

Helminthiasis and its Relationship with Lung Symptoms in Humans

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Abstract

The term “Neglected diseases” refers to the diseases caused by infectious and parasitic agents (e.g. helminths) that are endemic in low-income populations. While the development of more effective alternative therapies for the treatment of helminthiasis is neglected, information about forms of prevention and control provided to the population about these diseases is rather scarce, making prophylaxis and eradication difficult. Among the information that is not adequately shared with the population at risk of acquiring helminthiasis, those that refer to their symptoms are related as “common sense” information; however, some symptoms - which could alert the population about the possibility of helminthic infection, such as pulmonary symptoms - are generally unknown. Although, pulmonary symptoms are present in several helminthiasis cases and could provide evidence of infection; moreover, lung diseases are particularly prevalent in the tropics, frequently related to parasitic infestations. Thus, helminths could cause temporary or permanent lung damage basically, and usually, due to the presence of different evolutive forms of worms in this organ or due the presence of parasitic antigens trapped within the pulmonary vasculature. This review article aims to relate some human helminthiasis to the pulmonary symptoms in order to clarify the reasons for occurrence of pulmonary symptoms and to report the importance for population that lives in the tropics to gain this knowledge.

Keywords: *Helminths; Neglected Diseases; Helminthiasis; Lung Symptoms; Pulmonary Damage*

Introduction

The term “Neglected diseases” refers to the diseases caused by infectious and parasitic agents (e.g. virus, bacteria, fungi, protozoa and helminths); these diseases are endemic in low-income populations that live in developing countries in Africa, Asia and the Americas. These diseases are considered to be neglected because they do not grab the interest of multinational pharmaceutical companies in the research and development of the drugs intended to treat them. In addition, studies that aimed to research or discover efficient means of treatment and prevention are scarce, due to low investments made by drug development agencies [1,2]. Thus, some factors could explain why these illnesses are neglected, such as the close relation with poverty, geographic isolation of certain affected regions, absence of political “voice” of the affected population and lack of global financing to fight these diseases [3]. Besides, most neglected diseases are included in the list of tropical diseases (diseases that occur specifically or mainly in tropical areas, relating to hot and humid conditions).

In this context, helminthiasis cases stand out because many of them are common and prevalent in developing and tropical countries, causing what the World Health Organization (WHO) considers as “Disability Adjusted Life Years - DALYs” (the potential years of life loss due to

premature mortality and loss of productive years of life due to illness) [4]. While the development of more effective alternative therapies for the treatment of helminthiasis is neglected, information about forms of prevention and control provided to the population about these diseases are rather scarce, making prophylaxis, treatment and eradication difficult for these types of infections.

Among the information that is not adequately shared with the population at risk of acquiring helminthiasis, those that refer to their symptoms are related as “common sense” information, such as abdominal pain and diarrhea; however, these symptoms may or may not appear because it depends on the type and/or phase of the disease. Some symptoms - which could alert the population about the possibility of helminthic infection, such as pulmonary symptoms - are generally unknown by the population.

Pulmonary symptoms are present in several helminthiasis cases and these symptoms could provide evidence of infection, which is interesting for an infection diagnosis. According to Alvar, *et al.* [5] eosinophilic lung diseases are particularly prevalent in the tropics, frequently related to parasitic infestations. Moreover, helminths could cause temporary or permanent lungs damage.

This review article aims to relate the human helminthiasis to the pulmonary symptoms in order to clarify the reason why the pulmonary symptoms could occur and to report the importance for population that lives in the topics to gain this knowledge.

Why could some helminthiasis types cause lung symptoms?

Some helminthiasis types could cause lung symptoms and damage in the lungs basically, and usually, due to the presence of different evolutive forms of worms in this organ or due the presence of parasitic antigens trapped within the pulmonary vasculature.

Thus, helminths may be located in the lungs usually due to two different reasons:

1. **Group 1:** The need for larvae to migrate through the lungs to complete part of their development before growing into the adult form [6-11];
2. **Group 2:** Presence of eggs or larvae in the lung tissues, without transformation into another evolutive form, because they had been passively getting to this organ via blood or lymphatic circulation, or by erratic and occasional larval migrations. In these cases, humans could act as an erratic or accidental host, also acting as unusual intermediate host and, in order to complete the helminth life cycle, it would be necessary the transmission (e.g. the ingestion) by a definitive host [12-17].

