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PARASITIC NEMATODES IN HUMANS: EXPLORING THE HOST-PARASITE
DYNAMIC THROUGH HISTORICAL, BIOLOGICAL, AND PUBLIC HEALTH
EVALUATIONS OF INFECTION

By
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B.S. University of Kentucky, 2009

A Thesis
Submitted to the Faculty of the
School of Public Health and Information Sciences
of the University of Louisville
in Partial Fulfillment of the Requirements
for the Degree of

Master of Science

Department of Epidemiology and Population Health
University of Louisville
Louisville, KY

May 2012

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May 1, 2012

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ABSTRACT

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Erin Christine Welsh

May 1, 2012

This thesis investigated infection dynamics of parasitic nematodes at both the population and individual levels by exploring evolutionary and historical aspects of infection as well as how host-parasite interactions influence virulence. In particular, this thesis sought to answer questions of how host populations have influenced the spread of infection and how transmission determines infection virulence, with a final goal of understanding how eradication programs for parasites can be developed or improved with this knowledge. The host-parasite dynamic was explored throughout history, with particular focus on the ways host populations have shaped infection distribution in present, historic, and pre-historic times. Then, data for each nematode was systemically collected and presented for a comprehensive analysis of virulence and transmission mode. It was discovered that microparasitic principles of virulence can be applied limitedly to predict virulence of macroparasitic nematodes, and the relative virulence of each nematode can be explained partially by transmission mode.

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CHAPTER I

INTRODUCTION

In 1624, John Donne penned the words “No man is an island entire of itself; every man is a piece of the continent, a part of the main.” (1). Donne’s intent was to express the importance of human relationships; however unintended by the author, the phrase also has meaning for those who study the intricate interactions between man and the many single- and multi-cellular organisms to which he is host. It is estimated that in the human intestinal tract alone there are 10 to 100 trillion resident microbes (2). The presence of these microbes, along with countless others that inhabit the organs, surfaces, and orifices of the human body, may serve to aid their host in digestion or prevent the colonization of the body by pathogenic organisms (2). In return, microbes are provided with a home and energy resources which they use to survive and reproduce. The mutualistic relationship between microbes and their human hosts describes one type on a spectrum of inter-relationships between two organisms. Ranging from mutualism, in which both organisms benefit from an association, to parasitism, in which one \benefits while the other experiences a reduction in overall health and survival, this spectrum allows for a wide variety of ecological relationships. Close consideration of variation over this spectrum of inter-relationships also has powerful implications for the joint evolution of organisms by means of natural selection and adaptation, and for the dynamic fitness effects that come

to bear both on the individual organisms and on the differential qualities shared between them. Eukaryotic cellular life, as an example, is believed to have originated through a series of symbioses in which prokaryotic cells with particular functions were engulfed, acting as organelles as they evolved complete interdependence with the host cell (3).

As parasitic associations evolve, parasites acquire adaptations that allow them to effectively exploit their hosts (4). A parasitic relationship will evolve only if the parasite is able to use host resources to survive and reproduce (in or out of the host) without being eliminated by the host's defenses (4). Both prehistoric humans and their ancestors harbored a wide variety of both single- and multi-cellular parasites (5). The presence of these parasites had and continues to have a profound impact on the evolution of man, although the degree and outcome of these effects is variable among parasites and their hosts.

Microparasites include viruses, bacteria, and protozoa while macroparasites include multicellular organisms such as parasitic worms. In addition to differences in size, microparasites and macroparasites tend to produce characteristically different infections. Infections caused by microparasites are often acute in nature, and recovery is usually accompanied by protective immunity in the host, although exceptions to both of these characteristics are common (6). Macroparasites are generally associated with chronic infections that sometimes resolve in partial immunity, though reinfection is frequent (6). The selective pressures exerted upon hosts by these two types of parasites also differ. Although mortality directly due to macroparasites is less common than what is known for the more acute infections of microparasites, macroparasites can still have a significant effect on overall host health and thus, on the evolutionary fitness of their hosts

(6). If the burden of macroparasitic infection is high enough to cause disease, host fitness may be reduced directly or indirectly. In humans, such effects can include decreased productivity, lowered intelligence, temporary or permanent disability, poor nutrition, and anemia (7-17). Host fitness can be reduced through morbidity, with effects on host mating success, reproduction, general health, and mortality. The influence that a parasite has on host health is dependent upon a number of variables relating to the host, the parasite, and the environment.

Virulence, defined as harmfulness to the host, is a primary characteristic of infection that is influenced by host, parasite, and environmental variables (18-21). Virulence can be measured evolutionarily as decrements in host fitness. In order to develop effective strategies for the prevention or control of parasitic diseases, a thorough understanding of the factors determining virulence must be gained. Patterns of virulence in microparasites have been observed, but virulence patterns of macroparasites have been less well studied (22). The relatively complex life histories of macroparasites prevent simple generalizations for modeling their virulence borrowed from the better known example of microparasites. Rather, each macroparasite must be considered individually before making any assertions regarding the virulence patterns of macroparasitic infection.

The phylum Nematoda contains both free-living and parasitic worms (23). Parasitic nematodes are responsible for some of the most common infections of mankind (23). Although these worms share some general structural characteristics, great variation exists among parasitic worm species in life history, transmission mode, and infection virulence (23). Such wide variation in these traits, however, makes the group ideal for virulence research, and allows for comparisons among species that will lead to the

development of possible models for virulence. This thesis seeks to systematically collect and present data for a variety of nematodes that commonly infect humans. The collected data items will be used to identify possible factors of infection related to virulence and to evaluate the suitability of such factors of virulence among parasitic nematodes. Microparasitic models relating virulence to transmission mode will serve as a basis for comparisons among the macroparasitic nematodes (22). The suitability of these models for use with macroparasitic nematode infections will be tested.

Although much of the focus of this thesis is centered upon evaluating virulence in light of transmission mode and other parasitic characteristics, it is also essential to examine how host population dynamics have influenced infection rates throughout history and prehistory. Presently, nematode infections are extremely common; it is estimated that approximately one billion people worldwide are infected with at least one nematode (24). Economically undeveloped countries in tropical and sub-tropical regions of the world bear the highest burden of nematode infection, though this pattern was not always observed (5, 10, 24, 25). Comparing distributions of nematode infections among modern and ancient populations and combining this knowledge with information regarding changes in prehistoric and historic human population structure can provide insight into how present-day populations contribute to the spread of disease. The resulting inferences can be used to evaluate existing public health directives aimed at reducing infection and in the development of new programs.

Although parasitology as a field of study has existed for centuries, the incorporation of evolutionary theory into the field is in its infancy (4). The dearth of information regarding of virulence evolution in human multicellular parasites is an

obstacle to creating public health programs and to understanding why existing programs are ineffective. As the majority of nematode infections occur in the poorest regions of the world, research on the topic is difficult to conduct due to problems such as funding for surveillance. By delving into the current literature on human parasitic nematodes and examining the information with an evolutionary and public health perspective, new insights on the current state of disease caused by nematodes may be gained. This thesis will investigate the major human parasitic nematodes by reviewing what is known about the current and historic distributions of disease, life history, structure, and other biological traits for each nematode. This information will then be used to draw conclusions about the virulence of each infection. These infections will also be considered from the alternative point of view – that of the human host. Exploring the human-parasite relationship from prehistoric times to the present day may shed light on the evolution of both host and parasite and on the many ways in which human behavior alters patterns of infection. By identifying host and parasite factors relating to virulence, possible control strategies can be developed to reduce the significant morbidity caused by parasitic nematodes.

CHAPTER II

THE HISTORY OF NEMATODE INFECTION

Evidence for Prehistoric & Historic Infection

Although fossilized evidence of parasite infection is rare due to the strict conditions required by preservation, many records have been found that indicate parasitism is not a recently acquired adaptation for nematodes (26). Parasitic nematodes have been found in insects incased in amber dating 40-100 million years old (27, 28). Nematode parasitism in mammals is evidenced by the presence of preserved specimens in frozen woolly mammoths, horses, and a cave bear (26). The most common source of fossilized evidence of nematode parasites in humans is coprolites containing eggs, found in preserved remains or waste sites (5, 25, 29). Such findings are numerous in locations in both the Old and New World, dating back several thousand years (25, 29, 30). Archaeological findings of prehistoric nematode infection in humans can be used not only to describe the evolutionary and historic relationship between human and parasite, but also to inform about human behaviors relating to infection. Comparison of prehistoric geographic distributions of infection with patterns observed today can provide insight on how human behavior and the environment interact to encourage or inhibit infection in a population. In addition to archaeological evidence, mention of infection in texts of antiquity can show how aware ancient populations were of the worms and how affected they were by the disease. One great difficulty in the control of nematode infection in

modern endemic populations is the misunderstanding of the origin of the disease; many individuals do not associate guinea worm with unfiltered water, for instance, or lymphatic filariasis with mosquitoes, or hookworm infection with unhygienic conditions (31-34). Writings in ancient texts may help in hypothesizing how human behavior influenced the spread of nematode infections. For instance, a belief commonly held today about some nematode infections is that they are an unavoidable part of life and do not pose a serious health risk (32). This perception can help to perpetuate the infectious cycle, as those infected can expose other individuals to infection. In this section, archaeological findings and mentions in ancient texts will be reviewed for each of the major nematodes affecting humans.

Enterobius vermicularis

Enterobius vermicularis, commonly called the pinworm, is thought to have an extremely long evolutionary history with humans (35). This organism is termed an inherited parasite since it is believed to have infected pre-human primate ancestors and was not transmitted to humans from companion animals (25). This is supported by the finding of eggs in 10,000 year old coprolites in a cave in Utah (36). This finding also suggested an infestation rate similar to that seen today (36). Coprolites containing *E. vermicularis* eggs are common in New World archaeological sites in both North and South America (25, 37, 38). Desiccated eggs have been found in Chile, Peru, Mexico, Argentina, the United States (Arizona, Utah, Colorado, Tennessee, Oregon), and Greenland (25, 36-40). Although there is ample evidence of pinworm infection in the New World, archaeological findings in the Old World are scarce (25, 41, 42). The

reasons for this difference are not yet clear, although preservation conditions and incorrectly examined older samples are possible contributors (25, 42). Evidence of pinworm infection has been found in a few sites in the Old World, including Germany, China, Korea, and Egypt, although these are not as old as many of those found in New World sites (25, 41, 42). Despite the lack of archaeological findings in the Old World, it is nevertheless assumed that infection was common in this region (25, 41, 42).

The visual presence of worms and eggs in the feces would ensure that ancient populations were at least aware of infection with the worm, and historical writings confirm this (43, 44). Ancient Egyptian papyri contain mention of infectious worms, although designation of the modern-day equivalents of the worms is difficult (42, 45). In his writings on the natural history of animals, Aristotle discusses a worm which is believed to be pinworm, and Hippocrates also makes note of the infection in children (43, 46). Other notable historians and physicians also wrote of infection with the worm, including Avicenna and Galen (46). Such texts also illustrate the depth of knowledge a population possessed regarding infection with *Enterobius vermicularis*. Although many clinical features of the infection were long established, such as infection location and signs and symptoms, epidemiological characteristics of the worm were less clear. The mode of transmission was commonly thought to be spontaneous generation, and the true transmission mode was not established until the early 19th century (46).

Infection with *E. vermicularis* occurs when eggs are ingested (47). Infection rates are correlated with population densities, with higher rates occurring in dense populations with crowded living areas (25, 48). This feature of *E. vermicularis* classifies it as a cosmopolitan parasite, found most frequently in large cities or settlements in both historic

and modern times (25, 47-49). In order for the parasite to be established in a population, certain conditions regarding population density and size must be met (36). Variations in proportion of egg-containing coprolites in archaeological sites can be useful in determining changes in population size, hygiene habits, and crowding (37). Where the proportion of coprolites positive for pinworm eggs is high, it can be inferred that the population was both large and experienced a degree of crowding (50). The wide variation in location of fossilized eggs suggests that the geographic range of *E. vermicularis* infection was extremely widespread, essentially able to establish in any suitable human population regardless of environmental settings (5). Modern distribution of the parasite follows a similar cosmopolitan pattern, with infections common even in economically developed countries (51).

Trichuris trichiura

The human whipworm *Trichuris trichiura* is an intestinal parasite with a lengthy history of human infection (25, 35). Like *E. vermicularis*, *T. trichiura* is thought to be an inherited parasite, existing in and evolving with human ancestors (35). Coprolites, preserved latrines, and intestinal contents of mummies have provided ample evidence of prehistoric and ancient infection with this parasite in humans (5, 25, 35, 52-55). The oldest reported evidence of human infection with *T. trichiura* in the New World dates back approximately 7000 years, while a coprolite containing *T. trichiura* found in South Africa dated 10,000-7,000 years BP (25, 56, 57). Evidence of prehistoric whipworm infection is commonly found in tropical and sub-tropical regions in both Old World and

New World sites (25, 35). An extensive list of sites where *T. trichiura* eggs have been recovered can be seen in Goncalves et al 2003.

Despite the size of the worm and its obvious presence in infected individuals, there is surprisingly little written about the worm in ancient texts (44, 46). In fact, no mention of the worm can be found until the 14th century, but this and later reports went by the wayside until interest in the worm increased after Morgagni published his findings on whipworm in 1740 (46). That ancient physicians or historians appear to have not made note of the worm could indicate that disease caused by the worm was not considered enough of a nuisance to treat, or it could indicate that the worm was considered a symptom of a larger disease. It is unlikely that infected individuals or those who treated them were completely unaware of the worm. The author of the 14th century report of the worm hypothesized that the worm he observed (thought to be whipworm) was part of the life cycle of the roundworm *Ascaris lumbricoides* (46). Perhaps the absence of the subject of whipworm in historical writings could simply be a modern misunderstanding of the ancient texts. Nevertheless, archaeological evidence points to widespread *T. trichiura* infection, the presence of which affected the health status of ancient populations and provides clues regarding size, structure, and behavioral qualities of those populations infected (25, 35, 52, 54).

In order to perpetuate the infectious cycle, *Trichuris trichiura* eggs undergo a period of development outside of the host, in soil (58). The eggs, deposited in the soil in feces, require precise environmental conditions in order to embryonate and progress to the infectious stage (58, 59). This quality of whipworm restrains the geographic range of infection to those regions that fulfill the soil type, temperature, and moisture requirements

(58). Although the modern infection range is restrained to poor countries in sub-tropical and tropical regions, archaeological evidence suggests a different picture of whipworm infection in prehistoric and historic times (25, 52-54). Fossilized *T. trichiura* eggs have been found in locations such as England, Denmark, Austria, Norway, France, Prussia, and many other locations where infection today is uncommon due to environmental or economic conditions (10, 25, 58). This discrepancy in whipworm infection distribution is likely a reflection of crowded conditions and poor sanitation which allowed the worm to be easily transmitted (35).

The discovery of *T. trichiura* eggs in pre-Columbian coprolites has sparked a heated debate regarding the migration route of humans to the New World (5, 35, 55). The presence of pre-Columbian infection in New World populations implies that the parasite must have been brought over not with European explorers but with early human migrations (55). However, this is in contrast with the prevailing theory that humans traveled to the New World solely via Beringia, the land mass that existed approximately 20,000 years ago connecting Alaska and eastern Siberia (5, 35, 55). The inhospitable environmental conditions of the Beringia land mass would inhibit egg and larval development outside of the human host (35, 55, 57). This is supported by modern populations near this arctic region reporting no whipworm (35). Therefore, if humans had migrated solely through Beringia, *T. trichiura* could not be maintained in the migrating population, leaving no traces of whipworm infection in New World locations until post-Columbian contact (35, 55, 57). In addition, the parasite solely infects humans and so could not have been carried to the New World by infected animals (35). The presence of whipworm in pre-Columbian coprolites suggests a human migration in addition to the

Clovis migration across Beringia (35). This additional migration likely took place over 7000 years ago and occurred through a sub-arctic coastal route or a trans-Pacific voyage, possibly from Polynesia (35). Phylogenetic analysis of Old and New World whipworms could shed light on when *T. trichiura* was introduced to the New World, but studies reporting such findings are lacking. For a more in depth discussion of early human migrations and paleoparasitology findings, see Araujo et al 2008.

Ascaris lumbricoides

The most prevalent of human intestinal multi-cellular parasites is the human roundworm *Ascaris lumbricoides* (10, 60). It is also one of the largest, with lengths reaching more than 30 cm (7). Evidence of prehistoric infection is plentiful, with findings common in both Old and New World coprolites, latrine sites, and mummified remains (25, 35, 45, 54, 55, 61-66). Archaeological findings suggest pre-Columbian infection, as many samples have been recovered from North and South America in locations such as Peru, Brazil, Tennessee, Kentucky, Arizona, and Alaska (25, 61). Old World infection seems to be equally as common, with archaeological evidence originating from many sites in Europe and Africa such as France, England, Austria, Germany, Denmark, Belgium, Israel, and South Africa (25, 65). Initially, it was thought that *A. lumbricoides* may have arisen as a human parasite during the domestication of pigs from a common ancestor of *A. lumbricoides* and *Ascaris suum* (25, 67). However, this is disputed by the finding of *A. lumbricoides* in human coprolites in France predating the domestication of pigs (25). It is now thought that *A. lumbricoides* is an inherited parasite, like pinworm and whipworm, and that *A. lumbricoides* adapted to infect pigs, evolving into *A. suum*

(25, 35). However, the topic is still debated (25, 61). Both *Ascaris* species are very morphologically similar, which creates some difficulty in the distinction between the two in an archaeological sample (55). Generally, if the specimen is found at a latrine or in a human coprolite, it is assumed to be *A. lumbricoides*, although it is still unclear if the pig whipworm is able to successfully infect humans (7).

The great size of the worm ensured its recognition in ancient populations, and this is evidenced by the numerous references to the worms in ancient texts (44, 46). Early mentions of roundworm can be found in ancient Egyptian papyri as well as in Greek, Roman, and Chinese texts, dating back to approximately 400 BCE (44, 46). Although the worms were thought by many of these writers to cause a myriad of symptoms including disrupted sleep, laziness, blindness, swellings, and stomach pain, others noted that many infected individuals displayed no signs of disease (46). This led them to state that the worms were either neutral or beneficial to the host (46). This belief could have had implications for the continued transmission of roundworm but for the fact that the worms were thought to occur as a result of spontaneous generation (46).

Today, *A. lumbricoides* infects over a billion individuals, with highest infection rates occurring in tropical and sub-tropical regions (7). Archaeological evidence and experimental observations of egg durability indicate that roundworm is not restricted to those regions (7, 25, 54, 65). Like whipworm, roundworm eggs require certain environmental conditions in order for embryonation to occur (7, 68). However, *A. lumbricoides* eggs are much more durable in the environment and can last for months in undesirable conditions, which contributes to their widespread nature (7). This also explains why the presence of *A. lumbricoides* in pre-Columbian coprolites, latrines, or

mummified remains does not disturb the Beringia migration theory; the durability of the eggs would have allowed continued infection during a migration in conditions unfavorable to the development of other helminths (7, 35, 55). Although archaeological evidence indicates that infection was widespread in temperate regions as well as in tropical and sub-tropical regions, this pattern is not observed today (25, 44, 54, 65). The observed difference between historic and current infection distribution is likely a result of differences in population characteristics such as crowding, sanitation, and movement patterns (61).

The Hookworms: *Necator americanus* & *Ancylostoma duodenale*

Hookworms represent one third of the “unholy trinity” of tropical diseases affecting humans (10). The human hookworms *Necator americanus* and *Ancylostoma duodenale* are transmitted through direct contact. Eggs deposited in the soil in feces develop into larvae under favorable environmental conditions. Contact with an epidermal cut or hair follicle of an appropriate host allows the larvae to penetrate the skin and begin the infectious cycle within the host (9). Both species of hookworm are thought to be parasites inherited from human ancestors in Africa and are believed to have a very long co-evolutionary history with their sole host (52). The rich archaeological record of hookworm infection in prehistoric human populations suggests that infection was widespread where soil and moisture conditions would favor the development of the infectious stage (25, 30, 46, 52, 54, 62, 69). Coprolites and mummified bodies in both Old World and New World sites have yielded evidence of hookworm infection (25, 35, 70, 71). The majority of findings are located in North and South American sites such as

Brazil, Chile, Argentina, Peru, South Carolina, Tennessee, Alaska, and Kentucky (25, 70). The oldest of these, discovered in Brazil, is estimated to date to 7230 years before present, indicating pre-Columbian infection in the New World (69). The oldest finding in Old World archaeological sites is estimated to be 5,000 years old (30). Hookworm findings in Old World sites are mostly limited to European countries and are rarely present in Asian or African sites (25, 69, 72). The reason for this is not entirely clear but is likely due to unfavorable conditions for preservation rather than low or no infection rates in those regions (72). One difficulty faced by those studying fossilized evidence of hookworm infection is distinction between the two species of hookworm. Although largely similar in morphology and life cycle, *N. americanus* and *A. duodenale* differ slightly in transmission characteristics, life span, fecundity, and clinical disease (9). The ability to discern the specie responsible for infection is important in assessing early migration patterns of humans and how they correspond to modern species distributions (69).

In ancient times, hookworm infection did not go unnoticed. Although signs and symptoms accompanying hookworm infestation are not unique to that parasite alone, it is thought that several ancient texts refer to hookworm infection as the grouping of these symptoms (30). Early mentions of what could be considered hookworm infection must be considered lightly, however, for it is not known if the writers were aware of the connection between the worm and the symptoms (30). Nevertheless, several ancient Egyptian texts refer to a condition called *aaa* which modern historians believe signifies hookworm infection (30, 44). In addition, Chinese texts dating from 300 BCE mention a hookworm-like infection (30). Hippocrates and Lucretius also make note of a similar

condition (30). Despite the indications that ancient populations were aware of hookworm infection, without knowledge of the mode of transmission, infection rates would remain high provided an acceptable environment for growth. As with many other parasites, the route of transmission of hookworms would not be determined until the turn of the 20th century, a finding which spurred one of the largest eradication campaigns in history (46, 73).

Comparison of hookworm distribution between ancient and modern times allows for exploration into how human behavior and movement promoted or inhibited the spread of the disease in particular locations. Due to the environmental requirements of larval growth, hookworm distribution is fairly limited to sub-tropical and tropical regions, although infection has been found to occur in some temperate areas, both in the present and in the past (10, 25, 30, 60, 73). As the infection is largely spread by the deposition of contaminated feces in soil, countries with poor sanitation are most likely to report high levels of infection (8, 74). Regions whose low infection rates in modern times are in contrast with historic and prehistoric rates likely have improved sanitation measures preventing the infectious cycle from completing (10, 74).

As with the discovery of *Trichuris trichiura* eggs in New World coprolites, the prehistoric presence of hookworm infection in pre-Columbian North and South America supports the alternative migration hypothesis (30, 35, 52, 69). The necessary environmental conditions for larval development in soil could not have been met during the migration over Beringia, which is estimated to have lasted several generations (30, 69). Nor could hookworms have been brought over by animals, as the parasites exclusively infect humans (35). Although the archaeological evidence has been disputed,

recent findings lend support to the concept that migration must have occurred through another route besides or in addition to Beringia (30). An alternative hypothesis that would allow for the survival of hookworm and whipworm during the migration proposes a Pacific migration, possibly along the south coast of Beringia, a trans-Pacific voyage from Polynesia, and trans-Atlantic migration has also been considered (35, 57, 69). In addition to providing insight into the first peopling of the New World, these paleoparasitological findings suggest that humans were capable of long-distance aquatic navigation, an important factor in the historic spread of disease (69).

Strongyloides stercoralis

Infection with the threadworm *Strongyloides stercoralis* is common in subtropical and tropical regions of the world today (60, 75). The parasite is spread by a route similar to that of hookworms: through penetration of host skin by infective larvae (76). Two species of *Strongyloides* infect humans, *Strongyloides stercoralis* and *Strongyloides fuelleborni* (76). Of the two, *S. stercoralis* is more common (75, 76). *S. fuelleborni* is a zoonotic infection originating from non-human primates and is limited to regions in Africa and SE Asia, including Zaire, Zambia, and Papua New Guinea (44, 76). This zoonosis is medically important due to its high prevalence in infants in some regions and its association with mortality in those infected (75, 76). Parasitic *Strongyloides sp.* are unique in that they contain a free-living form in their life history (76). Furthermore, members of the *Strongyloides* genus reproduce by parthenogenesis while in the host, and autoinfection is common, which can lead to chronic infection despite a lack of exposure (76-78). The evolutionary origins of human infection with *S. stercoralis* are uncertain

regarding their heirloom (inherited) versus souvenir nature. The heirloom parasites previously discussed infect only humans, but *S. stercoralis* has multiple mammalian hosts (7, 9, 47, 76). This characteristic does not necessarily indicate a zoonotic origin of human strongyloidiasis, but it does make it difficult to determine with any certainty when *S. stercoralis* first parasitized humans and whether the infection originated in human ancestors or from contact with animals during the agricultural revolution.

