

A systematic review of human giardiasis in Bangladesh: public health perspective

Biplob Hossain (✉ bhossain@icddr.org)

icddr,b <https://orcid.org/0000-0002-4934-9866>

Humaira Rashid

International Centre for Diarrhoeal Disease Research Bangladesh

Zannatun Noor

International Centre for Diarrhoeal Disease Research Bangladesh

Mamun Kabir

International Centre for Diarrhoeal Disease Research Bangladesh

Sohag Miah

Shahjalal University of Science and Technology

Abdullah Siddique

International Centre for Diarrhoeal Disease Research Bangladesh

Rashidul Haque

International Centre for Diarrhoeal Disease Research Bangladesh

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Abstract

Background: Giardiasis identified as a leading cause of gastrointestinal pathogen in young children worldwide, is also common in Bangladesh. There has been an emerging evidence of an association between giardiasis and child growth. This systematic review focuses only on Bangladeshi children. Prevalence of giardiasis with its adverse health effects and the advancement of diagnosis has been reviewed.

Methods: A broad review of literature, electronic databases, and books within the time frame of 1970 and 2019 has been searched. Data published on giardiasis prevalence, outcomes (child growth, intestinal permeability, and diarrhea) and advances of diagnosis in Bangladesh has been searched.

Results: Both assemblages A and B genotypes of *Giardia lamblia* are responsible for human giardiasis in Bangladesh. Recent studies on Bangladeshi children suggested *Giardia* species infections has an adverse impact on poor child growth which have further characterized associations with altered gut epithelial barrier dysfunction, as well as diarrhea. Indeed emerging evidence indicates the key consequence of *Giardia* colonization is nutrient malabsorption.

Conclusions: In Bangladesh giardiasis remains a major public health concern, especially in children age <5 years but is considered as a neglected disease. In order to reduce the burden of giardiasis in developing countries such as Bangladesh, more focus is require to include this disease in public health policies.

Background

Giardiasis, one of the most frequent flagellated protozoan parasitic infection caused by *Giardia lamblia* (*Giardia duodenalis* and *Giardia intestinalis*), is considered to be a worldwide neglected disease (1). Giardiasis is more prevalent in children living in low hygiene settings with poor quality of water and overcrowding (2). In high-income countries, the prevalence of giardiasis in humans is low (1–7%), whereas in low-income countries it is highly prevalent (4–43%) (3, 4). It is one of the most common pathogens that causes diarrhea in people among developed and developing countries. The lifecycle of *Giardia* consists of two stages, trophozoites and infectious cysts. Transmission of giardiasis concede by the ingestion of infectious cysts, where 10 cysts is sufficient to acquire the illness. Clinical giardiasis causes vomiting, flatulence, abdominal pain, bloating and loss of weight following malabsorption (5, 6). Evaluation of *Giardia* contaminations that's asymptomatic, but it has the ability for the *Giardia* cyst transmission, differs from 5 to 15% (7). In Asia, Africa, and Latin America, 500,000 new cases of giardiasis are reported each year (8). *Giardia* infection prevalence rate less than 1% is intermittent, 1–10% is endemic and more than 10% is hyperendemic. According to the guidelines of the World Health Organization (WHO) there is sixteen endemic and four hyperendemic areas (9).

Giardia spp. can cause both acute and chronic diarrhea and can be presented as an asymptomatic infection (10) which leading to weight loss due to nutrients malabsorption (11). During acute *Giardia*

infection with diarrhea abdominal pain and the clinical manifestations of malabsorption are anticipated (12). On the other hand, chronic infection is associated with poor cognitive function as well as malnutrition and deficiencies in micronutrients including vitamin A, iron and anemia (10, 13, 14). The combination of these problems has an immense impact causing underweight and stunting in children. Although Bangladesh has made sustainable progress over the past few years, (15, 16) but we need to reduce the proportion of underweight children among under-5 children from 32.6–20% and stunting 36.1–25% to achieved sustainable development goals.

