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Trichostrongylosis: a zoonotic disease of small ruminants

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Abstract

In the present world a significant threat to human health is posed by zoonotic diseases. Helminth parasites of ruminants are one of the most common zoonotic organisms on the planet. Among them, trichostrongylid nematodes of ruminants, found worldwide, parasitize humans in different parts of the world with varying rates of incidence, particularly among rural and tribal communities with poor hygiene, pastoral livelihood and poor access to health services. In the Trichostrongyloidea superfamily, *Haemonchus contortus*, *Teladorsagia circumcincta*, *Marshallagia marshalli*, *Nematodirus abnormalis* and *Trichostrongylus* spp. are zoonotic in nature. Species of the genus *Trichostrongylus* are the most prevalent gastrointestinal nematode parasites of ruminants that transmit to humans. This parasite is prevalent in pastoral communities around the world and causes gastrointestinal complications with hypereosinophilia which is typically treated with anthelmintic therapy. The scientific literature from 1938 to 2022 revealed the occasional incidence of trichostrongylosis throughout the world with abdominal complications and hypereosinophilia as the predominant manifestation in humans. The primary means of transmission of *Trichostrongylus* to humans was found to be close contact with small ruminants and food contaminated by their faeces. Studies revealed that conventional stool examination methods such as formalin-ethyl acetate concentration or Willi's technique combined with polymerase chain reaction-based approaches are important for the accurate diagnosis of human trichostrongylosis. This review further found that interleukin 33, immunoglobulin E, immunoglobulin G1, immunoglobulin G2, immunoglobulin M, histamine, leukotriene C4, 6-keto prostaglandin $F_{1\alpha,}$ and thromboxane B_2 are vital in the fight against *Trichostrongylus* infection with mast cells playing a key role. This review focuses on the prevalence, pathogenicity and immunological aspects of *Trichostrongylus* spp. in humans.

Introduction

Parasites that we encounter in nature may be species-specific or may have a wide range of hosts. The latter are strenuous to control because they can lie dormant in their reservoir hosts for long periods of time before infecting other hosts. Similarly, zoonotic parasites are difficult to control and pose a concern to human health due to their proclivity for residing in diverse hosts (Allen *et al.*, 2017). Livestock helminths, among other zoonotic viruses, bacteria and other infections, are a cause of health concern for humans (Libera *et al.*, 2022). Helminth parasites that infect the livestock, significantly affect their health and reproduction (Rehman & Abidi, 2022). Although *Haemonchus contortus* is considered as the notorious parasite of livestock because of its reproductive potential and blood sucking ability, *Trichostrongylus* remains one of the most frequent and extremely pathogenic parasites in cattle, and because of its zoonotic potential, *Trichostrongylus* is dangerous to human health (Getachew *et al.*, 2007). Human infection by *Trichostrongylus* is more prevalent in the pastoral communities who raise livestock or eat vegetables that are fecundated with faecal ordure. Humans become infected after consuming food or water contaminated with faeces of the definitive host (ruminant and humans). Gastrointestinal symptoms with disparate morbidity may develop in some patients; however, most patients are asymptomatic but have eosinophilia as the only symptom (Buonfrate *et al.*, 2017). Till date, *Trichostrongylus* infections in humans have been reported only in a few parts of the world. The reason for such rarity in cases of human trichostrongylosis could most probably be the occurrence of asymptomatic infections and comparably less sensitivity of microscopic detection due to low egg-output (Buonfrate *et al.*, 2017). As a result, there could be many undiagnosed cases of *Trichostrongylus* infection in the human populations worldwide (Wolfe, 1978). *Trichostrongylus* is similar to hook worms, particularly *Ancylostoma duodenale* and *Necator americanus* concerning its transmission, pathophysiology and morphology at certain life-cycle stages; as a result, very little is known about the population biology and epidemiology of *Trichostrongylus* spp. (Yong *et al.*, 2007). There is lack of information regarding the global status of trichostrongylosis among humans. It is necessary to compile the pertinent scientific material and examine pastoral populations for the incidence of this parasite. Little to no work has been done on the pathogenicity and immune response to this worm in relation to humans. This review aims to compile literature about the: (a) pathogenesis of trichostrongylosis in humans; (b) immune response to *Trichostrongylus* invasion and its mechanism of action; and (c) epidemiology of this zoonotic parasite in relation to humans.

Life cycle and transmission

Using no intermediate host and exhibiting a direct life cycle, *Trichostrongylus* adults live in the gastrointestinal tract (GIT) at particular micro-niches depending on the species. Females lay eggs in the host's GIT which are then excreted with the faeces of the host. As soon as the eggs are in a favourable environment, they embryonate into the L1-larvae which moults two times and develops into the infective L3-larvae in about five days and may remain viable for about six months (Levine & Anderson, 1973). Throughout the summer months of June to August, most trichostrongylid larvae occur on the grass blades representing greater chances of infection in grazing animals (Crofton, 1948). Cattle become infected after consuming the L3-larvae while feeding on contaminated grasses. Once ingested, L3-larvae of *Trichostrongylus* spp. reach the predilection site, for example, the L3-larvae stage of *Trichostrongylus axei* inhabits the abomasum of ruminants where they complete their development and the adult worms then penetrate the lining of the abomasum. In some other species, the L3-larvae reach the small intestine and invade the crypts to complete their development into L4 and L5 larval stages. Depending on the species and the host, the prepatent period is usually three to four weeks (Janquera, 2017) but can extend up to two years (Ralph *et al.*, 2006). *Trichostrongylus colubriformis* lives in mucoid passages on the surface of duodenal and intestinal villi (Shaw *et al.*, 2003). Humans acquire trichostrongylosis when L3-larvae of *Trichostrongylus* spp. are ingested orally while consuming contaminated food. Application of night-soil (human excreta) or livestock faecal matter as manure and the resistant nature of the eggs gives rise to the propagation of this parasite in human populations (Sharma & Anand, 1997). Shady areas with high humidity and an abundance of grass are more favourable for the spread of *Trichostrongylus* (Watson, 1953).