Trematode of the genus *Schistosoma* consists in an especial case. Larvae (called “schistosomula”) need to get the lungs to complete their development and cycle of life. However, *Schistoma* eggs could be passively getting lungs via blood circulation, without transformation into other parasitic form [11]. Aiming to facilitate the comprehension about lungs symptoms and damage caused by *Schistosoma*, this helminth will be discussed in the first group (Group 1).

Moreover, microfilariae belongs to a third group (Group 3), that causes lung symptoms due the presence of parasitic antigens (Table 1).

	Reasons for the lung symptoms in humans	Helminth	General Lung Symptoms and Damages	General Prevention and Treatment	References
Group 1	Larvae need to migrate through the lungs to complete part of their development and their cycle of life.	<i>Ascaris lumbricoides</i> , <i>Ancylostoma duodenale</i> , <i>Necator americanus</i> , <i>Strongyloides stercoralis</i> , <i>Strongyloides fuelleborni</i> , <i>Schistosoma mansoni</i> , <i>Schistosoma japonicum</i> , <i>Schistosoma haematobium</i>	Pharyngeal irritation, cough, dyspnea, bronchitis, pneumonia eosinophilic, transdiaphragmatic penetration or symptoms of upper airway obstruction, pulmonary eosinophilia (Löeffler’s Syndrome). Symptoms could be followed by allergic manifestations, fever, nausea, vomiting and hoarseness. In the case of schistosomiasis: Katayama fever, infiltrative pulmonary pneumonia, pulmonary granuloma, Pulmonary Arterial Hypertension.	<p>Ascariasis* prevention:</p> <ul style="list-style-type: none"> • Personal and Food Hygiene • Environmental Sanitation • Health Education • Control of mechanic vectors (e.g. Diptera) <p>Ancylostomiasis*, Necatoriasis* and Strongyloidiasis* prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Protective measures to avoid human skin contact with sand or soil <p>Schistosomiasis* prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Avoid swimming in freshwater of endemic areas or that have the presence of the vector <p>*Treatment: Anthelmintic medications.</p>	[6-11,15,18-32]

<p>Group 2</p>	<p>Eggs or larvae are passively getting to lungs via blood or lymphatic circulation, or by erratic and occasional larval migrations in the lung tissues, without transformation into another parasitic form.</p>	<p><i>Capillaria hepatica</i>, <i>Capillaria aerophila</i>, <i>Toxocara canis</i>, <i>Toxocara cati</i>, <i>Dirofilaria immitis</i>, <i>Taenia solium</i>, <i>Echinococcus granulosus</i>.</p>	<p>Pulmonary abscesses, asthma, productive cough, pulmonary eosinophilia, presence of pulmonary nodules, cysts or fibrosis and calcifications (in the case of <i>Toxocara canis</i>, <i>T. cati</i> and <i>Taenia solium</i>), presence of hidatic cyst (in the case of <i>Echinococcus granulosus</i>) or cysticercos (in the case of <i>Taenia solium</i>).</p>	<p>Capillariasis** prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Food Hygiene • Control of rodents <p>Toxocariasis** prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Food Hygiene • Treatment of infected animals (e.g. dogs and cats) <p>Echinococcosis** prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Prevent dogs from feeding on the carcasses of infected sheep • Food Hygiene • Treatment of infected animals <p>Cysticercosis prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Health Education • Food Hygiene • Treatment of infected animals <p>Treatment: **Anthelmintic medications and surgical treatment.</p>	<p>[12-17,33-38]</p>
<p>Group 3</p>	<p>Presence of parasitic antigens trapped within the pulmonary vasculature.</p>	<p><i>Wuchereria bancrofti</i> and <i>Brugia malayi</i>.</p>	<p>Tropical Pulmonary Eosinophilia or 'Weingarten's Syndrome', nocturnal paroxysmal cough, asthmatics crisis, dyspnea. Symptoms could be followed by low fever, anorexia, weight loss and fatigue.</p>	<p>Filariasis prevention:</p> <ul style="list-style-type: none"> • Environmental Sanitation • Control of the vectors • Treatment of sick humans <p>Treatment: Anthelmintic medications and surgical treatment</p>	<p>[38,39]</p>

Table 1: Reasons for the lung symptoms that some helminths could cause in humans, prevention and treatment.

