Nematode Infections

Soil-Transmitted Helminths and *Trichinella*

Stefanie Knopp, PhD[a,b,*], Peter Steinmann, PhD[a,b], Jennifer Keiser, PhD[a,c], Jürg Utzinger, PhD[a,b]

KEYWORDS

• Soil-transmitted helminths • *Enterobius vermicularis* • *Strongyloides stercoralis* • *Toxocara* • *Trichinella* • Burden • Diagnosis • Control

KEY POINTS

- Soil-transmitted helminth and *Trichinella* infections belong to the "neglected tropical diseases" and the "neglected infections of poverty".
- Intestinal nematode infections considerably impact on people's health in the tropics and subtropics, and also occur in temperate and arctic regions of the United States and Europe.
- Early diagnosis and adequate treatment of infections at an early stage can help to avoid chronic morbid sequelae as infection progresses.
- Access to clean water, improved sanitation, personal hygiene, and food protection measures are key factors to avoid infection and transmission of intestinal nematodes.
- Diagnosis, prevention, and treatment of intestinal nematode infections gain importance in western travel clinics due to growing tourism, travel, migration, and food imports.

Intestinal nematode infections caused by soil-transmitted helminths (ie, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Trichuris trichiura*, and the 2 hookworm species *Ancylostoma duodenale* and *Necator americanus*), *Enterobius vermicularis*, *Toxocara* spp, and *Trichinella* spp belong to both the "neglected tropical diseases" and the "neglected infections of poverty."[1–3] Given the sheer number of the at-risk population

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[a] University of Basel, Petersplatz 1, CH-4003 Basel, Switzerland; [b] Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Socinstrasse 57, P.O. Box, CH-4002 Basel, Switzerland; [c] Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Socinstrasse 57, P.O. Box, CH-4002 Basel, Switzerland
* Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Socinstrasse 57, P.O. Box, CH-4002 Basel, Switzerland.
E-mail address: s.knopp@unibas.ch

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(more than half of the world's population) and the large amount of infected people (more than 1 billion), it is hard to understand why the diseases caused by intestinal nematodes are still widely neglected.[4] However, because of the increase in the tourist and food import industry, poverty-related crowding, and poor hygiene on one hand, and economic-, political-, and armed conflict-related migration on the other, nematode infections have recently gained renewed importance on the disease agenda in Europe and North America.[3,5–8]

The global burden attributable to common soil-transmitted helminthiasis (ascariasis, trichuriasis, and hookworm disease) is estimated at between 4.5 and 39 million disability-adjusted life years (DALYs).[9,10] For toxocariasis and trichinellosis no burden estimates are currently available.[11] Although these diseases can cause outbreaks and include severe manifestations with considerable fatality rates.[12]

This article reviews the epidemiology of intestinal nematode infections, including current distribution, life cycles, clinical features, and associated burden. Diagnostic approaches and treatment, and tools for prevention and control are discussed. Protective measures for travelers are highlighted (**Box 1**), and relevant information is given on vulnerable groups and case numbers in the United States (**Box 2**).

SOIL-TRANSMITTED HELMINTHS (*ASCARIS LUMBRICOIDES*, HOOKWORM, *STRONGYLOIDES STERCORALIS*, AND *TRICHURIS TRICHIURA*)

Life Cycle and Epidemiology

Common soil-transmitted helminths include the roundworm (*A lumbricoides*), 2 species of hookworm (*A duodenale* and *N americanus*), the whipworm (*T trichiura*), and the often neglected threadworm (*S stercoralis*).[2,13] The soil-transmitted helminths share many similarities in terms of transmission and epidemiology. For example, people become infected with *A lumbricoides* and *T trichiura* by ingesting fertilized eggs via consumption of contaminated food (eg, fruits and vegetables) or contact with contaminated hands. Worm larvae hatch in the intestine, and those of *A lumbricoides* penetrate the intestinal wall and migrate via the liver and heart to the lungs. From there, larvae are coughed up and swallowed, to re-enter the small intestine where they mature. Adult female *A lumbricoides* produce around 200,000 eggs per day (**Table 1**).[14–16] *T trichiura* develop in the intestine. Adult *T trichiura* attach to the mucosa of the large intestine. Females produce up to 5000 eggs per day.[2] The eggs of both species are excreted with the feces and undergo a maturation phase in the environment.