Female worms lay eggs in the small intestine of the host, and hatching also occurs within the host, a fact that makes preservation of *S. stercoralis* very difficult (79). Despite this, evidence of prehistoric infection of *Strongyloides* in humans and animals is present, particularly in the southwest region of the United States (25, 35, 71, 79-81). Findings in this region have been dated to approximately 400-1200 AD (25). *Strongyloides stercoralis* appears to have been a common infection in ancestral Puebloans, a group that occupied warm and dry regions of the United States, particularly in Utah, New Mexico, and Arizona (25). This finding is surprising considering the high moisture and shade environmental requirements for *S. stercoralis* larval survival and development, suggesting that those regions may have been wetter in prehistory (55, 76, 81). Infection in these regions must have been favored by increased transmission due to the behavioral patterns of humans, including poor sanitation (81). Old World evidence of *S. stercoralis* infection is scarce, but coprolites and mummified remains found in Egypt, the Netherlands, and Korea confirm the prehistoric presence of the parasite (25, 45, 82).

No mention of *S. stercoralis* infection exists in ancient texts (30, 46). While the adult stages of the previously discussed nematodes are visibly apparent when expelled from the host, *S. stercoralis* adults are much smaller, and larvae are barely visible to the

naked eye (30, 46). This quality, combined with the complex life cycle of the worms likely prevented the unambiguous identification of the parasite (30). Discovery of the parasitic worm was not made until the late 19th century, when French troops deployed to Vietnam presented with frequent gastrointestinal symptoms (46). Transmission mode and life cycle characteristics were not described until several years later (46). In recent years, *S. stercoralis* infection has garnered attention due to its predisposition to hyperinfection in immunosuppressed individuals (30).

Like *T. trichiura* and the hookworms, the environmental conditions required by *S. stercoralis* for development could not have been met during the migration across Beringia (35). Therefore, New World evidence indicating human infection with *S. stercoralis* in pre-Columbian times points to the necessity of an alternative hypothesis for human migration (35). However, the autoinfectious nature of the parasite allows for chronic infection despite a lack of exposure, and modern infections have been shown to last 65 years in individuals only transiently exposed (77). Although, as a trans-Beringia migration was estimated to span several generations, it seems unlikely that the parasite would have been able to be continuously infect sufficient proportions of a population to maintain the parasite (69).

Trichinella spiralis

Trichinella spiralis is an intestinal nematode that is acquired following the consumption of infected meat (11, 83). The majority of cases of human infection can be linked to the ingestion of raw or undercooked pork (84). Other sources of infection include ingestion of undercooked infected game meat, and this is usually the case for

hunters displaying signs of infection (11). Since the adult worm produces larvae rather than eggs, fossilized evidence of *T. spiralis* is scarce and usually is indicated by the presence of a cyst in preserved remains (11, 45, 55). The evolutionary origin of *T. spiralis* and its association with humans is unclear. Although humans are primarily infected due to their close association with domesticated pigs, several wild mammals have been shown to harbor *Trichinella sp.* (11, 85-87). Archaeological evidence in the form of cysts in preserved remains indicates prehistoric infection in both the Old and New World, in regions such as Egypt, South Dakota, and the Aleutian Islands (45, 55). An issue arises, however, in determining the *Trichinella* species responsible for the cyst (11, 86). Old World archaeological evidence of infection is likely due to *Trichinella spiralis*, while New World infections were likely a result of *Trichinella sp* infecting wild mammals (87). The domestication of pigs in Asia several thousand years ago is thought to have been the means by which the parasite spread through the population (87). New World populations were not introduced to domesticated swine until post-Columbian contact, so it appears as if these populations were exposed to *Trichinella* by consumption of wild mammal meat (87).

Infection with *Trichinella spiralis* is usually accompanied by symptoms, although the severity and type of symptoms is variable with the degree of infestation (11, 88). Descriptions of symptoms associated with trichinellosis in ancient texts suggest that ancient populations were aware of the disease and possibly the source of infection (44, 46). Some modern historians suggest that the association between the disease and consumption of pork was known to these populations and resulted in the Jewish and Islamic decrees against eating pig and pig products (44, 46). However, this avoidance

could also have been caused by the observation that contact with and consumption of pigs led to infection with the much more visible tapeworm (46). Regardless, faithful followers of these laws were protected from both parasites and were likely to have experienced a greater level of health in this regard (46). As with many of these nematodes, identification of the adult worm was not made until the 19th century, when parasitology as a field was gaining momentum (46). The mode of transmission as discovered shortly after identification of the worm and led to public health awareness of the dangers of consuming undercooked pork (46, 85, 89).

Human trichinellosis provides a unique insight into the influence of behavior on the distribution of infectious disease. The agricultural revolution was accompanied by several changes in population structure, mobility, and diet (50, 89). The rise in the Old World incidence of trichinellosis in ancient times is just one example of how this shift influenced patterns of infectious disease (87, 89). The lack of domesticated pigs in the New World provides an illustration of how widespread differences in human behavior can lead to alternative infection and exposure patterns of parasites (87).

Lymphatic Filariae: *Wuchereria bancrofti* & *Brugia malayi*

The two organisms *Wuchereria bancrofti* and *Brugia malayi* are responsible for lymphatic filariasis, a disease which is characterized by pain, swollen lymph nodes, and lymphedema of the extremities, termed elephantiasis (13). The modern geographic distribution of lymphatic filariasis follows the distribution of the mosquito vector, although it is concentrated in economically poor countries (13, 90). *W. bancrofti* is the more prevalent of the two, with *B. malayi* only infecting in regions of SE Asia, India, and

Malaysia (13). Archaeological evidence of lymphatic filariasis is scarce, though signs of microfilariae in mummified tissue has been found in one Egyptian mummy estimated to be 3000 years old (91). No traces of prehistoric infection with lymphatic filariae have been found in New World archaeological sites, though lymphatic filariasis is present in tropical regions of the Americas today (13). It is thought that the disease was absent in the New World during prehistoric times but experienced a rapid spread following Columbian contact due to the slave trade (44, 92). Prior to any public health interventions aimed at decreasing exposure to the disease vector, lymphatic filariasis existed wherever the vector could survive (44).

Although prehistoric indications of lymphatic filariasis in Old World countries are not heavily supported by archaeological evidence, writings from antiquity clearly indicate a disease which strongly resembles the condition (30, 44). The clinical manifestations of the disease are fairly obvious in those with mild and heavy infections, particularly when they present with elephantiasis, so ancient populations must have been aware of the disease (13, 44). Ancient Greek and Roman authors frequently mention a condition very similar to elephantiasis, although modern historians disagree about whether the texts refer to lymphatic filariasis or leprosy (44). A 4,000 year old statue depicting an Egyptian Pharaoh shows swollen limbs, suggesting that the ruler was afflicted with lymphatic filariasis (30). In addition, the discovery of 1,500 year old West African small figurines styled with similarly swollen limbs and genitalia suggests that the disease was not unknown to that region (30). Greek, Roman, and Arabic writers of antiquity appear to have been aware of the manifestation of elephantiasis and used different terms to distinguish it from elephantiasis caused by leprosy (30). One modern historian, BR

Lawrence, proposes a Southeast Asian origin of lymphatic filariasis (44). He argues that the parasite spread to Africa and the Pacific Islands, adapting to the mosquito-borne lifestyle during this time (44, 93). It was not until the late 16th century that lymphatic filariasis was reliably described in texts (30). From that time until the late 19th century, frequent mention of the disease is made, although the mode of transmission and life history of the parasite was still unclear (46). In 1877, parasitologist Patrick Manson discovered that the parasite was transmitted through the bite of the mosquito (30, 44). This finding was revolutionary in the identification of secondary hosts for parasites and allowed for the development of public health intervention programs aimed at halting transmission of the devastating illness (30).

Onchocerca volvulus

The filarial parasite *Onchocerca volvulus* is the causative agent of onchocerciasis, also called “river blindness” (14). The disease, spread by the bite of black flies, occurs in savannah and forested regions with warm temperatures and high moisture content, which allows for the growth and development of both the vector host and microfilariae in the host (15, 94). Intense infection with *O. volvulus* is usually associated with one of two outcomes, blindness or dermatitis characterized by intense itching (14). Interestingly, the occurrence of these conditions differs according to whether the infected individual was bitten by a forest-dwelling or a savannah-dwelling black fly (15). The bite of a savannah-dwelling black fly infected with *O. volvulus* is more likely to result in blindness, while forest-dwelling black flies are more likely to transmit the dermatitis form of the infection (15). Both of these debilitating outcomes of infection are caused by the host’s response to

circulating microfilariae and are not thought to be directly caused by the parasite (14). The obvious nature of these symptoms would probably have drawn the attention of ancient populations residing in endemic regions. However, since populations exposed to the disease are likely to present with one of the two possible main symptoms of infection depending on the source of the disease vector, they may not have realized that the blindness and the dermatitis were different forms of the same disease. Furthermore, blindness is not an uncommon affliction in endemic regions and may not have been noticed as an unusual or notable outcome of parasitic infection (44). The evolutionary origin of human infection with *Onchocerca volvulus* is uncertain, although the fact that humans act as the sole reservoir for the parasite points to the parasite being a souvenir from human ancestors (14).

Archaeological evidence of prehistoric infection with *O. volvulus* is lacking, probably due to the difficulty in preservation of the microfilariae or adult worms in human remains. Despite the dearth in paleoparasitology findings, historians estimate that infection became more common in regions of West Africa following the development of farming approximately 3,500 years ago (95). The need for a reliable source of water for agricultural practices and maintenance of domesticated animals led to increased exposure to black fly breeding grounds such as fast-moving rivers and streams (14). High levels of infection among groups residing near these areas have led in recent times to abandonment of rich fertile farmlands and is likely to have been a factor in population movement among ancient populations (44). Although individuals residing in regions of West Africa with high endemicity were aware of the dermatitis form of the disease, calling it “craw craw”, the parasite did not draw much notice until the African slave trade expanded the

geographic distribution of both parasite and vector to include the New World and parts of the Arabian peninsula (30, 92, 95). American onchocerciasis was thought to be caused by a form of *O. volvulus* with a long history of isolation from the African forms (96). However, genetic analysis of the parasites revealed that the American parasite is unable to be distinguished from the African savannah parasite, indicating a short shared history (96). This finding supports the hypothesis that the disease was brought to America through the slave trade (92, 96). Identification of the causative agent and the disease vector was not made until the late 19th century and the early 20th century, respectively (30). These discoveries allowed for the development of parasite control strategies aimed at reducing exposure to the disease vector (30, 44).

Loa loa

Similar to *Onchocerca volvulus*, *Loa loa* is a filarial nematode that is transmitted by mango flies of *Chrysops spp.* and results in ocular symptoms in infected humans, notably the migration of the adult worm across the eye (97). The geographic distribution of loiasis follows the distribution of the parasite's biting fly vector (98). Warm, moist, and shaded regions in Central and West Africa represent the regions with highest rates of infection, due to the environmental suitability of vector growth and development (99). Although modern agricultural practices appear to have influenced the distribution of the disease due to altering exposure to the vector, it is unclear whether ancient populations altered the environment in similar ways, particularly following the agricultural revolution (97, 100). Infection with the parasite is associated with the development of itchy nodules appearing on the face or head region or the extremities (97). The emergence of these

symptoms is a result of the host immune and allergic response to the presence of adult worms and microfilariae in the body (97). The overt presence of the worm during its migration across the human eye is not likely to have escaped the attention of ancient populations, although ancient writings recording the event do not seem to exist (30, 46). An ancient engraving thought to portray instructions for the removal of the worm from the eye has recently been disregarded as early mention of the worm and is now thought to be a depiction of torture (30, 46). The first recorded mention of the worm occurred in the late 18th century and concerned the observation of the migration across the eye and an unsuccessful attempt to remove it (30). Further research led to the identification of the biting fly as the parasite vector in the early twentieth century (46).

Dracunculus medinensis

The nematode *Dracunculus medinensis*, commonly called guinea worm, causes one of the most recognizable parasitic infections in humans. Once prevalent in many countries in Africa, Asia, and Latin America, dracunculiasis is now limited to a few regions in Africa, thanks to a global eradication initiative (16). The formation and rupturing of a painful swelling on a lower extremity and the subsequent emergence of the female worm from the foot are unique signs that visibly indicate an infection with guinea worm (16). Human infection begins after the consumption of water containing the parasite's secondary host, typically the crustacean Cyclops, but also the crustaceans Mesocyclops or Thermocyclops (16). The infectious cycle is perpetuated by the burning sensation caused by the blister, which induces the host to place the affected extremity into water (16, 17). Upon touching the water, the blister bursts, releasing millions of first

stage larvae which continue to mature in the secondary host (16). The status of *D. medinensis* as an heirloom or souvenir parasite has not been clarified. However, humans are thought to be the sole reservoir of guinea worm, a key to the successful eradication of the parasite (101). Previously, cats, dogs, horses, non-human primates, raccoons, and other animals were thought to be capable hosts of *D. medinensis* and to have influenced the transmission dynamics of the parasite (16, 101). However, the aforementioned animals can also harbor another species of *Dracunculus*, and reports of *D. medinensis* infection in animals are probably due a misidentification of these very similar worms (101). The lack of additional guinea worm reservoirs could point towards it being a souvenir parasite, inherited from human ancestors, although this has yet to be investigated.

Evidence of historical guinea worm infection is fairly abundant in the archaeological record. Autopsies and x-rays of ancient Egyptian mummies have revealed the presence of adult worms in tissue (30, 46, 102-104). The oldest reported piece of evidence comes from an ancient Egyptian female mummy dating to 1000 BCE (46). Writings suggesting ancient knowledge of the scourge date back even farther than archaeological evidence (30, 46, 105). The obvious signs of human guinea worm infection are not likely to have been missed by ancient historians and physicians, which is confirmed by the plentiful mentions of the parasite in texts of antiquity (30, 46, 105-107). One of the oldest medical writings known to exist contains what modern historians believe is a reference to the identification and treatment of the parasite (30, 46). Some passages in the Papyrus Ebers, written circa 1550 BCE, mention the emergence of larvae from a swelling and instructions for removal of the worm (30, 44, 46, 105, 108). If these

passages truly refer to guinea worm infestation, their inclusion in the text is intriguing (108). Writers of the Papyrus Ebers are believed to have recorded information about diseases affecting the Egyptian royalty (104, 108). Thus, the mention of guinea worm would appear to indicate that the disease did not solely afflict poor individuals (108). It also brings up the question of the origin of the worm. During the time the Papyrus Ebers was being written, significant trade was occurring between Egypt and regions south and west of the kingdom (108). Modern historians believe that this trade could have contributed to the spread of guinea worm either by introducing it to ancient Egypt or vice versa (108). The practice of monkey domestication in ancient times in central Africa has also been implicated in both the introduction of the parasite into humans as well as the spread of the disease (108).

Other ancient texts make reference to a condition resembling guinea worm infection, although the nature of the disease was a subject of debate among authors (30, 44). A notable mention of guinea worm in antiquity can be found in the Old Testament in the form of the “fiery serpents” that proved to be a terrible affliction for the Israelites during their exodus from Egypt (30, 44). Their exodus is believed to have occurred circa 1250 to 1200 BCE, although the text was likely composed around 700 BCE (44). The image of this “fiery snake” has been asserted by some to have inspired the design of the caduceus, the illustration of two snakes winding around a staff that is representative of the medical profession (17, 44). In addition, Assyrian, Greek, Roman, and Arabic medical texts make reference to the condition and its treatment (30, 44, 46). As these numerous mentions suggest, guinea worm was a very prevalent and notable infection in ancient times, and its geographical spread was likely advanced by the emergence of

widespread trade amongst afflicted regions (108). Medical interest in *D. medinensis* beyond endemic regions began to rise during the 16th century following the return of Europeans who had traveled among those regions and observed the illness (44, 46). The adult worm was identified in 1674 and named in 1758, although the manner of transmission was not elucidated until the late 19th century (44). The identification of contaminated water as the source of transmission forever altered the landscape of the disease. Following this breakthrough, water sanitation programs were widely implemented, and, although many areas still do not have a clean supply of water, public health education programs have nearly succeeded in making *Dracunculus medinensis* the second eradicated disease (109).

A Historical Perspective: Human Influence on Transmission of Nematodes

Approximately 10,000 years ago, humans experienced a major transformation in population structure, disease exposure, and migration patterns as a consequence of the shift from foraging to farming (110, 111). This period of change may have been precipitated by several factors including widespread climate change that led to a decrease in large mammal populations, which forced humans to seek alternative sources for food (110, 112). The domestication of plants and animals in the Fertile Crescent in western Asia allowed for the maintenance of larger populations with less mobility than hunter gatherers (110-112). Perhaps the most important outcome of the agricultural revolution is the drastic change in infectious disease exposure and transmission patterns (29, 111, 112). The increase in population density among farming populations allowed for the emergence and maintenance of many zoonotic parasites and pathogens, several of which

resulted in large-scale epidemics, leaving victims either dead or immunized (110, 111). This change is referred to as the first epidemiologic transition (112). In addition to the many zoonotic diseases originating from domesticated hosts, humans experienced an increase in heirloom parasites as some worms were able to take advantage of the high population density and sedentarism (110, 112). For instance, humans that settled near water sources created more opportunities for disease vectors that breed in water to feed on humans and transmit the parasite.

By their nature, macroparasites have longer reproductive stages and life cycles than microparasites, and usually cause chronic infection with no clear immunological outcome in the host (6). As a result, the agricultural revolution had a different impact on these parasites than on their smaller, unicellular counterparts. Nematodes, with their wide range of transmission modes and rich history with humans, are an ideal parasite group with which to view the impact of human behavior on disease and hypothesize about the potential effects humans have had on the evolution of virulence in these parasites.

Claims that hunter-gatherers were healthier than farmers are true to an extent, but the term 'healthier' is relative. Hunter-gatherers still experienced high levels of infectious disease and high adult mortality (113, 114). However, studies of modern hunter-gatherers show diversity in food acquisition and utilization, resulting in a generally higher level of nutrition than their farming counterparts (110, 115). This difference in nutrition has great implications for the effect of intestinal parasites on their host. Many of the soil-borne intestinal nematodes decrease the nutritional status of their host during feeding, resulting in conditions such as iron-deficient anemia (9). In addition to these dietary differences, patterns of infection between hunter-gatherers and farmers greatly varied, as previously

mentioned (110, 111, 116, 117). Prior to the agricultural revolution large-scale epidemics were uncommon, unable to be maintained in the small populations with infrequent and irregular contact with other groups (110). However, the agricultural revolution resulted in epidemics of acute diseases which leave victims dead or immune to future infection (110, 111). Hunter-gatherers were previously protected from infection from such pathogens, but their frequent movement could have brought them into contact with settlements, thus exposing them to epidemics (116). However, the relative ease with which they could move camp could have a protective effect by allowing them to avoid settlements known to be experiencing an epidemic (110). Modern nomadic groups display similar patterns of behavior, moving to avoid disease (116). While this can protect them from diseases of crowding, it can also leave them susceptible to outbreaks to which there is little to no herd immunity (116). In this section, the influence of changing host population dynamics following the agricultural revolution on the spread and distribution of nematode infections will be considered. Individual host dynamics will be discussed in Chapter III.

Soil-Transmitted & Direct Contact

The nematodes commonly referred to as soil-transmitted or direct contact parasites include the following: *Enterobius vermicularis*, *Trichuris trichiura*, *Ascaris lumbricoides*, Hookworms *Necator americanus* & *Ancylostoma duodenale*, and *Strongyloides stercoralis* (60, 118). Transmission occurs through ingestion of infectious larvae or eggs (*E. vermicularis*, *T. trichiura*, and *A. lumbricoides*) or through penetration of the host's skin by infectious larvae (hookworms and *S. stercoralis*). With the exception of *Enterobius vermicularis*, the aforementioned parasites spend part of their

developmental life cycle in the soil before they are able to infect another host (7, 9, 47, 58, 76). Primarily arboreal human ancestors probably would have experienced relatively low levels of infection with soil-borne parasites due to lessened exposure to contaminated feces. By defecating onto the forest floor from a point higher in the trees, primates would limit transmission of these parasites by reducing contact with infective larvae. The practice of defecating from low-hanging branches and seeking food and sleep higher in the canopy has been observed for several primate species and is argued to be a parasite avoidance behavior (119, 120). The transition from arboreal to terrestrial life in early human ancestors would have resulted in increased exposure to fecally-transmitted parasites and a correspondingly higher rate of infection.

The soil-borne parasites require a variable range of time in order to advance to the infectious stage and, upon reaching that stage, can survive for a certain length of time depending on environmental conditions (7, 60, 74, 76). Variations in durability among these species may play a role in virulence. Due to their durable nature, the transmission of these nematodes is not as reliant upon individual host mobility, and effective transmission may occur from a weakened or severely diseased host. On the other hand, mobility of the host population would greatly affect the soil-borne nematodes, particularly their ability to reach and maintain an infectious threshold in a population. Hunter-gatherer populations tend to move frequently in order to locate sufficient food and water (117). The soil-transmitted nematodes may not have enough time to be deposited into the soil, develop, and infect another host to continue the infectious cycle before their host population has moved on. Sedentary populations resulting from the agricultural revolution had generally low sanitation, and individuals were in frequent contact with

areas of refuse (110, 116). With these changes in population behavior, the soil-borne nematodes were able to be successfully maintained in a population with extremely high prevalence rates (110). *E. vermicularis* would not be as affected by the loss of host population mobility due to its direct transmission and relatively low environmental durability (47). Pinworm eggs require only six hours to embryonate and become infective, and the prospect of transmission is influenced only by sanitation characteristics, such as hand-washing, of those infected and exposed (47, 48). Therefore, it is reasonable to assume that *E. vermicularis* would not have been as affected by decreased mobility of the host population, except for the possibility of shorter generation times due to an increased effort in reproduction (121-123).

The soil-borne nematodes, on the other hand, experienced a tremendous increase in exposure to potential hosts as populations grew and became more stationary. The potential for parasite transmission grew as populations grew larger, more unhygienic, and more sedentary. Prior to the agricultural revolution, transmission of soil-borne nematodes was restrained by increased population movement. It does not seem likely that soil-borne nematodes would have been able to maintain a threshold of infection in a very mobile group of hunter-gatherers, and modern studies of nomadic tribes support this hypothesis (116, 117, 124). Nomadic tribes were found to have lower rates of soil-borne nematodes than settled groups (116). Prevalence rates of *T. trichiura*, hookworm, *A. lumbricoides*, and *S. stercoralis* in nomadic groups were reported to be 1.6%, 1.6%, 11.3% and 0%, respectively (116) These rates are in contrast with corresponding rates in settled populations, at 75.5%, 45.1%, 19.4%, and 2.9% (116). These findings could indicate that the movement of nomadic individuals prohibits the maintenance of infection by intestinal

helminths such as hookworms or it could indicate a greater level of hygiene in nomadic populations (116). Using these findings to make inferences about the disease state of prehistoric hunter-gatherer populations should be done with caution, however. Present-day nomadic tribes are not true representations of prehistoric hunter-gatherers. Many have descended from farmers, and few true hunter-gatherers exist; many nomadic tribes are pastoralists, maintaining domesticated herds as they move (116, 117). Furthermore, these individuals are a product of millennia of evolution following the agricultural revolution and respond to infection differently than their ancestors (110). These differences between modern nomadic tribes and prehistoric hunter-gatherers should be kept in mind when describing the disease state of ancient populations.

S. stercoralis is unique in its ability to cause autoinfection in a host, whereas the other soil-transmitted parasites must leave the host before being able to re-infect (76, 125). This characteristic of *S. stercoralis* is primarily responsible for deaths in infected individuals and can result in chronic infection despite the absence of exposure (46, 76). Aggregation of a species of parasite within a host can result in decreased average fitness and reproduction rate for the parasites if their size is large enough to cause a significant crowding effect (4). *S. stercoralis* adult females (no parasitic male exists) are relatively small, so autoinfection resulting in large numbers of worms would likely result in a correspondingly higher number of larvae produced, which increases the potential for infecting additional hosts (76). Whether *S. stercoralis* is an heirloom or a souvenir parasite has not yet been determined, but if it was inherited from human ancestors, the agricultural revolution may have altered the dynamics of infection. The increase in host population density would have exerted selection pressures on the parasite to increase

fecundity, likely as a result of increased autoinfection. This change, likely accompanied by a decrease in host fitness, may have increased the ease of transmission from sick hosts and thus the frequency of the more exploitative form of the parasite.

Transmission Through Ingestion of Contaminated Tissue

The only parasite whose transmission depends on the ingestion of infected tissue is *Trichinella spiralis* (11). Humans become infected when they consume raw or undercooked meat containing the Nurse cell-larvae complex (11). Today, pork is the most common source for human infection, but the consumption of infected game meat has also been reported to result in infection in developed countries (11, 83, 84). Before the advent of farming, humans probably experienced infection with *T. spiralis* by eating the meat of the animals they hunted (87). After the agricultural revolution, the common habit of keeping herds of domesticated pigs grossly increased human exposure to the parasite (87).