Methodology

Databases such as Google Scholar, PubMed, Scopus, Web of Science and ScienceDirect were searched to collect and review the published scientific research articles related to trichostrongylosis among humans. Terms such as *Trichostrongylus*, trichostrongylosis/liasis, zoonosis/es/tic, human, transmission, case/s, report, diagnosis, pathogenicity/sis, immunological, immune response, etc. were used in multiple combinations to search for relevant research articles. Further, the bibliographic section of research articles was also searched to extract relevant references. In addition to these, any other relevant research articles and/or case reports from other sources were also reviewed during the study. Research articles with information regarding number of cases in humans, method of diagnosis, symptoms, country name and/or pathogenesis and immune response were included in this study. Research articles related to other hosts were excluded. We used Endnote to compile the articles and then thoroughly read the papers to extract information such as year, country/region, number of cases, method of examination, mode of transmission, symptoms and any other important findings (table 1). Statistics from these articles are compiled in figs 3–5.

Pathogenicity

Human trichostrongylosis is typically a minor, subclinical condition as indicated by the fact that diagnosed cases have only been identified through screening. Nevertheless, heavier infection may result in emaciation, pain in the abdomen and diarrhoea along with slight anaemia and eosinophilia in adults while causing retardation of development in children (Hollo *et al.*, 1970). Persons with infection intensity of 24–300 eggs per gram (EPG) of faeces are symptomatic while an infection intensity below 24 EPG shows no symptoms (Ghadirian & Arfaa, 1975; Wolfe, 1978). In small ruminants the symptoms of trichostrongylosis are more severe causing 'black scour disease' which is characterized by dark green to black diarrhoea, that covers the crutch, hocks and legs. There is extreme emaciation in heavily infected sheep with wasting of musculature and negligible amount of renal and omental fat (Edgar, 1933). Craig (2009) reported that trichostrongylosis may lead to moderate anaemia as the worms may feed on the host's blood from mucosa of the gut. Histopathological studies carried out by Barker (1975) showed that *T. colubriformis* causes severe villus atrophy and plasma loss in the sheep gut. Acutely infected mucosa becomes flat, has stunted epithelium, with projecting crypts often leaking eosinophilic material, exhibiting hyperplasia with highly inflammated lamina propria due to cell infiltration. The intestinal epithelial surface has erosions and necrosis which may be most probably caused by operational movement of adult nematodes. In the case of *Trichostrongylus vitrinus*, exsheathed L3-larvae burrow through intestinal villi and form submucosal tunnels and when adults emerge out of these tunnels, they cause considerable damage to the mucosal layer (Beveridge *et al.*, 1989). Alterations in the intestinal morphology due to *Trichostrongylus* infection cause a decrease in the activity of enzymes such as alkaline phosphatase and leucine amino peptidase (Shayo & Benz, 1979). Though mildly pathogenic, *Trichostrongylus* may cause severe complications among young and weak livestock, sometimes proving fatal (fig. 1).

Immune response

The aim of the parasite is to establish itself successfully in/on the host without killing it. To do so, the parasite manipulates the immune response of the host, and either the parasite evades the host immune system by different mechanisms or it alters the immune response of host to make it ineffective. To counter this, the host tries to mount an effective immune response against the parasite to kill and expel it. Usually in helminth infection, T helper 2 or Type 2 response is initiated by the host. It includes expression of interleukin-4, interleukin-5, interleukin-9, interleukin-13, interleukin-21, interleukin-33 (IL-33) and proliferation and activation of plasma cells to secrete immunoglobulin E (IgE), ocytess and mast cells to secrete vasoactive amines. With respect to trichostrongylosis in humans, limited research has been conducted on immunological response. An *in vitro* study using a co-culture system of *T. colubriformis* and epithelial cell from humans showed that movement of *T. colubriformis* at the site of infection creates necrosis of intestinal epithelial cells. The necrosis in turn induces the release of intracellular contents, including IL33 which is elemental in the commencement of appropriate host response to gastrointestinal nematodes (Andronicos *et al.*, 2012). It has been found that after recurrent infections in natural conditions, sheep can develop immunity against *T. colubriformis*. In a natural foraging environment, the ability to withstand nematode establishment occurs after seven weeks of incessant infection (Dobson *et al.*, 1990). When a sheep is fed with *Trichostrongylus* larvae, most of them are expelled in less than 24 h under a hypersensitivity response known as rapid rejection (Miller *et al.*, 1985). The sheep shows resistance to *Trichostrongylus* by mounting an inflammatory response in gastro-intestinal mucosa which is evident by increase in mucosal mast cells and globule leucocytes (Miller *et al.*, 1985; Douch *et al.*, 1986). This inflammatory response seems to be genetically controlled and mast cells play a major role in resistance against *Trichostrongylus* (Gill, 1991). When treated with parasite antigen, mast cells from resistant sheep release around 39% of cellular mast cell protease (CMCP) as compared to less than 8% CMCP release by mast cells from sheep with primary infection of *Trichostrongylus* (Bendixsen *et al.*, 1995). Jones & Emery (1991) demonstrated that sheep immunized with *T. colubriformis* release a number of inflammatory mediators such as histamine, leukotriene C4, 6-keto prostaglandin $F_{1\alpha}$ and thromboxane B_2 on secondary infection with leukotriene C4 being the most predominant inflammatory mediator in expulsion of nematodes from intestines. In guinea pigs immunized with irradiated *T. colubriformis* larvae, release of biological amines (histamine and 5-hydroxytryptamine) and enteric plasma was found to be involved in resistance to secondary infections of this parasite (Steel *et al.*, 1990).