Hookworm and *S stercoralis* infections are acquired through skin penetration of the infective third-stage larvae (L_3), which are present in moist soil. Walking barefoot, playing on the ground, or farming and mining are known risk factors for acquiring these infections. Following host entry, the larvae undergo a journey through the vasculature, enter the airways, are swallowed, and finally reach the intestine, where hookworm larvae develop into adult male and female worms, whereas *S stercoralis* larvae mature into parthenogenetic egg-laying females.[8,17–19] Female *N americanus* produce between 9000 and 10,000 eggs per day and *A duodenale* between 25,000 and 30,000.[2] In contrast to the other soil-transmitted helminths, which do not reproduce within the host, *S stercoralis* infections are often perpetuated over long periods by autoinfection.[20] In that case, larvae hatch from eggs already in the gastrointestinal tract, develop into infective L_3, penetrate the intestinal mucosa, and migrate to the small intestine or to parenteral sites, eg, the lungs. *S stercoralis* can also enter a free-living nonparasitic life cycle ending in either infective L_3 (homogonic pathway)

Box 1
Protective measures against intestinal nematodes covered in this review

Ascaris lumbricoides and *Trichuris trichiura:*

- Avoid the ingestion of worm eggs
  - Peel or cook food
  - Boil drinking water
  - Wash hands with soap
  - Do not place small children directly on soil

Ancylostoma duodenale, Necator americanus, and *Strongyloides stercoralis:*

- Avoid skin penetration by larvae
  - Reduce skin contact with potentially infected soil
    - Wear closed shoes
    - Wear gloves for farming

Enterobius vermicularis

- Avoid the ingestion of worm eggs
  - Wash hands with soap
  - Regularly change and wash underwear with soap
  - Regularly change and wash towels, linen, and bed sheets with soap
  - Do not share linen and bed sheets; sleep in separate beds

Toxocara canis and *Toxocara cati*

- Avoid the ingestion of worm eggs
  - Wash hands with soap
  - Do not place small children directly on soil

Trichinella spp

- Avoid the ingestion of larvae
  - Do not eat raw or undercooked meat from domestic or sylvatic animals that has not been subjected to formal meat inspection

or free-living adults (heterogonic pathway) (**Fig. 1**), depending on environmental and genetic cues.[21]

Soil-transmitted helminth infections are particularly widespread in the tropical and subtropical regions of the world (**Table 2**). Indeed, social-ecological contexts govern the transmission of soil-transmitted helminths: warm and moist climate, which allow the development of helminth eggs and larvae, coupled with inappropriate hygiene, sanitation, and water.[25,26] The highest prevalence rates of soil-transmitted helminths occur in sub-Saharan Africa and southern and eastern Asia.[27,28] In general, school-aged children are at highest risk of infection with *A lumbricoides*, hookworm, and *T trichiura*.[29,30] Infection intensities of *A lumbricoides* and *T trichiura* peak in children aged 5 to 15 years, whereas hookworm infections may plateau in adulthood.[2] At highest risk of *S stercoralis* infections are individuals with altered cellular immunity, especially those receiving long-term steroid therapy, patients with lymphoma, kidney allograft recipients, travelers to endemic areas, and prisoners and other institutionalized people.[18] It is estimated that globally, more than 1.2 billion people are infected

Table 1
Characteristics of intestinal nematodes covered in the present review

	Infection Route	Adult Worm Location	Egg/Larvae Final Destination	No. of Eggs Shed by Female Worm Per Day	Life Span of Adult Worms	Intermediate Host/Vector	Time in Intermediate Host/until Eggs/Larvae become Infective
Ascaris lumbricoides	Ingestion of fertilized eggs	Small intestine	Eggs are passed with feces into soil	~200,000	~1 y	None	At least 8–10 d
Hookworms	Larvae penetrate skin	Small intestine	Eggs are passed with feces into soil and develop into infective larvae	*Necator americanus*: 9000–10,000 *Ancylostoma duodenale*: 25,000–30,000	5–7 y	None	~7 d
Trichuris trichiura	Ingestion of fertilized eggs	Large intestine	Eggs are passed with feces into soil	3000–5000	1.5–2 y	None	At least 12–15 d
Strongyloides stercoralis	Larvae penetrate skin; autoinfection	Small intestine	Larvae are passed with feces into soil	50	No number available	None	No number available
Enterobius vermicularis	Ingestion of fertilized eggs; autoinfection	Large intestine	Eggs attach to perianal skin and get into environment	16,000	~13 wk	None	~6 h
Toxocara canis and *Toxocara cati*	Ingestion of fertilized eggs	Small intestine	Eggs are passed with feces into soil	~200,000	~4 mo	Dog, cat	2–3 wk
Trichinella spp	Ingestion of encysted larvae contained in raw or undercooked meat	Small intestine	Larvae migrate to skeletal muscles and encyst	No number available	~4 wk	Mammals (particularly pigs), birds, reptiles	At least 18 d