This is the first systematic review on possible health issues of giardiasis in Bangladesh. We investigated articles that published in 1970 to 2019 which convey giardiasis as a major public health concern in Bangladesh, especially in young children aged < 5 years old. This review specifically identified the prevalence rate, child growth status and diagnosis of giardiasis in Bangladesh, the most frequently found assemblages in humans giardiasis and its adverse health outcomes.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Several international journal databases and Bangladeshi journals were searched from 1970 to 2019 which have been published in English. International databases include Web of Science, PubMed, PLOS One, journal of Clinical Infectious Diseases (CID), American Journal of Tropical Medicine and Hygiene (AJTMH), Google Scholar along with Bangladeshi databases such as Bangladesh Journal of Scientific Research (BJSR), Dhaka University Journal of Biological Science (DUJBS), Bangladesh Journal of Zoology (BJZ) and Bangladesh Medical Research Council (BMRC) and others has been searched. This review identified research studies related to Giardia infection and its adverse health effects across Bangladeshi population using keywords such as "Giardiasis", "Giardia infection", "Human", "Adverse effects/disorder", "Bangladesh".

In this review we excluded articles that did not had proper information. And the articles were also omitted that had only information related to experimental method, molecular and biochemical analysis of Giardia. In fact, papers were also removed from the consideration without full text access after searching in other databases. The last date searched was November 30th, 2019.

Results

Description of the studies identified:

We found 187 titles on the initial search, of which only 17 met the inclusion criteria and were finally included for this systematic review. Figure 1 shows the way to get the articles used in this review according to PRISMA. Thus, in this review we included possible health risk of giardiasis from 17 articles.

Epidemiology:

Giardia infection occurs worldwide (17) with the highest burden of giardiasis borne by people living in developing countries, particularly the tropics and subtropics, where hygiene and sanitation are inadequate like Bangladesh. Giardiasis was estimated to be as high as 20 to 40% in resource-limited settings with the highest infection rate among children under the age of 5 (18). Diarrhea associated with intestinal protozoal parasites such as Giardia, Entamoeba and Cryptosporidium has been one of the main reasons of child mortality in developing countries in sub-Saharan Africa and South Asia, including Bangladesh (19, 20).

In low and middle-income countries (LMIC) such as Bangladesh, the exact burden of giardiasis is difficult to quantify as the reports can vary by geographic region, study design, sample size, incubation, severity of symptoms, and the sensitivity of the diagnostic method.

In a large case-control study conducted on 2534 patients in Bangladesh, association between infection with G. lamblia genotypes assemblage A and assemblage B were tested, where significant odds ratio for diarrhea was observed for assemblage A infections whereas assemblage B infection was associated with asymptomatic Giardia infection (21). In another study performed in an urban slum of Dhaka, Bangladesh, shown 31.1% of children had at least one episode of Giardia lamblia diarrheal infection in first 2 years of age (22).

Pathogenesis of Giardia spp.:

Pathogenesis and host response of Giardia infection are not fully understood. Following the swallow of Giardia cysts from contaminated food, water or interaction with infected human or animal excystation occurs in the human intestine, which released two to four trophozoites. Trophozoites are attached to the epithelial surface of the intestine through ventral adhesive disk. Consequently, diarrhea occurs in response to this tight attachment. (See Fig. 2)

This pathophysiological process leads to Enterocyte apoptosis, intestinal barrier failure, activation of host lymphocytes and villous atrophy. As a results disaccharides deficiencies, small bowel malabsorption, hypersecretion of anions, and increased rates of intestinal transit occurs into the human body (23–31).

Giardiasis And Poor Child Growth:

Associations between Giardia infection and child growth impairments varied by study, population and location, but children in Bangladesh are consistently associated with poor child growth with Giardia infection burdens (Table 1).

