, Severens JL. Productivity loss related to neglected tropical diseases eligible for preventive chemotherapy: a systematic literature review. PLoS neglected tropical diseases. 2016;10(2):0004397.
61. Bowman DD, Montgomery SP, Zajac AM, Eberhard ML, Kazacos KR. Hookworms of dogs and cats as agents of cutaneous larva migrans. Trends in parasitology. 2010;26(4):162-7.
62. Guill MA, Odom RB. Larva migrans complicated by Loeffler's syndrome. Archives of dermatology. 1978;114(10): 1525-6.
63. Verweij JJ. Application of PCR-based methods for diagnosis of intestinal parasitic infections in the clinical laboratory. Parasitology. 2014;141(14):1863-72.
64. Wu X, Chen H, Gan T, Chen J, Ngo CW, Peng Q. Automatic hookworm detection in wireless capsule endoscopy images. IEEE transactions on medical imaging. 2016;35(7): 1741-52.
65. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. Jama. 2008;299(16):1937-48.
66. Vercruysse J, Behnke JM, Albonico M, Ame SM, Angebault C, Bethony JM, et al. Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. PLoS neglected tropical diseases. 2011;5(3):948.
67. De Clercq D, Sacko M, Behnke J, Gilbert F, Dorny P, Vercruysse J. Failure of mebendazole in treatment of human hookworm infections in the southern region of Mali.
68. Soukhathammavong PA, Sayasone S, Phongluxa K, Xayaseng V, Utzinger J, Vounatsou P, et al. Low efficacy of single-dose albendazole and mebendazole against hookworm and effect on concomitant helminth infection in Lao PDR. PLoS neglected tropical diseases. 2012;6(1):1417.
69. Albonico M, Bickle Q, Ramsan M, Montresor A, Savioli L, Taylor M. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. Bulletin of the World Health Organization. 2003; 81:343-52.
70. Demeler J, Krüger N, Krücken J, von der Heyden VC, Ramünke S, Küttler U, et al. Phylogenetic characterization of β-tubulins and development of pyrosequencing assays for benzimidazole resistance in cattle nematodes. PloS one. 2013;8(8):70212.
71. Diawara A, Halpenny CM, Churcher TS, Mwandawiro C, Kihara J, Kaplan RM, et al. Association between response to albendazole treatment and β-tubulin genotype frequencies in soil-transmitted helminths. PLoS neglected tropical diseases. 2013;7(5): 2247.
72. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. The American journal of tropical medicine and hygiene. 2008;79(6):856-63.
73. Montresor A, Awasthi S, Crompton DW. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. Acta tropica. 2003;86(2-3):223-32.
74. World Health Organization. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months: Geneva, 8-9 April 2002. World Health Organization; 2003.
75. Hotez PJ, Beaumier CM, Gillespie PM, Strych U, Hayward T, Bottazzi ME. Advancing a vaccine to prevent hookworm disease and anemia. Vaccine. 2016;34(26): 3001-5.
76. Albonico M, Smith PG, Ercole E, Hall A, Chwaya HM, Alawi KS, et al. Rate of reinfection with intestinal nematodes after treatment of children with mebendazole or

[DOI: 10.18502/tbsrj.v4i3.10515]

albendazole in a highly endemic area. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1995;89(5):538-41.
77. Hürlimann E, Silué KD, Zouzou F, Ouattara M, Schmidlin T, Yapi RB, et al. Effect of an integrated intervention package of preventive chemotherapy, community-led total sanitation and health education on the prevalence of helminth and intestinal protozoa infections in Côte d'Ivoire. Parasites & vectors. 2018;11(1):1-20.
78. Bartsch SM, Hotez PJ, Hertenstein DL, Diemert DJ, Zapf KM, Bottazzi ME, et al. Modeling the economic and epidemiologic impact of hookworm vaccine and mass drug administration (MDA) in Brazil, a high transmission setting. Vaccine. 2016;34(19): 2197-206.
79. Köhler P. The biochemical basis of anthelmintic action and resistance. International journal for parasitology. 2001; 31(4):336-45.
80. Steinmann P, Zhou XN, Du ZW, Jiang JY, Xiao SH, Wu ZX, et al. Tribendimidine and albendazole for treating soil-transmitted helminths, Strongyloides stercoralis and Taenia spp.: open-label randomized trial. PLoS neglected tropical diseases. 2008;2(10):322.
81. Xiao SH, Utzinger J, Tanner M, Keiser J, Xue J. Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations. Acta tropica. 2013;126(2):115-26.

[DOI: 10.18502/tbsrj.v4i3.10515]