During prehistoric times, transmission from humans could have occurred through cannibalistic or predator-borne means. Following the agricultural revolution, however, the parasite's presence in humans most likely resulted in a dead-end infection since the infectious cycle can only continue following the consumption of infected meat (11). Therefore, humans must have played another role in the transmission of *T. spiralis*. The infection was likely perpetuated amongst the swine by the farming practices of herders. The practice of feeding pigs infected pig and rodent carcasses results in high levels of infection among domesticated animals, and the practice was widespread until recently (84). Lower infection rates would have appeared in regions where religions forbidding

the consumption or keeping of pigs were dominant (46, 87). The implementation in recent decades of public health policy aimed at the reduction of unsanitary farming practices has resulted in a large decrease in the infection in the past decades (11, 126). The change in human exposure patterns to *T. spiralis* following the agricultural revolution illustrates how humans can influence the transmission dynamics of a parasite they do not directly transmit.

Vector-Borne

The filarial nematodes *Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa* are dependent upon insect vectors for transmission to humans (13, 14, 97). Prehistoric evidence of these infections is lacking, although poor preservation conditions of the environment and the parasite itself may be to blame (30, 44, 46). However, another prevailing hypothesis states that human infection by these parasites was not common until the agricultural revolution, when population density allowed the diseases to be maintained (127). The domestication of plants and animals necessitated that humans settle near reliable sources of water or create reservoirs of stagnant water, which are frequent breeding grounds for disease vectors (13, 14, 97). In addition, the steady presence of large numbers of domesticated animals attracted the presence of these insects. The increased availability of hosts for these vectors enabled a growth in both vector population size and geographic range (127). Diseases such as malaria flourished under these new conditions, and it is believed that resistance factors to malaria arose and were selected for during this time (127). In addition, the vectors and parasites adapted to

humans, becoming very specific (127). Evidence of an increase in vector-borne parasitic diseases as a result of the presence of farming can be found in the case of *Loa loa*.

The vectors of *Loa loa* are biting flies that usually reside in the high canopies of moist forest areas and feed on monkeys dwelling in trees (128). The vectors seek out humans to feed upon only when there is a sufficient clearing in the forest for them to detect the presence of humans (128). An increase in rubber plantations was found to be associated with an increase in loiasis among workers and those residing near the plantations (97, 100, 128). It was determined that the compositional differences of the rubber plantations, which included lower canopies and fewer monkeys, promoted the disease by increased biting activity of the vector on humans (128).

Research on modern-day nomadic tribes has shown that population movement is not a deterrent for infection with the vector-borne nematodes (116). The widespread distribution of vectors infected with nematodes places both nomadic and stationary populations at risk for infection (116, 127). However, nomadic tribes have been found to avoid moisture-rich regions during certain periods of the year, which is thought to be done in avoidance of disease vectors (116). Despite this, movement into areas with high vector prevalence is often necessary for the feeding and watering of the herds of nomadic pastoralists (116). One study found that onchocerciasis was present in nomadic pastoralists in rates as high as 5% following the movement of the group into savannah and rain forest areas during the dry season (116). Without infrastructural intervention and behavioral alterations decreasing exposure of humans to these disease vectors, significant and permanent change cannot be made in the fight against filarial nematodes.

Water-Borne

Infection with the guinea worm *Dracunculus medinensis* occurs when an individual consumes water containing copepods infected with the infective third-stage larvae of the parasite (16). Whether prehistoric humans were widely affected by the parasite is not known, but the changes associated with the agricultural revolution would have greatly altered the scope of infection. Pre-farming hunter-gatherer groups would shift their dependence on a particular water source as they moved. The source of infection within one of these mobile groups is not likely to have originated within the group itself but rather from another group. Maturation time inside the human host, from initial ingestion to production of larvae, is approximately one year (16). After the blister containing the larvae bursts in a pool of water containing the secondary hosts, the larvae are ingested by the copepods and take another two to three weeks to advance to the infectious stage (16). During this extra time required for the larvae to become infectious, the hunter-gatherer group could have already moved on, leaving the majority of members unexposed. The development of large settlements would have required a nearby reliable source of water which would be widely used by most members of the population. If one of these water sources became infected, the parasite would have a wide array of hosts to infect. The release of larvae from one infected member of a stationary farming population would result in the rapid spread of the parasite among the group. The advent of farming would have resulted in an exponential rise in cases of guinea worm among not only farmers but also hunter-gatherers. Mobile groups of hunter-gatherers were likely to come into contact with stationary groups and shared water sources, particularly during the dry season (116). Infection could have spread to the hunter-gatherers this way. Furthermore,

infected groups of hunter-gatherers or other mobile groups, possibly involved in trade, could have contributed to the geographical spread of the disease.

Studies investigating the health status of modern nomadic tribes have discovered prevalence rates of infection with *D. medinensis* reaching up to 65% (116). These findings are in line with predictions about how behavior of nomadic groups brings them into contact with infected water sources. Until the transmission mode of guinea worm was discovered, the infectious cycle continued unimpeded in areas with suitable environments for growth of copepods. Filtration of water is the most important preventative measure against infection with *D. medinensis*, and public health campaigns have nearly succeeded in the eradication of the parasite (129, 130). However, infection continues in some regions due in part to the movement of nomadic groups (116). Infected members of such groups can bring disease to regions where the parasite has been previously eradicated (116). This represents an interesting shift in how the behavior of nomadic groups influences transmission of the parasite. Before the agricultural revolution, the high mobility of nomadic groups did not favor the transmission of the parasite. However, nomadic groups today represent a major source of infection as groups with prevalence rates move amongst stationary groups and contaminate water sources (116, 124).

Impact of Nematodes on Human Evolution

The long-standing relationship between humans and nematodes has undoubtedly resulted in genetic variations in humans which relate to predisposition for infection or variation in the intensity of infection. Such variations have been found which contribute

to the parasite density within a host or the ability of the host to clear an infection (131-135). Recently, much research has investigated other implications these genetic variations might have on the health of a human host. The term “hygiene hypothesis” has gained momentum in discussions regarding the immunological impact on populations with low exposure to historically common infections, such as helminth infections (136-140). The hygiene hypothesis attempts to explain the apparent increase in the past century in allergic and autoimmune diseases such as asthma, particularly in developed countries (137, 139, 140). Supporters of the hygiene hypothesis believe that helminths tweak the host’s immune system, making it less likely to overreact and cause disease to the host (141). According to this hypothesis, the widespread reduction of helminth infections in these regions has led to an over-reactive immune system in which individuals may react strongly to innocuous particles (137, 140). The hypothesis appears to be supported by the observed inverse relationship between prevalence rates of autoimmune disease and parasitic infections (140). In addition, Crohn’s Disease sufferers experimentally infected with hookworm larvae were found to experience symptom reduction (142). However, the association of these findings with the hygiene hypothesis does not appear to take into consideration the basic immunological effect of intestinal nematode infections: intestinal nematodes compromise the host immune system in order to persist chronically (141). The observed alleviation of auto-immune disease symptoms in experimentally infected individuals is likely a by-product of parasitic infection rather than a direct interaction.

Although the hygiene hypothesis does not appear to explain sufficiently the apparent rise in auto-immune diseases by an absence of helminths, genetic and evolutionary considerations of the problem may shed some light. The shared evolutionary

history of humans and helminths has led to genetic variation in immune responses, and those that were protective against parasites were selected for (137). In some cases, the variation might represent an increased inflammatory response that could be indirectly tied to the presence of allergic diseases in a host (132). A variant associated with asthma has been found to be associated with lower *A. lumbricoides* worm burden (132). This could indicate that variation in Th2 response, known to be employed in the control of parasitic infections, was selected for because it protected against roundworm (132). This variant may now play a role in the increased inflammatory state present in asthma patients (132). It is unlikely, however, that the lack of infection alone has led to this over-reactive state. If that were the case, autoimmune disease would be expected to be much more prevalent. Instead, it is likely that the presence of a hyper-inflammatory genetic variant in some individuals manifests itself as an autoimmune disease when an individual is exposed to an antigen closely resembling a host molecule.

Although the evolutionary impact that nematodes have had on human evolution has only begun to be explored in depth, it is clear that the long evolutionary relationship between these organisms has resulted in immune system variations and responses important to disease frequency and distribution today. For example, studies conducted in the American South in the early 20th century revealed differences in hookworm prevalence and infection intensities between those with European ancestry compared to those with African ancestry (131). Specifically, those with African ancestry reported lower prevalence and lessened intensity of hookworm infection compared to those with European ancestry (131). Modern day differences in infection patterns should be explored

in more depth. In order to gain a clearer picture of the ways in which human evolution has been influenced by these parasites, widespread genomic analysis should be done, comparing regions with historically low levels of infection with those long endemic. This could result in the identification of genetic variants relating to the protection or suppression of parasitic infections and exploration of the impact of these variants today.

CHAPTER III

FACTORS AFFECTING VIRULENCE

Virulence patterns of infections with nematodes are understudied in parasitology, despite the fact that the topic has powerful implications for public health policy and practice. This section will explore the varying degrees of virulence of infections with nematodes and attempt to draw out patterns relating to virulence. First, the epidemiological, ecological, and biological aspects of each nematode will be discussed in depth, with special consideration to host, parasite, and environmental factors affecting transmission. The levels of virulence for nematodes will be compared first within transmission groups then among the groups themselves. Then, there will be a discussion on incorporating virulence patterns in the development of new or the assessment of old public health control or prevention strategies. The chapter will conclude with a discussion of future avenues of research involving nematode virulence. In general, this chapter seeks to explore why differing levels of virulence are observed among parasitic nematodes, to make predictions about patterns of virulence, and to apply findings to public health research and practice.

Mode of Transmission

The role of transmission mode in parasitic disease has been discussed briefly so far, but a more in depth investigation of how transmission relates to virulence is needed

in order to understand why different parasites affect their host more than others and how humans can manipulate transmission to decrease parasite virulence. For the purpose of this thesis, virulence will be considered a characteristic of infection and defined as the degree of harm a parasite causes to its host. Virulence represents a spectrum of parasitic relationships on the mutualism-parasitism spectrum mentioned previously, with the lowest to highest levels of virulence corresponding to the lowest to highest degrees of parasitism.

Scientists long believed that a host-parasite relationship will eventually lead to a harmonious state in which host nor parasite is negatively affected by the interaction, and that infections resulting in host death are indicative of a short shared history between host and parasite (143). This concept has in the past few decades been replaced by the idea that virulence is dependent upon factors affecting transmission (18). Parasites that severely debilitate or kill their host were thought to be inefficient; host death meant that the parasite lost its resource base for reproduction and transmission, so it was believed that it was in the best interest of the parasite to keep the host alive (143). However, this interpretation of the host-parasite relationship only holds if the parasite is dependent upon the survival or mobility of its primary host for transmission. If the parasite does not require its host to be mobile for transmission to occur, as in the case of vector-borne diseases, it is free to exploit the host severely without damaging its chance of transmission (144). Therefore, virulence is the result of a trade-off between the benefits of exploiting host resources and the negative effect of such exploitation on transmission.

Microparasites and macroparasites differ in size, life history, and the type of immune response they elicit in the host (145). In general, macroparasites are larger and

take longer to reproduce, which requires a longer time spent in a host (145). This requires that the host survive long enough for continued transmission to occur, which explains why parasitic nematodes are rarely as fatal as some microparasites. In addition, most of the parasitic nematodes previously discussed are able to reproduce within a host, but the offspring cannot directly infect the host without leaving the body, a characteristic which is in contrast with microparasites (118, 145). One exception to this is *Strongyloides stercoralis*, which can continually re-infect the host (76). Macroparasites are typically the cause of chronic infections whereas microparasites frequently, though not always, cause acute infections which are resolved by the host's death or clearance of the parasite by the host's immune system (145). Differences between these two types of parasites can influence the outcome of infection in a host and patterns of infection in a population (123). Nematodes represent a group of macroparasitic helminthic worms that infect humans. The various transmission modes of parasitic nematodes may influence the morbidity and mortality that they cause (16). Of the nematodes of major medical importance, direct contact, soil-borne, transmission through consumption of contaminated meat, vector-borne, and water-borne transmission modes are represented (118).

Transmission can be influenced by many factors both internal and external to the host-parasite relationship. Host behaviors may facilitate or inhibit the transmission of a parasite to another host (60, 99, 146, 147). One broad population-level behavior having great implications for transmission opportunities has already been discussed: the advent of farming resulting in sedentarism and larger populations (110, 111, 117). Both individual- and group-level behaviors may influence transmission. For example,

indiscriminate defecation by an individual infected with hookworm may increase exposure for a group of individuals residing nearby, and wars or political unrest resulting in infrastructural breakdown of water sanitation may increase the likelihood of guinea worm transmission (8, 74, 148). The previous section discussed how large-scale behavioral changes influence nematode distribution. This section's discussion of virulence will largely focus on the role of individual host behavior in nematode transmission.

In soil-borne, vector-borne, and water-borne parasites, environmental conditions can greatly influence the survival, development, and transmission of the infective stage of the parasite (149). Much research lately has been dedicated to predicting how climate change may influence the intensity and distribution of tropical diseases by widening vector habitat range and influencing human behavior (149, 150). The possible effects of climate change on nematode distribution and virulence will be considered in this section. A combination of factors, both internal and external to the host-parasite relationship, interacts to result in a level of virulence unique to each parasitic infection. This section will explore the virulence of each nematode infection by including a discussion on transmission mode in addition to host and environmental factors affecting transmission.

Several problems persist in the evaluation of virulence patterns for parasitic nematodes. Although the definition of virulence often includes the likelihood of host death, the term cannot be used readily for nematodes in that manner. Humans infected with nematodes rarely die as a direct result of the infection, so virulence must be assessed in additional ways (118). Also, studies examining the morbidity, mortality, or disability rates of nematode infections are infrequent and often unreliable. Furthermore, the

complex life histories of these parasites make generalizations or predictions regarding virulence difficult. The principles underlying microparasitic virulence cannot be easily applied to nematode infections due to the characteristically different types of infection, but the principles will be tested to evaluate how well they predict virulence in nematode infections. In order to combat these challenges, the author has created a generalized scale of virulence by incorporating both available mortality and morbidity estimates as well as aspects of clinical disease. Virulence was determined to be the level of harmfulness of a nematode infection, relative to other nematode infections. That the scale is a subjective creation of the author should be kept in mind during the discussion. Disease is different for each individual and each population may feel the effects of disease in varying intensities. Therefore, widespread application of this scale to affected populations should be done cautiously, with consideration of the population's culture, beliefs, and experiences. Despite these problems, the scale can be useful in discovering patterns of virulence and in identifying future avenues of research.

This upcoming section will focus largely on attempting to answer questions about the relationship between transmission mode and virulence in nematode infections. In particular, is there evidence to suggest that transmission mode influences patterns of virulence? Furthermore, how well can nematode virulence be predicted using the microparasitic model of virulence? What are the major problems with evaluating virulence in nematodes? Finally, how do humans influence transmission and thus virulence of nematodes? Addressing these questions will result in a more complete understanding of factors determining virulence in nematodes.

Soil-Borne and Direct Contact Nematodes

Comparative studies of transmission modes and virulence, defined as probability of the infection resulting in death in the host, have suggested that directly transmitted microparasites tend to be less virulent than vector-borne microparasites (22). However, the durability of the microparasite in the environment has been shown to influence the virulence of the parasite, with higher durability associated with higher levels of disease (151). Microparasites that are able to survive for long periods in the external environment do not have to rely as greatly on host mobility for future transmission (144, 151). Instead, they are able to put more energy into reproduction without hurting their chances of transmission (151). The causative agents of tuberculosis, smallpox, and diphtheria are very durable in the environment and cause correspondingly high mortality rates in hosts, while the less durable rhinovirus rarely results in host death (151). These durable microparasites are said to infect via 'sit-and-wait' transmission (22). This pattern between durability and virulence has been studied for many microparasites, but research on helminths is lacking (151).

The nematodes *Enterobius vermicularis*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma duodenale*, and *Strongyloides stercoralis* are transmitted through direct contact, either by the ingestion of infective larvae or eggs or the penetration of the host by the larvae (7, 9, 47, 58, 76). With the exception of *S. stercoralis*, these parasites must spend time outside of the host in soil or on the host's skin in order to develop to the infectious stage (7, 9, 47, 58, 76). Although re-infection by *S. stercoralis* can occur, the larvae must exit the host and exist as a free-living stage for a period of time in order to be transmitted to other hosts (76). The time needed for

development to the infectious stage is variable among these nematodes, as is larval durability. The length of time that larvae can survive outside of the host is of particular interest in a discussion of virulence. Following the principles of sit-and-wait transmission, one would expect to see an increase in virulence in soil-borne and directly transmitted nematodes corresponding to longer larval survival outside of the host. As durability increases, dependence upon the individual host for transmission would reduce, allowing for increased exploitation of the host.

Enterobius vermicularis

Distribution, Disease, & Immunity

The parasite *Enterobius vermicularis*, commonly called pinworm, most frequently infects school-aged children (48, 152). The difference in infection rates in children and adults is more likely to be a result of behavioral differences leading to exposure rather than acquired immunity (153). Infection is typically asymptomatic but can be associated with perianal pruritus, behavioral changes such as irritability, anorexia, and abdominal pain (47, 152). Fatality resulting from *E. vermicularis* infection is extremely rare (154). The virulence status of this parasite will be designated as being very low. Although immunity against *E. vermicularis* in humans has not been well studied, there is little to suggest that it is present (153).

Life Cycle

The life cycle of pinworm is direct, with transmission occurring via the ingestion of infectious eggs (47). Humans are the sole reservoir of infection (47). After being swallowed, pinworm eggs travel to the small intestine, where they hatch and develop into

second-, third-, and fourth-stage larvae (47). Approximately 4-6 weeks pass from ingestion of eggs to reproduction in the adult worms, and an additional 6 weeks is required for egg production (47). The eggs of *E. vermicularis* are deposited by the female worm onto the perianal region of the host at night (47). The eggs embryonate and become infective within six hours (47). Re-infection can occur if larvae hatch on the skin and crawl back into the colon (47). The nocturnal activity of the worm may have been selected for to provide the parasite with low levels of host activity so her presence is not noticed and to ensure that when the host wakes up, they are able to contaminate their hands with the infectious egg. The transmission cycle continues when an individual ingests the eggs, and re-infection of the same host is common (47, 48). Although embryonation of the egg can only occur if the ambient temperature is above 23°C, the eggs can remain viable for weeks if conditions are moist and cool (153). However, these conditions are rarely sustained long enough to prolong egg survival, and time outside of the host weakens the infective potential of the egg. After 1-2 days outside of the host, the egg experiences a sharp decline in infectivity (155). The low virulence and correspondingly low durability of *E. vermicularis* is in line with the prediction that durability in the external environment is positively correlated with virulence.

Environmental & Behavioral Risk Factors

Due to the life cycle characteristics of *E. vermicularis*, environmental variables such as rainfall or soil content do not strongly impact parasite development or survival. The survival of embryonated eggs is most strongly affected by temperature and moisture conditions (153). Host behavior plays a much bigger role in the transmission dynamics of pinworm. Close contact among potential and infected hosts is necessary for transmission

to occur (48). This indicates that host mobility is much more important than sit-and-wait transmission of *E. vermicularis*. The pinworm's relatively high reliance on host mobility for transmission would point toward it having low virulence, a prediction that is supported by epidemiological findings (47, 155). Poor personal hygiene, nail-biting, thumb-sucking, not washing hands before eating, and geophagia are also associated with pinworm infection (48, 156). These behaviors are more common in young children, which is in line with the observed infection age-curve for pinworms (156). Infection prevalence is also associated with family socioeconomic status, with lower socioeconomic status correlating to higher rates of infection (156). However, pinworm infection is not necessarily a disease of poverty. Transmission is dependent upon individual behaviors that increase or decrease exposure to the eggs. Since eggs are not transmitted by feces, infrastructural improvements in sanitation measures would not have significant effects on the transmission potential of the parasite (47). This is supported by the finding that *E. vermicularis* is the most common intestinal helminth in the United States (51).

Transmission Mode & Virulence

The low morbidity associated with pinworm infection can be explained in part by the transmission dynamics of the parasite. In order for transmission to occur, there must be close physical contact between an infected individual and a potential host, and the infected host must remain mobile (47). The relatively low durability of the worm also explains the need for host mobility and the observed low level of virulence. Transmission is favored by increased dispersal of the parasite, which requires host mobility. More virulent strains of the parasite would result in less mobile hosts, who would not be as

efficient in spreading the infection. Therefore, the strains that result in low host morbidity would be evolutionarily favored, which explains why these strains dominate today. Situations in which higher virulence would be selected for are possible. If transmission was no longer reliant upon host mobility, more virulent strains would hypothetically succeed.

Trichuris trichiura

Distribution, Disease, & Immunity

The soil-transmitted geohelminth *Trichuris trichiura* most commonly infects populations in tropical and sub-tropical poverty-stricken regions of the world and is found in highest levels in children (58). Mild infections are not usually accompanied by symptoms, but moderate and intense infections are associated with allergic symptoms, diarrhea, abdominal pain, vomiting, headache, blood loss, and weight loss (58, 59, 157). In children, intense infection is associated with *Trichuris* dysentery involving heavy diarrhea which leads to weight loss and rectal prolapse (58). The tendency of the parasite to induce frequent diarrhea in its host may play a role in broadening its transmission potential. By increasing the frequency and urgency of bowel movements, the infection may cause an individual to defecate indiscriminately, leading to contamination of a wider area. Individuals with chronic infection frequently present with a condition similar to inflammatory bowel disease, and long-term infection can result in side effects such as finger clubbing, anemia, and malnutrition (58, 59). Though morbidity resulting from infection can be debilitating, fatality is rare, with an annual global mortality rate of 10,000 (158). For these reasons, the virulence of *T. trichiura* is considered to be low.

Humans do not appear to show high enough acquired immunity to prevent infection or expel existing worms from the body (157).

Life Cycle

T. trichiura displays a direct life cycle, with infection resulting from the ingestion of embryonated *T. trichiura* eggs (58, 59). Following ingestion, the eggs travel to the small intestine and hatch into larvae. The larvae then undergo four molts before moving to the large intestine where they attach and complete maturation (58). It is here where sexual reproduction occurs, with a total timeline of initial ingestion to egg production of 60-90 days (58, 59). Eggs are deposited in the feces of the host, and embryonation commences under certain environmental conditions (58, 59). Embryonation occurs 18-22 days following deposition and is favored by shady loamy soil consisting of clay, silt, and sand, temperatures ranging from 25-34°C, and moderate moisture (58, 59). Although higher temperatures favor embryonation, they also reduce larval survival (154). In addition, exposure of the eggs to radiation can prevent further development of the eggs (58). *T. trichiura* eggs are fairly durable in the environment and have been found on a variety of surfaces (154).

Environmental & Behavioral Risk Factors

As discussed, temperature, moisture, soil content, and exposure to radiation affect the survival and development of *T. trichiura* eggs, thus affecting transmission (59, 159). Despite alterations in these conditions during seasonal change, infection prevalence is not likely to be as affected due to the chronic nature of the infection. During times of drought or cooling temperatures, larval development is impeded, so transmission is lessened and prevalence rates would remain stable (59, 159, 160). Altitude has been found to be

associated with *T. trichiura* infection, with lower infection rates occurring at higher altitudes (161). This finding is likely a reflection of unfavorable conditions for larval development and survival occurring at higher altitudes (161). Over the next century, climate change is predicted to result in warming temperatures and variable rain patterns (150). A temperature increase will result in more rapid larval embryonation but decreased larval survival (59, 150, 159). An increase in rainfall, likely to occur in eastern Africa, will favor larval survival and development while a decrease in rainfall, predicted to occur in southern Africa, will result in worse conditions for larval survival and growth (59, 150, 159).

Transmission of *T. trichiura* is favored by many human behaviors, particularly those relating to hygiene. Failure to wash hands after defecating, failure to wash vegetables before eating, and geophagia are associated with *T. trichiura* infection (10, 59, 162). Infrastructural components such as poor quality water, lack of latrines, and poor access to medical care have also been found to be associated with infection (59). Indiscriminate defecation can spread the disease both directly and indirectly. People may come into contact with the contaminated feces, acquiring infection that way. Additionally, flies can carry *T. trichiura* eggs, bringing them into contact with food, thus exposing humans (59). In areas where latrines are lacking or poorly assembled, chickens and ducks have been observed eating human feces (59). *T. trichiura* eggs pass through the birds and contaminate a wide area (59). Crowded conditions facilitate the transmission of soil-transmitted helminths by increasing exposure to the parasite (163, 164). Urbanization in undeveloped countries is accompanied by the growth of slums and shanties with poor water supply and unsanitary conditions (164). Such urbanization is

predicted to increase in the tropical and sub-tropical poor regions of the world where *T. trichiura* is endemic (164).

