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Breaking the Silos – Obstacles and Opportunities for One Health in Filariases

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Abstract

Despite major similarities in biology and transmission, human and animal filarial parasites exhibit a number of species-specific characteristics that prompt the question if a One Health approach is sui for filariases. We elucidate that applying the One Health concept to filariases is not motivated by the pathology of these diseases nor their geographic overlap and only to a minor extent by the zoonotic potential of animal filariases. Instead, the benefits of adopting a One Health view on this disease complex are evident in the areas of drug resistance, the well-being of humans and their pets, and even more importantly for the discovery of new anthelmintics and research on the basic biology of the host–parasite interface that may lead to entirely novel treatment strategies.

1.1 Introduction

Why should one combine chapters on scientific research and reviews into human and animal filariases in a single book? An obvious reason is that these parasites exhibit a number of biological similarities; the pathogenic filariae belong within the superfamily of Filarioidea and the same family of Onchocercidae [1], and they all cause vector-borne diseases (meaning that all are adapted to live in two very distinct kinds of hosts, arthropods, and mammals). However, the preferred sites of infection and thus the pathologies they cause are quite different, even within the same host [2, 3], and their respective competent vectors also differ a great deal in biology [4, 5]. In a more pragmatic approach, the present control methods are

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Human and Animal Filariases: Landscape, Challenges, and Control, First Edition.
Edited by Ronald Kaminsky and Timothy G. Geary.

quite different for human and animal filariases and product profiles differ substantially [6]; however, the currently applied control methods rely to a large extent on the same chemical class, the macrocyclic lactones [7–10]. The common history of chemical control of filariases relates back to the discovery and development of ivermectin, firstly for veterinary purposes but subsequently applied for control of human onchocerciasis and lymphatic filariasis. In addition, it is for good reasons that Satoshi Ōmura and William C. Campbell were awarded the 2015 Nobel Prize in Medicine for that breakthrough innovation. Even now, control programs for human filariases [7] rely on ivermectin (among other drugs), and many veterinary products [9] contain ivermectin or subsequently developed macrocyclic lactones as the active pharmaceutical ingredients.

The One Health approach is currently endorsed by many authorities and has become popular in the scientific public health community [11, 12]. The term "One Health" was first used in 2003 for the valuable consideration of a combined perspective on the emerging severe acute respiratory disease (SARS) [12]. Subsequently, the correlation and deep connections between human and animal health, including wildlife health, and the need for an interdisciplinary and collaborative approach to respond to emerging diseases, were clearly outlined (Wildlife Conservation Society One World-One Health www.oneworldonehealth.org Sept 2004) [13], although the principles of the One Health concept originated several decades ago as "One Medicine, One World" [11]. The concept has not been applied to the study of parasites as frequently or intensively as might be desired, and, in our experience, veterinarians, physicians, and parasitologists do not always work together to the extent that they could or should, despite the excellent chances for mutual benefit.

1.2 Indicators for "One Health" Diseases

The obvious indicators for a link between research in human and animal diseases are (i) the origin of the pathogen, (ii) shared geographic or microhabitats, and (iii) a zoonotic characteristic of the disease. A number of emerging infections can be traced to animals, including wildlife, such as the pathogenic avian influenza H5N1 or SIV/HIV, associated with changes in human activities [14–16]. More recently, it has been hypothesized that SARS-CoV-2 originated from a β-coronavirus in the sarbecovirus (SARS-like virus) group that naturally infects bats and pangolins [17–19]. The risk of exposure may rise when the hosts of the same pathogen share common close habitats, such as the distribution of *Escherichia coli* in cattle grazing next to a lettuce field. Furthermore, at least 60% of human diseases are multi-host zoonoses [20], including parasitic infections such as leishmaniasis, human African trypanosomiasis, schistosomiasis, soil-transmitted helminthiasis, and lymphatic filariasis. Many of these diseases have been grouped as "Neglected Zoonotic Diseases" [21].

