

Zoonotic Helminths and Their Influences on Humans

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Abstract. Zoonotic helminths are big health concerns for both human and animals. Such concerns are brought to attention only after Centres for Diseases Control and Prevention decided to categorize a few helminth-related infection as Neglected Tropical Disease. Over the years, researchers were only able to study the more prevalent zoonotic helminths due to the large variety of the species. However, as more and more people start to pay attention to helminths disease, more species have been found parasitic to human. Helminthes have been generally classified into three basic groups: Flukes (trematodes), Tapeworms (Cestodes), and Roundworms (Nematodes). According to the existing medical technology, although helminths are not fatal to human if properly treated, current medical treatment cannot grant complete immunity to both the parasites and the infection. There are still a large number of people in the world are infected. In fact, parasitic helminths have infected roughly 16% of the global population. In order to treat helminths more effectively, the focus has been shifted from traditional medication to molecular treatment and general genome manipulation. This article summarized physiology of different types of helminths, and emphasized the importance of understanding helminths by elaborating on a few previous studies on the more commonly studied species. Moreover, this article discussed some area of interest that could be further researched in the future.

Keywords: Helminths, Nemetados, Cestodas, Trematodes, Infection.

1. Introduction

Helminths are highly diverse; as clinical technique advances, many more different species of helminths have been discovered and studied. Over the years, helminths have been generally classified into 3 different groups, each of which consists of at least 50+ species scattering all over the world . In fact, parasitic helminths have infected approximately one sixth of the global population, posing significant healife cycle to both children and adults, and such large scale infections have induced roughly 14 million loss of the equivalent of one year of full health (DAYL) in 2000s [1]. Also, the roughly calculated helminth-infection-induced annual expense is roughly 2 billion USD in Europe alone [2]. Although the clinical and economical effect is evident, the study of these diseases is not yet emphasized, and World Health Organization (WHO) still classified most of these diseases as parts of the neglected tropical diseases (NTD) [2].

Although some specific anti-helminthic medicines have been developed and demonstrated promising clinical result, there are still issues with them. For example, these drugs do not grant immunity, and frequent use of the treatment has shown a trend in the increase of drug resistance [3]. In addition, there has been some promising results in vaccination studies to affect helminths growth at larvae stage, recombinant and epitope-based vaccine candidates did not otherwise [4-6]. In fact, many anti-helminthic vaccines are either still under development or under animal trials. Not until promising results are seen after that and acquired acknowledgement from the appropriate department, these vaccines will not be used on a global scale [6, 7].

Finding the best protective antigens is the key to successfully develop a vaccine. Usually, this requires an abundant amount of well-established transcriptomic, genomic, and databases, which is costly in both time and money. Moreover, a thorough understanding of helminths' physiology is necessary to correlate between the protective antigens and helminths themselves. Thus, to further extend research on helminth infections and develop effective medication or vaccination, such challenges must be overcome, starting with a summary of helminths' biology, including its physical structure, life cycle, transmission, and treatment [8].

2. General Overview Of Existing Parasitic Helminths

Parasitic helminths are large, multicellular and infectious organisms which live in and feed from their hosts and are capable of causing either discomfort or diseases. There are three main categories of parasitic helminths: Flukes (trematodes), Tapeworms (Cestodes), and Roundworms (Nematodes), where tapeworms and flukes can be further classified as one bigger category: flatworms (platyhelminths) [9].