Transmission Mode & Virulence

Humans become infected with *T. trichiura* through the ingestion of embryonated eggs that were deposited in soil in the feces of an infected individual (58). This represents a direct route of transmission, commonly called fecal-oral or soil-borne. Morbidity and mortality caused by *T. trichiura* infection is low, so the parasite can be described as having a low level of virulence (58). Transmission of *T. trichiura* is somewhat dependent upon host mobility, although less so than *E. vermicularis* due to its higher environmental durability. The higher durability of *T. trichiura* allows it to employ sit-and-wait transmission more than *E. vermicularis*, which results in increased host exploitation by *T. trichiura* and a relatively higher level of virulence. Theoretically, virulence could increase if transmission depended even less on host mobility, which would occur if a more durable variant of *T. trichiura* was selected for. If the parasite was largely transmitted by attendants to and from immobile individuals, one would expect the virulence to rise, as it has been shown to do in microparasites (22). However, the infection dynamic of macroparasites differs from microparasites, so selection pressures act differently on the virulence of the parasites. The durable nature of *T. trichiura* eggs can lead to exposure several months after deposition of the eggs in the soil, so an increase in attendant-borne transmission may not have a very strong effect upon virulence (59). Environmental durability has been found to be associated with virulence in microparasites, a finding which has thus far been mirrored in the nematodes (151).

Ascaris lumbricoides

Distribution, Disease, & Immunity

Ascaris lumbricoides is a soil-transmitted helminth with a global distribution, life cycle, and risk factors for infection closely resembling that of *T. trichiura* (7, 58). Countries in which ascariasis is endemic are typically poor and located within the tropical and sub-tropical regions of the world (7, 10). Like several of the other intestinal helminths, infection is most common in children (7, 68, 162). Infected individuals rarely show signs of infection unless the parasite load is high, but they can show reduced appetite and malnutrition from lessened intake of protein, fat, and nutrients (7). During initial infection, individuals may experience asthma, pneumonitis, and other respiratory symptoms (7). Once in the small intestine, diarrhea, abdominal pain, nausea, vomiting, anorexia, and other abdominal symptoms may appear (7). Host mortality resulting from infection is rare, although the WHO estimates approximate worldwide mortality from *A. lumbricoides* to be 60,000 individuals annually (154, 158). Despite this, very few individuals experience a high enough level of infestation to experience morbidity or mortality (154). The virulence of *A. lumbricoides*, though low in general, is higher than both *T. trichiura* and *E. vermicularis*. Research investigating the presence of immunity in humans has found that steady exposure likely results in some immunity. In areas where persistent infection is probable, individuals have shown high antibody titers with relatively low levels of egg production, indicating that an immune response is preventing the infection from progressing in intensity (68). Whether any populations are completely immune to infection is unknown, although it is unlikely due to the relatively low selection pressures placed on infected individuals.

Life Cycle

Infection begins when second-stage larvae are ingested from contaminated hands or food (7, 68). Once inside the small intestine, the larvae hatches and penetrates the intestinal wall, eventually migrating to the liver, where it feeds and continues to develop (7). The migratory phase of the parasite is not yet complete, and the larvae continue to the heart and lungs, where they travel to the trachea and are swallowed (7). Maturation of the larvae continues in the upper small intestine, where the larvae feed on digested chime (7, 68). Sexual maturation occurs in the six weeks following arrival in the small intestine and the female worm begins to produce hundreds of thousands of eggs per day (7). The non-embryonated eggs are deposited in the feces (7). If the eggs do not immediately come into contact with soil, they can survive in the environment for two months until proper conditions for embryonation are met (7). Survival and development of *Ascaris* eggs is favored by warm temperatures (21-30°C), although there is a tradeoff for development and survival, with faster development occurring at higher temperatures but with a lower chance of survival (165). Soil must be moist, but not too moist, and oxygen-rich (165). *A. lumbricoides* eggs are famous for their durable nature, with reports of infective eggs surviving up to 15 years (166). This high durability corresponds with the relatively high virulence of *A. lumbricoides*, compared with *E. vermicularis* and *T. trichiura*. The durable nature of *A. lumbricoides* eggs allows the nematode to use sit-and-wait transmission and rely less heavily on a mobile host, thus leading to increased host exploitation.

Environmental & Behavioral Risk Factors

As a soil-transmitted helminth, *A. lumbricoides* prevalence and distribution is dependent upon environmental variables such as temperature, moisture, and soil conditions (7, 68, 167). Seasonal or altitude variations in these factors can impact infection rate in humans. In a study in Bolivia, *A. lumbricoides* infections were found to be lower in higher altitudes (161). This finding suggests that the cooler temperatures and decreased soil moisture found at higher altitudes are unsuitable for larval survival and development (161). A recent study on the fecundity of *A. lumbricoides* in different regions of the world showed that mean egg count varied geographically (168). Fewer worms were required to output the same number of eggs per gram of feces in Mexico than in Madagascar, Nigeria, and Iran (168). This could be a result of differences in diagnostic measures used to determine mean egg count or it might indicate that fecal egg count is not useful in determining infection intensity (168). Further research is needed to determine if the observed differences in mean egg count per gram of feces actually point toward physiological differences in fecundity across countries or whether the finding was just an artifact of diagnostic technique. It should also be noted that worm fecundity is dependent upon the density of worms in an infection, with higher numbers of worms leading to lower individual rates of egg production (168, 169).

Lately, many studies have focused on the implications of climate change on the distribution of infectious disease. Due to the external life cycle requirements of *A. lumbricoides*, climate-change induced alterations in temperature and moisture could have profound effects on the survival, development, and transmission of larvae. Predicted increases in temperature would serve to increase the rate of larval development but would also negatively impact larval survival (150). As drought conditions are expected to rise in

regions of Central Africa, larval survival is predicted to decrease, resulting in fewer infections in one of most endemic regions (150).

Risk factors for *A. lumbricoides* infection depend largely upon behaviors leading to exposure. Unsanitary conditions and practices facilitate the fecal-oral transmission of the parasite (10, 68). A lack of latrines, geophagia, poor hand-washing practices, and indiscriminate defecation contribute to the spread of parasitic larvae as well as exposure (10, 68). Commonly, infection intensity in a population is distributed such that one individual carries the burden of the worms, and is primarily responsible for spreading the disease (10, 154). This intensely infected individual experiences a greater level of disease symptoms, a few of which can be debilitating (7). Frequently, human behavior and environmental variables can interact to increase the exposure potential of a population. For instance, a lack of latrines at a farming work site can lead to indiscriminate defecation by workers. Rain can spread the infective larvae to other workers as well as to agricultural products (160). Political unrest or wars can lead to infrastructural breakdown involving sewage or water treatment plants and a subsequent rise in diseases transmitted through the fecal-oral route, including *A. lumbricoides* (150, 160). Research has indicated that transmission of *A. lumbricoides* mostly occurs at home (170). Transmission between homes should result in more genetic mixing and more homogeneity in regions with small distances between homes (170). Variation in *A. lumbricoides* between homes should increase as the distance between homes increases (170). This finding has implications for the evolution of the parasite. For instance, a more virulent strain could be selected for in a household under certain conditions, but the movement of that strain out of that house is dependent upon the spacing of houses.

Transmission Mode & Virulence

Like *T. trichiura*, *A. lumbricoides* is transmitted directly through a fecal-oral route. The virulence of the parasite is dependent upon how much it relies on host mobility for transmission. The extreme durability of the eggs allows *A. lumbricoides* to rely less heavily on host mobility and more on sit-and-wait transmission. This durability allows for increased exploitation of the host and a corresponding higher virulence without a reduction in transmission potential. One would expect that an increase in *A. lumbricoides* virulence would be favored in situations where host mobility is minimally needed for transmission. For example, regions with ideal conditions for larval survival and development may report higher virulence since the long duration of egg survival in the environment would increase probability of transmission to a new host. The durable and virulent qualities of *A. lumbricoides* fit with the prediction that decreased dependency on host mobility for transmission leads to increased virulence. Comparisons among *E. vermicularis*, *T. trichiura*, and *A. lumbricoides* further illustrate this with the observation that high durability is associated with high virulence.

Hookworms: *Necator americanus* & *Ancylostoma duodenale*

Distribution, Disease, & Immunity

Hookworms, along with *T. trichiura* and *A. lumbricoides*, represent the “unholy trinity” of neglected tropical diseases (10). The parasites *Necator americanus* and *Ancylostoma duodenale* infect an estimated 576-740 million people worldwide, making hookworm infection one of the most common infections of mankind (10, 60). Areas of endemicity are concentrated in poverty-stricken tropical and sub-tropical countries (10,

171, 172). Of the two species, *N. americanus* is more prevalent, although the distributions of the two overlap in regions of Africa and the Americas (9). As is common with the other soil-transmitted helminths, lightly infected individuals rarely show signs of infection, and mortality is uncommon and typically not a direct result of infection (158, 172). Approximately 65,000 deaths annually are attributable to hookworm infection (154, 158). In initial stages of infection, the host may experience itchy, irritated skin and a rash at the site of the hookworm's entry, a condition called ground itch (8, 9). More heavily infected individuals can present with pneumonitis during the hookworm's migration (9). In the small intestine, the parasites feed on the host's blood, leading to the most common sign of hookworm infection, iron-deficient anemia (9). *A. duodenale* adults have been shown to cause ten times more blood loss and higher rates of anemia than *N. americanus* and are also the larger of the two (9, 173). Anemia most affects children and pregnant women, and physical and cognitive stunting has been shown in children chronically infected (8, 10, 174, 175). Children born to anemic mothers have lower birth weights and are often born prematurely (176). Intense infections in childhood can therefore have long-reaching implications for an individual's future educational and productivity potentials (174, 175). Considering mortality and morbidity estimates and clinical aspects of disease, hookworms can be considered to have a relatively low level of virulence but one which is higher than the previously discussed fecal-borne and direct contact nematodes. Studies have not shown the existence of inherent immunity to hookworm infection, although there appears to be a predisposition to infectious load (134, 177, 178). Furthermore, some individuals appear to show resistance to re-infection (134). However, infection

prevalence and intensity appear to increase with age, bringing these findings into question (171).

Life Cycle

Hookworm infection begins not with the ingestion of embryonated eggs, as is common with the other soil-transmitted helminths, but with the penetration and invasion of host skin by third-stage larvae (9). Upon entering the host, the larvae migrate in the bloodstream, through the heart to the lungs, where they travel up the trachea and are swallowed (9). The larvae travel to the small intestine, attach to begin feeding, and reach sexual maturity after undergoing two molts. It takes approximately 6-9 weeks for sexual maturity to complete after initial infection (9). Host defecation results in the deposition of eggs in the soil. Once eggs are deposited in soil, larvae develop within 48 hours (9). Two additional molts must occur before they can become infectious (9). Infectious larvae do not feed and are less durable than both *A. lumbricoides* and *T. trichiura* but are more durable than *E. vermicularis* (179). After developing to an infective state, hookworm larvae display a unique behavior. To increase the probability of contact with a potential host, larvae travel to a high point in their environment (9). This behavior reduces their need for host mobility in transmission, making up for the lower durability of hookworms. Thus, hookworms may be more effective at sit-and-wait transmission than *T. trichiura* or *A. lumbricoides*, which could help to explain hookworms' relatively higher virulence.

Environmental & Behavioral Risk Factors

Development of larvae is dependent upon soil type, moisture, and temperature, and larvae prefer warm, moist, loamy soil, especially freely drained and gray sandy soil (9, 74, 180). The optimal temperature for development is 20-30°C, but hookworm larvae

show resistance to higher temperatures (74). Larvae are susceptible to sunlight and survival is increased in shady areas (74). Infection rates are lower at higher altitudes, possibly due to the lower oxygen content, lower temperature, or lower density of hosts (74). Adequate rainfall is necessary for larval development, and larvae will seek out moisture lower in the ground, which can reduce transmissibility during drier seasons (74). Infection rates may show a degree of seasonality, with lower infection rates occurring during unfavorable conditions (180). Climate change is predicted to result in an increase in hookworm infection where rainfall increases and temperatures rise and a decrease in regions where drought is expected to be more frequent (150, 160). During highly unfavorable times for larval development, *A. duodenale* larvae in a host have been shown to migrate into skeletal tissue until conditions improve and maturation to sexual maturity can commence (9).

Regions where hookworm infection is endemic remain in a cycle of infection due to a combination of human behaviors and infrastructural failings leading to persistent and frequent exposure to infectious larvae (10, 74). A lack of access to clean water, latrines, and healthcare is associated with hookworm infection by maintaining an unsanitary environment in which larvae can develop (10, 74). Infected individuals who do not seek treatment continually contaminate the environment and help to perpetuate the infectious cycle (74). Indiscriminate defecation and the use of human feces as fertilizer also contribute to the presence of larvae in living and working areas (10, 146). Occupational exposure is common particularly for those individuals employed in agriculture or other fields that involve working outside (72). As is common with other soil-transmitted helminths, crowded conditions, common in poverty-stricken regions, represent a

significant risk factor for infection (32, 74). However, unlike the other members of the “unholy trinity”, hookworm transmission is not favored by increased urbanization due to the stricter environmental conditions required for larval development and the differing form of transmission (164, 181).

Differences Between *N. americanus* & *A. duodenale*

It is important to note the physiological and transmission differences between *N. americanus* and *A. duodenale* when considering factors relating to the virulence of these parasites. *A. duodenale* is the larger of the two and consumes more blood, causing more anemia than *N. americanus* (9). In addition, *A. duodenale* produces nearly three times more eggs than *N. americanus*, which could be directly associated with the observed increase in blood loss experienced by individuals infected with *A. duodenale* (9). While *N. americanus* can only be transmitted through penetration of host skin, *A. duodenale* has been found to employ other modes of transmission, including ingestion of larvae (74). Vertical transmission of *A. duodenale* has been suggested due to the high rate of neonatal infection in endemic regions, but evidence of larvae in the milk of nursing mothers has not been found (182). If vertical transmission of *A. duodenale* can occur, virulence would be expected to decrease as this method of transmission increased. Vertical transmission does not favor high virulence, as an increase in virulence would result in fewer potential hosts (22). Therefore, the variety of transmission routes possibly employed by *A. duodenale* would not allow increased transmission from a sick host relative to *N. americanus*. Research evaluating differences in larval durability between the two hookworm species could help to explain their differing virulence.

As previously mentioned, *A. duodenale* larvae in a host display a unique behavior if environmental conditions are unsuitable for larval development; they invade host skeletal tissue and lie dormant until conditions improve (9). The lifespan of *A. duodenale* is shorter on average than *N. americanus* at 1-2 years compared to 3-5 years, respectively (9). The differing disease intensities indicate different virulence levels between the two hookworm species, with higher virulence in *A. duodenale* than in *N. americanus*. Unfortunately, studies investigating environmental durability of each species are lacking, so the observed virulence differences have yet to be explained fully. It appears that egg production in these species is related to virulence, with increased host exploitation associated with increased fecundity (9). However, the shorter life span of the more virulent *A. duodenale* suggests that increased fecundity comes at a cost to adult worm survival within the host (9).

Transmission Mode & Virulence

In regions with high seasonal variation in rainfall and temperature, one might expect to observe more cases of *A. duodenale* infection due to the ability of the parasite to lay dormant within a host during unfavorable conditions. However, the long-lived quality of *N. americanus* within a host could overshadow any potential increase in the other parasite (9). In addition to environmental conditions, examining the role of human behavior in transmission of the two hookworm species might help to predict which species is more predominant in a population. Regions with poor hand-washing practices might see an increase in *A. duodenale* infections due to the oral transmission capability of this species. Unfortunately, studies reporting observable differences in the distributions of

these parasites are very rare due to the difficulty in distinguishing one species from the other (173).

Neither hookworm species is very reliant upon host mobility for transmission and can thus be transmitted from a sick host. Although hookworms are less durable than *A. lumbricoides* and *T. trichiura*, their ability to move to increase potential exposure to a host requires even less dependence upon host mobility. This may explain why hookworms, though less durable in the environment, are more virulent than *A. lumbricoides* and *T. trichiura*. The intermediate durability and migrating ability of hookworm larvae allows hookworms to use sit-and-wait transmission and increase host exploitation without reducing transmission potential.

Strongyloides stercoralis

Distribution, Disease, & Immunity

The threadworm *Strongyloides stercoralis* is responsible for 30-100 million infections worldwide, mostly occurring in the tropical and sub-tropical regions of the world where the climate is warm and humid (75). However, infection can also occur in temperate zones with poor sanitation such as parts of the USA, Europe, and Japan (75). Regions of Appalachia still experience relatively high levels of infection, with some counties in Kentucky reporting prevalence rates as high as 4% (76, 125). Infected individuals don't often show signs of infection, but during the migratory stage they may experience pneumonitis and larva curans (76, 125). Chronic infection can result in cutaneous, gastrointestinal, or pulmonary symptoms including diarrhea, abdominal discomfort, nausea, anorexia, and abdominal bloating (125). Hyperinfection, which is

common in immunocompromised individuals and dissemination is associated with disruption of mucosal patterns, septicemia, pneumonia, meningitis, and disseminated bacterial or fungal infection (125, 183). These bacterial infections are often the cause of mortality in hyperinfections (125). Overall, mortality from *S. stercoralis* infection is low, but the mortality rate for infected people requiring hospitalization is 16.7%, and the mortality rate for hyperinfected individuals can be as high as 87% (125, 184). The virulence level of *S. stercoralis* can be considered to be low to moderate due to morbidity and mortality qualities of infection. Although the human immune system does respond to infection with the parasite, complete protective immunity does not appear to exist (185-187).

Life Cycle

S. stercoralis can exist as either a parasitic worm or as a free-living worm (76, 188). Infection occurs when the third-stage parasitic larva comes into contact with a suitable host and penetrates the skin (76, 188). Upon entering the skin, the larva migrates through the bloodstream to the lungs where it moves to the trachea and is swallowed (76). The larvae mature in the small intestine (76, 188). Since there is no male parasitic worm, the female reproduces by parthenogenesis (76). The eggs produced hatch and proceed to the colon, where they undergo a second molt and either are deposited in feces or mature to third-form larvae, burrow into the mucosa and enter the circulation (76, 188). This is called autoinfection and can lead to chronic infection persisting long after a person has left an area of endemicity (76, 77, 188). The longest recorded infection lasted 65 years and was a result of autoinfection (77). Free-living stage worms mature to adult parasites after four molts if conditions are appropriate (76). Larvae require warm, moist, sandy, or

loamy soil in order for development to continue (76). The third-stage larvae can remain in soil for three days until glycogen stores have been exhausted (76). *S. stercoralis* larvae are able to move freely through aquatic environments which increases exposure to possible hosts (76). This quality of *S. stercoralis* larvae makes up for their relatively low durability and should be considered in discussions of virulence.

Environmental & Behavioral Risk Factors

Not much recent research has focused on investigating how climatic change regionally or globally might impact the distribution of *S. stercoralis*. However, using information about conditions for larval survival, larval response to changing weather patterns can be predicted. The warmer temperatures of global warming would serve to broaden the potential range of infection, and areas where rainfall is predicted to rise would likely experience more *S. stercoralis* infection (76, 150). Due to the unique ability of *S. stercoralis* to increase parasite load within one host (autoinfection) and cause chronic infection, environmental factors play less of a role in the geographic distribution of infection prevalence (76). However, these conditions do impact the ability of an infected individual in a non-endemic area to transmit the infection to others.

Similar to the other soil-transmitted helminth infections, *S. stercoralis* infection is highest in regions with poor sanitation (75). Lack of access to medical care and a lack of indoor plumbing facilitate the spread and transmission of the parasite (189). Crowded conditions appear to be associated with infection, and high infection rates have been reported in institutionalized patients (189). Hyperinfection is most likely to occur in individuals who use corticosteroids or immunosuppressive medication, have recently had an organ transplant, and in those infected with HTLV-1 (190, 191).

Transmission Mode & Virulence

Unlike the other human parasitic nematodes, parasite load in *S. stercoralis* infections can increase without continued exposure to infective larvae of *S. stercoralis* (76). In this way, *S. stercoralis* behaves more like a microparasite than a macroparasite. An increase in disease intensity is associated with an increase in parasite load, and death in the host usually results from disseminated hyperinfection (75, 125). *S. stercoralis* is somewhat dependent upon host mobility but also has a free-living stage that is fairly durable (76, 188). These factors can explain in part the low-to-moderate virulence of the parasite. The virulence of *S. stercoralis* could hypothetically increase if transmission was facilitated by an attendant, such as in an institution or a hospital with poor sanitation. However, research on such a phenomenon is lacking.

Nematodes Transmitted Through Consumption of Contaminated Meat

Parasites transmitted through consumption of contaminated meat can show variable amounts of virulence depending on the situation surrounding transmission. In some ways, the virulence of these pathogens or parasites resembles that of water-borne or predator-borne pathogens, but a thorough investigation of parasite life history should be made before characterizing virulence patterns of these parasites (22). *Trichinella spiralis* a nematode that transmitted through predation, cannibalism, and scavenging (118). This quality of *T. spiralis* should be considered in predictions of *T. spiralis* virulence.

Trichinella spiralis

Distribution, Disease, & Immunity

Although *T. spiralis* infection rates have declined over the past decades, the parasite still poses a great threat to regions with poor food quality control (11, 84). Estimating prevalence is difficult because the infection is not reportable in many countries, although reports indicate a global distribution (11, 126). Typically, everyone who is infected with *T. spiralis* displays some symptoms, the severity of which depends upon the degree of infection (11). In one study, the proportion of infected cases that reported symptoms was 99% (88). Symptoms change over time and are often non-specific, making diagnosis difficult (11, 12). Initially, the infected individual experiences gastroenteritis with diarrhea, abdominal pain, and vomiting, followed by enteritis (11, 12). A week after infection and several weeks beyond, the infected individual will experience fever, myalgia, bilateral periorbital edema, muscle tenderness, and circulating eosinophilia (11, 12). When the larvae invade muscle tissue, other symptoms can result, including myocarditis and neurological symptoms (11, 12). Mortality resulting from infection is fairly uncommon though high relative to other nematode infections, with case-fatality rates ranging from 0.2-2% (84, 192). Fatal trichinellosis is usually caused by cardiac, pulmonary, or neurological complications, especially myocarditis (193, 194). The relatively high mortality rate of *T. spiralis* classifies it as having high virulence for the purposes of this thesis. Infected humans are able to mount an immune response against larval *Trichinella*, but complete protective immunity in humans is not known (195).

Life Cycle

Infection with *T. spiralis* is initiated when raw or undercooked meat containing the Nurse cell-larvae complex is consumed by an appropriate host (11, 196). The larvae

are released from the tissue and travel to the small intestine, where they embed themselves (11, 196). The larvae embed within a row of columnar epithelial cells, which makes them intra-multi-cellular organisms (11, 196). The larvae then undergo four molts until maturity is reached (11). *T. spiralis* produces live offspring rather than eggs, and production continues until the host displays immunity (11). Newborn larvae disperse into the circulatory system and embed in various tissues and cells, seemingly randomly, using environmental cues not yet determined (11). If larvae enter skeletal muscle cells, they induce changes in the host tissue which support the growth of larval development, called Nurse cell formation (11). The Nurse cell-parasite complex can live indefinitely within the host (but usually results in calcification), and infection must be continued by the death of the host and consumption of the host tissue by another suitable host (11). The Nurse cell-larva complex can survive in extremely decayed host tissue for several months and is thus transmitted effectively through both carnivory and scavenging (197).

Environmental & Behavioral Risk Factors

The largest risk factor for trichinellosis is consumption of raw or under-cooked pork (83, 196). In a study conducted in China, 94% of trichinellosis cases could be traced to this source (84). Infection is perpetuated in pork, the major reservoir of *T. spiralis*, through farming practices such as feeding pigs infected pork and rodent carcasses and garbage (84). Several countries including France and Italy have experienced *T. spiralis* outbreaks following consumption of infected horse meat (197, 198). The horses responsible for transmission were thought to become infected by consumption of infected meat scraps (197). Socioeconomic status does not appear to be directly associated with infection. Both developed and poor countries experience infection (83). Recently in the

US, there has been a shift in the source of trichinellosis outbreaks, with infection coming more often from raw or undercooked game meat rather than from commercial sources (11). Although there does not appear to be a difference in infection rates between the sexes, trichinellosis occurs more often in adult populations, likely due to cultural differences in eating styles (85).

Transmission Mode & Virulence

Since *T. spiralis* in humans results in a dead-end infection in present times, humans do not play a direct role in altering the virulence of the parasite (11). In order for the parasite to be transmitted, consumption of infected flesh must occur (11). Humans are most commonly infected by the consumption of undercooked pork or game meat containing infective cysts (11, 84). Domestic swine or wild animals harboring the parasite are infected by the same route: ingestion of infected tissue (199). Humans facilitate the transmission of the parasite to domestic swine by feeding them infected pig and rodent carcasses (84). This can favor higher parasite virulence because parasites that develop more cysts within a host will be more likely to kill their host and thus more successful in being transmitted. Hypothetically, humans could also promote reduced virulence in domestic swine by isolating infective carcasses and preventing other pigs to feed on them, thus preventing the transmission of infective cysts. An increased virulence will also be favored by high rates of cannibalism or scavenging in host species, both wild and domestic (200, 201). Parasite influence on host behavior can effect the early death of the host by making it more easily caught (18, 202). *T. spiralis* could have a similar influence on wild hosts, thus facilitating transmission of the parasite.

