Trichuriasis

Subjects: Zoology
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Trichuriasis is the clinical disease of animals infected with the parasite of the genus *Trichuris*. This review attempts to present information on *Trichuris* spp. infestation in neo-tropical rodents that are utilized for meat consumption by humans

Keywords: agouti ; lappe

1. Introduction

The neo-tropics is a geographical region located in the western hemisphere between the Tropic of Cancer and the Tropic of Capricorn. Geographical territories present within this zone include the southern parts of North America, all of Central America, the northern parts of South America, and all of the Caribbean[1]. Animals that are present in this region can be categorized into three groups: imported domesticated animals[2], domesticated animals originating from the neo-tropics[3], and non-domesticated neo-tropical animals[4]. For the purpose of this review, neo-tropical rodents that are included belong to the domesticated and non-domesticated groups. Domesticated neo-tropical rodents, such as the guinea pig, are utilized in South America for their meat and are reared in captivity to provide meat protein for rural villages. The guinea pig is able to utilize household waste and provide income and food for these communities[5][6]. Neo-tropical rodents on the verge of domestication are the agouti, lappe, and capybara. These animals have been reared in captivity in South America and the Caribbean for their meat [1]. These animals have been able to breed in captivity: the agouti produces four offspring per year [7] the lappe produces two offspring per year[8], and the capybara can produce eight offspring per year[9][10]. These animals are ideal in that they can utilize local feed resources and are adapted to local conditions of high heat and humidity. The meats produced by these rodents are highly nutritious, with high protein values and low fat and cholesterol concentration[11][12][13][14]. *Trichuris* spp., also known as whipworms, have parasitized many domesticated species, causing enteritis, diarrhea, and weight loss [15]. *Trichuris* spp. adults live in the caecum and colon; this predilection site has occurred due to evolution. The life cycle is direct; eggs with characteristic bi-polar plugs are passed in the feces and take two to three weeks to become infective (Figure 1) [16]. Animals become infected by the ingestion of infective eggs[16]. However, there has been limited information on the effects of *Trichuris* spp. on neotropical rodents (domestic and semi-domestic). Thus, the objective of this review is to summarize the species of *Trichuris* that parasitizes these rodents, the effect of this parasite on these animals, and the zoonotic potential of this pathogen.