Giardia had a considerable negative correlation with linear growth in a cohort study of malnutrition and enteric disease (MAL-ED), which lasted for the first 2 years of life up to 5 years in some cases. Giardia infection was associated with smaller reductions in the length-for-age z score (LAZ) in quantity instead of prevalence using the exposure criterion (32). In another case-control study on Bangladeshi children

showed that Giardia infection was significantly related to undernourished cases after age, sex, and diarrhea were modified and further adjusted to sociodemographic factors (33). Similarly, from a prospective birth cohort study in Dhaka, 7% of children were Giardia positive (stool specimen) with a decreased LAZ score in the first 6 months of life as an early life risk factor (34). Moreover, infection with Giardia before 6 months of age was associated with a decrease in LAZ - 0.29 (95 percent CI, - 0.64 to 0.07) and a decrease in weight-for-age z score (WAZ) at 24 months of age - 0.29 (95 percent CI, - 0.53 to - 0.05) indicating a stunted growth rate (35). In addition, evidence of elevated Giardia-specific IgM titre (GSIgM) was found in a longitudinal study of 298 rural Bangladeshi infants associated with poor WAZ and weight-for-height z score (WHZ) (P = 0.015 and 0.039 respectively) (36). This findings suggest that infection with Giardia could be a potential obstacle to poor child growth up to 2 years of life and a crucial window of childhood vulnerability that is rarely recorded in a focused manner.

Table 1
Health effects of giardiasis found in Bangladeshi children

Authors Name	Sample Size	Age	Prevalence rate	Effects	Reference no.
Rogawsk ET et al., 2018	923	0–2 years	21.4%	Poor linear growth	(32)
Fahim SM et al., 2108	265	0–2 years	14.6% at 7 months of age. 8.2% at 15 months of age. 1.6% at 24 months of age.	Intestinal inflammation and increased intestinal permeability	(37)
Rogawsk ET et al., 2017	2089	0–2 years	13.6%	Persistent infections contribute to intestinal permeability and stunted growth	(35)
Platts-Mills JA et al., 2017	964	6–23 months	Case:22.4% and Control: 12.4%	Associated with malnutrition	(33)
Donowitz JR et al., 2016	629	0–2 years	7% at 6 months of age and 74% of cohort stool	Risk factor for stunting at age 2	(34)
Mondal D et al., 2011	147	0–12 months	34%	Defect in mucosal immunity	(38)
Mondal D et al., 2009	289	2–5 years	–	No significant association	(39)
Lutfun Nahar et al., 1999	198	6–59 months	31% single infection, 7.7% double infection and 2.8% triple infection	Association with malnutrition	(40)
Goto R et al., 2008	298	3–15 months	1%	Elevated GSIGM associated with poor WAZ and WHZ	(36)

Giardiasis And Intestinal Permeability:

Infection with *Giardia* has been correlated with altered human bowel architecture and experimental models (28, 41, 42). In this regard, Bartelt et al. identified *Giardia* as a "stunting" pathogen (42) resulting in malabsorption of glucose, sodium and water in the body and decreased production of disaccharides

(43–48). In MAL-ED study, Giardia infection was associated with high level of lactulose: mannitol (L: M) ratio, indicate of increased gut permeability. A similar study in rural area of Bangladesh reported that burden of giardiasis prevalence was correlated with greater level of intestinal permeability (49). Similarly, Goto et al. found that intestinal permeability function is impaired by elevated acid glycoprotein (AGP) as an indication of routine re-infection in rural Bangladeshi children along with elevated Giardia IgM titers (36).

Additionally an observational study of Bangladeshi infants of an urban area indicated giardiasis was associated with the intestinal barrier disruption (38). Furthermore, another prospective longitudinal study confirmed that giardiasis was significantly associated with concentrations of fecal myeloperoxidase (MPO) and alpha-1-anti-trypsin (AAT) in children under the age of 2 and was also significantly associated with score of environmental enteric dysfunction (EED) (37). Most of these studies showed evidence that giardiasis was associated with intestinal permeability. Improvements in analytical techniques have allowed the identification of Giardia in human samples associated with intestinal permeability. Study in Bangladesh to date has clearly demonstrated the relationship between human Giardia infection and abnormal gut permeability.