T. spiralis infects an extremely wide range of host species (11). Transmission of the parasite through scavenging and carnivory is likely responsible for this low host-specificity. In this way, *T. spiralis* is similar to *Toxoplasma gondii*, a protozoan transmitted by a wide variety of animals through predator-prey interactions (198, 203). *Toxoplasma gondii* infection results in low virulence in predator species and high virulence in prey, which enables the transmission of the parasite from a sick host (203). Although *T. spiralis* can be transmitted by predation, different virulence levels are not observed among host species. *T. spiralis*'s virulence pattern cannot be considered to result from predator-prey interactions due to the parasite's ability to be transmitted through scavenging as well as predation and cannibalism (11). This method of transmission would favor increased exploitation of the host, as the infectious cycle can only be continued following host death. The Nurse cell-larva's extended survival in decomposing tissue also allows for increased host exploitation. This combination of transmission characteristics predicts a relatively high level of virulence, a prediction which is confirmed by case fatality estimates.

Vector-Borne Nematodes

Parasites affecting humans that are solely transmitted by vectors are predicted to be highly virulent because they do not depend on the mobility of their human hosts for transmission (18, 22). This pattern has been observed in many vector-borne pathogens (22). The life cycle and virulence patterns of the vector-borne nematodes, *Wuchereria bancrofti* & *Brugia malayi* (lymphatic filariae), *Onchocerca volvulus*, and *Loa loa* are discussed in the following section.

Lymphatic Filariae: *Wuchereria bancrofti* & *Brugia malayi*

Distribution, Disease, & Immunity

The filarial parasites *Wuchereria bancrofti* and *Brugia malayi* are endemic in regions where the environment and climate are suitable for the survival of their disease vectors (13). *W. bancrofti* causes 90% of lymphatic filariasis cases worldwide, whereas *B. malayi* is responsible for only 10% (204). *B. malayi* cases are most common in regions of SE Asia (13). Generally, countries located in tropical and sub-tropical regions of the world are suitable for the survival and transmission of the disease, with 40% of cases occurring in sub-Saharan Africa (10). The parasites cause a condition in humans known as lymphatic filariasis. The majority of people who are infected with *W. bancrofti* or *B. malayi* display no symptoms, even though they have apparent circulating microfilariae (13). Acute lymphadenitis results when the adult worm dies, eliciting an inflammatory response (13). Acute lymphadenitis is accompanied by fevers and swellings around lymph nodes (13, 205). Of the individuals who experience acute lymphadenitis, some will develop elephantiasis, which includes lymphedema of arms, breasts, and genitalia (13, 205). The tissue involved in the swelling becomes pitted and firm, ultimately with the loss of elasticity of the top layer of skin (13). Much of the symptomology associated with lymphatic filariasis is directly caused by the host immune response and is not directly elicited by the parasite (13). Disease resulting from infection can be debilitating to those infected and can significantly impact productivity (90). In addition, the obvious presence of lymphedema in those infected is associated with significant social stigma (206). Infected individuals are often shunned by friends, family, and potential employers

and often do not marry (206). Using mortality, morbidity, and clinical disease data, virulence is considered moderate.

Though many studies have investigated immunity to lymphatic filariae in humans, the nature of immunity is not known. Women of childbearing age appear to show an increased resistance to lymphatic filariasis and show higher antibody positivity to adult worms (207). The subject of acquired immunity in humans is controversial, but studies have reported herd immunity in endemic populations, with herd immunity appearing earlier and at a higher level in areas with a high biting frequency (208). Individual acquired immunity may not be long-lasting, however (208). Another study has indicated that acquired immunity may only be attained in populations where transmission is moderate to high (209). Infection intensity has been shown to be different in areas of low transmission as compared to those of high transmission (209). In areas with high transmission, infection intensity decreases with age while in low transmission areas, infection intensity increases with age (209).

Life Cycle

Both *W. bancrofti* and *B. malayi* are transmitted to humans through the bite of a mosquito (13). Several species of mosquitoes are capable of transmission, including *Culex pipiens sp.*, *Anopheles gamibae*, *Anopheles polynesiensis*, and *Aedes aegypti* (13). The ability of these mosquitoes to effectively transmit the parasite is variable, which could play a role in regional disease distribution (210). Infection begins when an infected mosquito bites an appropriate host, and infective larvae located in the mouthparts of the mosquito crawl into the open wound (13). Once in the body, the larvae migrate through the subcutaneous tissue to the lymphatic system, where they mature into adults after one

year (13). The most common sites of infection are in the lymphatics of the extremities and in the male genitalia (13). Mating follows maturation, and the newly born microfilariae migrate to the bloodstream from the lymphatic system, although they are present in peripheral blood only during the night (13). The microfilariae are present in the lungs during the day when the host is more active (13). In order for the infectious cycle to continue, the microfilariae must be transmitted to a mosquito before 1.5 years, the lifespan of the microfilariae (13). A mosquito becomes infected when it takes a bloodmeal from an infected host. Once ingested, the microfilariae penetrate the stomach wall and migrate to the insect's thoracic flight muscles (13). The microfilariae develop into third-stage larvae after three molts and become infective after 10-20 days in muscle tissue (13). Infective larvae move to the mouthparts of the mosquito, from which they are deposited onto the skin of the host during a bite (13).

Environmental & Behavioral Risk Factors

The environmental requirements for *W. bancrofti* and *B. malayi* are dependent upon those of the disease vectors. A study using GIS to model infection distribution found that the temperatures at which infection is common lie within the range of 22-30°C (147). At temperatures below 22°C, the microfilariae are unable to penetrate the mosquito gut, and at temperatures higher than 30°C, the microfilariae experience higher mortality (147). Places with higher rainfall also experience higher infection rates due to the potential for mosquito breeding sites (147). Both urban and rural environments are suitable for the mosquito vectors of lymphatic filariasis, and urbanization has resulted in an increase of urban vectors (13, 147, 211). The predominant mosquito species are different in each area, which can alter disease distribution if transmission potential of

each species is different (147). *Culex* mosquitoes are the more prevalent vector in urban and semi-urban areas, while *Anopheles* mosquitoes are more prevalent in rural areas of Africa, and *Aedes* mosquitoes act as primary vector in some Pacific Islands (13).

Transmission Mode & Virulence

Human behavior does not play as large a role in transmission of lymphatic filariasis as in other non-vector borne diseases. Rather, infrastructural factors relating to mosquito exposure and prevalence are more responsible for disease transmission (147). Endemic regions are generally poorer and have low quality sewage and water treatment facilities, which would provide ample mosquito breeding grounds (147). In addition, houses in these regions rarely have screened windows, so transmission can occur both inside and outside the home (147). The microfilariae of these parasites circulate in the peripheral blood at night but remains confined to the lungs during the day (13, 212). This feature of the parasite is likely an adaptation to the biting habits of the mosquito disease vectors (212). Therefore, human behaviors that expose them to night-biting mosquitoes will increase the potential for transmission of the microfilariae.

The virulence pattern of vector-borne pathogens has been well studied (18). These pathogens tend to result in higher host mortality rates (18). This is because these pathogens do not depend on host mobility for transmission so they are able to increase host exploitation without experiencing a loss in transmission potential (18). Using this logic, one would expect that vector-borne parasites would display a similar degree of virulence. If this was the case, regions where host behavior, infrastructure, and environmental conditions allowed for frequent and year-round exposure to mosquitoes would favor more virulent strains of *W. bancrofti* and *B. malayi*. Reduced virulence could

occur as a result of alterations in transmission patterns. For instance, ecological variation in vector distribution and habitat could result in different levels of virulence. Mosquito species in regions with moderate seasonal variation may experience a periodic die-off, which would limit exposure to hosts and favor host survival. Infections in these regions may display low virulence in relation to more seasonally stable areas. In addition, vector species distribution could affect virulence patterns if some species are more effective at transmission than others. If individuals in endemic regions improved sanitation measures, reduced standing water, and applied screens to doors and windows, overall exposure to mosquitoes would decrease, as would the virulence of the parasite. These changes would favor the survival of longer-lived, less virulent parasites. The virulence of lymphatic filariae fits with the model of vector-borne microparasitic virulence, in which increased virulence is favored by vector-borne transmission.

Onchocerca volvulus

Distribution, Disease, & Immunity

The nematode *Onchocerca volvulus* is responsible for a condition known as river blindness, which mainly affects people in tropical and sub-tropical regions of the world (14, 213). Like the other vector-borne parasites, disease distribution follows vector distribution, and poor countries in sub-Saharan Africa and Latin and South America are most commonly afflicted (14). The species of black fly that plays host to the parasite is *Simulium spp.* (14). The disease displays a highly focal distribution due to its vector-borne nature (14, 214). *O. volvulus* is responsible for a wide spectrum of disease. Infection with *O. volvulus* typically results in two general types of symptoms clusters,

those affecting the skin and those affecting the eyes (14, 15). In general, forest-dwelling black flies transmit a strain of *O. volvulus* that causes onchodermatitis, and savannah-dwelling black flies transmit the blinding form of the parasite (15). The two forms of disease are caused by two genetically distinct strains of *O. volvulus* located in geographically distinct regions (215).

The dermatitis form of infection is characterized by intense itching, sometimes severe enough to result in suicide (14). Affected regions of skin show a rash with small elevations, and the skin loses elasticity and atrophies (14). Skin depigmentation can occur, which makes the infection visibly apparent and can contribute to the disease's stigma (14). The most debilitating result of infection is blindness, which results from host response to microfilariae and occurs most commonly in those 30-40 years of age (14). In highly endemic regions, up to a third of individuals may experience blindness resulting from infection, which can have a severely negative effect on the productivity of a population (216). The degree with which the host responds to dead and dying worms and microfilariae is directly associated with the intensity of pathogenesis (14). Although infection rarely results in death, it is estimated that 5% of deaths in highly endemic regions are attributable to the effects of onchocerciasis (217). In addition, it causes severe disability that can greatly affect an individual's reproductive potential (218). The virulence level of *O. volvulus* can be considered moderate to high. Immunity in humans has been observed, with a small number of individuals in an endemic zone remaining infection-free (133). Studies have indicated that the absence of infection in some individuals is not a reflection of differing host attractiveness to the parasite vector (219).

The source of immunity is unclear, whether it is through antenatal exposure, exposure to cattle onchocerciasis, or genetic variation in the histocompatibility complex (133).

Life Cycle

Infection begins when immature larvae are deposited onto the skin after the fly bites a susceptible host (14). The larvae enter the body through the bite wound and migrate to subcutaneous tissue, where they continue development until they are able to mate (14). The length of time from deposition to final development is typically one year (10). This might have to do with seasonal variation in environmental suitability for mosquito breeding. The development of the larvae is accompanied by the growth of fibrous nodules and an angiogenic response, which is thought to provide nutrients as well as the means to dispose of waste (14). Nodules are commonly located near bony prominences, such as the hip (10). Location of the nodules differs between Africa and Central American infections, with nodules on the upper part of the body appearing more frequently in Central America as opposed to Africa, where they are found on the lower part of the body (14). This is likely due to differences in biting habits caused by clothing styles in each region or in variation in biting location preference by resident mosquitoes (14). It is in the subcutaneous tissue where the female worms begin producing microfilariae (14). The microfilariae migrate out of the nodules to other parts of the body (14). The microfilariae are typically found in skin and the lymphatics but can also travel to the peripheral blood, urine, and sputum (10).

The infectious cycle continues when a black fly takes a bloodmeal containing microfilariae (14). Development of the larvae continues in the hemocele and flight muscles in the thorax of the fly (14). Following 6-8 days of additional development and

two molts, the larvae migrate from the muscles to the proboscis of the fly, from which they are deposited onto the skin of a host during a blood meal (14).

Environmental & Behavioral Risk Factors

There are two general groups of vectors: forest-dwelling and savannah-dwelling, and disease symptoms and outcomes differ between the two groups (15). Deforestation has an impact on the distribution of the vectors, with savannah-dwelling vectors being found in previously forested regions (15). The rainy season in some regions has been shown to be associated with an increase in the adult fly population due to the increase in available food (15). Humidity is also found to be associated with an increase in fly density and can lead to a higher biting rate (15). Breeding sites of the black fly vector are fast-moving mountainous streams in tropical and sub-tropical regions of Africa and South and Central America (14). Climate change involving rising temperatures is predicted to increase the transmission potential of the disease due to an increase in the disease vector populations (149). Urbanization may not have as large of an effect on the disease since black flies only breed near fast-moving mountainous streams, so vector presence within a city is likely to be low (14).

As *O. volvulus* is transmitted through the bite of a black fly, risk factors associated with onchocerciasis are those that increase exposure to the disease vector (14, 15, 94). Those that live within the habit range of the disease vector are most at risk for infection (14, 15, 94). Studies have shown that the highest rates of infection occur in adults aged 20-39 who are employed in farming occupations (94). This occupation increases the level of exposure to the vector, which is found to bite more frequently in open farmland rather than near rivers (94). However, black flies breed in fast-moving

mountainous streams, which are popular sites for human settlement (216). The high rates of blindness endured by these populations can prompt a migration away from rivers (216). This movement often means that the population must try to subsist off of poorer quality farmland, lowering the overall health and nutritional status of these individuals (216).

Transmission Mode & Virulence

As a vector-borne parasite, *O. volvulus* does not need to rely on host mobility for transmission, so virulence is predicted to be high. Virulence of *O. volvulus* can be considered to be moderate to high due to the significant morbidity and mortality commonly resulting from infection (14). However, the two strains of the parasite cause a difference in disease severity depending on the ecological origin of the fly (15). The forest-dwelling black flies transmit the strain of parasite that causes onchodermatitis, a skin affliction which is less devastating than the blinding form transmitted by savannah-dwelling black flies (15). The difference in virulence between these two ecological regions may be a reflection of vector and human behavioral differences. Bite frequency is highest in open farmland and lowest in shaded, forested regions (94). The low vector-human contact in forested regions may be due to the presence of other primates available to bite or poor detection of human hosts. The relatively low virulence of the non-blinding strain may be due to this decreased probability of host contact, which would disfavor increased host exploitation.

The blindness caused by the parasite can significantly affect both an individual and a population. Blindness most commonly occurs in those in their working prime, aged 30-40, and greatly affects the health and productivity of an infected individual (14).

Transmission of *O. volvulus* does not depend on host mobility because the black fly is able to transfer infective microfilariae from one host to another without the host moving (14). Therefore, this mode of transmission would favor increased exploitation of the host without lowering transmission potential. An increase in virulence would be favored by extremely accessible human hosts, from the point of view of the fly. Populations that settle near streams or deforested regions, have no screens on their doors or windows, go outside at night frequently, and work outside are more likely to come into contact with the black fly vector and thus favor an increase in virulence. Reduced virulence would be favored by the reversal of these conditions. It appears that the virulence pattern of *O. volvulus* fits with microparasitic models of virulence.

Loa loa

Distribution, Disease, & Immunity

The filarial nematode *Loa loa* affects 13 million people in tropical and subtropical countries in Central and West Africa (97, 98, 220, 221). Loiasis generally results in low morbidity but is reported to be the third highest reason for hospital visits in regions of hyperendemicity (220). Most of the signs and symptoms of infection are a result of the host's allergic inflammatory response to the presence of worms and microfilariae in the body (97). Some individuals do not exhibit overt clinical signs of infection, instead displaying a slightly decreased allergic response; measured microfilariae response in these individuals is typically high (97). Calabar swellings are a recognizable sign of loiasis and appear on the face or head region and the extremities in response to the presence of adult worms (97). These swellings are usually accompanied by itching and

irritation (97). Periodically, adult worms can migrate across the eye of an infected individual, which can be a startling but obvious indicator of infection (97). More serious complications can result from migrating adult worms (97). Those living in endemic regions are largely asymptomatic, despite having high levels of microfilariae in the bloodstream while those briefly exposed show more reactive allergic responses to the infection (97). The majority of people experience at least some level of symptoms, usually itchiness and swellings (222). The virulence level of *L. loa* can be considered to be low to moderate compared to the other vector-borne nematodes, as it does not cause significant disability in hosts.

Humans appear to show a level of immunity to loiasis, particularly those in endemic areas (97). The number of microfilariae produced per adult worm decreases after a certain amount of time, likely in response to an increased immunological response by the host (223). However, this decrease is compensated for by an increase in adult worm population, leaving the total microfilarial circulating rate somewhat stable (223). This suggests that there is an adaptive immune response in those chronically infected (223). Additionally, the difference in symptom intensity and allergic response strength in those that live in endemic areas compared to those that are only periodically exposed also suggests a protective immunity present in endemic individuals (97). Some individuals are known to have at least one adult worm yet show no circulating microfilaremia, a condition known as occult filariasis (224). There is also some evidence to suggest that genetic factors play a role in the susceptibility or resistance to *L. loa* infections (225).

Life Cycle

The bite of an infected *Chrysops sp.* mango fly is the initial step in infection with *L. loa* (97). The infective third-stage larvae are released from the mouth of the fly into the bite (97). The larvae migrate to sub-cutaneous tissue, where they mature in 1-4 years and produce calabar swellings (97). The worms mate while in the subcutaneous tissue and release sheathed microfilariae (97). The microfilariae can be widely dispersed in the body and have been found in blood, spinal fluid, urine, sputum, and lungs (99). The microfilariae exhibit a behavior known as diurnal periodicity, in which they circulate in the bloodstream at different times of day corresponding to the feeding habits of the vector (97). The infectious cycle continues when a mango fly, *Chrysops sp.*, feeds on an infected individual, ingesting blood containing sheathed microfilariae (97). Once inside the fly, the microfilariae lose their sheaths and penetrate the fly's midgut (99). The larvae then enter the thoracic muscles, where they mature to third-stage larvae (99). These infective larvae migrate to the mouthparts of the fly, from which they are released into the bite wound (97).

Environmental & Behavioral Risk Factors

The environmental settings required for the survival, development, and transmission of the parasite are dictated by the vector. The flies responsible for carrying the parasite live and breed in moist shaded areas, such as in the canopy of the rain forest, near streams, or in rotting wood (99, 220). The flies feed during the day, which corresponds to the period in which microfilariae are present in the peripheral blood (97, 220). The flies are particularly attracted to the smell of wood smoke and the presence of carbon dioxide, and infection rates have been found to be higher near rubber plantations and in those employed at rubber plantations (100). The survival and development of both

vector and parasitic larvae is favored by higher temperatures, and transmission may not occur if the temperature is too low (226). Climate change resulting in increased global temperatures would favor the development and transmission of the parasite and would likely result in higher rates of infection (227). In addition, increased rainfall in certain areas would favor the development of the vector (99, 220). However, the effects of climate change on the distribution of the disease are likely to be counteracted by urbanization. Deforestation, an activity frequently associated with human expansion into unsettled lands, would result in a loss of vector habitat and thus a decrease in infection rates (228).

Transmission Mode & Virulence

As a vector-borne parasite, *Loa loa* is predicted to have relatively high virulence since it does not depend on host mobility for transmission. However, infections with *Loa loa* are generally not severe and rarely result in death (97). It is important to explore why this parasite is not in complete agreement with principles of microparasitic virulence. Differences in vector ecology and behavior may contribute. The mango fly disease vector occupies high canopies of warm and moist forests and generally feeds on hosts that also live at that height (99, 220). Thus, humans are infrequently exposed to the vector, and *Loa loa* virulence is kept low, as it is not in the interest of the parasite to exploit the host highly. Rubber plantations have lower canopies than the traditional forest habitats of the vectors, and the flies are more likely to detect and feed on humans rather than other higher-dwelling primates (128). A rise in rubber plantations has led to an increase in biting frequency and infection in workers and villagers living near the plantations (97, 100). In such areas where human exposure to the disease vector is high and consistent,

Loa loa virulence would be expected to rise. Although *Loa loa* does not directly match the predicted pattern of virulence, its deviation can be explained in part due to these differences in vector habitat and exposure to humans.

Water-borne Nematodes

The virulence of pathogens transmitted by ingesting contaminated water is dependent on many factors. Foremost among them is the degree to which the pathogen can rely on unclean water to facilitate transmission (22). In regions with poor water sanitation, the more virulent strain of a pathogen has been found to dominate, while in areas with cleaner water, the less virulent strain is more common (22). Predicting the virulence level of water-borne nematodes is more difficult due to the longer reproductive time and more complex life cycle of the parasites. The transmission dynamics and life history traits of the water-transmitted nematode *Dracunculus medinensis* are discussed in the following section.

Dracunculus medinensis

Distribution, Disease, & Immunity

One of the most infamous nematodes affecting humans is *Dracunculus medinensis*, also called guinea worm. Historically, infection rates were extremely high, but thanks to the global eradication program, fewer than 2,000 cases of guinea worm remain today, with cases appearing mainly in Ethiopia, Mali, and Southern Sudan (10, 109). Human guinea worm infection results in great pain and discomfort for nearly all infected, so the morbidity of those infected is high (16). The infection is rarely fatal, but

some individuals may die from septicemia resulting from secondary bacterial infections (16, 229). It is estimated that approximately 1% of guinea worm cases result in death (16). During the year that the worm matures in the human host, the host displays no outward signs or symptoms of infection (16). The first sign of infection is the blisters and ulcers that appear on the lower extremities (16). Prior to the blister rupturing or during removal of the worm, the host may exhibit an allergic reaction (16). Death of the worm while still in the host results in calcification which can cause joint problems (16). It is estimated that half of all infected individuals experience symptoms so painful and uncomfortable that they are effectively disabled for a span ranging 5-13 weeks (16, 17). The virulence of *D. medinensis* is considered to be moderate to high due to the disabling and infrequently fatal outcomes of the disease. There is little to no evidence of immunity to guinea worms in humans, and re-infections are common (16).

Life Cycle

Infection begins when a human host consumes water contaminated with *D. medinensis*-infected *Cyclops*, *Mesocyclops*, or *Thermocyclops* copepods (16). The copepod hosts are digested in the small intestine of the human and the third-stage larvae are released (16, 230). The larvae penetrate the walls of the small intestine and migrate through the connective tissue, undergoing an additional two molts until they reach maturity (16, 230). After mating, females move through subcutaneous tissue until they reach the extremities (230). There, the females induce an ulcerated and painful papule (16). To ease the pain of the blister, the host often will place the affected region in water, which causes the papule to rupture, releasing larvae (16, 230). The released larvae are ingested by the copepod secondary host, in which they penetrate the hemocele and

mature to third-stage infective larvae (16). The maturation process in the copepod takes approximately 2-3 weeks while the maturation in the human host takes approximately one year (16). The timespan of development is thought to be an adaptive feature of the parasite. It takes one year from initial infection to emergence, which ensures that environmental conditions are fit for the survival and further transmission of the parasite (17).

Environmental & Behavioral Risk Factors

The survival and development of the parasite and its secondary host are dependent upon temperature and rainfall affecting the habitat of the copepod (231). The copepod thrives in stagnant ponds and other sources of non-running water (129, 231). Chance of infection is greatly influenced by the amount of water in the pond, which is influenced by rainfall (231). Shallow ponds increase exposure because of the higher density of infected secondary hosts (231). This is reflected in the infection's seasonality, with infection rates peaking during the dry months when more contaminated water is consumed (231). Infection rates are also influenced by geology (231). Ponds with more permeable rock will house a greater density of infected secondary hosts (231). Climate change is not likely to play a large role in the distribution of guinea worm due to the intense eradication effort that is intended to stop guinea worm transmission by the end of 2012 (109). Urbanization, with its associated increases in standing pools of water and increased population density, probably played a role in the spread of *D. medinensis* and continues to disrupt the eradication effort (116). Nomadic bands are found to have fairly high rates of infection, and interaction between these populations with poor urban areas can expose a previously parasite-free zone (116).

Population movement is an example of how large-scale human behavior can play a role in the distribution of *D. medinensis*. Individual behaviors can also impact the risk of transmission. A lack of education in water sanitation practices, such as not filtering water, increases exposure to the infective agent (130). The use of filters should lower risk of infection, but filters are usually used only in the home, so individuals who drink from contaminated sources outside of the home are at risk (130). This can explain why farming as an occupation is associated with increased infection rates (130). Beliefs and practices common in endemic regions may also increase risk of infection or prolong symptoms (129). Many individuals do not filter water after it rains and believe that infection is not a state of disease but a natural part of the body (129).

Transmission Mode & Virulence

The virulence of water-borne pathogens is predicted to increase as water transmission increases (22). This is because waterborne transmission does not depend on host mobility, so increased pathogen reproduction would be favored at the expense of host health (22). The most highly virulent strains are expected to be predominant in regions where water transmission is high, particularly in areas with little to no access to clean water (22). Guinea worm is found only in regions with poor water sanitation (130). The moderate level of virulence associated with guinea worm infection can be explained in part by its transmission via contaminated water. With this mode of transmission, *D. medinensis* does not have to rely heavily on host mobility for transmission. Potentially, one individual could contaminate a water source that could lead to high infection rates in those who use the water.

Guinea worm virulence would be expected to increase as water sanitation decreased, following from principles of microparasitic virulence. However, dynamics of microparasitic virulence evolution may not apply as directly to macroparasites. In microparasites transmitted by water, virulence is expected to rise as the potential for water transmission increases and dependence on host mobility for transmission decreases (22). However, increased water-borne transmission of guinea worm does not necessarily result in lessened reliance on host mobility for transmission. The infected host completes the infectious cycle by immersing a parasite-caused blister, which releases millions of larvae into a water source (16). Therefore, *D. medinensis* depends upon host mobility for transmission, which limits the virulence of the parasite. Increased exploitation of the host would result in lessened transmission.