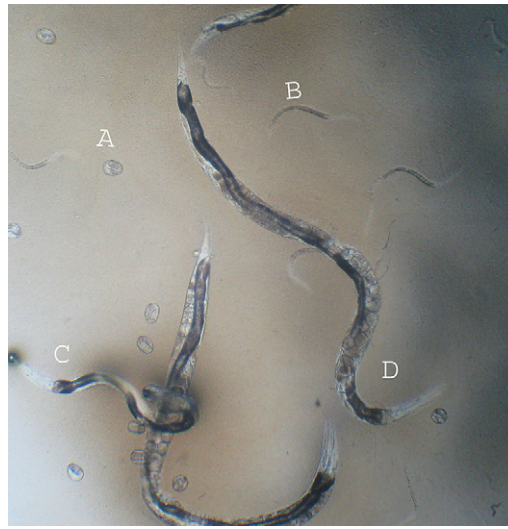

Fig. 1. *Strongyloides stercoralis* eggs (A), larvae (B), and free-living male (C) and female (D) adult worms on a Koga agar plate. (*Courtesy of* Hanspeter Marti, PhD, Swiss Tropical and Public Health Institute, Basel, Switzerland.)

with at least one soil-transmitted helminth species[2] and that more than half the world's population is at risk of infection.[14,22] In the developing world, particularly in rural settings, multiple-species soil-transmitted helminth infections are common.[31] In Europe, most infections are caused by *A lumbricoides* and *T trichiura* and occur in the poorest areas, mostly in Eastern and Southern Europe.[8] In the United States there is a high probability that ascariasis, trichuriasis, and strongyloidiasis are still important parasitic diseases (**Box 2**).[7] Parasitic gastrointestinal infections must also be considered in travelers, particularly in those returning from South America, sub-Saharan Africa, and South Asia.[39]

Clinical Features

Soil-transmitted helminths arguably are among the world's most important causes of physical and intellectual growth retardation.[2] The morbidity associated with soil-transmitted helminth infections depends on the intensity of infection, which is a function of the number of worms harbored in the human host. Common are intestinal symptoms such as abdominal pain, and general malaise and weakness. Heavy *A lumbricoides* infections can cause nutritional deficiencies and growth retardation as a result of lactose intolerance and malabsorption of vitamin A and possibly other nutrients.[2] In infected children partial intestinal obstruction can occur, which is typically associated with signs and symptoms of peritonitis. In adults, *A lumbricoides* worms can enter and block the ampullary orifice of the common bile duct, causing hepatobiliary and pancreatic disease symptoms. Fever tends to animate adult worms to move and emerge from the nasopharynx or anus. Adult worms might also enter the appendix, leading to acute appendicular colic and gangrene of the appendix tip. This process leads to symptoms similar to appendicitis, hence differential diagnosis is required.[2] An intense inflammatory response against *A lumbricoides* larval antigen in the lungs can result in verminous pneumonia.

Heavy chronic infection with *T trichiura* can cause inflammation and colitis. Chronic disease signs include diarrhea, impaired growth, anemia, and finger clubbing. The

Table 2
Epidemiology and burden of intestinal nematodes covered in the present review

	Geographic Distribution	No. of People at Risk	No. of Infected People (Million)	Global Burden (DALYs) (Year of Estimate)
Ascaris lumbricoides	Worldwide in at least 112 countries; particularly in sub-Saharan Africa, the Americas, South and East Asia	4.5 billion[14,22]	807–1221[2]	1,851,000 (2004)[23]
Hookworm			576–740[2]	1,092,000 (2004)[23]
Trichuris trichiura			604–795[2]	1,012,000 (2004)[23]
Strongyloides stercoralis	Worldwide in at least 70 countries; particularly in Southeast Asia, Latin America, sub-Saharan Africa, and parts of the southeastern United States	No number available	30–100[2]	No number available
Enterobius vermicularis	Worldwide	No number available	No number available	No number available
Toxocara canis and *T cati*	Worldwide	No number available	No number available	No number available
Trichinella spiralis	Worldwide	No number available	>10[24]	No number available

Box 2
Intestinal nematode infections in North America

Most nematode infections occur, yet are largely neglected, in the United States,[3] where prevalences are highest among poor people, ethnic minorities, women, and children.[32] The United States Gulf Coast, including Louisiana, Mississippi, and Alabama as well as neighboring regions of Texas and Florida, are considered most vulnerable in terms of neglected disease occurrence.[2,3,28,33]

Ascaris lumbricoides

- Appalachia, American South
- Refugees, Mexican-born migrant workers, African American populations
- <4 million cases[3,10,12,34]

Trichuris trichiura

- Appalachia, American South
- Refugees
- 13% of schoolchildren in Clay County (Eastern Kentucky)[35,36]