Helminths and lung symptoms: group 1

In the first group some Nematoda are present (Figure 1), which need to perform a pulmonary cycle (also called as “cycle of Looss”, in reference to the first researcher - in 1901 - that elucidate the life cycle of a hookworm, that have a lung phase) to complete their development (larval form into adult form) [6].

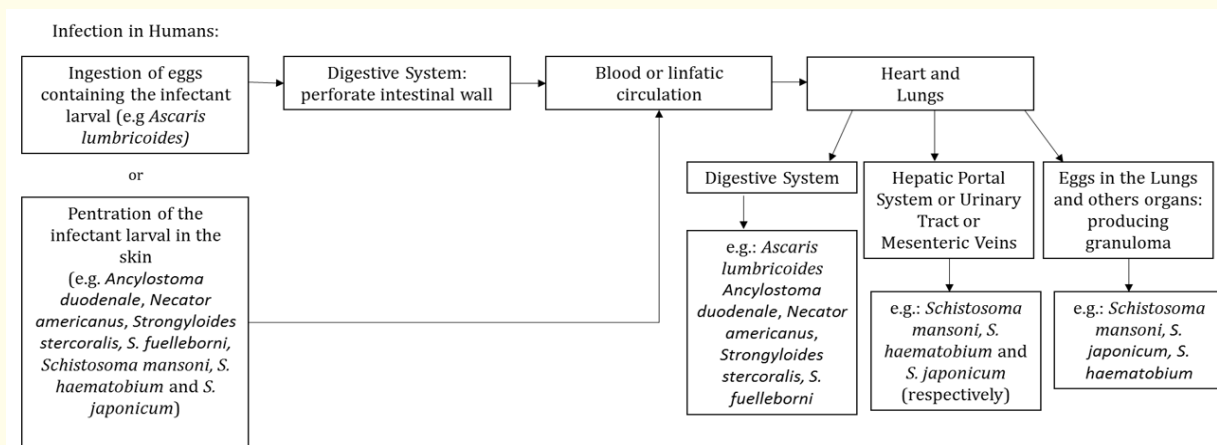


Figure 1: Group 1 helminths life cycle in humans.

Ascaris lumbricoides, for example, has a monoxenous life cycle and humans are its hosts. Eggs of *A. lumbricoides* are disposed in the environment with the feces of the infected hosts; and the eggs could contaminate water and food. Humans could ingest the eggs (e.g. eggs present on food or water) containing the infectious larvae; these larvae will hatch in the host's digestive system and then they will perforate the intestinal wall and reach the lymphatic vessels as well as the mesenteric and portal veins; finally it will reach the liver. From the liver, the larvae are taken to the heart by the vena cava, and from the heart, it reaches the lungs, where it will perforate the blood capillaries, entering the alveolus and doing moults (L3-L4-L5). The larvae named L5 leaves the alveoli up through the bronchial tree and trachea, reaching the pharynx. Then, it could be expelled by coughing or be swallowed, arriving in the stomach and later in the intestine, where it will become an adult worm inside this organ [8,7,21,29]. For low intensity infections, no major alterations are observed in the human organism [29]. However, in the case of high intensity infections, especially among children, lesions may occur in the liver and lungs (with hemorrhagic spots on both organs), causing fever as well as lungs symptoms (e.g. cough dyspnea, eosinophilia, bronchitis, asthma, pneumonia eosinophilic, transdiaphragmatic penetration or symptoms of upper airway obstruction). The pulmonary symptomatology occurs in approximately 6 to 10 days after the ingestion of eggs. Infectious bacterial complications from parasitic migration and associated aspiration are rare [8,9,22].