Table 1.1 Differences and potential synergies for human and animal filariases

Differences	Common/ different	Human health	Animal health
Geography	Different	Predominantly tropical, subtropical countries	Heartworm endemic areas in North America, etc.
Financial resources of involved communities	Different	Resource-limited; most drugs are donated	Heartworm control products are a major component of AH revenue, as well as for veterinary clinics
Treatment schedules	Different	Ideally once/year	Monthly to yearly
Zoonotic potential different for some species	Different	*D. repens*; *D. immitis* in human only anecdotal	—
	Different	—	No known animal reservoir for *W. bancrofti*
	Different	—	No animal host confirmed for *O. volvulus*, but related cattle species exist (*O. ochengi*)
Primary life stages targeted for chemotherapy	Different	L1, adult fertility	L3/L4, L1
Vectors	±: overlapping mosquito species, but flies not relevant for heartworm	Mosquitoes/ black flies	Mosquitoes
Possible synergies			
Zoonotic potential for some species	+	*Brugia malayi, Brugia pahangi*	Cats
	+	*Onchocerca lupi*	Dogs, cats
	+	*Dirofilaria repens*	Dog
Current drugs	+	Ivermectin, moxidectin, doxycycline, and diethylcarbamazine	Macrocyclic lactones, arsenicals, and doxycycline
Drug targets	+	Table 1.3	Table 1.3
Vaccine targets	+ Common epitopes	*O. volvulus*	*D. immitis*
Vector control	± for mosquitoes	For LF	For *D. immitis*
Costs	+ low cost of goods	Affordable for public health resources of local communities	Competitive margins for animal health industries
Diagnostics	+ Common protein or nucleic acid technologies	All human filariae	*D. immitis*

1.3 Zoonotic Characteristics of Human and Animal Filariases

Although eight filariae species have been reported to infect humans [22, 23], the zoonotic potential of filarial parasites appears to be limited. They all rely on insect vectors for transmission, but most of them express a more or less strict host specificity such that each species is confined to a single or few specific definitive and intermediate hosts [12]. The human pathogenic species *Brugia malayi* and *Brugia pahangi* can also infect cats, but the epidemiological significance of this alternative host is not known. Nevertheless, they are grouped as lymphatic filariases in the Neglected Zoonotic Diseases list [21], and cats can serve as competent hosts for *B. malayi*, with reported prevalence reaching as high as 20% in endemic feline populations [24]. Other than *Onchocerca volvulus*, the cause of onchocerciasis, only one other species in this genus, *Onchocerca lupi*, can use humans as host, although it is far more commonly found in dogs and cats (Table 1.1). The medical significance of this parasite has only recently been appreciated. *O. lupi* infection is now also proposed as an emerging zoonosis [25, 26]. Infections of humans with the canine pathogen *Dirofilaria immitis* occur, but the parasites almost never mature into adult stages and are described mostly as anecdotal, single case reports. However, the usually non-pathogenic species *Dirofilaria repens*, with a primary canine host, has higher zoonotic potential than *D. immitis*. Human infection is usually characterized by subcutaneous nodules, but larva migrans-like symptoms may also occur and, notably, larvae may reach the eye, becoming visible in the conjunctiva. Some reports have described the presence of microfilariae in humans [27].

1.4 Are Human and Animal Filariases Suitable for a "One Health" Approach?

Applying the One Health concept to filariases is not motivated by common pathological manifestations of these diseases nor their geographic overlap and only to a minor extent by the zoonotic potential of animal filariases (Table 1.1). Instead, the benefits of adopting a One Health view on this disease complex are evident in the areas of pharmacology of antifilarial drugs (including drug discovery and drug resistance), the use of common technology platforms for diagnosis and vaccine control, aspects of vector biology, and implications for the well-being of humans and their pets. Research on the basic biology of the host–parasite interface that may lead to entirely novel treatment strategies also illustrates the great potential of a One Health approach to filariases.

1.4.1 Pharmacology of Antifilarial Drugs

As reviewed in this volume [7–10], chemotherapy of human and veterinary filariases relies to a significant extent on the use of macrocyclic lactones, in particular the prototype of this class, ivermectin. Although ivermectin has some

filariid species- and host-specific effects [28, 29], the drug has microfilaricidal and temporary sterilization effects against human and veterinary filariae. Although microfilaricidal activity may be due to inhibition of secretion of parasite-derived immunomodulatory factors, a mechanistic explanation of the prolonged but reversible inhibition of fertility caused by the drug remains elusive. In contrast, the activity of ivermectin against L3 and L4 larvae of *D. immitis*, the basis for its use as a heartworm disease preventative, is not fully duplicated in *O. volvulus* or LF parasites, for unknown reasons. Although the microfilaricidal effects of diethylcarbamazine are evident against veterinary and human filariae, macrofilaricidal effects are only pronounced in LF parasites. The basis for the discrepancy between the profound pathology associated with killing of microfilariae in onchocerciasis and heartworm infections, but not in LF, is yet unresolved. Thus, although many commonalities are observed for antifilarial chemotherapy in human and veterinary medicine, the differences could provide a basis for comparative studies that may illuminate strategies for safer and more effective interventions.