The Role of Transmission in Nematode Virulence: Conclusions

Virulence, defined as the amount of harm caused by a parasite to its host, emerges as a characteristic of infection from a combination of host and parasite factors. Individual variation in host susceptibility, inter- and intra-specific interactions among concomitant infections, life-history traits, and ecological characteristics affecting transmission play a role in determining the level of virulence of a parasitic infection. All of these factors should be considered both separately and together for a complete assessment of what components determine virulence. This chapter presented epidemiological and life history descriptions of major nematode infections and addressed a principle component determining virulence: mode of transmission. In particular, this chapter sought to make and test predictions of nematode virulence by using the collected information and

drawing from microparasitic models of virulence. By establishing what factors influence infection virulence, public health interventions can be developed which aim to promote the evolution of reduced virulence.

Assessing nematode virulence is problematic. Observational studies of changing virulence are not feasible due to the comparatively low rate at which these macroparasites evolve. Morbidity and mortality caused by nematodes is difficult to measure, and estimates are often out of date or incomplete. With no clear and reliable scale for measuring host deaths or disease burden, one must evaluate virulence by comparing the virulence levels of parasites relative to one another. This method is useful for determining virulence in an individual infection. However, it does not account for community and individual perceptions of disease. For instance, some populations residing in regions endemic for nematode infection may consider infection to be a minor inconvenience while others may view the same disease as a serious health issue. It is important for public health researchers and practitioners to remember this when evaluating the burden of disease in a population. Disease assessment in this thesis attempted to minimize subjectivity in its discussion of virulence by focusing mostly on morbidity and mortality measurements. For this thesis, a scale of virulence was created using available morbidity and mortality data as well as manifestations of clinical disease for each nematode. Nematode virulence was determined to be high or low relative to the other nematodes being considered. The resulting scale is somewhat crude and subjective but is informative in discussions of virulence patterns and evolution.

The soil-borne nematodes *E. vermicularis*, *T. trichiura*, *A. lumbricoides*, *N. americanus*, *A. duodenale*, and *S. stercoralis* display low to moderate virulence (7, 9, 47,

58). These parasites are transmitted either through the ingestion of infective larvae or eggs or by the penetration of host tissue and subsequent invasion by parasitic larvae (118). One characteristic shared by these nematodes is that their larvae or eggs must leave the host for a period of time before they are able to infect another host (118). The larvae or egg can develop to the infectious stage in soil or on the host, although the amount of time required for progressing to infectivity is variable. Survival outside of the host also differs among these nematodes, which may play a significant role in determining parasite virulence.

In microparasites, virulence is expected to increase as reliance on host mobility for transmission decreases (22, 151). The pathogens responsible for smallpox and tuberculosis are both highly virulent and highly durable in the external environment, employing a method of transmission known as sit-and-wait transmission (151). Increased exploitation of the host by these pathogens does not negatively affect their potential for transmission as they are able to survive outside the host long enough to come into contact with a new host (151). Based on this virulence pattern, direct contact and soil-borne nematodes are expected to display variable levels of virulence depending on their durability in the external environment, with higher durability associated with higher virulence. This was found to be the case for the soil-borne and direct contact nematodes discussed. The least virulent parasite, *Enterobius vermicularis*, was also the least durable. Hookworms were considered to be the most virulent nematode of the group, although not the most durable. However, the ability of hookworm larvae to seek out high points to increase potential contact with a host makes up for its lower durability and makes it the least reliant on host mobility for transmission.

The soil-borne and direct contact nematodes display a clear pattern of virulence, with higher virulence being favored by low reliance upon host mobility for transmission. This pattern strongly reflects that of microparasites that employ sit-and-wait transmission. The non-durable nematode *E. vermicularis* depends heavily on host mobility for transmission and exhibits a correspondingly low virulence, whereas more durable nematodes such as *A. lumbricoides* are also more virulent. In this group, higher virulence is favored by increased durability and, in the case of hookworm, the ability to move to increase the chance of transmission.

Trichinella spiralis is a nematode transmitted to humans through the consumption of infected animal tissue, commonly swine or wild game (11). The transmission pattern of *T. spiralis* cannot be classified as predator-borne as it is transmitted by scavenging, cannibalism, and predation. Therefore, all host species are predicted to experience a similar level of infection virulence. *T. spiralis* does not require that the host be mobile for transmission, and its durable nature is evidenced by its ability to survive for months in rotten tissue (197). In fact, the parasite would benefit from the host's death, as transmission can only occur following consumption of infected tissue. Therefore, *T. spiralis* is predicted to have a relatively high level of virulence, since host death favors transmission. This is confirmed by the moderate mortality rate and disease manifestations experienced by infected individuals (193-195). Since the infection must be perpetuated by the ingestion of contaminated meat, infected humans represent a dead end host (11). Humans can aid in the transmission of the parasite by feeding the carcasses of infected pigs and rodents to their domestic swine herds (84). This practice would favor increased virulence, as the parasite would be easily transmitted to a large number of new hosts.

Vector-borne pathogens are among the most virulent, as they rely very minimally on host mobility for transmission (22). These microparasites are able to increase host exploitation without suffering a decrease in transmission potential (22). It would be expected that the macroparasitic nematodes would display a similar pattern of virulence. Several common nematodes are transmitted by an insect vector. *Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa* are filarial nematodes affecting humans that are transmitted via the bite of an infected fly or mosquito (13, 14, 97). Lymphatic filariasis, caused by *W. bancrofti* or *B. malayi*, and onchocerciasis, caused by *O. volvulus*, are associated with moderate levels of virulence, while loiasis, caused by *L. loa*, displays less virulence. The moderate level of virulence can be explained by the vector-borne transmission mode of the parasites. Transmission of these filarial nematodes relies less on host mobility than the soil-transmitted nematodes because the insect vector is able to transport the infectious microfilariae to other hosts without the initial host moving. Therefore, an increase in virulence is favored, and the increased exploitation of the host does not negatively impact transmission.

The virulence of these vector-borne nematodes, though not directly caused by the worms, should differ according to the exposure level of individuals to the vector (22). The mosquito and black fly vectors responsible for lymphatic filariasis and onchocerciasis transmission, respectively, have a wider geographic range with fewer environmental requirements than that of the loiasis vector, the mango fly (13, 14, 99, 147, 220). This in part explains the wider distribution and higher prevalences of lymphatic filariasis and onchocerciasis compared to loiasis. In addition, the loiasis vector prefers to remain in moist, canopied forests, and people may only be exposed to the bite of the

worm when working in such areas (97, 99, 100). The positive correlation with infection and age supports this (224). Virulence patterns of the vector-borne nematodes appear to correspond with those of microparasites transmitted by vectors, with an increase in virulence favored by increased vector-borne transmission.

Research on water-borne pathogens indicates that virulence is predicted to increase as transmission increases (22). The virulence of water-borne parasites is more difficult to predict due to the difference in life history traits of macroparasites compared to microparasites. *Dracunculus medinensis* is a moderate to highly virulent nematode that spreads through the ingestion of water containing copepods infected with the larval form of the parasite (16). The process from initial infection to the development of a blister containing larvae takes approximately one year (16). The female worm directly induces this blister, whose intense burning sensation provokes the host to place the blister in water to provide relief, releasing millions of larvae (16). Therefore, *D. medinensis* is somewhat reliant on host mobility for transmission, which limits its ability to increase host exploitation at the risk of losing transmission potential. In this way, guinea worm is dissimilar to water-borne pathogens, which rely less on host mobility as water-borne transmission increases. *D. medinensis* is an example of how the dynamics of microparasitic virulence evolution may not apply directly to macroparasites.

Examining the role of transmission mode in nematode virulence has led to a tentative but usable framework for predicting virulence levels of parasites relative to each other. In addition, inferences can be made regarding virulence and mode of transmission. The nematodes discussed are transmitted in a variety of ways and display differing levels of virulence depending on the method of transmission employed. In general, it appears

that soil-borne and direct contact nematodes are the least virulent, followed by the vector-borne filarial nematodes, water-borne *D. medinensis*, and *T. spiralis*, transmitted through the consumption of contaminated meat. The observed differences in virulence can be explained by the extent to which a certain transmission group depends upon host mobility for transmission. For example, *T. spiralis*, the most virulent nematode does not rely on host mobility for transmission, and transmission is actually favored by host death.

Many difficulties arise when studying the virulence patterns of nematodes and hypothesizing how virulence might increase or decrease depending on situational differences relating to behavioral and environmental factors. For instance, nematodes often have complex life histories, and a change in one stage of the life cycle can have repercussions on fecundity, transmission, and host health. Furthermore, the virulence patterns observed in microparasites are not applicable to macroparasites due to differences in life history traits and infection dynamics. These factors must be taken into account when attempting to explain why a parasite or group of parasites displays a particular virulence. The intricate relationship between host, parasite, environment or vector requires that each factors relating to virulence in each parasite should be considered individually. Mode of transmission undoubtedly plays a large role in determining the level of virulence of a parasite, but other factors, relating to both host and parasite must also be considered.

Within-Host Dynamics of Infection

Parasitic nematodes disproportionately affect sub-tropical and tropical economically poor regions of the world, and most individuals residing in endemic areas

experience concomitant infections (10). Over one billion people are estimated to be infected with at least one of the “unholy trinity” of intestinal nematodes, roundworm, whipworm, and hookworm (10, 60). Several of these species may occupy the same region of the body and interspecies interactions could impact the virulence of the parasites (7, 9, 21). Furthermore, the density of an individual parasite species within a host can impact the overall virulence of that parasite population (21, 122). In order to gain a complete understanding of factors relating to parasite virulence, the interspecies and intraspecies interactions within a host must be considered. Few studies have investigated these interactions extensively in nematode infections, but much work has been done on concomitant infections in other hosts (21, 122, 232-236). However, interspecific interactions in filarial nematodes have not been well investigated; most of these studies examine the interactions between intestinal helminth species (234).

Intraspecific interactions within a host can have an impact on the virulence, fecundity, and population structure of a parasitic infection (168, 169, 233). Studies on intestinal nematodes have shown that an increase in parasite density leads to decreased individual fecundity, likely a result of intraspecific competition for resources (168, 169). Additionally, some adult intestinal helminths have been shown to provoke the host immune response to react to antigens associated with incoming larvae but not to the already present adult population, effectively inhibiting incoming larvae from developing in the host (233). In research on the human immune response to hookworm infection, a similar reaction to incoming larvae was found (134). The increased presence of IL-5 in the host was aimed at preventing the establishment of new larval populations while the adult worms were able to evade this attack (134). It is not known whether this immune

response is elicited by the hookworm or if it is a feature of partial immunity in the host (134). Regardless, intraspecies competition is an important factor in the population dynamics of an intestinal helminth infection.

Concomitant infections involving nematodes occupying the same region inside a host are likely to involve some degree of species interactions. This interaction can manifest itself as competition for host resources and subsequent domination of one species over another involving a significant reduction in the population size of one species (234). In addition, interspecies competition may result in one species altering how it uses resources or where it is located, called a functional change (234). The reverse of this situation can also be seen, wherein one species sufficiently suppresses the host immune response so that exploitation by a second parasite species is possible (4). This might be the outcome favored when the species are not in direct competition for resources. A natural state of suppressed immune response in human hosts is commonly seen, particularly in intestinal nematode infections, which could explain why multiple infections with these parasites are extremely common and typically last for years (10, 134, 178).

This immunosuppressive effect of intestinal nematode infections can not only impact populations of other intestinal parasites, but can influence the susceptibility of the host to other diseases as well. Therefore, individuals can be infected with multiple parasites and pathogens, but due to the downregulatory effects of intestinal helminths on the host's immune system, the host may display lessened signs of disease (237-239). On the other hand, high rates of intestinal nematode infection have been found to be associated with high rates of other diseases (240). Conflicting findings such as these have

been found for malaria and concomitant infection with intestinal nematodes (238-240). In some cases, individuals infected with intestinal nematodes were found to have reduced malaria symptomology, whereas in other cases, high rates of intestinal nematode infection were associated with an increase in the severity of malarial symptoms (238-240). The reason for these inconsistent findings is unclear, although it is believed to be caused in part by the downregulation of the Th1 immune response, used against malaria, in favor of a stronger Th2 response, used against helminths (241). In the cases in which a lessened malarial disease state is observed, the suppression of symptoms may not be associated with a lower malaria parasite count. Rather, the host immune system simply may not be responding to the protozoan as it normally would. Treatment resulting in a reduction in intestinal nematodes in a host may therefore subsequently cause an upswing in malarial signs and symptoms and an overall decrease in the health status of an individual, which is an important implication for public health.

The “unholy trinity” of geohelminths, *T. trichiura*, *A. lumbricoides*, and the hookworms, often appear simultaneously in one host (10, 242). *A. lumbricoides* and hookworms spend their adult life in the small intestine while *T. trichiura* occupies the large intestine (7, 9, 58). This variation in location of infection likely reduces both contact and competition between *T. trichiura* and the other intestinal helminths and could help to explain why concomitant infections are common. Both *A. lumbricoides* and the hookworms occupy the small intestine, though, which should lead to competition for space and resources. However, adult *A. lumbricoides* use the food bolus of a host for resources while hookworms feed on host blood, thus reducing their competition for resources and explaining why these infections commonly occur together (7, 9). Despite

this, these parasites may still be in competition for space or other resources, and this competition can have significant impacts on the parasite densities or functions of different species within a host (4, 234).

In a study of concomitant intestinal helminth infections in rabbits, researchers found that parasite populations were limited in the presence of multiple species and that elimination of one species via antihelminthic treatment resulted in a large increase in another species (232). The presence of multiple species of helminths in a host led to a suppression in parasite population for all species (232). Once the competition was removed, the increase in space and available resources allowed for the establishment of new larval populations (232). The increase in parasite population and associated virulence following treatment of one species would not be possible without continuous exposure to the infectious stage of the remaining species. This upswing observed for one parasite species has great implications for the use of antihelminthics in the medication of human parasite infections. In individuals infected with multiple parasites, treating one infection can lead to an increase in the virulence of the unaffected parasites (232, 242). This should be kept in mind when designing and distributing antihelminthic drugs. These findings clearly show the need not only for effective treatment but also for reduction in exposure.

Implications for Public Health

Parasitic nematodes display a wide variety of transmission modes and levels of virulence. With knowledge about environmental and behavioral factors that impact transmission patterns of the parasite, predictions can be made regarding changing patterns

of virulence. Public health workers can in turn use these predictions to develop and implement strategies for prevention and control of parasitic disease. While discussing possible ways to promote a reduction in virulence, it is important to consider the cultural and social aspects of the target population. Public health programs aimed at reducing nematode virulence may work in some populations but fail to succeed in others. Much of the difficulty in controlling nematode infections stems from life cycle and disease characteristics caused by the nematodes. For instance, most infections are largely asymptomatic, and one infected individual may spread the disease to many others without being targeted for treatment. In addition, the durable soil-borne nematodes may perpetuate in a population following treatment due to their prolonged survival in the external environment. Such considerations should be made while developing treatment or control plans for parasitic nematodes.

Most of the nematode infections discussed occur largely in poverty-stricken countries in the tropical and sub-tropical regions of the world (10, 60, 118). Historical writings and archaeological evidence indicate that the distribution of these diseases was once much more widespread and many countries with little to no infection today were formerly heavily infected (25, 30). The reason for this shift in endemnicity is probably due to a number of factors, the most important being infrastructural changes during the past century resulting in decreased exposure in wealthy countries (73). For example, improvements in sanitation, housing quality, and access to healthcare changed the landscape of nematode infection by reducing transmission and exposure (73). Large-scale eradication campaigns probably led to a swifter reduction in nematode prevalence, as in the hookworm eradication program instituted by the Rockefeller Center in the early 20th

century (73). However, the decline in infections was also likely a side effect of the increased sanitation measures, improved housing quality, and healthcare revolution that occurred during the economic growth in these countries.

Parasitic nematode infections are largely infections of poverty, as evidenced by their absence in wealthy countries and their concentration in undeveloped regions (10). Although they are not a significant cause of mortality, these infections are responsible for significant morbidity and diminished productivity potential in endemic regions (10, 60, 175). One of the most devastating features of these infections is their ability to keep affected regions mired in poverty (10, 74). Sanitation and housing quality of a region cannot improve without significant reduction in parasitic infections because of the significant and negative effect the infections have on an individual's productivity. It is clear that public health directives aimed at lessening the burden of nematode disease in these populations will not succeed unless significant and permanent improvement in the conditions of poverty in these regions are not also made (10, 74).

Due the wide variety in transmission modes employed by these nematodes, each mode must be considered individually when developing strategies for prevention or control. *E. vermicularis*, *T. trichiura*, *A. lumbricoides*, *N. americanus*, *A. duodenale*, and *S. stercoralis* are transmitted through direct contact or ingestion of eggs (118). For those nematodes, improvements in overall sanitation should reduce infection rates by lessening exposure. In particular, these measures could include the construction and maintenance of latrines at home and at work, improved access clean water for hand-washing, and education on unhygienic practices that can lead to infection (10, 74). Control of the infections through access to medical facilities for diagnosis and treatment should result in

decreased transmission of the parasite. The combination of sanitation measures and antihelminthic treatment will interrupt the infectious cycle of these directly transmitted and soil-borne parasites, but the interruption will not be sustained unless permanent improvement is made on both counts. In these nematodes, durability appears to be associated with virulence, with higher durability corresponding to higher virulence. Hypothetically, reduced virulence could occur if decreased durability was selected for, but any reduction in virulence would be miniscule, as it is already fairly low in this group. Furthermore, implementation of such a plan would be very difficult.

T. spiralis is a nematode transmitted by consuming contaminated meat whose global prevalence has decreased greatly over the past decades (11). Much of this reduction is a direct result in the improvement of food quality control and agricultural practices (11, 126). In order to maintain this downward trend, it is important to identify the source of infection. Most commonly, infection occurs following the consumption of infected tissue from domestic swine, but in developed countries, game meat has become an important source (11, 83, 84). Thorough inspection of the meat should reduce exposure from domestic swine (11). Those consuming game meat should cook the meat thoroughly in order to inactivate the cysts (11). Humans cannot directly influence the evolution of virulence in humans, but they can promote lessened virulence by improvements in agricultural practices such as preventing the consumption of infected carcasses by other members of the herd. Since humans are a dead-end host, treatment of the infection should be limited to humans because it is unlikely to result in the evolution of resistant strains of the parasite.

Vector-borne illnesses in undeveloped countries are difficult to control and reduction in infection prevalence is difficult to maintain (10). The filarial parasites *W. bancrofti*, *B. malayi*, *O. volvulus*, and *L. loa* are transmitted to humans through the bite of a fly or a mosquito (13, 14, 97). Reductions in these infections require that the population at risk lessens their exposure to the disease vector. This can occur by fitting doors and windows at home and at work with screens and the use of mosquito nets (10). However, these practices are difficult to implement and do not ensure complete protection from the vector (10). In addition, many individuals in endemic regions work outdoors and are thus exposed to the bite of the disease vector (10). Bug repellent and pesticides are commonly used to supplement other forms of exposure reduction, but the emergence of resistant vectors makes any improvement in infection control short-lived (10). A combination of exposure reduction in the form of screens and nets in addition to rapid diagnosis and treatment of infection should reduce the overall prevalence of the filarial nematodes. Humans are the sole reservoir for *W. bancrofti*, *O. volvulus*, and *L. loa*, so disruption of the infectious cycle in a region and maintenance of practices designed to limit exposure should result in an overall reduction of infection. The measures aimed at reducing infection by limiting exposure should result hypothetically in a decrease in virulence of the vector-borne nematodes. However, macroparasitic evolution occurs much more slowly than microparasites, so any reduction in virulence would not likely be observable.

The water-borne nematode *D. medinensis*, once widely distributed in tropical and sub-tropical regions of Africa and Asia, is in what is hoped to be its final years of activity before being consigned to history books as the second globally eradicated human disease (229). Consumption of water containing infected copepods initiates the infectious cycle

within a human host (16). Therefore, water sanitation practices should effectively inhibit the transmission of guinea worm. However, individuals afflicted with the infection frequently do not have access to clean water, nor are they aware of the manner in which the parasite is transmitted (10). These factors contributed to the historic widespread distribution of guinea worm. Much of the global campaign for eradication focused on teaching populations at risk about the benefits of filtration, which can be done using a simple clean cloth, and overall improvement in water sanitation (229). Eradication was not completed within the original goal of the program due to many factors including difficulty in community participation as well as access to transient populations (116, 229). The struggles and (hopefully) eventual success of the eradication program will continue to provide numerous lessons in how a multi-step approach to a parasite control or prevention program can be most effective.

Future Research

This thesis includes one of the first thorough examinations of the relationship between nematode virulence and transmission mode. By comparing virulence between and among nematodes, hypotheses regarding virulence patterns among nematodes were able to be tested. This resulted in the development of general principles of virulence that can be applied to nematodes. However, wide generalization of these findings is not recommended. Further research is needed to verify these findings and to develop a more refined model for predicting virulence in nematodes. In particular, the gaps in knowledge regarding mortality and morbidity rates of nematodes should be addressed. Having precise and accurate statistics for these characteristics is necessary to create a reliable

scale for virulence in nematodes. In addition, exploring the biomechanical pathways involved in host exploitation would provide interesting insight into how these parasites may manipulate their host to facilitate transmission. By evaluating host exploitation strategies among regional strains of a nematode, the relationship between virulence, transmission, and host exploitation could be concretely illustrated. Furthermore, research into the relationship between host exploitation and parasite fecundity should be explored.

This field of research would benefit from interdisciplinary research involving public health, evolutionary biology, and parasitology. Broadening the analysis of nematode virulence by investigating nematodes infecting other animals would add to the discussion of virulence evolution in nematodes. A thorough examination of in-host dynamics of infection may aid in understanding how virulence may be impacted by parasite density. Other future questions may consider the impact of climate change on the distribution and transmission of these parasites. Experimental studies testing environmental durability of soil-borne and directly transmitted nematodes could provide a more precise measurement of species, and possibly strain, durability. Ecological assessment of vector habitat and range could help to explain patterns in infection distribution and prevalence and how these may change as vector habitat widens or shrinks. In addition, measuring the transmission potential of each parasite vector may reveal regional differences in virulence or transmission rates. A public health perspective is necessary to understand the spread of a disease in a population and what can be done to reduce infection. An interesting question that could be addressed in public health research is determining whether there are any differences between morbidity or mortality rates in regions exposed to different control or treatment strategies.

Clearly, the field of virulence evolution in nematodes contains many possibilities for future research, with both broad and specific aims. The interaction between multiple disciplines allows for an examination of these problems from multiple perspectives and would result in a more comprehensive understanding of the relationship between nematodes and humans.

CHAPTER IV

CONCLUSION

This thesis set out to explore the relationship between parasitic nematodes and their human hosts by investigating the historical and modern-day significance of each infection. In addition, this thesis addressed the relationship between nematode virulence and mode of transmission in order to create a framework with which to make predictions about virulence. First, a historical evaluation of each infection helped to illustrate how host population-based changes can alter parasite frequency and distribution.

Delving into archaeological evidence of parasites in humans and investigating mentions of the diseases in ancient texts is useful in understanding how large-scale changes in human behavioral patterns forever changed the shape of nematode infection. Humans and parasitic nematodes have a long shared history which has had profound effects on parasite evolution and distribution as well as human health and evolution over the course of their relationship (25, 30, 44). During the past 10,000 years, changing patterns in environment and human behavior have resulted in altered host-parasite dynamics in which the intensity and range of parasitic infection has shifted (110, 111, 243). The degree and direction of these shifts depends upon the ability of each parasite to be transmitted effectively within a population under these changing parameters. The agricultural revolution began approximately 10,000 years ago in western Asia and led to an immense change in human population structure and movement (110-112). This shift from foraging to farming led to larger and more stationary human settlements and in

turn, set the stage for widespread infection effectively maintained by the increase in population density (111, 243). Parasitic nematodes were among those organisms that experienced a massive upswing in infection rates. The more crowded conditions and decreased population movement that occurred as a result of the agricultural revolution favored the transmission of inherited nematodes as well as those newly introduced into human populations from the domestication of animals (110, 111, 243). Studying the shifting patterns of nematode infection over time can provide insight into factors that promote or inhibit the establishment and persistence of nematode infection in human populations. These findings can then be used to inform public health officials about the multi-faceted nature of parasitic infections and help them to make steady and continuous progress in the control of these devastating diseases.

A central question to this thesis was whether nematode virulence could be predicted by examining dynamics of transmission and life history characteristics. The virulence patterns of each nematode were examined in order to gain a clearer understanding of the nature of the relationship between transmission mode and virulence. Hypotheses for each nematode were based in part on the microparasitic model of virulence evolution (22). Evaluation of these predictions led to a basic framework of nematode virulence and transmission. Durability in directly transmitted and soil-borne nematodes was found to be positively correlated with virulence. The unique transmission features of *T. spiralis* make host mobility entirely unnecessary, which corresponds to the relatively high virulence of this parasite. The virulence of vector-borne nematodes fit well with the prediction that a lessened reliance on host mobility would be associated with an increase in virulence. The water-borne *D. medinensis*, though virulent, was not

found to strictly follow the dynamics of virulence evolution as predicted in microparasitic models. The investigation of nematode virulence and transmission mode, though lacking in many aspects, represents a starting point at which many questions can be asked in order to gain a more comprehensive understanding of factors affecting virulence.