Hookworm *(Ancylostoma duodenale, Necator americanus)*

- Believed to be eliminated from the American South where in the early twentieth century highly endemic areas existed, but no large studies have been conducted since the 1970s[7]
- Refugees, Mexican-born migrant workers[3]

Strongyloides stercoralis

- Appalachia, American South
- Refugees, older white men with underlying chronic illnesses, poor white Appalachians
- 68,000 to 100,000 cases[3,14]

Enterobius vermicularis

- Most common worm infection in the United States
- Children younger than 18 years; people who take care of infected children; institutionalized people; no association with any particular socioeconomic level, ethnic group, or culture
- 42 million cases[37]

Toxocara canis and *Toxocara cati*

- Inner cities, American South (Mississippi Delta and the Cotton Belt), Appalachia
- Impoverished, socioeconomically disadvantaged children, rural children, inner-city children, Hispanics, African Americans
- 1.3 to 2.8 million cases[3]
- ~14% of the United States population has been infected (Centers for Disease Control and Prevention [CDC])

Trichinella spp

- Arctic Alaska, Canada
- Inuits, people from poor rural areas or tribal lands
- Between 2002 and 2007, an average of 11 cases per year were reported to CDC
- Incidence rate of Arctic trichinellosis (*Trichinella nativa*) in Alaska: 1.8 cases per 100,000 per year[38]
- Incidence rate of Arctic trichinellosis (*Trichinella nativa*) in the northernmost region of Canada: 11 cases per 100,000 per year[38]

most serious manifestation of heavy *T trichiura* infection is chronic dysentery and rectal prolapse.[40]

The attachment of hookworm to the intestinal mucosa and blood feeding causes bleeding, which can result in (iron-deficiency) anemia.[2] Of note, *A duodenale* take up larger amounts of blood than *N americanus*, which is explained by the larger size of the former hookworm species. Children and women of reproductive age, who have low iron reserves, are at particular risk of anemia. In pregnant women, severe iron deficiency can have a negative impact on the mother, fetus, and newborn baby.[41] The skin penetration of hookworm larvae results in ground itch, a local erythematous and papular rash accompanied by pruritus.[17] The lung passage of hookworm larvae results in less severe pneumonitis compared with that caused by *A lumbricoides* larvae.

S stercoralis infections might create cutaneous, gastrointestinal, or pulmonary symptoms. The extremely motile larvae may invade the skin in the perianal region (autoinfection), causing serpiginous, urticarial rashes termed larva currens (**Fig. 2**).[18,42] Hyperinfection and dissemination of *S stercoralis* can result in edema and infiltrates of the lung, whereas larvae penetrating the intestinal walls can carry enteral bacteria that are the cause of septicemia, meningitis, or pneumonia.[18,42]

Diagnosis and Treatment

As discussed in detail in the article by Rosenblatt and colleagues elsewhere in this issue, the diagnosis of soil-transmitted helminthiasis is based on the microscopic detection of eggs or larvae in fresh or fixed stool samples. The most widely used technique in epidemiologic surveys for the diagnosis of *A lumbricoides*, hookworm, and *T trichiura* is the Kato-Katz technique,[43,44] whereby a thick smear of a defined volume of stool (usually 41.7 mg) is stained and cleared with a malachite green or methylene blue and glycerol-soaked cellophane coverslip, and eggs are enumerated under a microscope by experienced laboratory technicians. The ether-concentration, McMaster, and FLOTAC techniques are also suitable for the diagnosis of soil-transmitted helminth infections.[45–47] *S stercoralis* larvae cannot be diagnosed with the aforementioned techniques. The Koga agar plate[48] and Baermann[49] methods allow the detection of *S stercoralis* larvae in fresh stool samples. Immunologic or serologic approaches for diagnosis have been investigated but are not widely used, as they are not able to distinguish past from present infections and suffer from considerable cross-reactivity between serum antibodies and antigens from different nematode species. Polymerase chain reaction (PCR) assays for the identification of molecular nematode markers in stool samples are very specific and sensitive, but are not yet

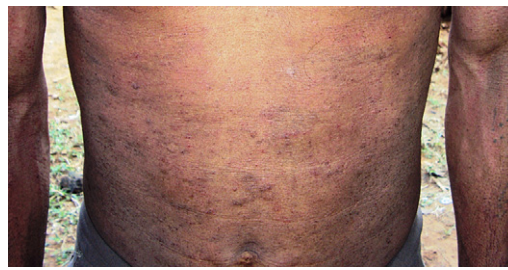

Fig. 2. *Strongyloides stercoralis* hyperinfection. (*Courtesy of* Hanspeter Marti, PhD, Swiss Tropical and Public Health Institute, Basel, Switzerland.)

routinely applied for individual patient management or in epidemiologic surveys because of technical constraints in resource-poor settings and their high costs.