1.4.2 Drug Resistance

Drug resistance is a well-known and urgently considered obstacle in animal health, particularly for livestock but also more recently for companion animals. Producers of small ruminants and cattle have experienced the disastrous effects of drug-resistant gastrointestinal nematodes, even to the point of forced abandonment of sheep farming in some areas with high-level resistance to all available anthelmintics. This major stressor has resulted in considerable investment in research to understand, monitor, and combat the issue of drug resistance in livestock animals [30]. These methods are now being applied to supplement human STH control programs, as concerns about the development of resistance to albendazole and mebendazole are heightened by the expansion and intensification of mass drug administration programs. In this case, extensive molecular biology work has clearly identified three alleles in a nematode beta-tubulin gene that cause benzimidazole resistance, and it is possible to monitor for the presence and spread of these alleles in human STH species [31]. Recently, one of these alleles (a change from phenylalanine to tyrosine at residue 167 of the beta-tubulin gene) has been reported to be present in *Ancylostoma caninum* (hookworms) in dogs in the United States [32], proving that benzimidazole resistance is a threat in hookworms and encouraging intensified monitoring for this mutation in areas that receive intensive treatment with these drugs for human STH infections.

A similar situation has developed in canine heartworms; recent experiments have proven that macrocyclic lactone-resistant *D. immitis* populations have appeared in the United States [33]. These resistant populations can break through previously effective macrocyclic lactone regimens, and microfilariae of these parasites are unaffected by these normally effective drugs. A mixture of genomic and phenotypic assays has conclusively demonstrated that resistant populations are genetically distinct from wild-type parasites and support the hypothesis that the phenotype of macrocyclic lactone resistance is multigenic. Although genomic analyses have not

yet been able to conclusively identify the genes that cause this phenotype, single nucleotide polymorphisms (SNPs) have been found that can identify resistant parasites with high confidence. The phenotype extends to all members of this drug class, but further work is needed to define the quantitative shift in sensitivity and to determine if the extent of resistance is the same for all macrocyclic lactones. At this time, new drugs or drug regiments that are fully effective against resistant parasites have not been identified or confirmed.

Although resistance to macrocyclic lactones has been suspected in human filariases (particularly in *O. volvulus*; [33]), the lack of a convenient laboratory host for these parasites has greatly limited the opportunity for experimental validation. It is to be hoped that, once the genes responsible for resistance to macrocyclic lactones in *D. immitis* are identified, research can be initiated to characterize and monitor them in populations of *O. volvulus* that have been intensively treated with ivermectin.

1.4.3 Antifilarial Drug Discovery

Almost all medicines used in veterinary practice were originally developed for human use, with the notable exception of antiparasitic drugs, many of which were developed for use in animals (Table 1.2). The examples include the majority of drugs used to treat coccidian infections of poultry and, particularly, anthelmintics. Indeed, only one drug used as an anthelmintic in animals was originally discovered in a human-use screening operation: diethylcarbamazine [10], which was discovered

Table 1.2 Anthelmintics discovered for AH, which were repurposed for HH

Active ingredient	Indication for animal health	Year of market entry	Indication for human health
Thiabendazole	GI nematodes	1964	Derivatives in use (mebendazole, albendazole, and flubendazole)
Albendazole	GI nematodes	1981	Lymphatic filariases GI nematodes Tapeworms (*Taenia* and *Echinococcus*)
Pyrantel	GI nematodes	1970s	GI nematodes
Oxantel	GI nematodes	1970s	GI nematodes
Ivermectin	GI nematodes, heartworm, arthropods	1981	Filariases, mites, lice
Moxidectin	As for ivermectin	1990	Onchocerciasis
Praziquantel	Tapeworms	1975	Schistosomiasis, other trematodes
Triclabendazole	*Fasciola* spp.	1983	*Fasciola hepatica*

All but diethylcarbamazine and doxycycline.

in a program looking for drugs for the treatment of lymphatic filariasis and only later transitioned for use as a heartworm preventative in dogs (now replaced by macrocyclic lactones for this indication).