The impact that these parasitic infections has on present populations cannot be understated. More than one billion people are currently infected with at least of the parasitic nematodes discussed and many more are at risk (10). Although infections with these parasites rarely result in host mortality, significant and long-lasting morbidity is a common outcome (10, 13, 14, 175). Public health prevention and control strategies often do not seem to account for the influence of evolution on the modern epidemiological patterns of infection or for the impact that those programs might have on the evolution of the parasite or its vector. For instance, the use of insecticides can lead to the evolution of resistance in insect vectors and the growth of a more widespread and difficult to control infection (10). Also, widespread antihelminthic treatment may result in short-term improvement in infection rates, but unless significant effort is put forth to reduce the transmission of the parasites, a permanent reduction in infection cannot be made (10, 60, 74). For these reasons, it is imperative that public health workers understand how transmission mode, human behavior, and infrastructural components interact to influence the state of disease in a host.

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Table 1. Prevalence and Geographical Distribution of Nematodes

Nematode	Geographic location	Prevalence	Productive days lost
<i>Enterobius vermicularis</i>	Worldwide, temperate and tropical climates	300 million	No data available
<i>Trichuris trichiura</i>	Asia, sub-Saharan Africa, tropical countries of Americas	604-795 million	1.2 million DALYs
<i>Ascaris lumbricoides</i>	Tropical and sub-tropical regions; highest in Asia	807-1221 million	1.2 million DALYs
<i>Necator americanus</i> & <i>Ancylostoma duodenale</i>	Tropical and sub-tropical regions; used to be more widespread	576-740 million	1.8 million DALYs
<i>Strongyloides stercoralis</i>	Tropical and sub-tropical regions; can also be found in temperate zones	30-100 million	No data available
<i>Trichinella spiralis</i>	Worldwide; highest in regions with poor food quality control	11 million, but only 10,000 infections reported each year. Non-reportable illness in many countries, making prevalence estimates difficult	No data available
<i>Wuchereria bancrofti</i> & <i>Brugia malayi</i>	Tropics; 40% of cases occur in sub-Saharan Africa, also occurs in Asia and Americas	120 million; most infected with <i>W. bancrofti</i> ; 10-20 million infected with <i>B. malayi</i>	5.78 million DALYs
<i>Onchocerca volvulus</i>	Mostly in sub-Saharan Africa, also in Yemen and countries in Latin America and South America	18-37 million	484,000 DALYs
<i>Loa loa</i>	Central and West Africa	13 million	No data available
<i>Dracunculus medinensis</i>	Ethiopia, Mali, and South Sudan; used to be much more prevalent but eradication campaign disrupted infection in previously endemic countries	1,793 cases as of 2010	Average period of disability ranging 5-13 weeks
References	(7, 8, 10, 11, 13, 14, 48, 58, 60, 73, 75, 97, 98, 109, 126, 213, 220)	(10, 13, 14, 51, 58, 60, 75, 97, 109, 126)	(59, 60, 90, 218, 229, 244)

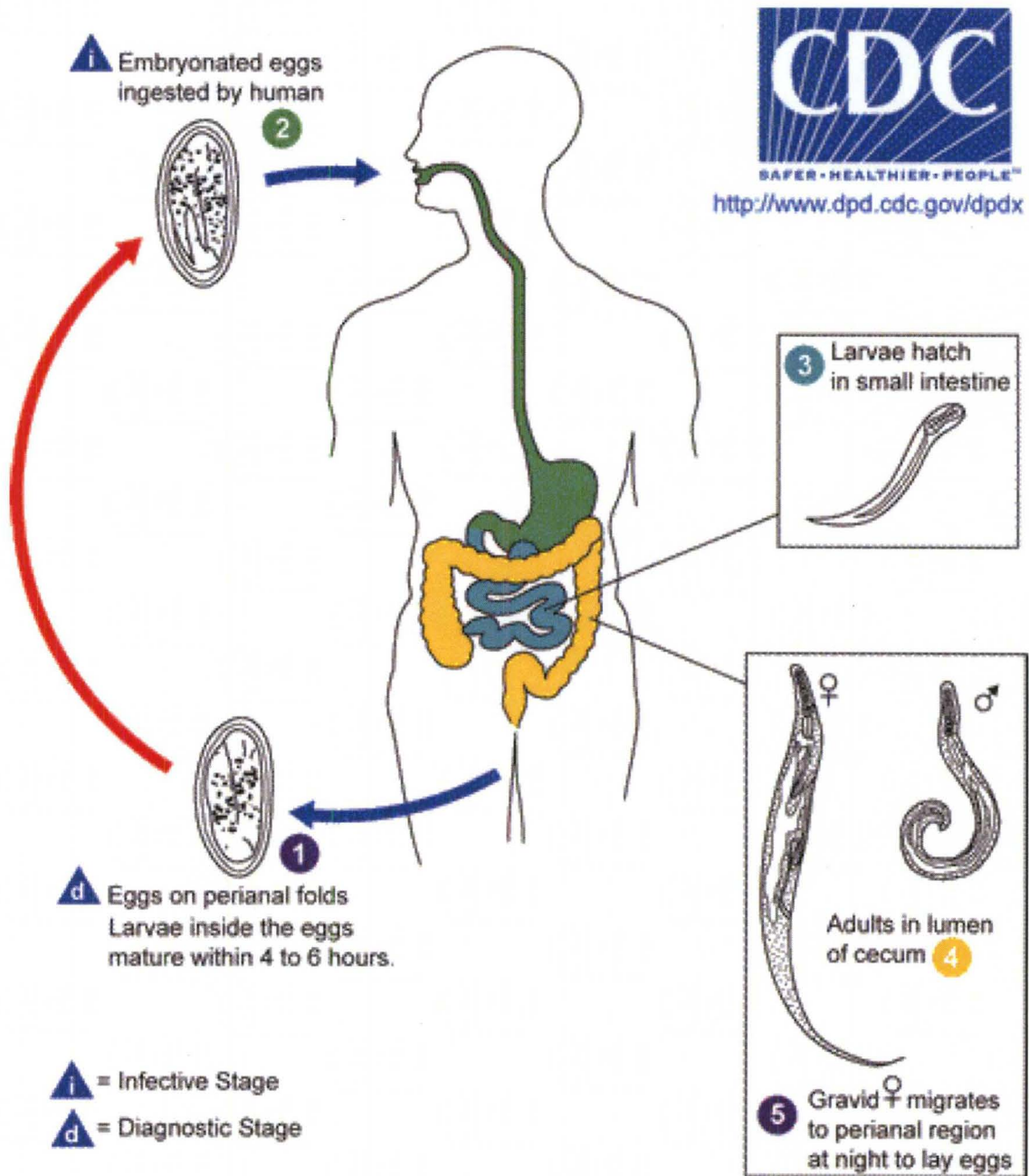
Table 2. Mode of Transmission, Morbidity, and Hosts

Nematode	Virulence level	Main cause of morbidity	Mode of transmission	Hosts
<i>Enterobius vermicularis</i>	Low	Perianal itching; complications from aberrant infection	Fecal-oral; ingestion of eggs	Humans
<i>Trichuris trichiura</i>	Low	Diarrhea, abdominal pain, vomiting, headache, blood loss, weight loss	Fecal-oral; ingestion of eggs	Humans
<i>Ascaris lumbricoides</i>	Low	Diarrhea, abdominal pain, nausea, vomiting, anorexia	Fecal-oral; ingestion of eggs	Humans; pigs may serve as animal reservoir
<i>Necator americanus</i> & <i>Ancylostoma duodenale</i>	Low to moderate	Ground itch, pneumonitis, iron-deficient anemia; anemia can result in physical and cognitive stunting	Penetration of host skin by infective larvae; <i>A. duodenale</i> can be transmitted orally	Humans
<i>Strongyloides stercoralis</i>	Low to moderate	Diarrhea, abdominal discomfort, nausea, anorexia. In hyperinfection, disruption of mucosal patterns, secondary bacterial and fungal infections, can result in mortality	Direct contact; penetration of host skin by infective larvae	Humans, non-human primates, dogs
<i>Trichinella spiralis</i>	Moderate to high	Abdominal symptoms, fever myalgia; when larvae invade muscle tissue myocarditis and neurological symptoms can result	Ingestion of infected tissue	Humans, domestic and wild swine, rodents, wild mammals
<i>Wuchereria bancrofti</i> & <i>Brugia malayi</i>	Moderate	Acute lymphadenitis, elephantiasis in lower limbs and genitalia, tropical pulmonary eosinophilia	Bite of infected mosquito	<i>W. bancrofti</i> : Humans, mosquitoes <i>B. malayi</i> : Humans, monkeys, felines, mosquitoes
<i>Onchocerca volvulus</i>	Moderate	In dermatitis form, depigmentation of skin and loss of skin elasticity. In ocular form of disease, blindness can occur	Bite of infected blackfly	Humans, blackflies
<i>Loa loa</i>	Low	Itchy and irritating Calabar swellings in head region or extremities	Bite of infected mango fly	Humans, mango flies
<i>Dracunculus medinensis</i>	Moderate	Formation of extremely painful, debilitating blister on lower extremity; can result in months of disability	Ingestion of water contaminated with infected copepods	Humans, <i>Cyclops</i> copepods
References		(7, 9-14, 16, 17, 47, 68, 76, 97, 125, 157, 172, 175)	(7, 9, 11, 13, 16, 47, 58, 76, 97)	(7, 9, 11, 13, 16, 47, 58, 76, 97)

Table 3. Biological and Life Cycle Features of Nematodes

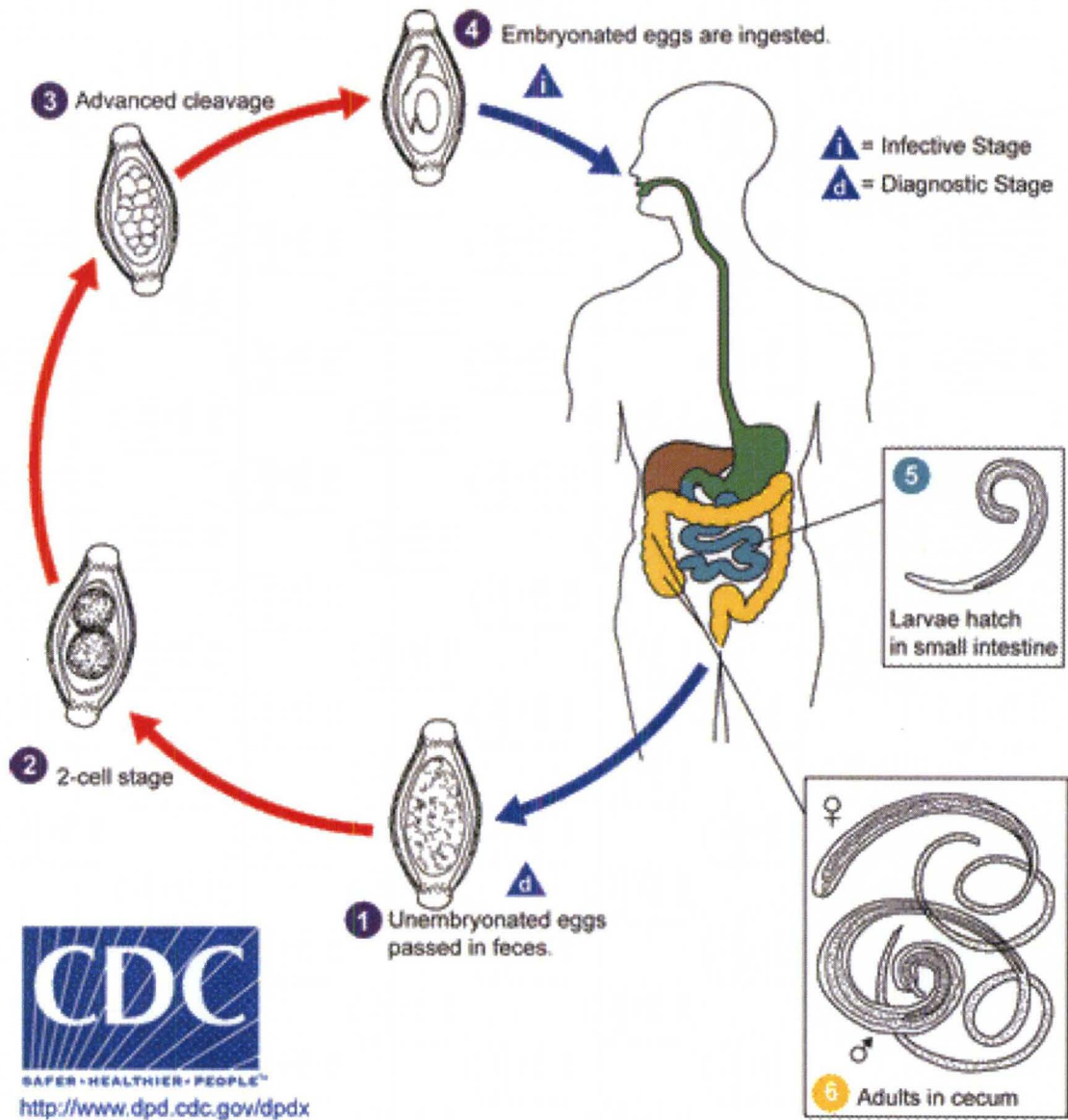
Nematode	Virulence level	Size of adult (length)	Prepatent Period	Eggs/microfilariae produced per adult female/day	Average life span of worm	Maximum life span
<i>Enterobius vermicularis</i>	Low	Female: 8-13mm Male: 2-5mm	3-6 weeks	10,000	8-10 weeks	2 months
<i>Trichuris trichiura</i>	Low	Female: 30-50mm Male: 30-45mm	60-90 days	3,000-5,000	1.5-2 years	1-2 years
<i>Ascaris lumbricoides</i>	Low	13-18 cm	67-76 days	200,000 eggs	1-2 years	1-2 years
<i>Necator americanus</i>	Low to moderate	5-13mm	42 days	10,000 eggs	3-5 years	14 years
<i>Ancylostoma duodenale</i>	Low to moderate	5-13mm	39 days	28,000 eggs	1-2 years	15 years
<i>Strongyloides stercoralis</i>	Moderate to high	2mm	18-30 days	50 eggs	Unknown due to autoinfection	Longest recorded is 65 years
<i>Trichinella spiralis</i>	Moderate	Female: 3mm Male: 1.5mm	7 days	Depends on host immune response; 500-1,500 over lifetime	Nurse-cell complex can exist as long as host stays alive	Nurse-cell complex can exist as long as host stays alive
<i>Wuchereria bancrofti</i> & <i>Brugia malayi</i>	Moderate	Female: 4-10cm Male: 2-4cm	0.5-1 year	10,000 microfilariae	4.5 years for adult 1.5 years for microfilariae	6-8 years
<i>Onchocerca volvulus</i>	Low	Female: 40cm Male: 3-5cm	9-15 months	700 microfilariae	8-10 years for adult	14-18 years
<i>Loa loa</i>	Moderate	Female: 60mm Male: 32mm	1-4 years	10,000 microfilariae	Many years	17-20 years
<i>Dracunculus medinensis</i>	Low	Female: 100cm Male: 40mm	1 year	Female's uterus contains 1-3 million larvae	1 year	1 year
References		(7, 8, 11, 13, 14, 16, 47, 58, 76, 97)	(13, 16, 47, 58, 59, 76, 97, 166, 245, 246)	(7, 9, 13, 14, 17, 47, 58, 76, 198, 223, 245)	(9, 11, 13, 14, 16, 47, 58, 97, 165, 245, 247)	(9, 11, 16, 46, 58, 97, 246, 247)

Figure 1. Life Cycle Illustration of *Enterobius vermicularis* (248)



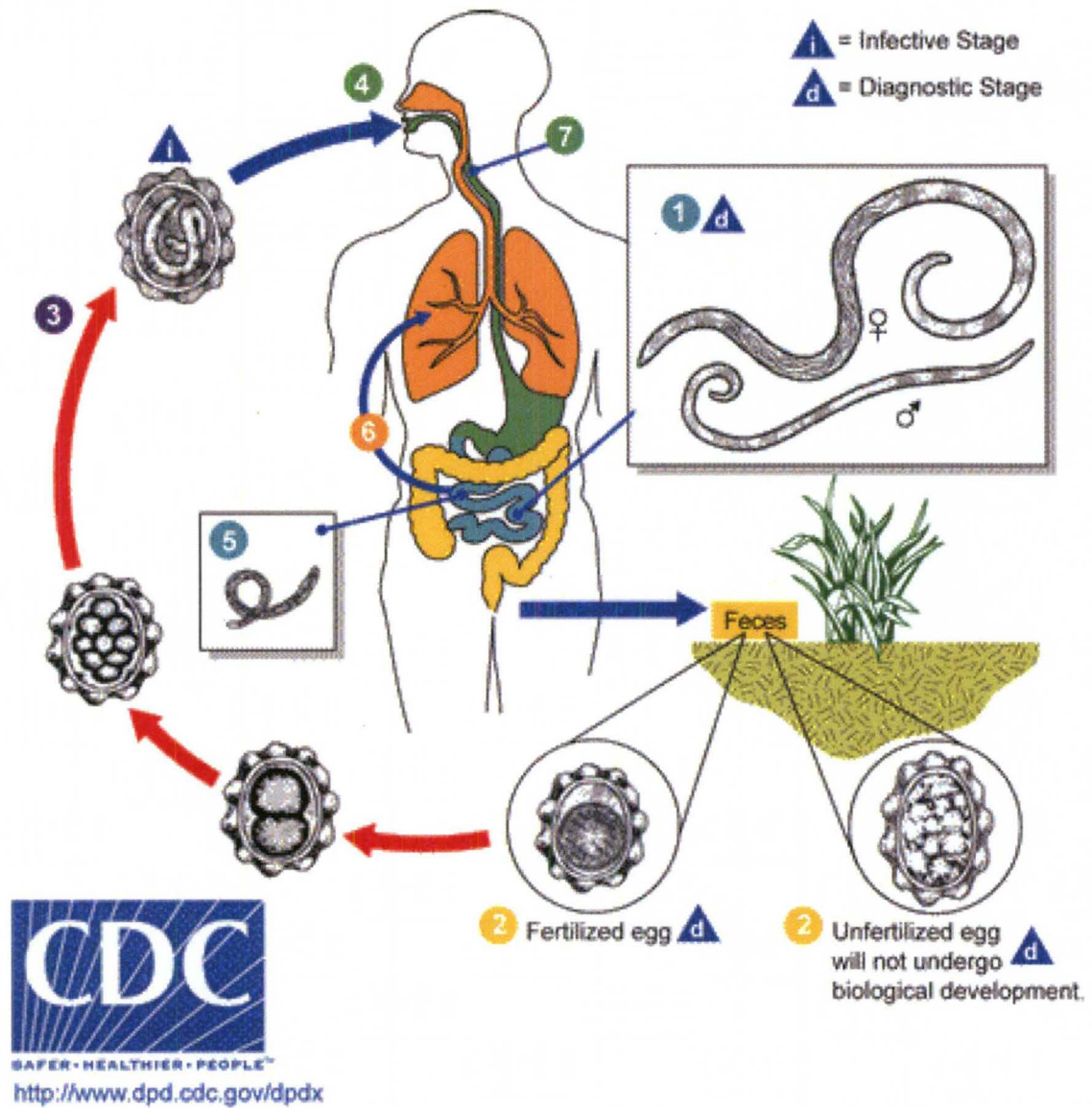
This image was taken from the CDC's Enterobiasis website (248).

Figure 2. Life Cycle Illustration of *Trichuris trichiura* (249)



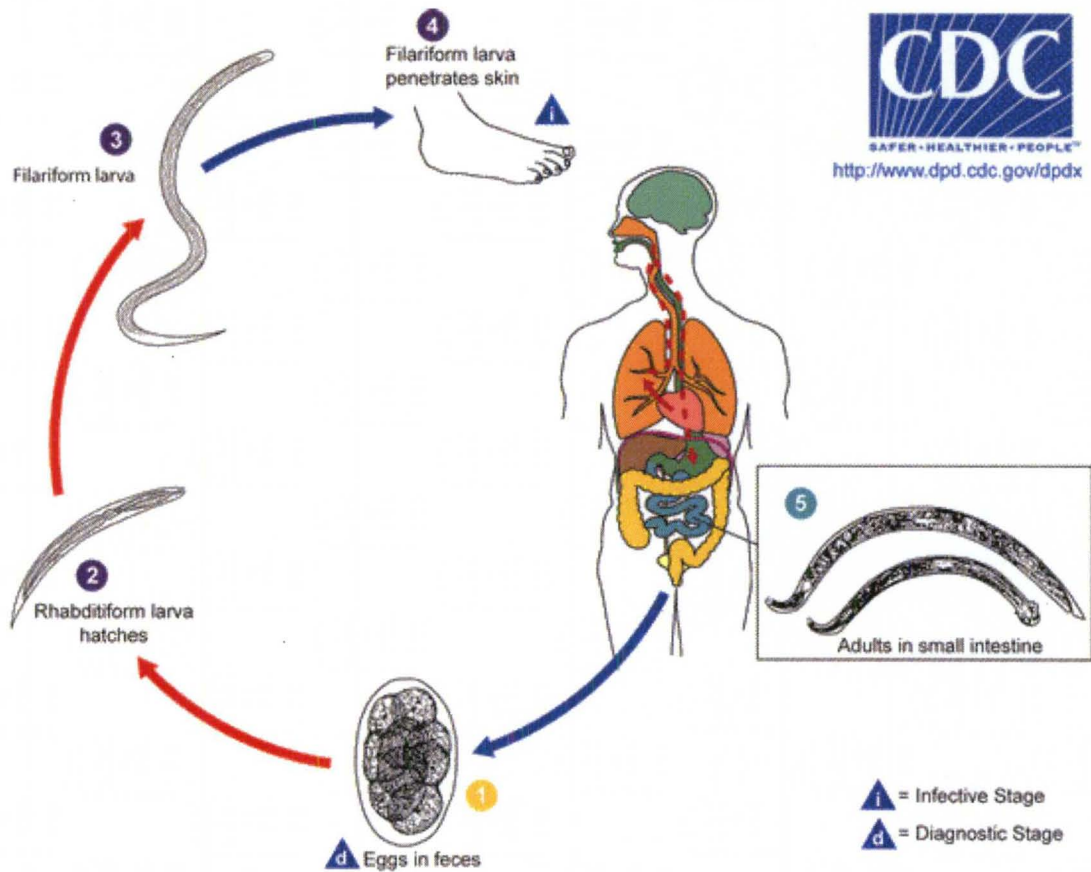
This image was taken from the CDC's Trichuriasis website (249).

Figure 3. Life Cycle Illustration of *Ascaris lumbricoides* (250)



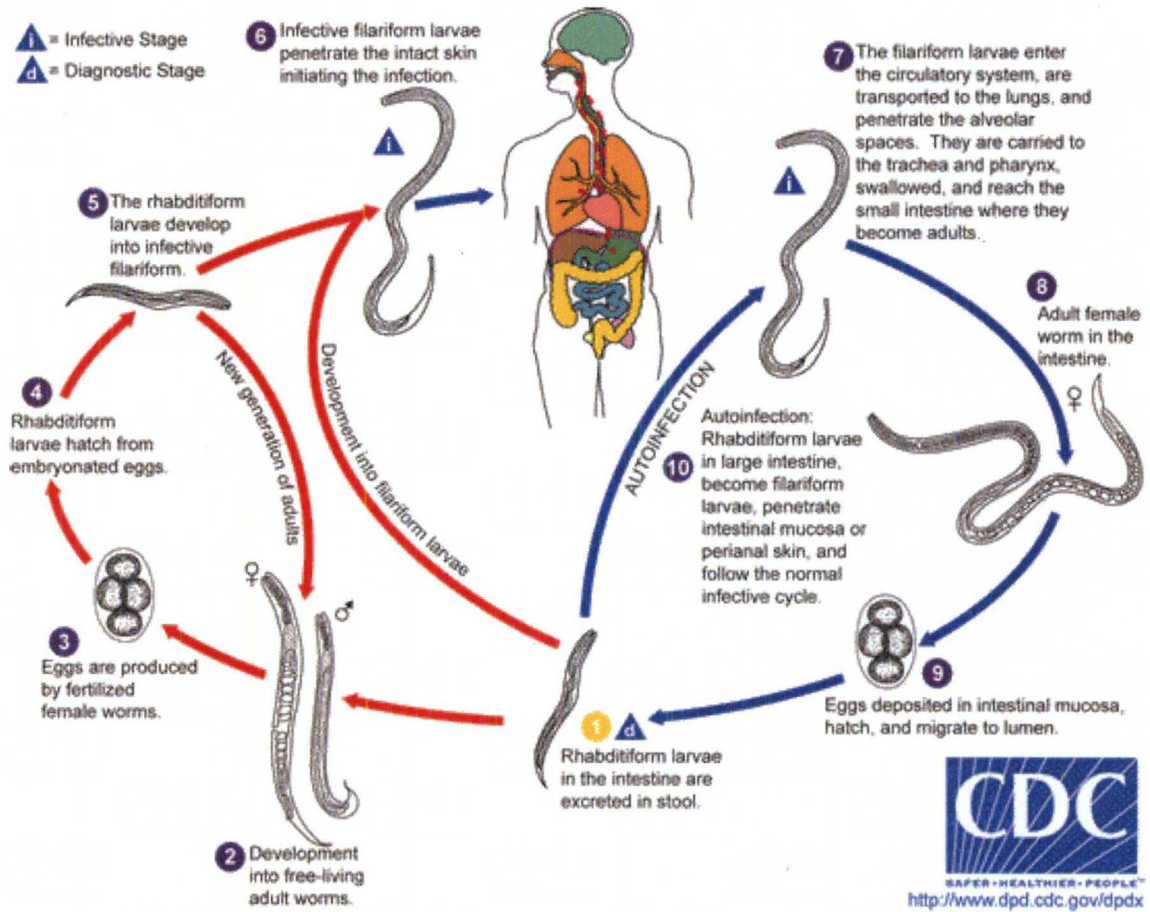
This image was taken from the CDC's Ascariasis website (250).