The 2 benzimidazoles albendazole and mebendazole, and the macrocyclic lactone ivermectin, are the recommended drugs for soil-transmitted helminthiasis.[14,34,50] In preventive chemotherapy programs targeting ascariasis, trichuriasis, and hookworm disease, albendazole and mebendazole are used in single oral doses of 400 mg and 500 mg, respectively.[34,51] For trichuriasis, a randomized controlled trial performed in the People's Republic of China found high cure and egg reduction rates after triple-dose albendazole or mebendazole.[52] Indeed, 3-day courses of albendazole (400 mg per dose) or twice-daily mebendazole (100 mg per dose) is the recommended treatment scheme by physicians in special travel clinics in the North.[2,50] It was recently shown that a combination therapy of mebendazole (single oral dose of 500 mg) plus ivermectin (200 μg/kg) is more efficacious than single mebendazole and albendazole against *T trichiura.*[53] Ivermectin (200 μg/kg) is the treatment of choice against *S stercoralis*, but multiple doses of albendazole are also efficacious.[4,54]

Control and Prevention

Soil-transmitted helminthiasis control programs rely on the regular administration of anthelmintic drugs (mainly albendazole and mebendazole) to school-aged children or entire communities (when prevalence rates in the school-aged population are above a predefined threshold) to prevent morbidity. This strategy, termed preventive chemotherapy, also has an impact on transmission. Such programs have been implemented in many endemic countries following the 2001 World Health Assembly resolution 54.19, which urged all endemic member states to annually administer anthelmintic drugs to at least 75%, and up to 100% of all school-aged children at risk of morbidity by 2010.[4,55] However, in 2009 the global treatment coverage was estimated to be only 31%, far below the target set for 2010.[56] Besides these efforts, the community-wide administration of ivermectin or diethylcarbamazine (DEC) plus albendazole, in the context of programs to control lymphatic filariasis or onchocerciasis, has an impact on soil-transmitted helminths, including *S stercoralis*, but the effectiveness should be monitored more closely. Additional measures to prevent soil-transmitted helminth infections are the provision of improved sanitary infrastructure, safe water, abstaining from night-soil use for farming (commonly practiced in Southeast and East Asia), and adequate personal and food hygiene as well as wearing shoes. Results from a recent systematic review and meta-analysis suggest that people having access to sanitation have an approximately 50% lower risk of soil-transmitted helminth infection than those without.[26] Individuals can avoid *A lumbricoides* and *T trichiura* infections by peeling or cooking their food, boiling drinking water, and by consistent use of soap for hand washing (the mnemonic saying "cook it, peel it, or leave it") (see **Box 1**). Travelers should also be alerted to the risk of soil-transmitted helminth infections and the simple prevention measures. Hookworm and new *S stercoralis* infections (cave at: autoinfections are possible) can be prevented by reducing skin contact with potentially infected soil, for example by wearing closed shoes or gloves, and by placing infants on mats.

ENTEROBIASIS (*ENTEROBIUS VERMICULARIS*)

Life Cycle and Epidemiology

E vermicularis, also known as pinworm, is transmitted directly from person to person, but autoinfection is also possible. The most common ways of infection are via dust, food, hands, and water contaminated with eggs.[57] The adult worms live attached to the mucosa in the cecum and large intestine of humans. At night, female worms

migrate out of the anus of their host and deposit their sticky eggs on the perianal skin. The eggs become infective within hours. If eggs are ingested, larvae hatch and mature to adult worms within 2 to 4 weeks[57] (see **Table 1**).

E vermicularis occur worldwide and infect millions of people, mainly children (see **Table 2**). Infections are most prevalent in temperate regions but also frequently occur in the tropics. It is the most common helminth infection in the United States.[58] Overcrowding in families, kindergartens, and schools as well as inadequate personal and community hygiene are the key risk factors for transmission. Children are at highest risk of infection; prevalences usually peak in children aged 5 to 10 years.

Clinical Features

E vermicularis infections are mostly asymptomatic. Reported symptoms include intense pruritus in the perianal area that can lead to insomnia, restlessness, and irritability.[57] In women, adult female pinworms can migrate to the genital tract, causing granulomas in the uterus, ovary, and the fallopian tubes, and pelvic peritoneum.