Serum IgE levels have been found to escalate following nematode infections (Shaw *et al.*, 1999). Shaw *et al.* (2003) found *T. colubriformis* aspartyl inhibitor (Tco-API-1) as a strong allergen that produces an overwhelming IgE response in sheep, when produced endogenously by nematode; however, when administered separately, Tco-API-1 does not evoke IgE response. In response against *T. colubriformis*, serum immunoglobulin G1 (IgG1) and immunoglobulin M (IgM) titres elevate significantly by 35 days of infection with IgG1 being more persistent than IgM (Douch *et al.*, 1994). IgG1 and immunoglobulin G2 (IgG2) levels in gut associated lymphoid tissue were observed to be greater in Merino sheep during *T. colubriformis* larval rejection (McClure *et al.*, 1992). Treatment with the corticosteroid dexamethasone has been found to inhibit the progress of nematode resistance and reversibly reduce the expression of existing resistance in sheep, as indicated by higher faecal egg count and persistent weight loss. Dexamethasone functions by decreasing the production of leukotrienes and preventing the advent of mast cells in intestines (Douch *et al.*, 1986, 1994) and eosinophils in serum (Buddle *et al.*, 1992). Sheep also counter the nematodes by increased numbers of circulating antibodies and increased number of antibodies in the mucus of the intestine (Dawkins *et al.*, 1988; Adams *et al.*, 1989; McClure *et al.*, 1992). Rabbit develops resistance against *Trichostrongylus retortaeformis* through three ways *viz*: self-cure; inhibition of larval development; and prevention of establishment of infective larval stages (Michel, 1952). All of these findings reveal that inflammatory response involving an interplay of different immune mediators including IL33, IgE, IgG1, IgG2, IgM, histamine, leukotriene C4, 6-keto prostaglandin $F_{1\alpha,}$ and thromboxane B_2 is vital in the fight against *Trichostrongylus* infection with mast cells playing a key role (fig. 2).

Prevalence of *Trichostrongylus* in humans

Few investigations on *Trichostrongylus* have revealed its widespread occurrence in human communities around the world. Watson (1953) reported that 48 million people were infected with *Trichostrongylus* spp. globally. However, researches on the epidemiology of *Trichostrongylus* proclaim a global distribution but low prevalence of infection in humans (Ghadirian & Arfaa, 1975; Cancrini *et al.*, 1982; Millington *et al.*, 1989; Boreham *et al.*, 1995; John & Petri, 2006; Ralph *et al.*, 2006; Yong *et al.*, 2007). Ghadirian & Arfaa (1975) estimated 67%, 86% and 71% prevalence of trichostrongylosis among humans in Isfahan, Bakhtiari and Khuzestan regions of Iran, respectively, with primary species being *Trichostrongylus orientalis and T. colubriformis*. Watthanakulpanich *et al.* (2013) found 36.9% prevalence in Thakamrien Savannakhet, Laos. *Trichostrongylus* infections often become misreported due to the resemblance of their eggs with those of hookworms, for example, in Lahanam Laos, 2011, 93.5% of positive hookworm cases were of *Trichostrongylus* (Sato *et al.*, 2011). Joe (1947) reported 36.42% prevalence in Java, Indonesia. Very low prevalence of 0.5% and 1.2% was reported in Chile and Brazil, respectively (Torres *et al.*, 1972; Souza *et al.*, 2013). Heydon & Green (1931) also reported a very low prevalence (0.3–0.4%) of trichostrongylosis in Queensland, Australia. Infection of *T. orientalis* has been reported in Armenia, China, Japan and Korea (John & Petri, 2006). Species such as *T. axei*, *Trichostrongylus capricola*, *T. colubriformis*, *T. orientalis*, *Trichostrongylus probolurus*, *Trichostrongylus skrjabin* and *T. vitrinus* have been found associated with infections in humans with *T. axei*, *T. colubriformis* and *T. orientalis* being the most common species which infect humans, mostly obtained via close contact with livestock (Ghadirian & Arfaa, 1975; Millington *et al.*, 1989; John & Petri, 2006; Ralph *et al.*, 2006; Yong *et al.*, 2007). In Japan, the most predominant species among humans is *T. orientalis* which is also found in China and Korea (Miyazaki, 1991). Buonfrate *et al.* (2017) reported four clusters of *Trichostrongylus* infection in Italy. Multiple cases were reported from different regions of Hungary from time to time as mentioned by Hollo *et al.* (1970). El-Shazy *et al.* (2006) reported 2.6% prevalence of trichostrongylsis in Dakahlia, Egypt. Females of age group 41–50 have been found to be more susceptible to trichostrongylosis than males (Watthanakulpanich *et al.*, 2013) (figs 3–5).