However, relatively little investment was made in the animal health industry to discover new drugs for heartworm infections over the past 20 years. The most important reason for this status was the excellent record of efficacy and safety of the macrocyclic lactones, which greatly reduced the opportunity for new medicines to penetrate an already well-satisfied market. Furthermore, the necessity to maintain the long heartworm life cycle in dogs to detect efficacy endpoints requires much longer discovery programs than for GI nematodes, for example, and greatly limits the ability of academic researchers to operate in this area (along with animal use regulations that restrict the use of dogs for exploratory research). Finally, the marked consolidation of the animal health industry has led to a significant overall decline in the amount of private resources that can be devoted to the discovery of new drugs for prevention of heartworm disease.

Instead, significant investment has more recently been targeted for the discovery of new anthelmintics with macrofilaricidal activity for human use, especially for onchocerciasis, for which control programs that rely solely on the microfilaricidal action of ivermectin (and now moxidectin) may not achieve the goals of control programs in a cost- and time-effective manner. These efforts have led to the identification of several compounds that are in clinical trials or are candidates for such trials, including the veterinary anthelmintic emodepside, which has antifilarial activity in many animal models, auranofin, imatinib, and several antibiotics with anti-*Wolbachia* activity [10, 34, 35]. Although these compounds have known mechanisms of action, their antifilarial activity was discovered in phenotypic and infected animal models. Among them, only emodepside has been reported to have activity against *D. immitis* [36]. It is also important to recognize that other veterinary anthelmintics, such as monepantel [37] or derquantel [38], may have utility for filariases; further research is needed to support or reject this possibility.

Until recently, it has not been possible to maintain *Wuchereria bancrofti*, *O. volvulus*, or *D. immitis* in convenient laboratory rodent hosts to permit transition from *in vitro* to *in vivo* assays before testing promising compounds in dogs, a major limitation in the ability of academic or small industrial labs to participate in heartworm drug discovery programs. In the absence of such models, scientists commonly rely on surrogate filariid species maintained in permissive rodent hosts (e.g. *Litomosoides sigmodontis* in mice or *Brugia* spp. in jirds; see Ref. [39]) to identify compounds with promising antifilarial activity. These models can identify compounds with preventative activity, as well as microfilaricides and macrofilaricides, and represent a significant synergy in the One Health context. As reviewed in Ref. [39], novel immunosuppressed rodent models now permit more facile drug screening studies for *D. immitis* (mice and rats) and *O. volvulus* (mice). It remains somewhat challenging to procure infective larvae of *O. volvulus* for routine use, but this is simple for *D. immitis*, and it is possible that the heartworm screens could be used to generate and characterize new compounds with high likelihood of activity against the relevant stages of human filariid species.

It is important to emphasize in this regard that there is a disconnect between the life stages targeted for antifilarial chemotherapy in human and veterinary medicine. The overwhelming emphasis in veterinary medicine is to discover compounds that prevent maturation to adult parasites by targeting L3 and L4 stages as they develop in the host. Microfilaricidal activity is permissible but is not generally a therapeutic priority and can be a drawback (as seen with diethylcarbamazine). Adulticidal activity is clearly a drawback, as killing adult heartworms can lead to significant pathology in the host. In contrast, available human antifilarial drugs primarily target microfilariae, both in the host and developing in the adult female parasite, and preventative chemotherapy is not practiced or practical for these infections. In the absence of proven resistance to ivermectin, the emphasis has been on finding drugs that safely kill adult parasites. Thus, much research on potential drug targets in human filarial parasites may be applicable to heartworms, but it remains to be seen if the macrofilaricidal compounds now under evaluation for human filariases will find ready applications in veterinary medicine for heartworm prevention.

1.4.4 Discovery of Common Drug Targets

Because of their parasitic nature and their close phylogenetic relationship, human- and animal pathogenic filarial share some common drug targets (Table 1.3). The list includes targets for which activity against both human and animal filariids has been demonstrated, at least *in vitro*. There are chances that interference or inhibition of other targets in one filarial species, e.g. *D. immitis*, may be evident and relevant in other species. Activity in a particular mechanism-based screen cannot guarantee that the compound would be suitable for use against all filarial species as other parameters must also be met, such as stage of the life cycle, proper pharmacodynamics and pharmacokinetic characteristics, and safe toxicological profile in the respective host. Nevertheless, activity against a specific target could offer a valuable starting point for a drug discovery program with therapeutic implications for all filariases.

Table 1.3 Selected drug targets shared by animal and human pathogenic filariae.