Human Giardiasis Associated Diarrhea:

According to the new Global Burden of Disease Survey, approximately 2.39 billion cases of diarrhea occurred worldwide and approximately 0.53 million children under five years of age died each year (19, 50). Diarrheal diseases are still very common among children under 5 years old in Bangladesh (51). In Bangladesh, Haque et al. reported intestinal protozoal parasites are significantly associated with diarrheal diseases, especially Giardia, Entamoeba and cryptosporidium (20). Several studies conducted in Bangladesh using diarrheal stools also found that Giardia spp. are responsible for diarrheal diseases (52–54). From May 2004 to April 2006, Haque et al. conducted a prospective case control study at the Dhaka hospital of the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) found that in case patients with diarrhea G. lamblia assemblage A was more prevalent than in healthy control subjects (20% vs. 5%; $P < 0.001$) (20). Another, Haque et al. study reported 11% pre-school children were infected with Giardia lamblia which one is second highest after Shigella flexneri (11.6%) in diarrheal stool (55). Table 2 shows the prevalence rate of giardiasis in diarrheal stool by different test methods.

Table 2
Prevalence of Giardia spp. infection in diarrheal stool in Bangladesh

Authors Name	Sample Size	Age	Prevalence rate	Test Method
Haque et al., 2005	1305	All ages	7.7%	EIA
Suman et al,2011	266	< 5 years	3.8%	EIA
Kabir et al.,2018	832	< 2 years	31.1%	TaqMan Array Card Assay
Alam et al.,2011	77	All ages	79.22%	EIA
Haque et al.,2003	289	2–5 years	11%	Microscopy

Advances In The Diagnosis Of Giardiasis:

Current Giardiasis diagnostic methods in Bangladesh include microscopic identification of Giardia cyst and trophozoites, enzyme-linked immunosorbent assay (ELISA) detection of antigen, rapid Quik Chek, and polymerase chain reaction (PCR) detection of DNA. In order to diagnose Giardia spp. properly, a combination of tests are often required. Microscopy has been historically the most commonly used but has limited diagnostic use and is no longer recommended as a reliable method of diagnosing giardiasis. While qualified microscopists in only one stool specimen will reduce the inaccuracy of Giardia detection (56). Yet microscopy does not differentiate between two Giardia human infecting large genotypic assemblages (A and B). On the other hand antigen detection technology has improved and is easy to use to resolve some of the drawbacks of stool microscopy. Only 35 Giardia cysts were detected by microscopy in a recent study of 157 stool samples compared with 127 showed positive results for Giardia cyst-specific antigen by Giardia II ELISA package (Techlab, Blacksburg) (57). Similarly, a cohort study of 229 Bangladeshi children found that ELISA's antigen detection test was 100% sensitive and accurate compared to 94.5% and 99.8% respectively for microscopy (58). Currently there are rapid antigen test for the diagnosis of giardiasis in stool sample are available. Juliana et al. compare three rapid antigen tests for Giardia using ELISA as a reference standard in this issue, the Giardia Quik Chek (Techlab) had 100% and 98.8% sensitivity and specificity respectively (59). This sample panel included both symptomatic and asymptomatic stool specimens from 117 Bangladeshi children. Additionally in comparison with real-time PCR as a reference standard Giardia Quik Chek shown sensitivity and specificity 78% and 100% respectively. Stool PCR is extremely sensitive and it is considered as a gold standard for diagnosis of giardiasis. The use in routine diagnostic laboratories of these molecular diagnostic tests such as real-time PCR is still limited.

Discussion And Perspective

This systematic review observed the most common reported health consequences for Giardia infections in Bangladesh based on quality literature search. Although the search strategy accepted only 17 full

articles out of 187 papers these were quality warranting inclusion.