Discussion

Different studies on the incidence of *Trichostrongylus* prove that this parasite is prevalent among small ruminants worldwide and sporadically occurs in humans that live in close contact with these ruminants. This review, which included almost all cases of *Trichostrongylus* infection that had been reported and documented in the literature worldwide, showed that trichostrongylosis occur in people occasionally. A systematic review of *Trichostrongylus* infection in Iran by Rahimi-Esboei *et al.* (2022) showed its prevalence to be 0.01%. However, in rural communities the prevalence is found to be higher (3.13%) (Sharifdini *et al.*, 2020). With ten species of *Trichostrongylus* reported in human beings, Iran has been a hotspot of human trichostrongylosis; globally, 11 species of *Trichostrongylus* have been linked to humans (Sharifdini *et al.*, 2017b). The metrics indicate that *T. colubriformis*, followed by other species, is the predominant species infecting humans around the world (Lattes *et al.*, 2011; Phosuk *et al.*, 2013; Watthanakulpanich *et al.*, 2013; Gholami

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Table 1. Reported cases of human trichostrongylosis globally in scientific publications from 1938 to 2022.

Species number	Location	Number of cases reported in humans	Findings	Reference
1.	Louisiana, United States	01	*Trichostrongylus colubriformis* was found in the appendix of a girl suffering from recurrent pain	Chenken & Moss (1938)
2.	New South Wales, Australia	01	strongyle type eggs were collected from faecal sample of a four years old girl. Larvae from eggs were cultured and fed to rabbit which produced adult worms of *T. colubriformis*	Heydon & Bearup (1939)
3.	Democratic Republic of Congo	03	parasitological stool examination of three persons with abdominal symptoms and eosinophilia showed *Trichostrongylus* infection in them	O'teal & Magath (1947)
4.	Baghdad, Iraq	04	four persons with anaemia and epigastric pain were diagnosed with trichostrongylosis	Jawad (1952)
5.	United States	02	stool examination of two patients suffering from abdominal pain, diarrhoea and weakness, revealed *Trichostrongylus* infection with profound eosinophilia	Wallace *et al.* (1956)
6.	United Kingdom	03	three women aged 21, 23 and 27 years with epigastric pain, weakness, dizziness and anaemia reported positive for *Trichostrongylus* spp. All cases were introduced from other countries	Markell (1968)
7.	Israel	59	through stool analysis, 59 cases of trichostrongylosis were found between 1967 and 1971 in Israel. All of the cases, nevertheless, originated in Asia. Patients experienced nausea, abdominal pain and other associated symptoms	Cotin *et al.* (1972)
8.	Isfahan, Iran	40	*Trichostrongylus capricola* outbreak was reported in tribal population of Isfahan, Iran, with 22.5% prevalence among *Trichostrongylus* infected population	Ghadirian *et al.* (1974)
9.	Tunisia	01	54 years old woman complaining about abdominal cramps was diagnosed with trichostrongylosis by stool examination	Bouchekoua *et al.* (1977)
10.	Khuzestan, Iran	06	ether formalin stool examination of six persons showed *Trichostrongylus* infection. Oxantel–pyrantel was given to patients to resolve the infection	Farahmandian *et al.* (1977)
11.	Morocco	01	56 years old woman with asthenia, weight loss and pain in the lower limbs was diagnosed with *Entamoeba* and *Trichostrongylus* infection after stool examination. Species identified was *Trichostrongylus vitrinus*	Poirriez *et al.* (1984a)
12.	India	35	In 1981, ten and 1982, 25 cases of *T. colubriformis* were reported among tribal children using direct faecal smears, brine flotation and formol-ether concentration approaches	Poirriez *et al.* (1984b)
13.	Queensland, Australia	05	stool examination of five persons with high eosinophilia revealed *Trichostrongylus* eggs. Two of the persons suffered from abdominal pain and diarrhoea. Pyrantel embonate resolved the eosinophilia and infection	Boreham et al. (1995)
14.	Tasmania, Australia	01	seven years old refugee from Sudan was diagnosed with trichostrongylosis after formalin-ethyl acetate concentration (FEAC) stool examination	Bradbury (2006)
15.	Sydney, Australia,	02	stool microscopy of two persons with abdominal pain, nausea and diarrhoea revealed *Trichostrongylus* infection which showed mebendazole resistance. Colonoscopy of one person revealed mild terminal ileitis. Intestinal biopsies of both persons showed an inflammatory cell infiltrate, including profound eosinophils. Both of the persons had pet goats which were the source of infection	Ralph *et al.* (2006)
16.	France	01	FEAC stool examination of a 47 years old woman with stomach aches, abdominal bloating and occasional diarrhoea detected *Trichostrongylus* eggs, which were further identified to be of *T. colubriformis* by internal	Lattes *et al.* (2011)

(*Continued*)

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Table 1. (*Continued.*)