2.1. Cestodes' Physiology

Cestodes (tapeworms) acquired the name from their ribbon-like shape at their adult stage. However, their bodies are not exactly continuous, and are connected by many similar small segments. An adult tapeworm is made of a scolex (head), a neck and a strobila. The scolex can have the shape of a sucker, hook, or groove, which allows tapeworms to firmly attach onto the surface, such as intestinal wall of the infected host, and is the only mean for tapeworm to absorb nutrient as tapeworms do not have a digestive tract and mouth. The neck continuously produces small segments, known as proglottids, and these proglottids are the major components of the strobila (main body). As tapeworms mature, proglottids are then pushed toward the tail of tapeworms. Each of these proglottids contain both male and female reproductive organs, and when the most distal proglottids are filled with embryonated eggs, they detach and then are excreted by the host. Many cestodes have complicated life cycles, including one or two intermediate stages in which larvae grow in some other hosts and a definitive (final) stage where tapeworms grow and reproduce in human body. Two common cestodes that have been studied are *Hymenolepis nana* and *Taenia solium*. *H. nana*, known as dwarf tapeworm, is highly prevalent in poor rural regions as high as 55%, and infects over 75 million people worldwide [10]. Usually, *H. nana* uses beetles and fleas as intermediate hosts. Unlike *H. nan*, *T. Solium* uses pigs as intermediate hosts, who develop a symptom called cysticercosis, and then infects human [11]. Figure 1 demonstrated the complete life-cycle of *T. Solium* [12]. At first stage, eggs are excreted via feces by infected hosts. In second stage, when pigs ingest feces with eggs, cysticerci develops in tissues. At the last stage, if human ingests undercooked meat with cysticerci, infection begins and *T. Solium* completes the life-cycle.

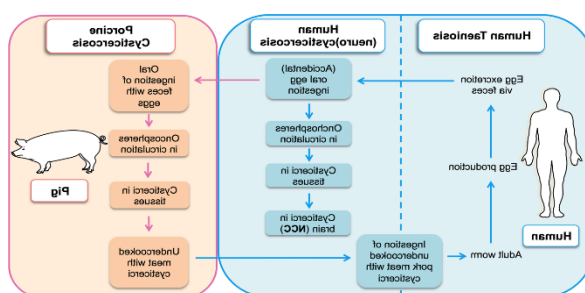


Figure 1 Block Diagram of *T. solium* infection with different stages

2.2. Trematodes' Physiology

Trematodes (flukes) were known for their flat and elongated shape; thus, they were part of the platyhelminths category, just like tapeworms. However, their physical structures differ from that of tapeworms. Adult flukes have an anterior and ventral sucker, followed by an incomplete digestive tract used to absorb nutrients from hosts [13]. Moreover, flukes have a tough syncytial tegument on the outside that helps nutrient adsorption and protect them from digestive enzymes produced by hosts. Also, flukes do possess an excretory system, even though most excretion occurs through the tegument. Similar to tapeworms, flukes usually have a definite host such as human and an intermediate host typically snails, demonstrated in Figure 2 [14]. These types of life process are also referred as digenean (two-host) life cycles. At first stage, eggs are excreted via feces by infected hosts. In second stage, when feces with eggs reaches freshwater and ingested by fish or snails, cercaria develops and eventually fleets out into water again. At the third stage, when fish ingests cercaria and consumed by human, infection begins and marks the completion of the cycle. Species of flukes with zoonotic

characteristics are classified based on the location where flukes parasitize on, such as lung, liver, and intestine. Particularly, liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, are studied thoroughly over the years. WHO even classified these as a part of NTD due to its prevalence. Based on a study done by B. Sripa, et, *O. viverrini* alone has infected about 12.39 million people in 2018 in four major endemic countries [14]. Similarly, Based on a study done by J. Chai, et, *C. sinensis* alone has infected about 14 million people, with an average of 2.04% infection rate across all types of helminthic infection over 15 provinces in China [15].