Figure 4. Life Cycle Illustration of Hookworms *Ancylostoma duodenale* & *Necator americanus* (251)



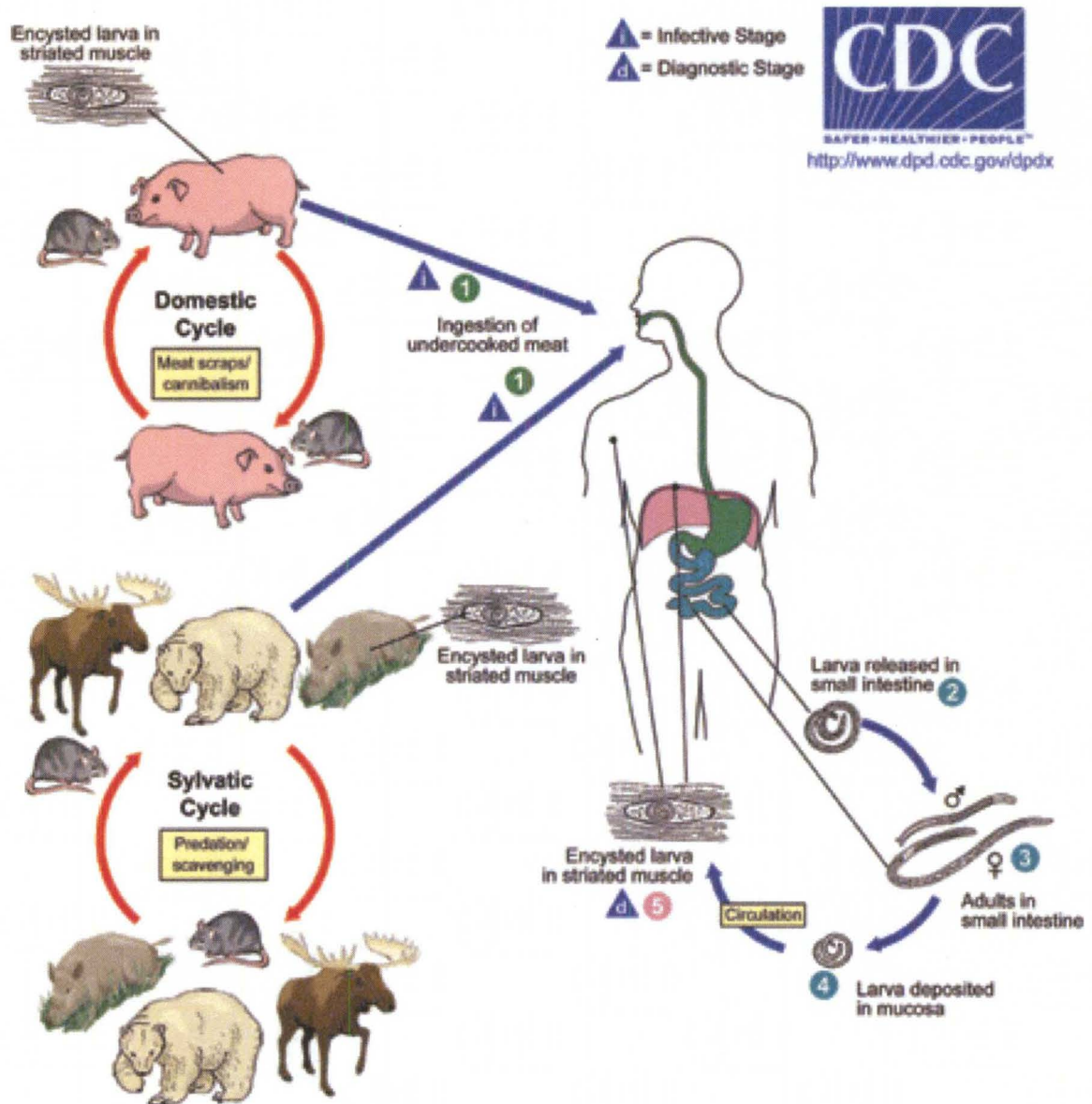
This image was taken from the CDC's Hookworm website (251).

Figure 5. Life Cycle Illustration of *Strongyloides stercoralis* (252)



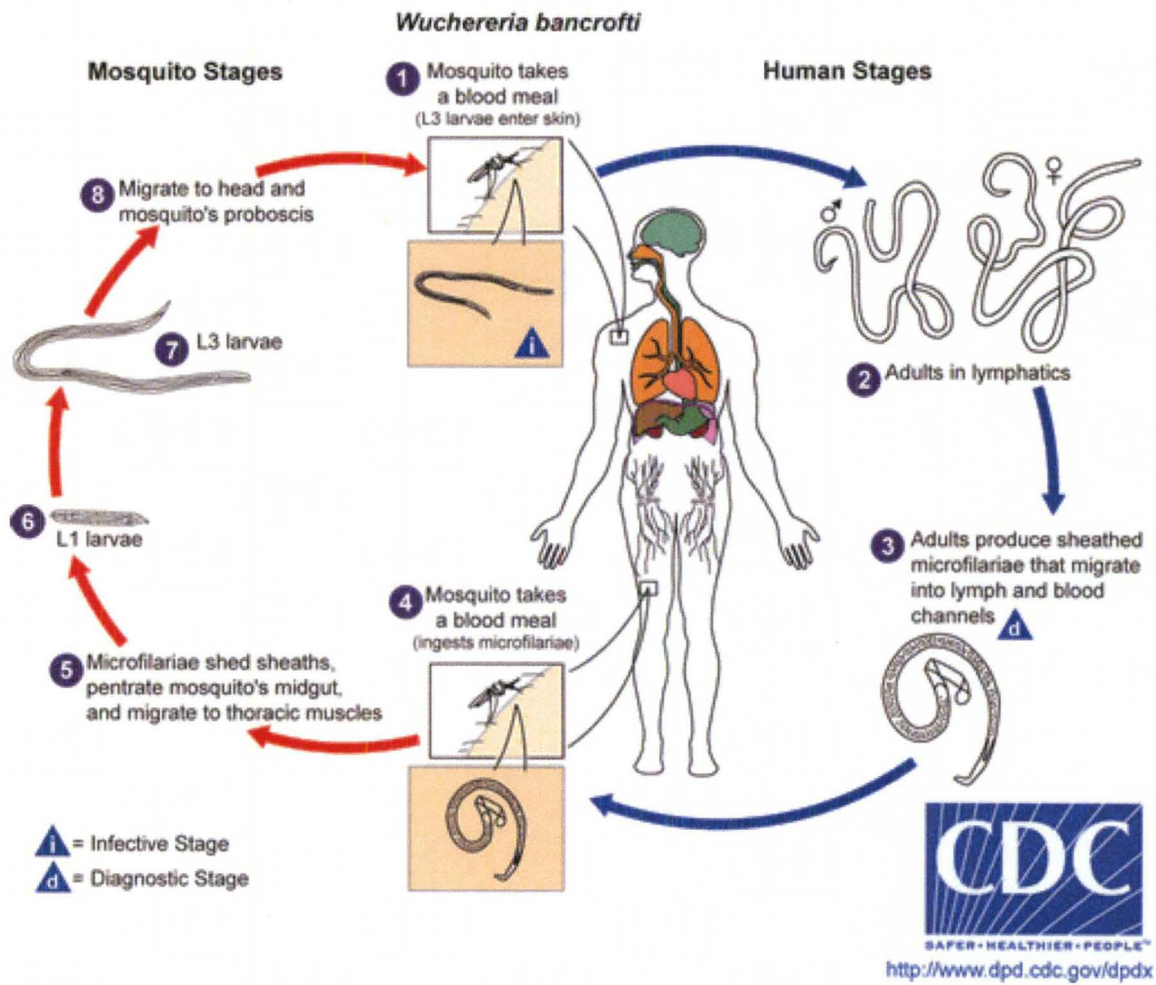
This image was taken from the CDC's Strongyloidiasis website (252).

Figure 6. Life Cycle Illustration of *Trichinella Spiralis* (253)



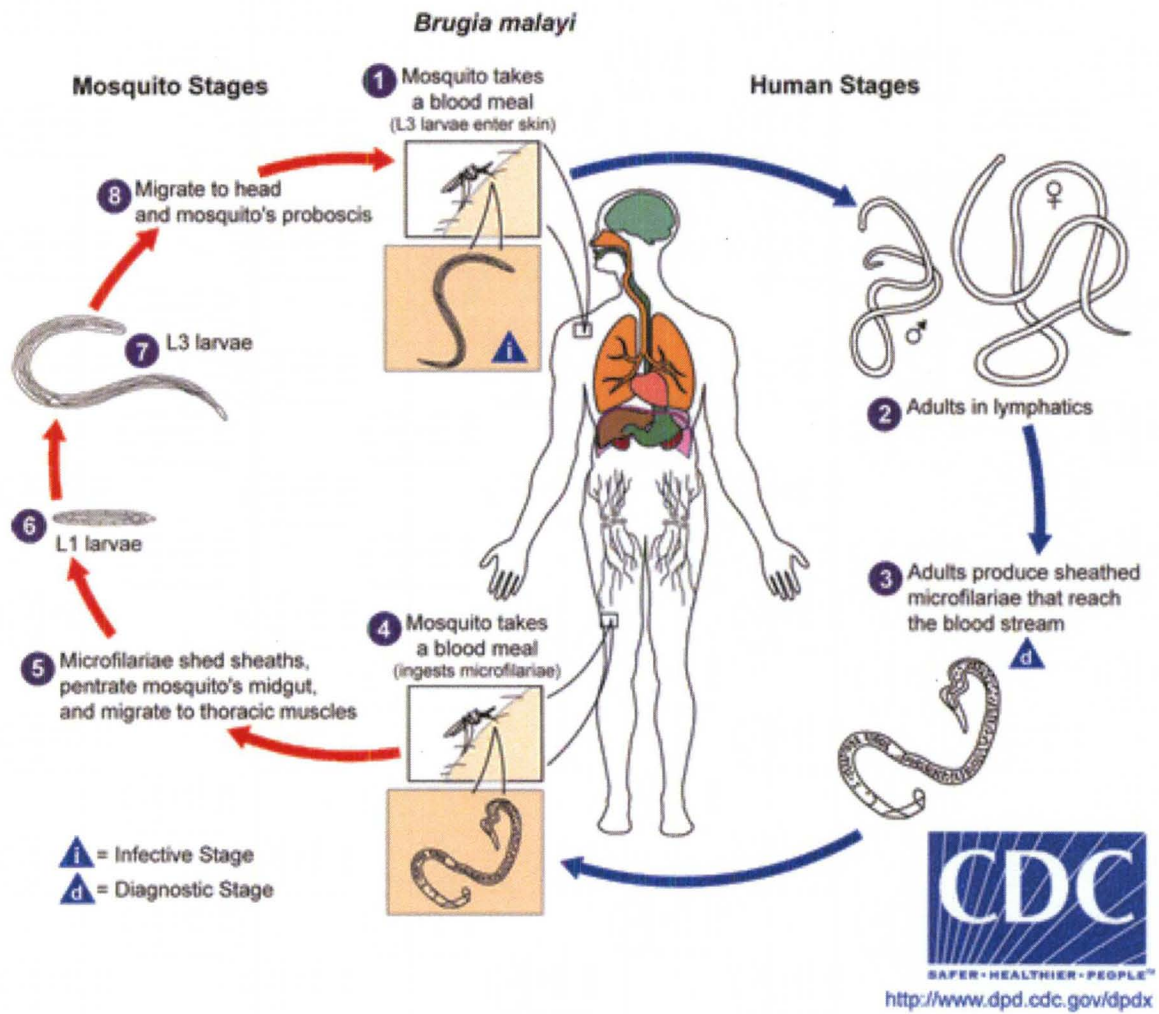
This image was taken from the CDC's Trichinellosis website (253).

Figure 7. Life Cycle Illustration of *Wuchereria bancrofti* (254)



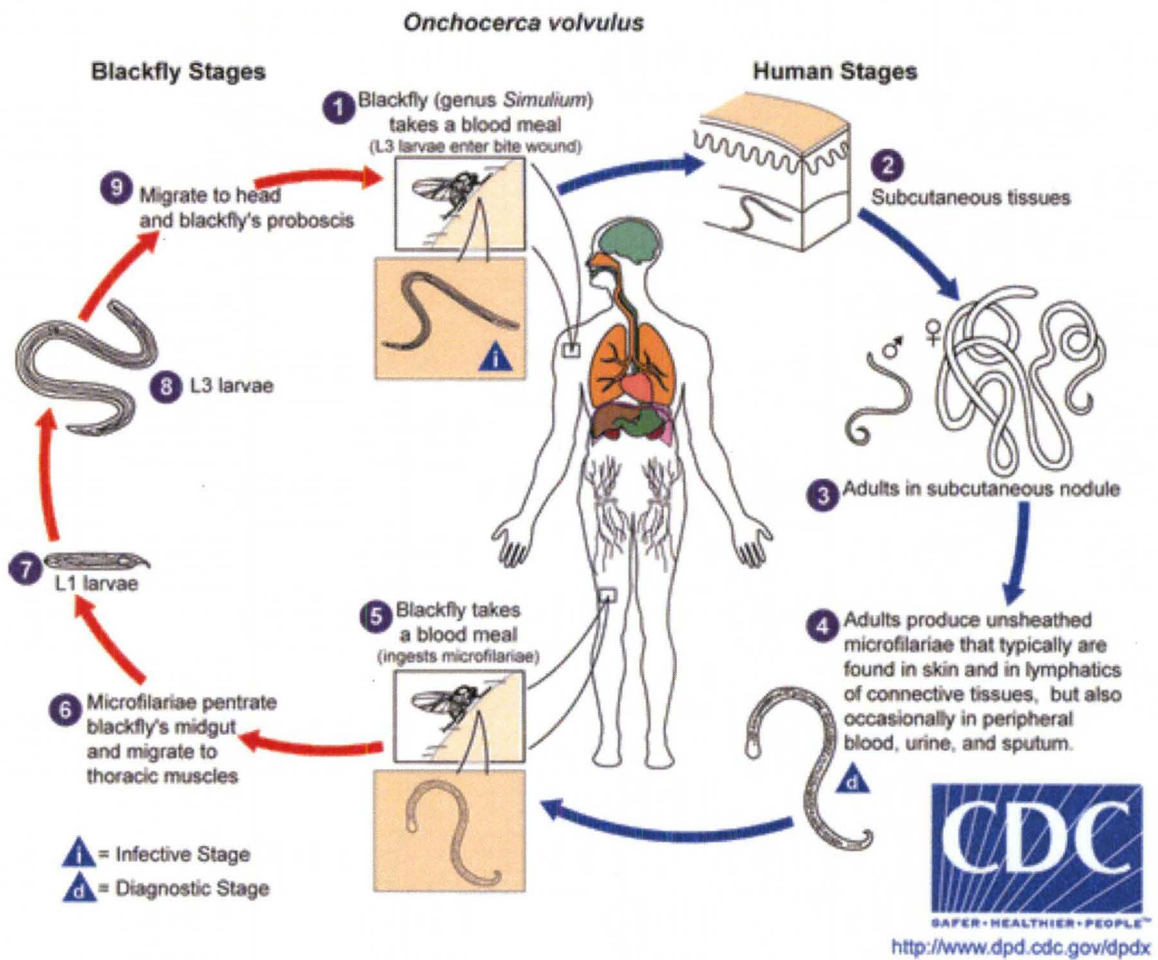
This image was taken from the CDC's Filariasis website (254).

Figure 8. Life Cycle Illustration of *Brugia malayi* (254)



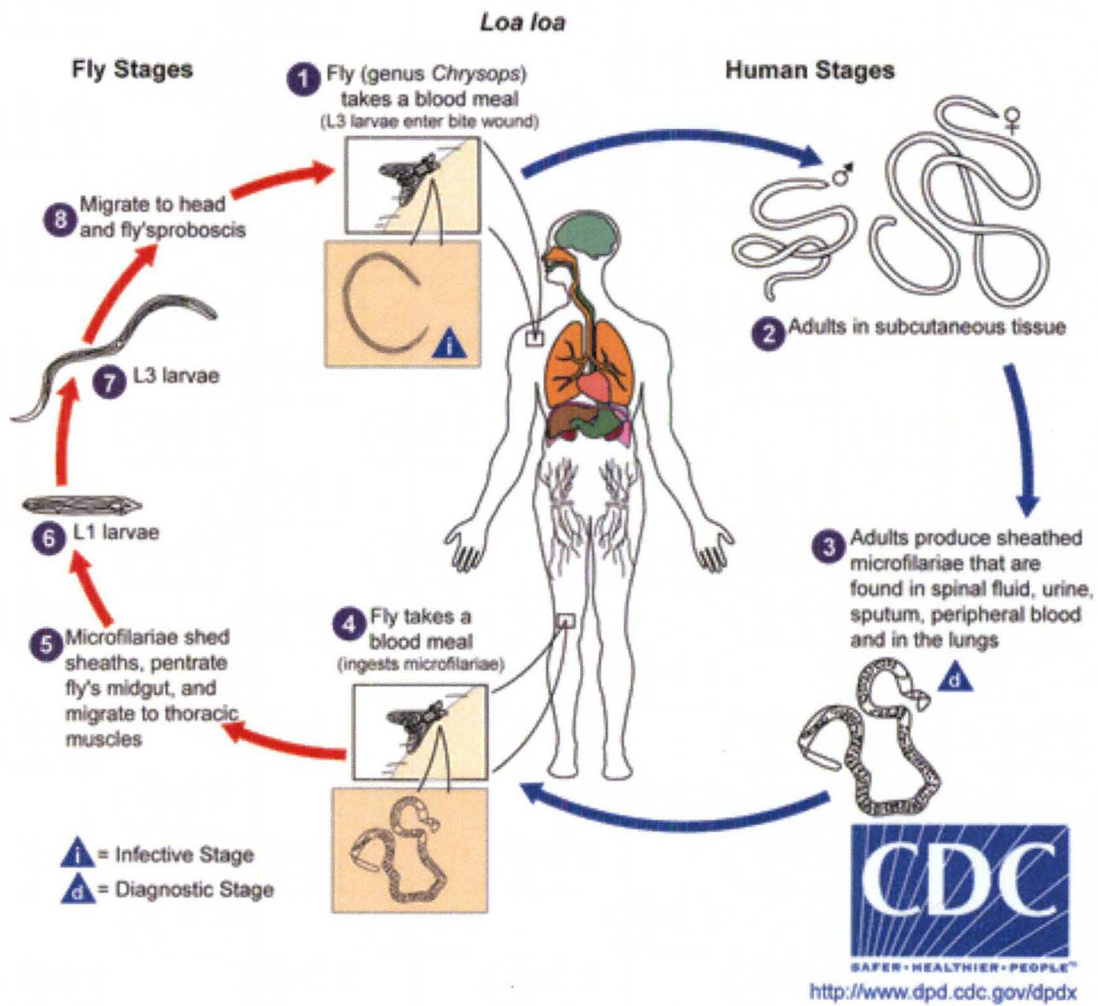
This image was taken from the CDC's Filariasis website (254).

Figure 9. Life Cycle Illustration of *Onchocerca volvulus* (254)



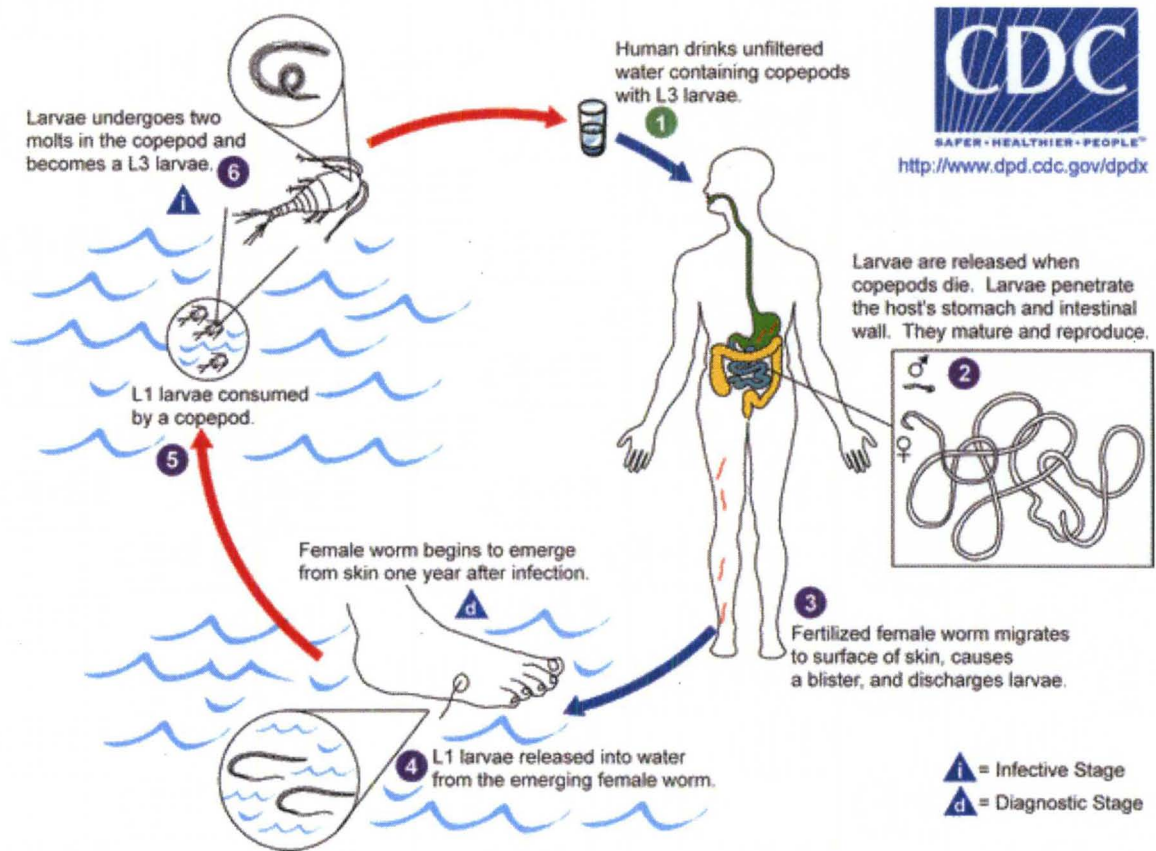
This image was taken from the CDC's Filariasis website (254).

Figure 10. Life Cycle Illustration of *Loa loa* (254)



This image was taken from the CDC's Filariasis website (254).

Figure 11. Life Cycle Illustration of *Dracunculus medinensis* (255)



This image was taken from the CDC's Dracunculiasis website (255).

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NATIONAL MEETING

PRESENTATIONS: Welsh EC, McGeeney TJ, Zierold KM. Healthy communication between parents and working teens and its influence on work-related injury. 139th Annual APHA Meeting, October 2011

Welsh EC, McGeeney TJ, Zierold KM. Evaluation of safety training for teenagers in regards to dangerous situation response for injury prevention. 139th Annual APHA Meeting, October 2011

Welsh EC, McGeeney TJ, Zierold KM. Knowledge of US child labor laws and influence on work-related injury among working teenagers. 139th Annual APHA Meeting, October 2011

Welsh EC, McGeeney TJ, Zierold KM. Use of dangerous equipment in the workplace and safety training: Effects on work-related injury in teenagers. 139th Annual APHA Meeting, October 2011

Welsh EC, McGeeney TJ, Zierold KM. Racial differences in supervision among teens injured at work. Eliminating Health and Safety Disparities at Work Conference (NIOSH), September 2011

McGeeney TJ, Welsh EC, Zierold KM. Quality of supervision and injury among teenagers in the workplace. 139th Annual APHA Meeting, October 2011

McGeeney TJ, Welsh EC, Zierold KM. Injury severity among working teenagers as related to safety training. 139th Annual APHA Meeting, October 2011