In addition to *A. lumbricoides*, others Nematoda also need to perform the pulmonary cycle in order to complete their development, for example Hookworms (e.g. *Ancylostoma duodenale*, *Necator americanus*), *Strongyloides stercoralis* and *S. fuelleborni* (specie of *Strongyloides* found sporadically in Africa and Papua New Guinea) [8,40]. For these nematodes, the infective larvae (called filariform stage or L3) can penetrate in the skin of the definitive host (humans) being transported by the blood and lymphatic vessels to the heart and lungs, where it will perform moult (L4). L4 larvae causes the same pulmonary symptoms related for *A. lumbricoides* [8,22]. According to Bethony, *et al.* [8], the oral ingestion of *A. duodenale* larvae could also result in “Wakana Syndrome” which is characterized by nausea, vomiting, pharyngeal irritation, cough, dyspnea, and hoarseness.

The condition characterized by pulmonary eosinophilia, allergic manifestations, fever, bronchitis and pneumonia due the parasite lung phase is called “Loeffler’s Syndrome” (a type of simple pulmonary eosinophilia) [9]. This syndrome causes an eosinophilic pneumonitis that is self-limited and transient (1 to 2 weeks) and the symptoms could be related to pulmonary alveolar edema [9]. When there is cough with mucus, larvae can also appear in this mucus. Loeffler’s Syndrome manifestations are most common in children infected by nematodes, related with the development of the immune system, nutritional status and easiness to the exposition to re-infections [26,29].

Other example for helminth of the first group is *Schistosoma mansoni*. This Trematoda may present two parasitic forms in the lungs: schistosomula (larvae) and the eggs [24].

The infection of *S. mansoni* is due to the cercariae penetration into the skin of the definitive host (e.g. humans), getting transformed into schistosomula that, when entering in the bloodstream, are passively carried to the heart and lungs (Figure 1). From the lungs, the schistosomula can travel through the alveolar capillaries and be carried to the heart via small circulation; then rises in the aorta to gain the systemic circulation, arriving in the hepatic portal system, where it must reach in order to become an adult worm. Another form is through transtissular way (e.g. perforation of alveoli and pulmonary parenchyma) crossing the pleura and the diaphragm, reaching the peritoneal cavity, perforating the capsule and liver parenchyma and reaching the hepatic portal system [19,24,25,30].

This stage of schistosomula migration is considered to be part of the schistosomiasis acute phase. Pulmonary symptoms such as generalized lymphadenitis, fever (called “Katayama fever” or toxemic schistosomiasis - a febrile manifestation that occurs in nonimmune patients, as a response to the systemic hypersensitivity reaction against the schistosomula migration) and enlargement of the spleen can be noticed [24,41]. Congestion and rupture of alveolar capillaries could occur, with the production of small pockets of hemorrhage within the alveoli. In general, the reaction around the schistosomula is minimal and temporary. Although pulmonary involvement is uncommon, the symptoms have been described among population living in endemic areas [24].

There is no transformation of the schistosomula into another parasitic form [19,30], however, schistosomula needs to pass through the lungs probably because the parasite became more resistant to the immunological system of the host (“mechanism of scape”) and due to acquires a more elongated shape [20]. During this period, respiratory symptoms and other signs with ephemeral or more persistent duration, such as dry cough, dyspnea and mucous expectoration could occur. Chest x-ray may show dense strands and thickened vascular weave [19].

Schistosomula of other species of *Schistosoma*, such as *S. japonicum* and *S. haematobium* (major agents of schistosomiasis in humans, besides *S. mansoni*), also migrate to the lungs, causing the same pulmonary symptoms of *S. mansoni* [25].

Still regarding *S. mansoni*, adult females oviposit in the mesenteric veins. The eggs need to cross the intestinal wall reaching the lumen, then they are taken to the environment in order to complete their life cycle. However, some eggs could cross the intestine but other eggs could stay within the intestinal wall, where they will incite the granulomatous reaction; other eggs are passively taken to other organs, especially the liver, but they can also reach other organs, such as the lungs. There is a formation of inflammatory reactions around the eggs retained in the tissues, named granuloma, in these organs (more present in the liver). These inflammatory reactions promote the appearance of fibroses that affect the performance of the organ, characterizing the chronic phase of the disease. Thus, granuloma causes a permanent damage in the lungs [24,25]. Moreover, *Schistosoma mansoni* eggs are highly immunogenic and Loeffler’s Syndrome could be present [28].