Diagnosis and Treatment

Pinworm infections are usually diagnosed using the adhesive-tape method for detection of ova, segments of adult worms, or intact worms (**Fig. 3**).[59] For this test, a transparent adhesive cellulose tape is placed on the subject's perianal area in the early morning before the individual showers or uses the toilet.[37] The tape is subsequently attached to a microscope slide for microscopic examination.[60] The eggs can be stained deep blue with lactophenol cotton blue, facilitating the detection and identification.[61] The threadlike, light-yellowish to white adult worms with a long, thin, sharply pointed tail may also be observed in the stool.[37]

Albendazole and mebendazole are efficacious against *E vermicularis*. Recommended regimens are single oral doses (mebendazole, 100–400 mg; albendazole, 100–400 mg) that are repeated after 1 week, to target worms that have developed from autoinfection.[57] Whether symptoms are present or not, it is advisable to treat all members in a household where an infection has occurred as family members are usually also infected with *E vermicularis*.[37]

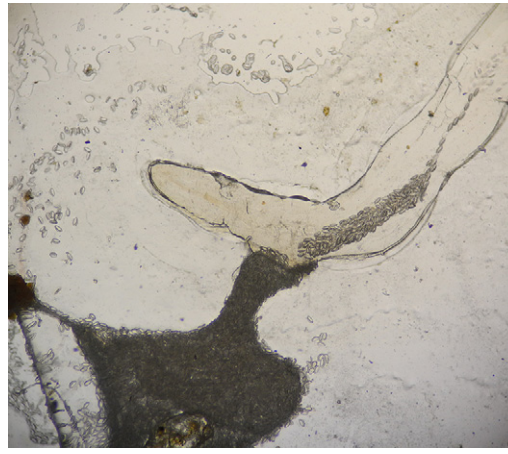

Fig. 3. *Enterobius vermicularis* adult female worm shedding countless eggs on an adhesive tape. (*Courtesy of* Tobias Schindler, BSc, Ifakara Health Center, Bagamoyo, Tanzania.)

Control and Prevention

In households or institutions where more than one individual is infected or repeated symptomatic infections occur, simultaneous treatment of all members along with a thorough cleaning of the rooms, towels, and bed linen is recommended. Individual and household hygiene, for example the regular washing of hands and linen, towels, and underwear with soap, is of major importance in preventing infections (see **Box 1**).

TOXOCARIASIS (*TOXOCARA CANIS* AND *TOXOCARA CATI*)

Life Cycle and Epidemiology

Toxocariasis is a zoonosis. The definitive hosts of *T canis* and *T cati* are dogs and cats, respectively. Humans are accidentally infected by ingesting *Toxocara* eggs containing infective L_3 or by eating raw or undercooked tissue with encapsulated L_3 of paratenic hosts such as cows, sheep, or chickens.[62] After egg ingestion the L_3 hatch in the small intestines, penetrate the intestinal wall, and are carried by the blood stream to the liver, and in some cases to the lungs, muscles, eyes, and/or the central nervous system. Humans are accidental hosts in which larvae fail to develop into reproducing adult worms but instead encapsulate in an arbitrary environment.

Similarly, in dogs and cats the L_3 encyst in tissues but can be reactivated in pregnant bitches, and reach their final destination in the dog's intestines either in the adult animal or after crossing the placenta, infecting fetuses. In the intestine of a definitive host, the female worm produces up to 200,000 eggs per day, shed with the feces[62] (see **Table 1**). In the environment, eggs embryonate and develop to L_3 within 2 to 3 weeks.

Toxocara infections occur wherever cats and dogs are kept. In the United States, toxocariasis is considered one of the most common human parasitic worm infections, while in developing countries it might pose an even greater public health problem.[63] However, the importance of toxocariasis in public health, including global and regional burden estimates, remains to be determined (see **Table 2**).[11]

Risk factors for infection include poverty, overcrowding, illiteracy, rural residence, and pica/geophagia.[64] Children playing on grounds contaminated with dog or cat feces and people having soil-related occupations are at particular risk of infection.[63,64]

Clinical Features

Toxocara infections in humans can remain asymptomatic, but larvae in tissues and organs can also cause severe local inflammatory reactions that result in both mechanical and immunopathologic damage, which are the basis of toxocariasis.[63,64] The 2 classic clinical syndromes in humans are (1) visceral larva migrans (systemic disease caused by larval migration through major organs) and (2) ocular larva migrans (disease is limited to the eyes and optic nerves). Larvae migrating through the liver and lungs are the cause of visceral larva migrans, which results in hepatitis and pneumonitis and might progress to hepatomegaly and pulmonary infiltrates or nodules accompanied by cough, wheezing, eosinophilia, lymphadenopathy, and fever. If larvae enter the central nervous system, they can cause meningoencephalitis and cerebritis, manifesting as seizures.[63] The migration of larvae through the eye (ocular larva migrans) results in inflammation and permanent ocular damage[63,64] Common and less severe symptoms known as covert and common toxocariasis in children and adults, respectively, resemble asthma and include wheezing, pulmonary infiltrates, and eosinophilia.