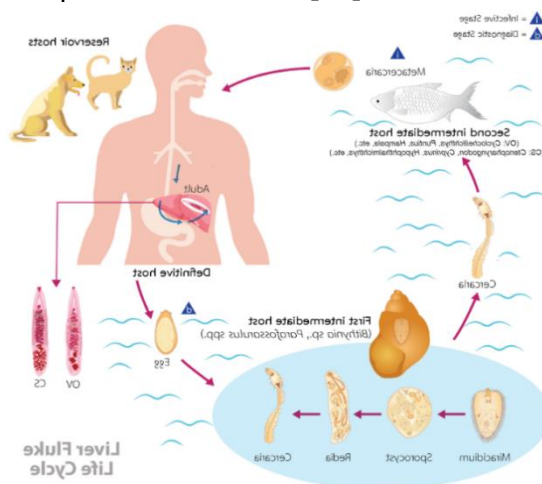


Figure 2 Block Diagram of Liver Fluke Life Cycle with different stages

2.3. Nematodes' Physiology

Nematodes are slender, segment-free worms. Unlike the other two helminths mentioned above, nematodes have free living organisms as well as parasitic species. The standard size of Nematodes varies from 0.1-2.5 mm to 1m in length, and the free-living species often have longer size. Physical structures of nematodes can be identified with two major components, each of which has distinct features. The head of nematodes is radially symmetrical and has a series of sensory bristles around the mouth which usually has multiple layers of lips with teeth found on the inner surface. A thick collagenous cuticle shields the rest of the bilaterally symmetrical body. The cuticle consists of three layers: an outer layer - cuticular layer, an epidermal layer, and muscular layer. Cuticular layer is the most outer layer, it is thick and smooth. And can divided into other three layers: cortex layer, fiber layer and matrix layer. The function of cuticular layer is to protect the body, resist the corrosion of digestive juices in the host body. The next layer is epidermal layer it is the syncytium composed of many lines of epithelial cells, it is distributed in roundworm's both sides of the body, back and central abdomen. The epithelial cell layer also get thickens to form the lateral line, dorsal line and ventral line; In the thickness dorsal and ventral lines are arranged with dorsal and ventral nerve cord; In the thickness lateral lines are the excretion tube, and through the epidermal layer cells the tubes can secrete substances to form cuticular membrane. The third layer is muscle layer, this is the most inner layer, composed of a single longitudinal muscle. The muscle cells can be divided into two parts: on the top is the protoplasmic part containing the nucleus, on the base is the contractile part containing the myofibrils. Because of there are only longitudinal muscles and no annular muscles in roundworms, so their body can only be bent, not telescopic. Then is the pseudocoel, which filled with body cavity fluid, its role is: transport nutrition, and form a turgor pressure between body wall and viscera to maintain a certain body shape. Nematodes also have a relatively simple digestive system similar to the other two, consisting of the mouth, pharynx, intestine, rectum and anus. They can directly feed on semi-digested substances in the host body, so they can be directly absorbed and utilized without digestion. Therefore, they do not have special digestive glands, and there are microvilli in the intestinal lumen, which can increase the absorption area. Lastly, nematodes have a long tubular reproductive system that reproduces sexually and through fertilized eggs. Three most common nematodes found are *Trichuris trichiura*, *Ascaris lumbricoides*, and *Necator americanus duodenale*.

WHO also classified these helminths as soil-transmitted helminths. In a study of prevalence of nematodes' infections in United Republic of Tanzania, infection from *Trichuris trichiura* has the highest ratio of 15%+ across youth and teenagers shown in Figure 3 [16]. *Ascaris lumbricoides* is one of the most common m NTD nowadays and have affected nearly 1.2 billion of individuals in the world. *Trichuris trichiura* is the major health concern for human in the world, and is more common in the poor areas lack of medical care. *Necator americanus duodenale* have been affecting 430 million individuals in the global, and once been parasite directly through skin they usually stay in a person's small intestine for years.

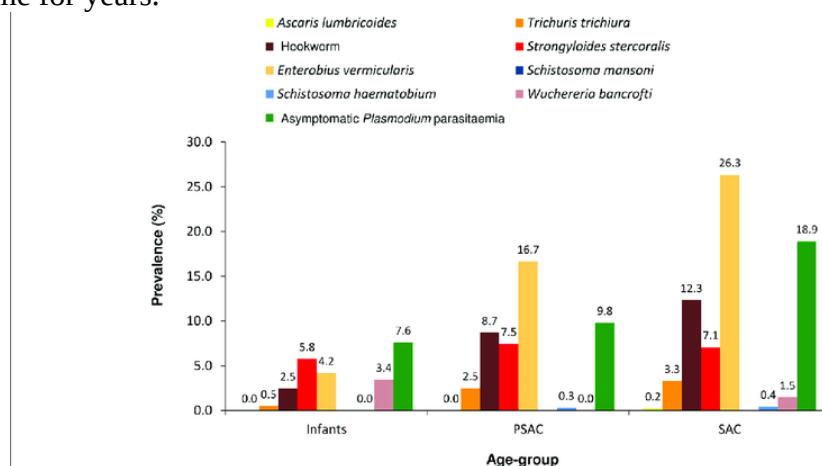


Figure 3 Prevalence of nematodes' infections in infants, youth (PSAC) and teenager (SAC) from United Republic of Tanzania, Bagamoyo district