Pulmonary manifestations of granuloma such as dry cough, hoarseness and dyspnea, resemble the so-called “infiltrative pulmonary pneumonia” or, sometimes, pulmonary tuberculosis. Increased blood vessels pressure, including pulmonary vessels (Pulmonary Arterial Hypertension) and ‘cor pulmonale’ are a consequence of granuloma. Eggs of *S. japonicum* and *S. haematobium* also caused the same symptoms in the lungs [18,19,23-25,27].

Due to the presence of pulmonary symptoms, the set of symptoms and damage caused in the lungs by the genus *Schistosoma* is called as ‘Pulmonary Schistosomiasis’, more commonly caused by *Schistosoma mansoni* [28].

Helminths and lung symptoms: group 2

In the second group, there are worms which larval forms or eggs are passively taken via blood or lymphatic circulation to the lungs; either the larvae have migrated or were occasionally carried out via circulation to the lungs. In these cases, the helminths will not develop another parasitic form in the lungs (Figure 2).

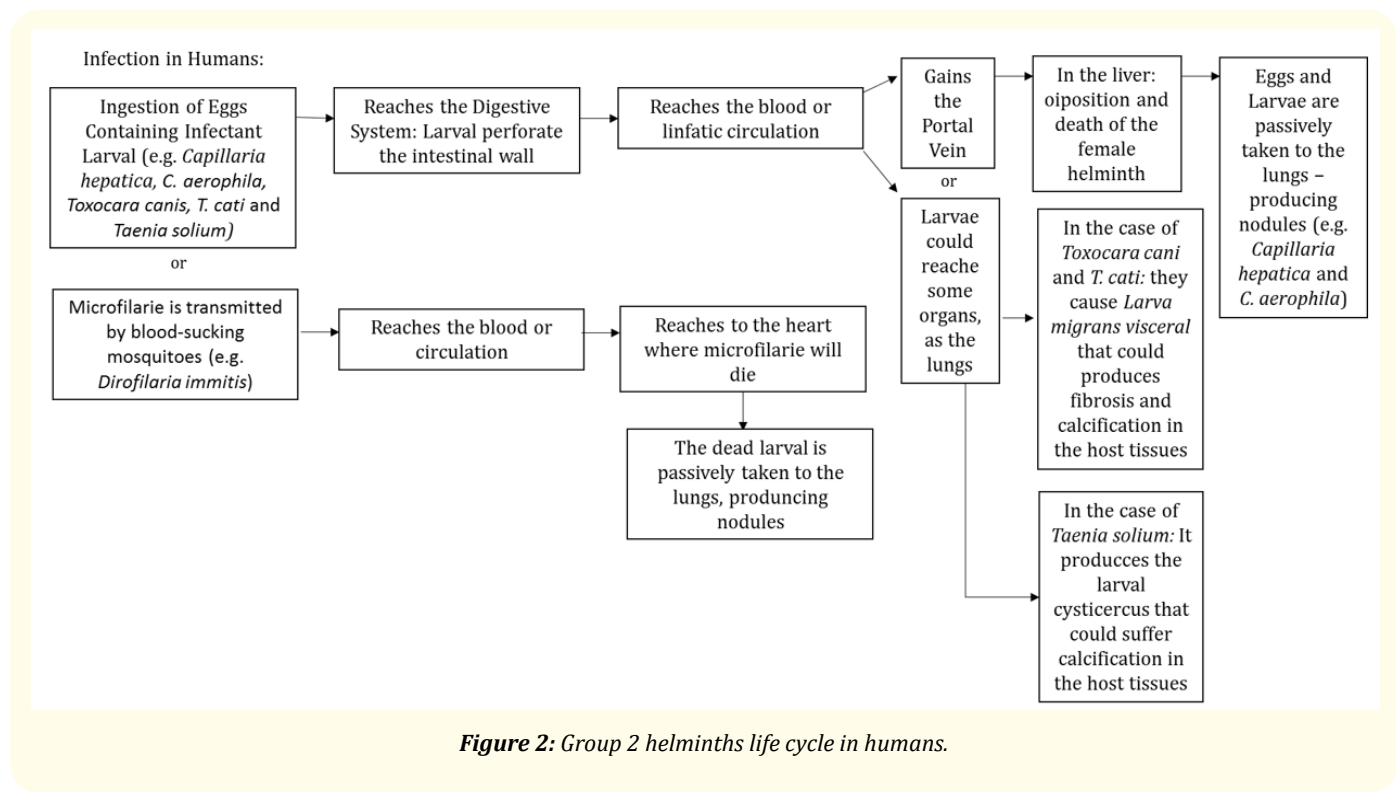


Figure 2: Group 2 helminths life cycle in humans.