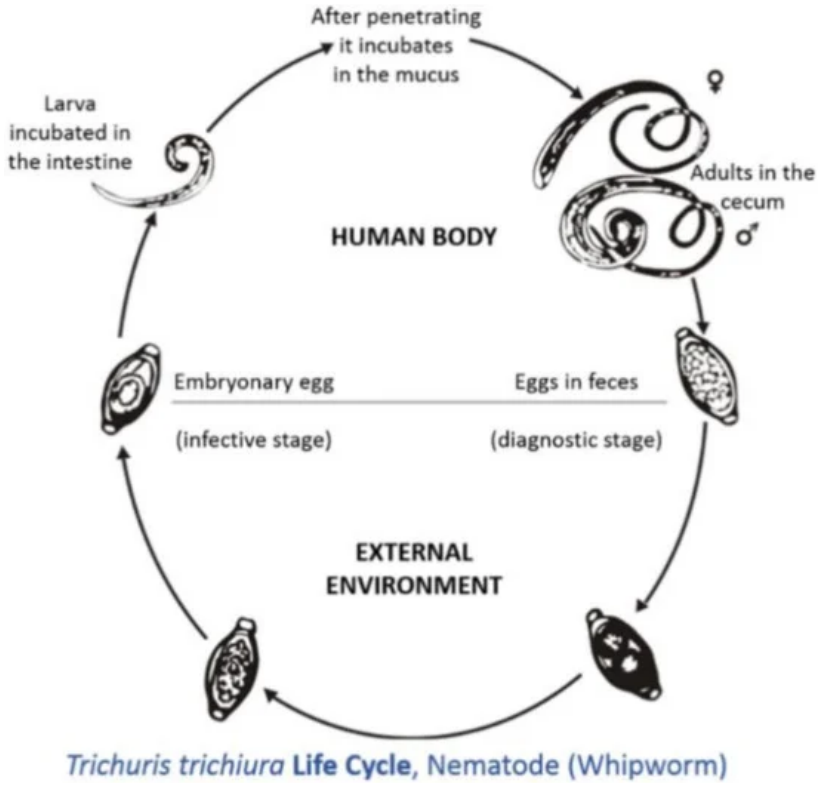

Figure 1. Life cycle of *Tichuris trichiura* (taken from[17]).

2. *Trichuris* spp. of Veterinary and Public Health Importance

2.1. Trichuriasis of Man

Trichuriasis is one of the major infectious diseases of children in developing countries[18]. *Trichuris trichiura* is a major, soil-transmitted helminth targeted by the World Health Organization in their mass drug administration program for pre-school and primary school children in endemic developing countries[18]. There have been several cases of trichuriasis reported in humans. In some cases, it has been due to three *Trichuris* spp.: *T. trichiura*, *T. vulpis*, and *T. suis*. Humans have been infected with *T. vulpis*, and the diagnosis was made based on the morphology of the eggs and vulva from an adult female[19]. Molecular techniques were used on *Trichuris* spp. egg present in feces to identify *T. suis* and *T. trichiura* in human populations from Thailand[20]. *T. suis* has been experimentally given to humans, and the author stated that feces were negative for *Trichuris* eggs 40 days post-infection[21]. Experimentally treated patients showed no symptoms of gastrointestinal distress[21]. In contrast to the previous studies, Kradin et al.[22] showed that iatrogenic infection with *T. suis* resulted in a persistent active infection in man. Pathological findings from colonic biopsies showed several round helminths beneath the ileocecal mucosa epithelium [22].

Trichuris trichiura has human and non-human primates as its natural hosts[23]. Mixed infections with various *Trichuris* spp. in humans have been documented. There have been cases of mixed infections with *T. vulpis* and *T. trichiura* [24][25]. The identification of the species of *Trichuris* spp. was based on the morphology of eggs[24] and polymerase chain reactions of the helminth eggs [25]. *Trichuris trichiura* and *T. vulpis* was also found in the stool samples of dogs that roamed around the community. This shows that dogs are key to the transmission of *Trichuris* spp. to humans, but further work needs to be done to validate this finding[25].

Infections with *T. vulpis* have been reported in children and adults [19][26][27]. However, all cases of trichuriasis in humans caused by *T. vulpis* have had some association with dogs, and the diagnosis was made based on morphology of eggs present in the feces. Clinical signs reported in humans are abdominal discomfort, epigastric pain, nausea, vomiting, diarrhea, and poor appetite[24]. Patients with *T. vulpis* [24][26][27] and *T. trichiura*[19] have been treated with mebendazole and albendazole with improvements of clinical signs [19][24][26][27]. However, in vivo studies on albendazole and mebendazole have shown little efficacy against *T. trichiura*[28]. At 14 days post-treatment, there was no difference in the disease prevalence seen between treatments of patients with 400 grams of albendazole [28]. Therefore, alternative anthelmintic treatment against *T. trichiura* should be investigated. Ivermectin has been used to treat *Trichuris* spp.; however, it is very ineffective, as these parasites have become resistant to this drug. However, due to the increased prevalence of anthelmintic resistance, the drugs used to treat trichuriasis should be done with caution.