Species number	Location	Number of cases reported in humans	Findings	Reference
			transcribed spacer 2 (ITS2) rDNA sequencing. The infection was transmitted from contaminated strawberries fertilized with sheep manure	
17.	New Zealand	03	three persons in Cornwall, United Kingdom, with abdominal pain, diarrhoea, weight loss and eosinophilia revealed *Trichostrongylus* sp. infection through parasitological stool examination. Albendazole resolved the eosinophilia and infection after six weeks. They had contracted the infection from a sheep farm in New Zealand	Wall *et al.* (2011)
18.	Thailand and Lao People's Democratic Republic (PDR)	08	five symptomatic persons from Thailand and three from Lao PDR showed *Trichostrongylus* infection upon stool examination by FEAC technique. Molecular identification of third stage larva obtained through agar plate culture technique revealed two species of *Trichostrongylus*, *viz*: *T. colubriformis* and *Trichostrongylus axei*	Phosuk *et al.* (2013)
19.	Guilan Province, Iran	08	eight persons in Guilan Province, Iran, with varying degree of weakness, backache, abdominal complications, diarrhoea, urticaria, dyspepsia and low-grade fever showed *T. colubriformis* and *Trichostrongylus vitrinus* eggs on stool examination	Ashrafi *et al.* (2015)
20.	Thailand	41	Srinagarind Hospital, Thailand, reported 41 cases of human trichostrongylosis from 2005–2012 through stool examinations using the standard FEAC technique. Most of the patients had abdominal symptoms with profound eosinophilia	Phosuk *et al.* (2015)
21.	Mazandaran Province, Iran	33	33 persons with medical complications were examined with FEAC technique and found positive for trichostrongylosis. Molecular identification by ITS2 rDNA sequencing revealed *T. colubriformis* (29 samples) and *T. axei* (four samples)	Gholami *et al.* (2015)
22.	Gakenke, Rwanda	159	conventional stool examination combined with the polymerase chain reaction (PCR) approach was used to diagnose 159 cases of *Trichostrongylus* spp. in children from a rural area of Rwanda	Irisarri-Gutiérrez *et al.* (2016)
23.	Mazandaran Province, Iran	07 51	five males and two females with clinical symptoms were examined and reported positive for trichostrongylosis. Molecular identification confirmed *T. colubriformis* infection. Out of 132 suspected cases, 51 persons were found positive to *Trichostrongylus* infection using the highly sensitive multiplex restriction enzyme-PCR technique. three species, *T. colubriformis*, *T. axei* and *Trichostrongylus vitrines* were reported	Sharifdini *et al.* (2017a) and Mizani *et al.* (2017)
24.	Northern Italy	11	from 2010 to 2015, Centre for Tropical Diseases of Negrar Verona, Italy, reported four family outbreaks of trichostrongylosis (total 11 cases). Most of the patients suffered from abdominal pain, diarrhoea and had profound eosinophilia. All four families had a history of eating vegetables contaminated with sheep faeces	Buonfrate *et al.* (2017)
25.	Guilan Province, Iran	41 60	41 individuals were found to be positive for *Trichostrongylus* infection using formalin-ether approach. three species were reported in this study, *viz*: *T. colubriformis*, *T. vitrinus* and *Trichostrongylus longispicularis*. The latter species was reported for the first time in humans. 60 persons from Guilan Province, Iran, with abdominal complications were infected with *Trichostrongylus* sp. Identification of *Trichostrongylus* was done through FEAC technique and nutrient-agar plate culture	Sharifdini *et al.* (2017b) and Ghanbarzadeh *et al.* (2019)

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Table 1. (*Continued.*)

Species number	Location	Number of cases reported in humans	Findings	Reference
26.	Mazandaran province, Iran	12	12 persons with abdominal complications were diagnosed with trichostrongylosis by cellophane thick smear method	Babamahmoodi *et al.* (2020)
27.	Langroud district, Guilan Province, Iran	07	seven members of a family in Guilan Province, Iran, were diagnosed with trichostrongylosis after coproparasitological examination. Most of them experienced abdominal pain, diarrhoea, low grade fever, night rigors, allergic manifestations including urticaria and weight loss. ITS2 rDNA identification revealed *T. colubriformis* species	Ashrafi *et al.* (2020)
28.	Guilan Province, Iran	47	a cross-sectional study of 1500 individuals from 31 villages of Fouman region was done using different stool examination methods to estimate intestinal parasitic infections. *Trichostrongylus* spp. was found in 3.13% of individuals	Sharifdini *et al.* (2020)
29.	La Araucanía region, Chile	07	coproparasitological examination of 7 persons from rural La Araucanía region, Chile, proved positive to strongylid eggs. ITS2 rDNA sequencing further confirmed the *T. colubriformis* infection. Infected persons suffered from varying degree of diarrhoea, reflux, vomiting, meteorism and eosinophilia	Hidalgo *et al.* (2020)
30.	Valdivia, Chile	03	a person in Valdivia, Chile, reported with persistent diarrhoea for three weeks. Along with him, two other members of his family also proved positive for *T. colubriformis* infection on stool examination	Torres *et al.* (2021)
31.	China	01	a sheep herder from China presented with severe persistent diarrhoea, abdominal pain, weakness and hyper-eosinophilia. On stool examination, he was positive for *T. colubriformis* infection	Du *et al.* (2022)

et al., 2015; Hidalgo *et al.*, 2020; Torres *et al.*, 2021; Du *et al.*, 2022) with Iran reporting the highest number of cases.

Most cases of human trichostrongylosis around the world have been revealed following a parasitological stool examination particularly using the FEAC technique on persons with gastro-intestinal complications (diarrhoea, abdominal pain, weakness and loss of appetite) and eosinophilia. In family outbreaks of tri-chostrongylosis, some family members with hypereosinophilia