2.4. Survival Of Helminths In Human Body

One unique feature of helminths researchers has been studying over decades is how helminths are able to survive in hosts' body without being digested or excreted. Helminths secrete enzymes that help them better adapt in human's small intestine. There have been three types of enzymes found that are solely devoted to better adaptation. First type, categorized as Kunitz-type protein, is a type of inhibitor produced by the roundworms that suppress the activity of trypsin and protect them from the host's proteases. Second type, known as Haemanthus galactose and contains glycoprotein complex (H-gal-GP), can be found in the intestinal striated border. It is a complex that composes two or more enzymes and is capable of digesting efficiently. It can cleave primary parts of the Haemanthus blood meal into pieces small enough for highly efficient degradation. Third type, AsPrx is an antioxidant enzyme, which is generated during aerobic metabolism and is the key element that can fight with the oxygen radicals. It also helps roundworm to defend against host's immune cell assault.

3. Transmission And Symptom

Tapeworms' transmission can be complex. Initially, eggs excreted by infected definite hosts are ingested by animals such as cattles and pigs. The eggs then hatch inside hosts' intestines, forming cysteri. Infected animals got slaughtered and eaten. If not fully cooked, the meat migrates to the intestine, and cysteri releases protoscolices which attached to the intestinal wall. Then, proglottids are grown slowly until worms fully mature and kickoff the last couple proglottids fully of embryonated eggs. There also have been cases where fish is infected by tapeworms and infects human afterwards. *D. latum*, the largest parasitic tapeworm, is extremely prevalent in regions where freshwater fish is a popular dish such as Japan and Northern Europe. (sushi, ceviche, smoked or pickled fish).

Flukes' transmission happens after one or two intermediate hosts' infection. Liver flukes for instance has two intermediate stages. First, the embryonated eggs are excreted by adult worms and released into fecal matters from definite host. Eventually, once these matters reach fresh water and are consumed by organisms such as snails, eggs start to hatch and produce miracidia. It then begins

to develop to form sporocysts, which begin asexual reproduction and end up producing cercariae. Once cercariae gets away from the hosts, it then attaches to the skin of freshwater fish, entering its second intermediate stage [14]. When human ingests infected fish, he becomes the definite host and symptom starts to develop.

Nematodes' transmission and infection are similar to others, which can be categorized into a few stages. Figure 4 shows the complete life-cycle of the few common nematodes [17]. During the first stage, fertilized roundworm eggs get into human body through the mouth. Then it is transferred to human's small intestine, and undergoes biological development. Once it fully matures, this is when infection begins, and it starts to lay eggs in human's intestine. If roundworms and eggs are excreted through faecal matter, it goes back to first stage and the cycle continues. Otherwise, host will start to feel severe discomfort such as abdominal pain, nausea and upset stomach.

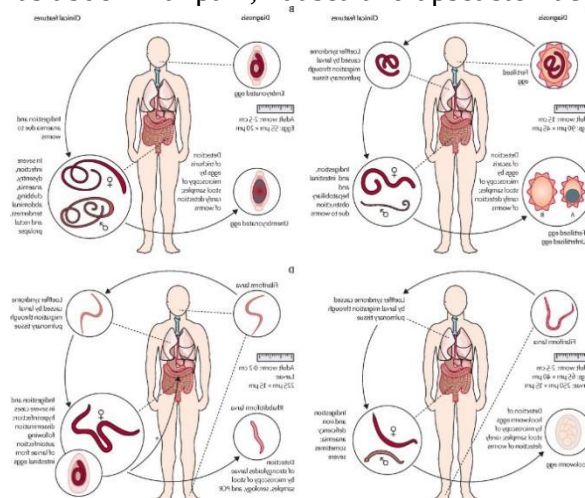


Figure 4 Transmission of (A) *A. lumbricoides*, (B) *T. trichiura*, (C) *A. duodenale*, and (D) *S. stercoralis*