2.2. Morphological and Molecular Identifications of Trichuris spp.

2.2.1. Morphological Identification of *Trichuris* spp. in Pigs, Dogs, Cats, Humans, and Non-Human Primates

Morphological analysis of *Trichuris* spp. has been used for identification within various host species. *Trichuris trichiura* infection has been investigated in humans, non-human primates, and pigs, but based on morphological analysis, the *T. trichiura* found in humans and non-human primates were indistinguishable[29]. In pigs, *T. suis* was differentiated from *T. trichiura*, based on the lack of peri-cloacal papillae in adult specimens. In female specimens, there were no morphological differentiation between *T. suis* and *T. trichiura*[29]. Ruminants evaluated in India using morphological analysis identified *T. ovis* as the major parasite [30]. [

Further research was done in domestic cats in St. Kitts. Based on the size of the *Trichuris* spp. identified, authors believed that it was *T. campanula*, but based on the vulva structure the authors confirmed it was *T. serrata*. In conclusion, the authors, identified the parasite as *T. serrata*, but recommended that molecular studies must be done in order to reliably identify this parasite[31]. In dogs, male and female adult *T. vulpis* could be identified based on nine parameters (including body length, length of cuticular processes, and width of body at tail part)[32]. Male *T. vulpis* can be distinguished from other species by spicule sheath ornamentation (the dimensions of the spicule) [32].

Recently, the morphometric approach analyzing the adult worms and eggs of *Trichuris* spp. of non-human primates were analyzed[33][34]. Morphometric data on the adult worms showed that features present in the females made them indistinguishable for species characteristics, but adult male worms may be used to differentiate *Trichuris* populations[33]. Geometric morphometric analysis is a new diagnostic tool that can be used to differential *Trichuris* spp. present in non-human primates. However, further data must be collected to determine the sensitivity and specificity of this diagnostic tool[34]. Combination of various techniques, such as the use of molecular and morphological analysis, should be performed for confirmation of various *Trichuris* spp. [33].

2.2.2. Molecular Identification of *Trichuris* spp. in Domestic and Non-Domestic Ruminants

Molecular techniques have been used to identify various *Trichuris* spp. in their animals or human hosts. Such techniques have been applied to *Trichuris* spp. found in ruminants (both domesticated and non-domesticated). Four *Trichuris* spp.—*T. discolor*, *T. ovis*, *T. globulosa* and *T. skrjabini*—have been identified as inhabiting the caecum and colon of ruminants[35][36][37][38][39][40][41][42][43][44][45][46]. One of the major discoveries was the identification of *T. globulosa* and *T. ovis* as the same species by isoenzymes [35], using second, internally transcribed spacer ribosomal DNA (ITS2 rDNA)[38] and ITS1-5.8S-1TS2 [37]. Further molecular analysis was done comparing *T. ovis* and *T. discolor*, where the entire mitochondrial DNA (mtDNA) was analyzed[42], and with the use of internally transcribed spacers 1, 2, and 16S, partial DNA sequencing (ITS1, 2, 16rDNA) was completed[44]. Based on mtDNA and rDNA, *T. ovis* and *T. discolor* can be classified as two different species.

Trichuris skrjabini, found in small ruminants (sheep and goats), was characterized using isoenzymes [36], ITS1-5.8S-1TS2 [37], and cytochrome oxidase subunit 1 and mitochondrial 16S rDNA [39]. Authors have stated that *T. skrjabini* is an independent species but has close relations to other *Trichuris* spp. that parasitize small ruminants. *Trichuris discolor* has been identified in domestic ruminants with the use of molecular techniques; however, it was recently identified in wild ruminants, such as the roe deer (*Capreolus capreolus*), sika deer, (*Cervus nippon*), red deer (*Cervus elephus*), fallow deer (*Dama dama*), and mouflons (*Ovis orientalis musimon*)[43][44][45]. In wild ruminants, *T. discolor* was identified with use of ITS1-5.8S-1TS2[43][44][45], but in cattle different populations of *T. discolor* in Iran, Spain, and Japan were investigated using 16S partial gene mtDNA, as well as ITS1 and 2 [43]. Callejon et al. [43] noted that there were specific populations of *T. discolor* groups based on geographical location. The author noted that one reason may be due to two cryptic species of *T. discolor* from Japan and Iran, as well as another from Spain.