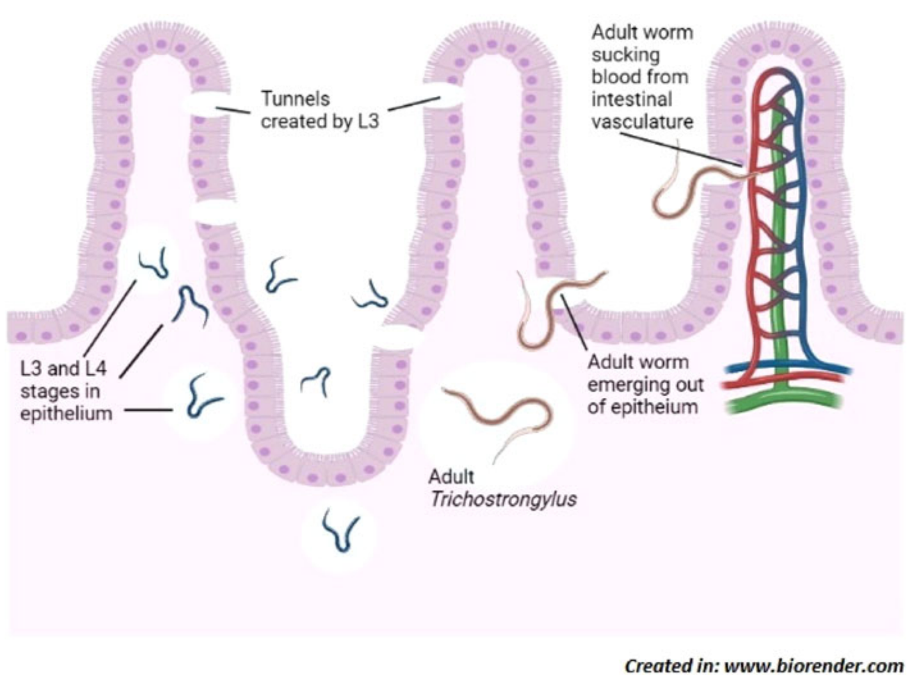

Fig. 1. Activity and development of *Trichostrongylus* sp. in intestine of host; L3-larvae stages burrow through epithelium resulting in damage to intestinal villi and enteritis. Then adults emerge out through tunnels into the lumen of intestine and occasionally suck blood from the intestinal vasculature which leads to anaemia.

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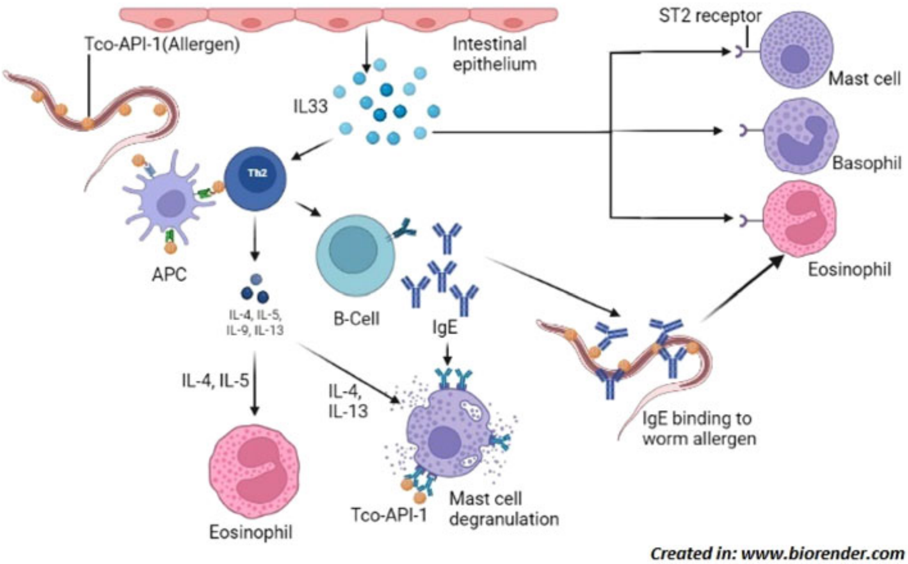

Fig. 2. Induction of Th2 immune response; *Trichostrongylus colubriformis* expressing allergen Tco-API-1, that is presented to Th2 cells by APC which releases cytokines (IL-4, IL-5, IL-9 and IL-13) that activate other cells including mast cell, eosinophil and B-cells. B-cells produce allergen specific IgE which bind to worm surface by Fab region and eosinophil by Fc region to induce their degranulation in order to kill the parasite. Allergen can also bind to mast cell bound IgE to cause their degranulation. In addition, damaged intestinal epithelial cells release IL-33 which binds to ST-2 receptor expressed by cells such as mast cell, basophil and eosinophil to cause their degranulation. Abbreviations: Tco-API-1, *Trichostrongylus colubriformis* sspartyl inhibitor; Th2 cell, T-helper 2 cell; APC, antigen presenting cell; IL, interleukin; Fab, fragment antigen-binding; Fc, fragment crystallizable; ST-2 is an IL-33 receptor belonging to the IL-1 family.