Example of the second group are the nematodes *Capillaria hepatica* and *C. aerophila* that cause capillariasis. Capillariasis is a zoonotic disease which circulates among wild carnivorous and omnivorous mammals. Human infection occurs by accidental ingestion of eggs containing the infective larvae that hatch in the intestine and migrate from the portal vein to the liver, where it will become the adult worm. Genuine infection occurs by the ingestion of material contaminated with embryonated eggs, which reach the host’s cecum, hatch, and release larvae, migrating to the liver via portal circulation, where they will remain until becoming adult. In the parenchyma hepatic, the adult female lays eggs that remain encapsulated and are not excreted with feces. After laying the eggs in the liver, adult worms die and are disintegrated by the host’s immune system, while the eggs are preserved in the hepatic parenchyma. The release of eggs into the environment may occur when the host dies, due to the disintegration of the carcass. In this sense, predation and cannibalism are also important for the capillariasis transmission [13,17].

Occasionally, larvae and eggs of *C. hepatica* and *C. aerophila* present in the liver could migrate or could be passively carried to the kidneys and lungs causing abscesses (some of them containing eggs) and pulmonary capillariasis [13]. Pulmonary capillariasis is a rare

disease, however it is severe in humans. Lalosevic, *et al.* [37] described a cryptic case of pulmonary capillariasis in a Serbian woman that resembled a bronchial carcinoma. Symptoms of pulmonary capillariasis are related to asthma, productive cough and pulmonary eosinophilia [33].

Toxocara canis and *T. cati* - nematodes examples of the second group - are intestinal parasites of dogs and cats, respectively, that cause *visceral larva migrans* in humans. The human host gets infected by ingesting eggs of the parasite (e.g. present in contaminated food and water). In the intestine, larvae will cross the intestinal wall and will be passively taken to other organs (e.g. liver, central nervous system, musculature, eyes and lungs). In these organs, it could occur fibrosis and calcifications. In the lungs, the symptoms described are asthma, cough, eosinophilic pneumonia and the respiratory distress syndrome [38].

Dirofilaria immitis, another Nematoda, causes dirofilariasis, a zoonotic disease which most common presentation is a pulmonary nodule that mimics lung cancer in humans [36]. Microfilariae of this worm is usually transmitted by blood-sucking mosquitoes, like *Culex*, *Aedes* and *Anopheles*, to the dogs - the typical definitive host. Then, the microfilariae transmitted to the definitive host will migrate to the subcutaneous or subserous tissues, doing molts. The L5 reaches the heart through the venous circulation and in this organ (in the right ventricle), microfilariae will transform into the adult form in the dogs. The insect vector could also bite humans that will act as an accidental host for *D. immitis*. Because humans are not the normal host for this parasite, microfilariae will not survive in human subcutaneous tissues and consequently in the human organism; so the immature forms of the worms will migrate to the heart. In the heart, microfilariae will not complete the life cycle and will die in this organ; microfilariae death will be passively carried to the lungs by small circulation. In the lungs, the death microfilariae will be attached to the minor vessels, producing pulmonary symptoms like embolism [14,34,35] and also producing a lung solitary nodule that will mimic a lung cancer [36]. The set of these symptoms in humans are called as Pulmonary Dirofilariasis [34].