2.2.3. Molecular Identification of *Trichuris* spp. in Cats, Dogs, Pigs, Humans, and Non-Human Primates

Trichuris spp. has also been identified molecularly in pets, such as dogs and cats. In cats it is associated with typhlitis, which also occurs in other animals[46]. Identification of *T. serrata* (cats) and *Trichuris vulpis* (dogs) was accomplished through the use of 18S rDNA (cats) and enzyme-linked immunosorbent assay (ELISA) and ITS1-5.8S-1TS2 (dogs)[47][48]. Comparative genetic studies were done of the *T. vulpis* found in dogs and *T. suis* found in pigs (wild and domesticated). There was a difference seen in amplified ITS1-5.8S-1TS2 rDNA between the *T. vulpis* found in dogs and *T. suis* found in pigs. Interestingly, *T. suis* collected from wild pigs (*Sus scrofa scrofa*) and domestic pigs (*Sus scrofa domestica*) showed no sequential genetic differences[49].

Several non-morphological processes were used to identify *T. suis* found in pigs using isoenzymes[50], ITS 1 and ITS2 regions of rDNA [51], large mitochondrial subunits and ITS2[52], and nuclear ribosomes (18S, ITS2)[18]. Due to the zoonotic potential of *T. suis* and its morphological similarity to *T. trichiura* previous molecular studies have been done in both human and non-human primates[53][54][55]. *Trichuris* spp. was taken from pigs (wild and domestic) and non-human primates (*Colobus guereza kikuyensis* and *Nomascus gabriellae*) and analyzed by amplification of rDNA (ITS1-5.8S-1TS2). The authors confirmed that the *T. suis* found in pigs was genetically different from *T. trichiura* in *Colobus guereza kikuyensis* and *Nomascus gabriellae*[53]. Nissen et al. [54] conducted a similar study to Cutillas et al.[53], but *T. suis* and *T. trichiura* were identified in pigs and humans in Uganda. The gastrointestinal tract of pigs only contained *T. suis*, while in humans *T. trichiura*, *T. suis*, and a heterozygous type was identified [54]. This showed that the use of ITS 2 and β-tubulin allowed the identity of several species of *Trichuris* in humans to be highlighted.

The research done by Cutillas et al. [53]and Nissen et al.[54] highlights the fact that humans and non-human primates may be infected with several species of *Trichuris* that are generally classified as *T. trichiura.* This was seen with *Trichuris* spp. samples taken from the wild Japanese macaques (*Macaca fuscata*), where the *Trichuris* spp. identified had genetic (18S rDNA) dissimilarity compared to those found in humans [56]. This new hypothesis sparked scientists to investigate this phenomenon at a molecular level (Figure 2). Ravasi et al.[57] investigated the genotype of human and non-human primates in Central Africa. Sequencing of the rDNA (ITS1-5.8S-1TS2) revealed two *Trichuris* genotypes that infect both humans and non-primates[57]. Ghai et al.[58] found similar results to Ravasi et al.[57], but three *Trichuris* genotypes were identified as circulating within human and non-human primates. Humans were infected with two genotypes: one genotype that was only common to human samples (Group 1), and another genotype that infected humans as well as non-human primates (black-and-white colobus (*Colobus guereza*), blue monkeys (*Cercopithecus mitis*), grey-cheeked mangabeys (*Lophocebus albigena*), l'hoest monkeys (*Cercopithecus lhoesti*), olive baboons (*Papio anubis*), red colobus (*Procolobus rufomitratus*), red-tailed guenons (*Cercopithecus ascanius*), and the chimpanzee (*Pan troglodytes*)) (Group 3). The intermediary group (Group 2) had a *Trichuris* genotype that affected non-human primates (black-and-white colobus (*Colobus guereza* and the red colobus (*Procolobus rufomitratus*)[58]. Furthermore, this new species of *Trichuris* was found in the Francois' leaf monkey (*Presbytis francoisi*) and the *Colobus guereza kikuyensis* using mtDNA, rDNA, and morphometry[59][60].