Diagnosis and Treatment

As no adult worms develop in the paratenic human host, no *Toxocara* eggs can be found in human feces, and hence the identification of infection relies on biopsies and, particularly, on serodiagnosis. The commercially available and most useful test for the diagnosis of visceral and ocular larva migrans caused by *T canis* and *T cati* is the enzyme immunoassay (EIA) using standardized *T canis* excretory-secretory (TES) antigens from infective-stage larvae.[63,65] A limitation of the indirect TES enzyme-linked immunosorbent assay (ELISA) for antibody detection is its cross-reactivity with other nematode infections. Hence, positive screening results from the ELISA should be confirmed by applying a TES Western blot, which visualizes *Toxocara*-specific low molecular weight bands (24–32 kDa).[11] Of note, antibody detection tests are not able to distinguish between past and present infections, because antibody titers can remain high in the absence of disease and after treatment, limiting their applicability. The detection of parasite DNA in humans is not very sensitive and reliable, because *Toxocara* does not replicate in the human host and larvae are encapsulated in tissue.[11] However, the detection of parasite DNA in soil samples and in definitive and paratenic animal hosts is possible with new PCR tests, and might be useful for the assessment of environmental contamination and the prevalence of infections in animals.[66,67]

Albendazole (500 mg given twice a day for 5 days) is the current first-line treatment for visceral larva migrans.[62] DEC has also been used to treat *Toxocara* infections. Indeed, DEC might be more effective than the benzimidazoles, but also more readily elicits major adverse reactions. Ocular toxocariasis should be treated in combination with steroids to reduce the inflammatory response.[11] Albendazole treatment (800 mg/d for adults and 400 mg/d for children) for 2 to 4 weeks kills persisting larvae.[68]

Control and Prevention

The public health importance of *Toxocara* infections remains to be elucidated, which will require national surveillance systems that are not yet in place in most countries. Measures to control transmission and prevent infections include: (1) sensitization of the general public, particularly pet owners, to raise awareness for the disease and its transmission; (2) regular deworming of puppies, adult dogs, and cats to reduce environmental contamination with *Toxocara* eggs; (3) improvements in the urban and rural sanitation structure to lower transmission between animals and humans; and (4) promotion of adequate personal hygiene (ie, hand washing), to prevent fecal-oral transmission of eggs (see **Box 1**).[11,63,64]

TRICHINELLOSIS (*TRICHINELLA* SPP)

Life Cycle and Epidemiology

Trichinellosis (trichinosis) is a zoonotic disease. The life cycle of the parasite includes an intestinal and a muscular phase. Humans, as well as pigs, rodents, and other animals, are infected by the ingestion of raw or undercooked meat containing encysted larvae.[69] During digestion, the *Trichinella* larvae are released into the stomach and subsequently penetrate the mucosa of the small intestine, where they develop into adult worms (see **Table 1**). Starting after 1 week and for a period of 3 to 4 weeks, adult female worms produce larvae, which cross the intestinal wall, spread via the blood vessels, and finally settle in striated skeletal muscles where they encyst after 4 to 5 weeks, but remain viable for several years.[69]

Trichinella infections occur worldwide (see **Table 2**). There are at least 8 *Trichinella* species, infecting a wide range of host species (mammals, birds, and reptiles),

including humans. Among them, *Trichinella spiralis* is considered the most important in causing human trichinellosis.[70] Because approaches for the diagnosis and reporting of trichinellosis are not yet standardized, there is a lack of information on the global burden, current distribution, and incidence of trichinellosis in both animals and humans.[5,12] Estimates put forth more than 10 years ago suggest that globally, at least 10 million people are infected with *Trichinella*.[24] Autochthonous cases have been reported in 55 countries,[5] and accidental infections occur in areas and countries where people eat raw or undercooked meat that has not undergone testing for trichinellosis, and was imported from an endemic region.

Clinical Features

The clinical signs, symptoms, and course of disease vary between *Trichinella* species [69] and depend on the number of adult worms and larvae.[5] Trichinellosis includes a wide spectrum of clinical appearances ranging from asymptomatic to fatal.[5] In the acute phase of the disease, adult worms and particularly migrating larvae are responsible for the course of disease. The migration of larvae to their final destinations provokes acute immunologic, pathologic, and metabolic disturbances, which manifest as eosinophilia, increased levels of immunoglobulin E and muscle enzymes, diarrhea, abdominal pain, fever, myalgia, cutaneous rash, eyelid or facial edema, vasculitis, and intravascular thrombi.[5,69] In the acute infection, and because of the penetration and residency of larvae in the muscle, modifications of the cells and their environment are common.[5,69] More serious trichinellosis manifestations include cardiovascular, neurologic, ocular, respiratory, and digestive complications, which usually develop within 2 weeks after infection, and are more often seen in elderly and inappropriately treated people than in other population segments.[69] In pregnant women, *Trichinella* infections can cause abortion or premature delivery.[69]