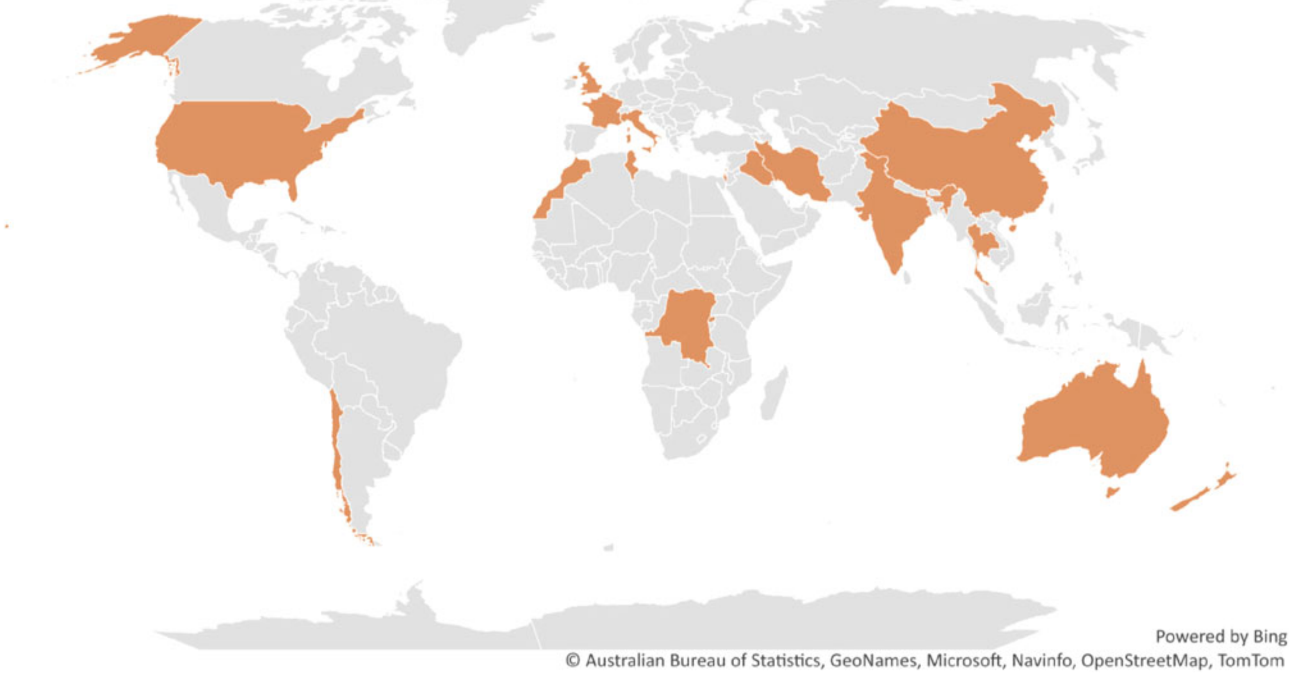

Fig. 3. Countries (coloured) with reported cases of *Trichostrongylus* infection in humans; Human infection by *Trichostrongylus* spp. is documented in several countries and is not limited to any one geographical area. Comprehensive inspection of hookworm patients may indicate otherwise in nations where *Trichostrongylus* has not yet been reported, as trichostrongyle eggs are frequently mistaken for hookworm eggs.

prove negative for *Trichostrongylus* eggs on stool examination which can be attributed to a long prepatent period of the parasite, that is, four months to two years (Wolfe, 1978; Boreham *et al.*, 1995; Ralph *et al.*, 2006). Saraei *et al.* (2019) showed a higher sensitivity of FEAC (95.8%) than the agar plate culture method (90.1%) in diagnosis of trichostrongylosis. However, a recent study showed that among conventional parasitological stool examination techniques, Willi's method is more sensitive (91.7%) followed by the agar plate culture method (52.8%), Harada–Mori culture (40.3%), FEAC (37.5%) and 5.6% for the wet mount technique (Pandi *et al.*, 2021). The same study showed the polymerase chain reaction (PCR) assay to be highly sensitive (97.2%) and specific in diagnosing human trichostrongylosis. Recently, Mizani *et al.* (2017) the devised restriction enzyme-PCR assay for the detection of *Trichostrongylus* species, which has higher specificity to detect even 10 pg/ml of DNA from the sample. Arbabi *et al.* (2020) developed the PCR-high resolution melting assay for the diagnosis of *Trichostrongylus* species with higher specificity in differentiating *T. colubriformis*, *T. capricula*, *T. vitrinus* and *T. probblorous*. Most research to date has used the FEAC approach to diagnose human trichostrongylosis, which has lower sensitivity than Willi's method in

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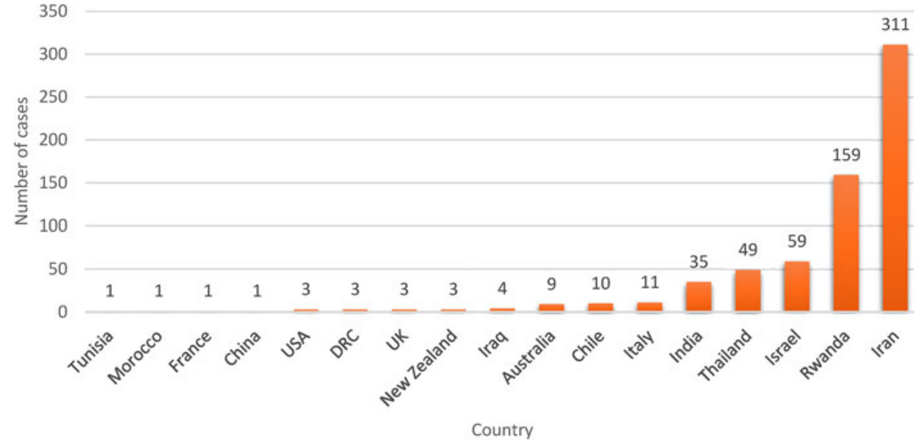

Fig. 4. Human trichostrongylosis case count by country. It is evident that Iran has reported the highest number of cases of *Trichostrongylus* among humans, which can be attributed to higher screening among human populations in part and the rest for pastoral livelihood of people in rural areas of Iran.