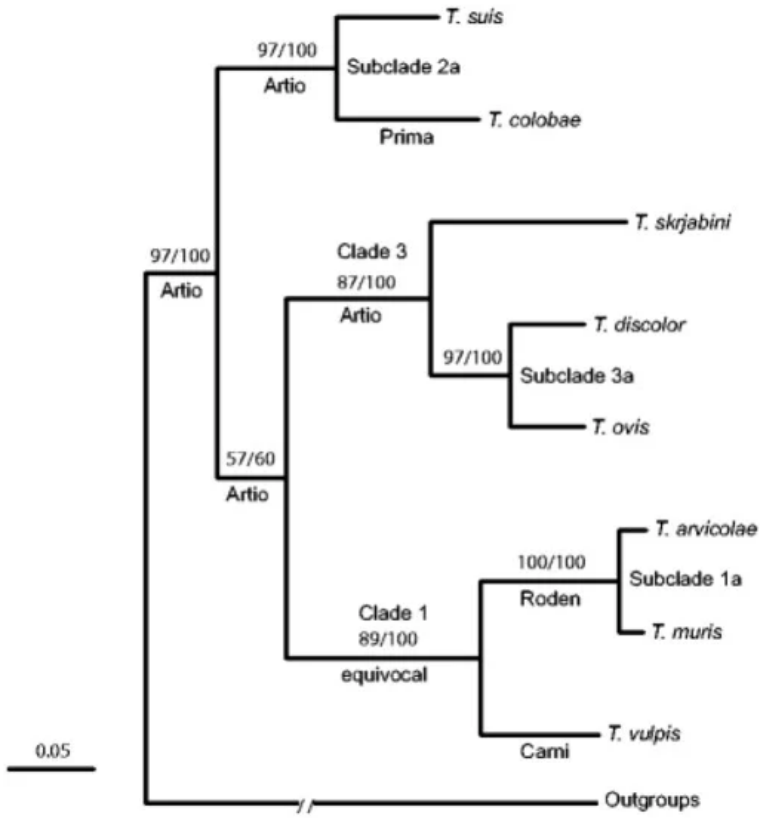

Figure 2. Phylogenic tree of *Trichuris* spp. (taken from Cutillas et al. [53]).

2.2.4. Molecular Identification *Trichuris* spp. in Rodents

Trichuris spp. has been found in domestic livestock and pets, but there are also species that are specific to rodents. The initial molecular research that was done on the *Trichuris* spp. present in rodents focused on European rodents [61]. *Trichuris muris* was identified in Murid rodents in Europe with the use of rDNA (ITS1-5.8S-ITS2). It was found that two lineages had occurred, due to geographical distribution. One was found in northern Spain to Denmark, and the other in

the Southern Europe (Croatia, Romania, and Turkey) [61]. In recent years, several new species of *Trichuris arvicolae* have been found in Arvicolinae rodents using multi-local enzyme electrophoresis[62]and rDNA (ITS1-5.8S-ITS2)[63]. Further investigations were done in the phylogeographic analysis of *T. arvicolae* in Europe, using the mtDNA cytochrome subunit 1 gene (cox1) and rDNA (ITS1-5.8S-ITS2). Nuclear genetics (ITS1-5.8S-ITS2) suggest that *T. arvicolae* show two geographic and genetic lineages (Neoarctic and Palaearctic). Mitochondrial results gave further details into the Palaearctic region, giving three geographic and genetic lineages (Northern Europe, Southern and Eastern Europe, and Italy and France) [64].

Scientists also investigated *Trichuris* present in Sigmodontinae rodents in South America (Argentina). New species, such as *Trichuris novonae*, were identified based on morphological analysis [65]. Another species that was identified morphologically was *T. pardinasi* [64]. Based on molecular characteristics, using ITS2 (rDNA), a new species named *Trichuris bainae* was identified[66]. Molecular analysis using cox1 and mitochondrial cytochrome b (cob) on the *Trichuris* spp. found in Sigmodontinae rodents found three clades corresponding to three different species, which were *T. pardinasi*, *T. bainae*, and *T. navonae*)[67]. Further to this, *T. massoiai* was identified in *Holochilus chacarius* (Cricetidae: Sigmodontinae) using morphological mitochondrial (cox1 and cob) and nuclear (ITS2) markers [68].