Taenia solium, another example of the second group; the presence of the larval forms (cysticercos) in human organs (due to the ingestion of parasite eggs) is called cysticercosis. When humans are infected with eggs of *T. solium* (e.g. through the ingestion of contaminated water and food), the embryo that emerges from the egg could perforate the intestinal wall. Then, the embryo enters the bloodstream and it is passively taken to any part of the organism, such as the brain, eyes, muscles, and rarely in the lungs, heart and bones where they will remain in the form of cysticercos, without formation of a new parasitic form. In this case, the human body is acting as an intermediate host of the worm (the usual intermediate host is swine); so, larval forms would only grow into the adult form if the cysticercos was ingested by the definitive host [14,31]. The clinical manifestations caused by cysticercosis depend on the amount, location, size and phase of the cysticercos. However, there is a need for further studies about pulmonary cysticercosis.

Another example of worms of the second group is the *Echinococcus granulosus*. Usually, this worm's definitive hosts are dogs that could have the intestine parasitized by the adult worms. The eggs of the parasite are eliminated in the environment with the host's feces, contaminating water and food. The normal intermediate host of this helminth is the sheep, but humans can be infected with the eggs when ingesting them, being the erratic host. In humans, the development of a hydatid cyst occurs in the viscera (mainly liver and lungs). The definitive host, when ingesting carcass of sheep containing the hydatid cyst, can become infected and then will develop the adult worm. In humans, the presence of the hydatid cyst in the lungs may compress the bronchi and alveoli because of the large dimensions that the cyst may reach. Drowsiness may appear to physical exertion, as well as coughing with expectoration. Thus, disruption of these cysts is not uncommon, leading to the spread and growth of new cysts in other parts of the organism [15,32].

Microfilariae and pulmonary symptoms: group 3

Pulmonary symptoms could also be caused by some helminthiasis that are related with the presence of parasites antigens trapped in the vessels of the lungs. In this case, antigenic constituents of microfilariae (e.g. *Wuchereria bancrofti* and *Brugia malayi*) are trapped in

the pulmonary vasculature, causing Tropical Pulmonary Eosinophilia ('Weingarten's Syndrome'). The typical symptomatology includes a period of 1 to 2 weeks of low fever, anorexia, weight loss, fatigue and non-productive nocturnal paroxysmal cough. Asthmatic crisis with wheezing dyspnea are frequent. Tropical Pulmonary Eosinophilia could still involve cardiac and central nervous system symptoms [38,39].

Conclusion

As discussed in this article, dry cough as well as other pulmonary symptoms (that could cause low, high or permanent lung damage), are quite common symptoms for several helminthiasis cases. Moreover, helminthic parasitic pneumonias and lung involvement are common in the tropics with few exceptions; they most commonly occur in the western world and are severe diseases of immunocompromised hosts [38,39].

The knowledge about helminthiasis and the set of symptoms are essential factors to control these diseases. Moreover, these diseases are generally possible to be eradicated, and one of the forms of prevention and eradication occurs through the health-education, informing the population about such diseases (Table 1). According to Busato., *et al.* [42] it is important to carry out socio-educational actions with the population in order to inform them about the types of parasitosis, preventive measures, contamination and elimination cycle, correct symptoms and treatments for elimination of these parasites, since they are little known by the community.

Recently, a study carried out in a public school of children's education in a county of the State of São Paulo (Brazil) revealed the knowledge about parasitology in the school community (parents or tutors, teachers and other employees, and scholars - children) through a questionnaire. At this region of study, there are cases of acute diarrheal disease (disease caused by different etiological agents, among them, the helminths). A total of 476 people answered the questionnaire, composed by 12 teachers, 09 employees, 264 students and 191 parents/tutors. The evaluation of the questionnaire showed that there is a great deal of fragility in the knowledge about some symptoms caused by parasites, such as cough, which was unknown to all teachers (100% were unaware) and to most of the employees (78%) [43]. Thus, due to the fact that these diseases are neglected, the population becomes uninformed mainly about symptoms, which contributes to the continuity of the cycles and consequently the transmission of such helminthiasis types. Moreover, there is an urgent need to overcoming the common sense about helminthiasis symptoms. In this sense, Araujo., *et al.* [2], makes a correlation between different types of neglected diseases and the existence of a neglected communication about them. According to these authors, health communication usually privileges the institutional speech but ignores the context, contributing to increase in the negligence - technical and political - for some diseases [44].

Conflict of Interest

The author declares there are no conflicts of interest.

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