4. Treatment

The treatment for helminths' infection can be case by case. Over the years, specific medication has been developed to target designated worm type. Neurocysticercosis (NCC), for example, a symptom developed when human is infected by *T. Solium*, varies based on the individual and tapeworms' characteristics. The two main anti-helminthic drugs used are albendazole (ABZ) and praziquantel (PZQ). PZQ has also been proven to be effective as a treatment to cure infection from flukes. Similarly, to treat roundworms, usage of ABZ and mebendazole is also effective. Because of the unique enzymes that helminths produce to help themselves survive, medication developed to treat these infections primarily tackles on how to reduce effectiveness of these enzymes. ABZ, for example, is a derivative of benzimidazole. It can be rapidly metabolized and decomposed in vivo, and then selectively and irreversibly inhibit the uptake of glucose by intestinal nematodes, resulting in the depletion of endogenous glycogen and death of nematodes. It also blocks the production of adenosine triphosphate which is the cell's main energy source, and then leading to the death of the parasite. Mebendazole, on the other hand, causes the degeneration and destruction of intestinal parasite cell structure, resulting in intracellular transport blockage, gradual dissolution of cytoplasm, and then cause the final death of the parasite. Nonetheless, such medication are not fully effective as they do not grant human full immunity to either the helminths or infection. Moreover, drug resistance has been found to certain types of helminths, such as liver flukes [18]. Consequently, some studies have dedicated effort on to transgenesis in these zoonotic helminths. Figure 5 shows historical milestones in the transgenesis of zoonotic helminths [1]. Nevertheless, current genome manipulation is still imperfect due to the specific complication of helminths' biology as well as their complex life process. Particularly, comprehensive and robust transgenic lines that identify attributions critical to helminths'

development, infection and survival is yet needed to breakthrough the current state-of-art methodologies [8].

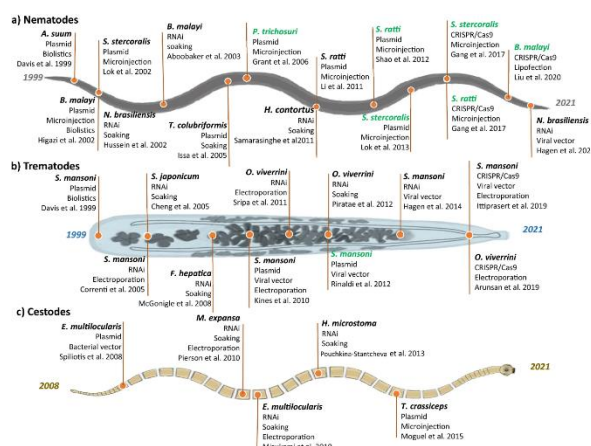


Figure 5 The transgenesis of zoonotic helminths Timeline on the different species of (a) nematodes, (b) trematodes and (c) cestodes

5. Conclusion

Even though tremendous studies have been done on physiology of zoonotic helminths, and development of anti-helminthic drugs, the understanding of helminths is far not enough; The immunology of helminths remains unknown due to the wide diversity within species and lack of sampling sizes. Current methodologies cannot grant human complete immunity and prevent human from second infection. As technology advances, the focus of the treatment to these helminths infections should slowly migrate from traditional medication to cytototherapy or genetic modification. If, with thorough studies on physiology of helminths, a suitable protective antigen, which shares the same attributes of that of the helminths, is found, it can be used to assist human body to effectively target helminths and excrete or digest them. Also, gene editing, such as CRIPSR-Cas9, can be helpful in treating helminths infection if genes of helminths can be modified to prevent them from reproduction.

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