Callejon et al. [41][69] investigated nuclear (18S, triose phosphate isomerase) and mitochondrial (cox1, cob1) genes from *Trichuris* spp. from nine various host species *(Colobus guereza kikuyuensis*, *Papio hamadryas*, *Homo sapiens*, *Sus scrofa domesticus*, *Capra hircus*, *Canis lupus familiaris*, *Bos taurus*, *Mus domesticus*, and *Myodes glareolus*) from Spain. The data show that *Trichuris* spp. could be divided in three clades: Clade 1 = *T. arvicolae*, *T. muris*, and *T.vulpis*; Clade 2 = *T. suis*, *T. colobae*, *T. trichiura*, and *T*. spp. ex *Papio hamadryas*; Clade 3 = *T. discolor*, *T. ovis*, and *T. skrjabini*[69].

2.3. Immunomodulatory Effect of Trichuris spp.

Trichuris spp. has been used in the treatment of gastrointestinal autoimmune diseases, such as inflammatory bowel disease, Crohn's disease, and ulcerative colitis [70][71][72]. *Trichuris suis* (pig whipworm) had been experimentally given to humans with no overt sign of gastrointestinal illness. The eggs produced from the feces remained constant, and only a low percentage of these eggs embryonated in vitro[21]. Some authors also noted that treatment of patients with inflammatory bowel disease, ulcerative colitis, and Crohn's disease with *Trichuris suis* showed improvement in gastrointestinal signs, and in the management of disease the subjects were given ova every three weeks [70][71][72]. Surprisingly, Kradin et al.[22] noted that a patient that underwent treatment for Crohn's disease using *T. suis* had adult worms beneath the ileocecal mucosal epithelium. This case does raise concerns about persistent infection from *T. suis* in man [22].

Further work was done on the use of excretory secretory products of *T. suis* in rats[73]. The investigation of the use of excretory products of *T. suis* in swine epithelium cells was used as a model to be used in humans. It was noted that the excretory secretory products (ESPs) elicited the production of interleukin (IL)-6 and IL-10, which have been identified as anti-inflammatory cytokines that inhibit Th-1 responses. This proved that ESPs from *T. suis* have immunomodulatory effects and can be used as candidates in the treatment of inflammatory bowel disease[73]. The use of ESPs from *T. suis* may be safer than the actual treatment with ova.

Subsequent research was done on the immunomodulatory and immunogenic effects of the proteins and ESPs of *Trichuris trichiura* and *Trichuris muris* [74][75][76]. Proteins were analyzed from adult worm extract and fragments of *T. trichiura*. These extracts and fragments were placed in cell cultures of human peripheral blood monocytes, and elicited the production of IL-10, IL-12, and TNF-α. Some fractions showed the inhibition of IL-5 production. The downregulation of IL-5 is a feature of a Th-2 response[74]. Santos et al. [74] concluded that protein fractions of *T. trichiura* can be used in the treatment and prevention of allergic and autoimmune diseases. Immunogenic research was also conducted on the ESPs of *T. muris*, and specific immunogenic proteins were identified. The structure of one such protein was Tm16, which was characterized and could be used in the production of a vaccine[75]. Shears et al.[76] noted that ESPs from *T. muris* elicited production of IL-9 and IL-13 when inoculated into rats. Eleven immunogenic proteins from the ESP of *T. muris* were also identified, and these could be used in the production of a vaccine [76]. Recent studies show that there is tremendous potential for *Trichuris* in human autoimmune disease, as well as vaccine development in rural countries where trichuriasis infections are prevalent.

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