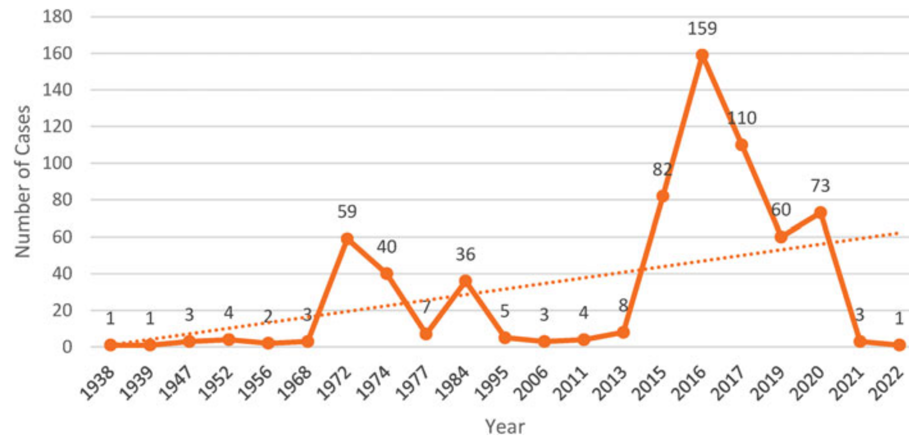

Fig. 5. Year wise human trichostrongylosis cases reported in the scientific literature from 1938 to 2022. Between the years 2015 and 2020, the number of cases is comparatively higher because of increased testing in rural human communities. Investigations in other pastoral communities of the world may detect more infections of trichostrongylosis.

conventional methods. Therefore, many more cases of trichostrongylosis can be discovered if human populations are screened using highly specific PCR along with the conventional Willi's and FEAC approaches.

Even though helminth zoonoses are declining globally, research has shown that warming caused by climate change, in particular, may eventually lead to a rise in helminth infections. The cause of this is that warming would lessen these helminths' larval arrest including *Trichostrongylus*, and so lengthen the time of year when the free-living larval stages would be active. This would result in a rise in the rates of inadvertent human and livestock ingestion of larval stages, as well as the rates of infection (Dobson & Hudson, 1992; Mas-Coma *et al.*, 2008). This review indicates that contamination of food (vegetables) by livestock faeces is the main source of trichostrongylosis among humans which is further enhanced by rainfall due to dispersal of faecal material (Ghadirian & Arfaa, 1973; Ashrafi *et al.*, 2020; Hidalgo *et al.*, 2020). Along with close proximity to livestock, consumption of untreated wild aromatic plants, use of animal dung as fuel (common among rural residents), unhygienic eating practises, use of livestock manure as fertilizer, weakened immune system and advanced age are some other risk factors linked to the rising incidence of human trichostrongylosis (Ashrafi *et al.*, 2020; Rahimi-Esboei *et al.*, 2022). In light of many proven ill effects of chemical fertilizers, organic farming with use of animal dung as fertilizer is becoming common among rural areas which could further increase the incidence of human trichostrongylosis and other zoonotic diseases in the near future (Ashrafi *et al.*, 2020). Livestock being our most important source of meat and dairy must be monitored for helminth infections regularly through parasitological stool examination and be given periodic anthelmintic doses in order to prevent spillover of helminthiasis to humans. Proper hygiene decreases the rate of helminth infection greatly (Vaz Nery *et al.*, 2019). Even though developed countries with advanced health care and proper hygiene have managed to curb the helminth infections, the 'hygiene hypothesis' and related studies have correlated the decrease in helminth infections with the increase of inflammatory and autoimmune diseases among human population as research proves that helminth infection in early stages of life are important contributors to the proper development of the immune system (Rook, 2012). With an increasing trend of anthelmintic resistance among different helminths, immunological studies among small ruminants in the direction of identifying potential antigenic proteins for the development of a vaccine against *Trichostrongylus* and other economically important nematodes in general are necessary. Pathogenicity has not been investigated in humans due to minimal number of infections. However, in sheep, *Trichostrongylus* causes high morbidity ranging from diarrhoea, severe degradation of intestinal wall to even mortality, which is more obvious in lambs. With the advent of new zoonotic diseases in the world, studies are needed to be conducted over these neglected mild pathogenic parasites to better understand their zoonotic potential and accordingly devise management strategies in the future.

Conclusion

The purpose of this review was to compile data regarding human trichostrongylosis in order to gain insights into the epidemiological, immunological and pathogenic aspects of *Trichostrongylus* species among humans. It was found that trichostrongylosis occurs among pastoral communities across the globe particularly in tropical countries. The majority of cases have been identified by traditional faecal examination techniques such as FEAC, however with the development of highly precise PCR-based approaches, it is important to combine these advanced techniques with traditional ones to accurately identify *Trichostrongylus* and other zoonotic helminths infecting humans. Most of the cases have been linked to the close association with the small ruminants or consumption of contaminated food. More investigations on human trichostrongylosis have led to an upsurge in instances being reported in recent years. With the recent finding of *Trichostrongylus longispicularis* among humans in Iran, the number of species associated with humans in this genus has increased to 11.

Further investigations are needed to be done to know the zoonotic potential and disease status of trichostrongylosis around the world. With meagre pathogenic studies and lack of information regarding the mechanism of immune response against *Trichostrongylus* spp., these two fields have remained unexplored; further research is needed in this direction to gather insights about the histological and physiological changes associated with human trichostrongylosis. Ruminants being an important source of food and other products, close association of humans with these domesticated animals is inevitable. In light of the emergence of new species of *Trichostrongylus* in humans, it is crucial to study their pathogenicity and zoonotic potential. Furthermore, it is recommended to devise proper management strategies in order to check the transmission of such zoonotic parasites in the future.

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Conflicts of interest. None.

Ethical standards. We, as authors of this review article, have made every effort to conduct a thorough and unbiased evaluation of the literature on the topic at hand. We have taken care to ensure that all sources are properly cited. We have also strived to maintain objectivity and accuracy in our interpretation of the data, and have not allowed personal biases to influence our conclusions. It is our hope that this review article will provide readers with a fair and comprehensive overview of the current state of knowledge on the subject.

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