What decides whether a flagellated *Giardia* spp. protozoan is a harmless parasite or a damaging pathogen or not? The true clinical adverse effects of pediatric giardiasis are not clear, but current prospective studies have reported a high burden of giardiasis diarrhea and subclinical infections are associated with child growth retardation. Recent worldwide laboratory work to understand the relationship between *Giardia* infection and health issues indicates new research lines.

In many regions of the world including Bangladesh, giardiasis is considered the most frequently reported intestinal parasite protozoan across humans, but giardiasis remains a neglected disease. Long-term *Giardia* infection can result in complications, such as damage to the cells that line the intestines. Morbidities associated with *Giardia* have been gradually established over the past decades, including extra-intestinal symptoms and long-term consequences (60–62). A cross-sectional study examined the role of giardiasis in the development of growth and psychomotor, suggesting an adverse impact of *Giardia intestinalis* infection (63). Another study in rural Malaysia reveals *Giardia* infection has significantly associated with the weight of children (64). Many epidemiological studies showed that childhood growth retardation has been associated with giardiasis in developing countries (65–69). Recent data from Bangladeshi children found similar results indicating that infection with *Giardia* could be a potential barrier to children's development (32–34, 40). The prospective MAL-ED birth-cohort study give us a special opportunity to explore the relationship among giardiasis and child growth (35).

The worst symptoms of *Giardia* infection are associated with damage to the absorptive small intestine mucosa, along with an impaired intestinal immunity that contributes to chronic infection. Recently published data from children in Bangladesh suggested a correlation between giardiasis and increased the risk of intestinal permeability as well as an immune defect (35, 37, 38). Although an observation by Scott et al. showed that small intestinal gut permeability increased of *Giardia* infected mice without any morphological damage to the intestinal mucosa, which is independent of T-cell and is secondary to reorganization of cytoskeletal F-actin and tight-junction ZO-1 protein (70). To understand the relationship among infection and intestinal permeability, more studies are needed in children with *Giardia* infection.

Diarrheal diseases is a crucial problem in public health that particularly affects children in Bangladesh (71). The bidirectional correlation between malnutrition and diarrheal mortality has been known for decades (72, 73). Enteric infections such as *Giardia* spp. cause a significant proportion of global malnutrition. (73). Although more studies are needed to determine the actual health effects of giardiasis. Recently, an increased number of *Giardia* spp. has been identified in Bangladesh, especially in children.

This systematic review has few limitations including the number of articles observed. As we followed a strict number of inclusion criteria for this review, resulted a large number of articles removed from the consideration, because of their reports were incomplete or inappropriate. Several articles demonstrated diarrheal related health problems in generally without analysis of etiological agent individually especially for *Giardia* spp. were also excluded.

Conclusions

Giardia spp. is one of the most frequent flagellated protozoan parasite infecting human in Bangladesh especially in children. Recent studies suggested that giardiasis adverse health effects are acute diarrhea, poor child growth and increased intestinal permeability, which can contribute many systemic disorders. However, prevention remains difficult, sufficient awareness should be given for preventing *Giardia* infection in children in Bangladesh to improve their health status.

Declarations

List of abbreviations:

WHO-	World Health Organization
PRISMA-	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
LMIC-	Low and Middle-Income Countries
LAZ-	Length-for-age Z score
WAZ-	Weight-for-age Z score
GSIgM-	<i>Giardia</i> -specific Immunoglobulin M
MAL-ED-	Malnutrition and Enteric Disease
AGP-	Acid Glycoprotein
MPO-	Myeloperoxidase
ELISA-	Enzyme Linked Immunosorbent Assay
PCR-	Polymerase Chain Reaction
AAT-	Alpha1 Anti Trypsin
EED-	Environmental Enteric Dysfunction

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The authors declare they have no competing interests.

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BH conceived the study. BH and HR wrote the analysis plan. BH conducted the literature review, analysis and wrote the first draft of manuscript. HR, SM and AS reviewed the first draft manuscript and suggested additional analyses. ZN and MK reviewed the final draft manuscript and provided critical comments. BH finalized the manuscript which was subsequently approved by all authors.