Diagnosis and Treatment

The most reliable technique for diagnosing *Trichinella* infections is the ELISA, in combination with a Western blot.[69] Among the commercially available ELISA kits, only those showing no cross-reactions with other nematode antigens should be used.[69] However, anti-*Trichinella* antibodies usually cannot be detected at the onset of clinical signs. If a rapid confirmation of infection is required, counterimmunoelectrophoresis or latex agglutination tests can be applied which, though quick, are not commonly used because they are less sensitive and specific than ELISA. Trichinelloscopy allows determination of the intensity of infection (1000 larvae/g muscle tissue is considered a very heavy infection) and the species or genotype of the parasite. For this purpose, a small muscle sample is compressed between 2 microscope slides and examined under a light microscope at a magnification of 50× to 100×. However, this method is not very sensitive for detecting low-intensity infections. Additional diagnostic possibilities are the histologic examination of muscle tissue after hematoxylin-eosin staining, and the digestion of muscle tissue with pepsin (1%) and hydrochloric acid (1%) to detect early-stage larvae and late-stage (encapsulated) larvae, respectively. In general, as highlighted in the article by Rosenblatt and colleagues elsewhere in this issue, the diagnosis of trichinellosis in humans should be based on: (1) clinical picture (recognition of the signs and symptoms of trichinellosis); (2) laboratory findings (nonspecific laboratory parameters, ie, eosinophilia and muscle enzymes, antibody detection, and/or detection of larvae in a muscle biopsy); and (3) epidemiologic investigation (identification of source of infection and origin of meat, outbreak studies).[5,71]

Trichinellosis should ideally be treated at an early stage of infection to avoid serious complications. The anthelmintic drugs albendazole (400 mg twice daily for 8–14 days)

and mebendazole (200–400 mg 3 times a day for 3 days, followed by 400–500 mg 3 times a day for 10 days) are recommended as first-line treatments.[5] Neither albendazole nor mebendazole are efficacious against all larval stages. Of note, mebendazole is particularly poorly absorbed in the gastrointestinal lumen and reaches only low plasma levels.[69] Severe symptoms should be treated with steroids, for example with prednisone (30–60 mg per day for 10–15 days).[5] Steroids must always be used in combination with anthelmintics, because they can increase the larval burden by delaying the expulsion of worms from the intestine.[69]

Control and Prevention

Trichinella infections in humans can be prevented at the individual level by avoiding the consumption of raw or undercooked meat and meat products from both domestic and sylvatic animals not tested for *Trichinella* larvae through formal meat inspection (see **Box 1**). At the population level, farming pigs under strict veterinary control and use of certified animal feed is important.[5]

In the United States and the European Union, there is a legal requirement to report trichinellosis cases. For example, the European Commission regulation no. 2075/2005 requires meat inspections for farmed and wild animal species that are susceptible to *Trichinella* infection (ie, domestic pigs, horses, and wild boars) and are slaughtered for consumption.[5] In the United States, a program to certify *Trichinella*-free pork production is being evaluated.[72] Despite these efforts, the movement of people (migrants and travelers), livestock, wildlife and, potentially, infectious food products increase the risk of spreading trichinellosis, illustrating the need for a rigorous testing and reporting system as well as good interaction between the public health and veterinary sector in affected countries.[5]

SUMMARY

Intestinal nematode infections, including soil-transmitted helminths, *E vermicularis*, *Toxocara* spp, and *Trichinella* spp inflict a considerable, yet underappreciated, public health burden not only on deprived populations in the tropics and subtropics but also in temperate and arctic areas of Europe and North America. The detection of light-intensity infections with the available diagnostic tools is generally not very sensitive and/or specific. Hence, the development of more accurate diagnostic methods, suitable for large-scale population screenings as well as for individual patient management, is essential for adequate surveillance and monitoring of the incidence and prevalence of disease in endemic countries, and in countries with a flourishing tourist and food import industry. The recognition and treatment of infections at an early stage can help avoid chronic morbid sequelae as infection progresses. While available anthelmintic drugs show moderate to good efficacy against some intestinal nematode species when administered at single oral doses within preventive chemotherapy programs (eg, albendazole and mebendazole),[73] other infections require multiple dosing or combination therapy and several disease outcomes cannot be inverted. Adopting preventive measures, first and foremost adequate food and personal hygiene, is hence key to the avoidance of infection and transmission of intestinal nematode infections.

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