Target	Function	References
Glutamate-gated chloride channels	Secretion, fertility	[10]
Intestinal proteases	Specific digestive enzymes of parasitic nematodes involved in feeding process	[40]
Peptide GPCRs	Motility, development, and feeding	[41]
sloK channel	Motility	[36, 42, 43]
Wolbachia	Viability and development	[35]
Kinases	Viability	[10, 34]

1.5 Insights into Host–Parasite Interactions: New Therapeutic and Diagnostic Opportunities

Current control of filariases in both human and veterinary medicine relies on drugs discovered empirically; except for diethylcarbamazine, all were discovered for use in other indications (trypanosomes, gastrointestinal nematodes, and bacteria). As noted, our understanding of the molecular pharmacology underlying their therapeutic benefit remains incomplete, and indeed, our understanding of the basic biochemistry and physiology of filariid parasites has been little advanced over the past decades. In part, this reflects the difficulty of maintaining sufficiently large numbers of parasites at all stages of the life cycle in laboratories, as culture systems that can replicate the life cycle in the absence of hosts have not been developed. The use of surrogate (non-target) filariid species is necessary even now as it is quite challenging if not essentially impossible to obtain living specimens of, for instance, adult *O. volvulus*, *W. bancrofti*, and *D. immitis*. The situation is made more complex by the fact that we do not know if parasites removed from the host and placed in culture accurately reflect their biology *in situ* and for how long they are useful surrogates *in vitro* (see, for example, Ref. [44]).

However, the development of sensitive and highly quantitative technology platforms for genomic, proteomic, metabolomic, transcriptomic, and microRNA (miRNA) analyses is revolutionizing our ability to interrogate the host–filariid parasite interface and the molecular language that serves to maintain or prevent the establishment of a chronic infection. Comparative studies may eventually provide insights into the basis for host–parasite specificity, focusing on the species-specific molecules that are essential for enabling a chronic infection (possibly including proteins, metabolites, and/or non-coding RNAs). Work in model or surrogate filariid species may allow rapid extrapolation to medically important species, an important benefit of a One Health paradigm. Some advances have been made in our ability to perform functional genomics experiments in filariae [45], but more intensive investment in this area has the potential to radically transform our understanding of the host–parasite interface and to reveal new targets and novel strategies for prevention and control of these infections in humans and animals.

Clinically important advances may be expected from these studies, not only in terms of new targets for chemotherapy [46]. Identification of critically important immunomodulatory proteins can lead to the rational selection of vaccine antigens; by neutralizing those proteins, we may be able to convert permissive into non-permissive hosts for pathogenic filariid species. Similarly, obtaining the menu of abundantly secreted parasite-derived proteins and nucleic acids can be expected to offer new strategies for stage- and species-specific diagnosis of pathogenic species in field-friendly, cost-effective platforms. New vaccines and diagnostics can rationally be evaluated in lab animal models before development for use in people and/or dogs and cats.

1.6 Health Benefits

Although the direct health benefits of chemotherapy for human filariases are obvious and profound, the indirect human health benefits of chemotherapy for prevention of heartworm disease should be included in a consideration of the One Health landscape around filariid parasites. In many parts of the world, companion animals, particularly dogs and cats, have been integrated into family life, sometimes to the extent that pets are considered to be family members. The pet–owner bond, particularly as it relates to the well-being of these animals, contributes to a large extent to the overall life experience of the involved people, and as such, healthy pets can contribute to human health by providing many positive psychological and physical benefits for their owners [47–49]. Thus, although treatment of human filariases leads to direct improvements in the well-being of communities, families, and individuals, significant health benefits are also apparent in companion animal owners who are free from worry over possible heartworm infections and pet ill health.

1.7 Conclusions

Despite significant differences in vectors, tissue location, pathology, and strategies for control, the phylogenetic and pharmacological similarities among the important filarial species that parasitize humans and animals merit the application of a One Health approach to their study. Much can be learned about their diagnosis, physiology, biochemistry, and host manipulation strategies in comparative analyses that will benefit researchers, physicians, and veterinarians, as well as scientists who strive to develop better tools to control them. Research on filarial parasites that cause neglected tropical diseases and heartworm has for too long been focused on empirical discovery of diagnostics and treatments; very little emphasis has been placed on understanding the complex biology of the host–parasite interface from which novel approaches may emerge. The research highlighted in this book identifies areas of work that will benefit scientists in both sectors and can encourage joint efforts to enhance our ability to eliminate these parasites as significant health burdens.

Acknowledgment

We are thankful to JakobZinsstag for critical reviewing of the manuscript.

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