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Emerging Infections and Parasitology Laboratory department of Infectious Diseases Division of the International Centre for Diarrheal Disease Research, Bangladesh; Dhaka, Bangladesh.

Authors details:

¹Rashidul Haque

Senior scientist and head, Emerging infections and parasitology laboratory, IDD, icddr,b

¹Biplob Hossain

Research officer, Emerging infections and parasitology laboratory, IDD, icddr,b

¹Humaira Rashid

PhD Student and Research Fellow, Emerging infections and parasitology laboratory, IDD, icddr,b

¹Zannatun Noor

Deputy Project Coordinator, Emerging infections and parasitology laboratory, IDD, icddr,b

¹Mamun Kabir

Research Investigator, Enteric and Respiratory Infections Department, IDD, icddr,b

¹Abdullah Siddique

Senior Research officer, Emerging infections and parasitology laboratory, IDD, icddr,b

²Sohag Miah

Student fellow, Shahjalal University of Science & Technology; Sylhet-3114, Bangladesh

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Figures

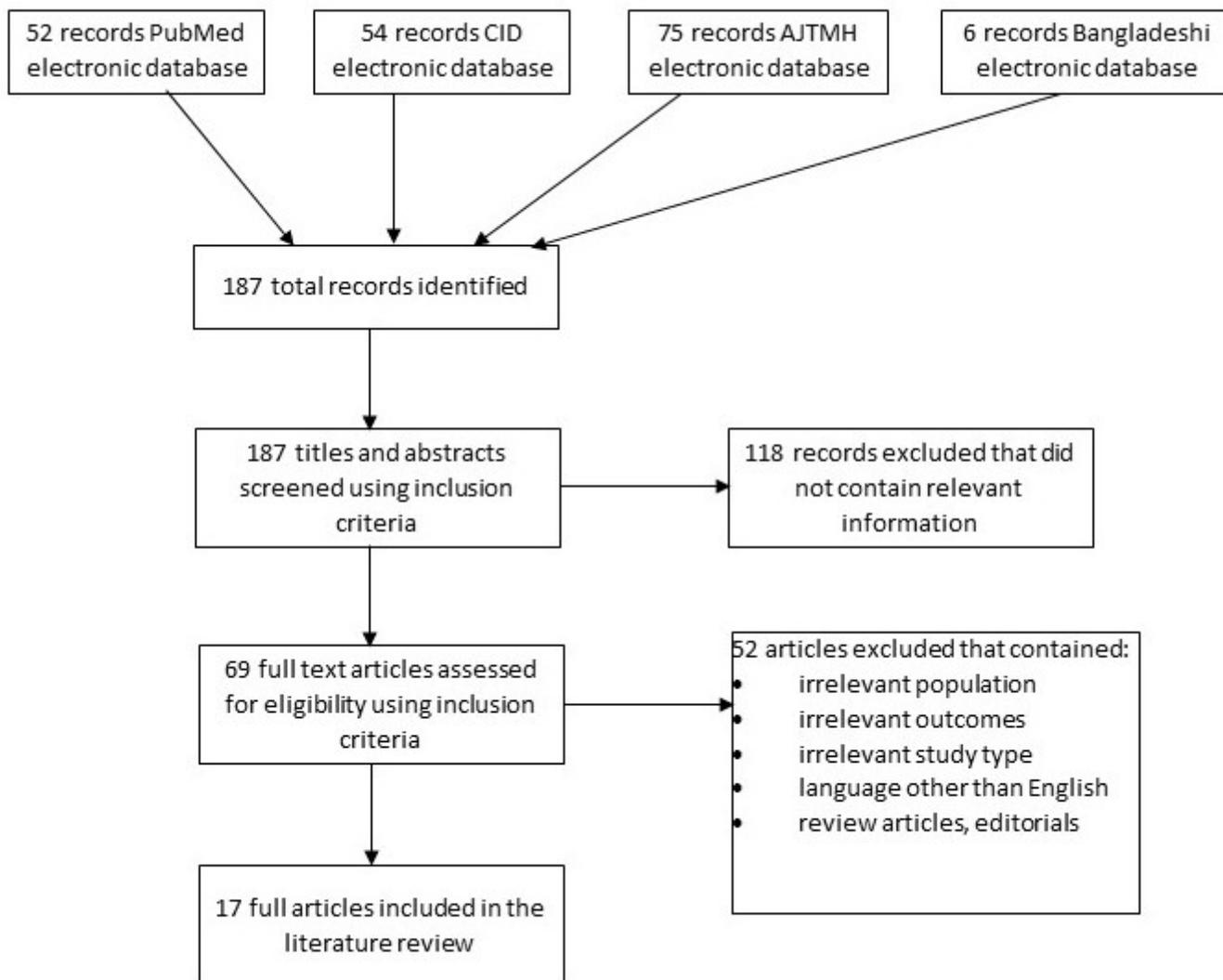


Figure 1

Flow diagram for systematic review: The PRISMA flow diagram for the systematic review outlining the search for the database, the number of abstracts reviewed and the full texts included.

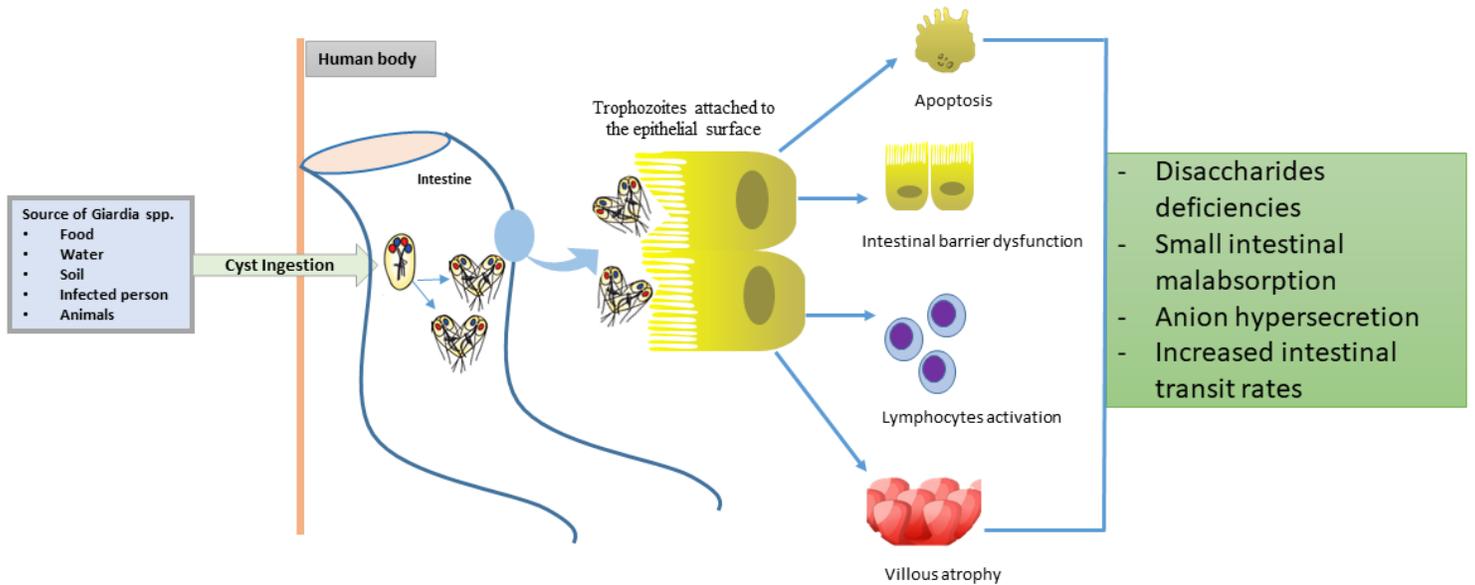


Figure 2

Clinical features and manifestation of Giardia spp. infection

Supplementary Files

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