The relevance of studying insect-nematode interactions for human disease

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Abstract

Vertebrate-parasitic nematodes cause debilitating, chronic infections in millions of people worldwide. The burden of these so-called “neglected tropical diseases” is often carried by poorer socio-economic communities in part because research on parasitic nematodes and their vertebrate hosts are challenging and costly. However, complex biological and pathological processes can be modelled in simpler organisms. Here we consider how insight into the interactions between entomopathogenic or insect-pathogenic nematodes (EPN), their insect hosts and bacterial symbionts may reveal novel treatment targets for parasitic nematode infections. We argue that a combination of approaches that target the nematodes, as well as the interaction of the pathogens with insect vectors and bacterial symbionts, offer potentially effective, but underexplored opportunities.

[113 words]

KEYWORDS: vertebrate-parasitic nematodes, entomopathogenic nematodes, inter-species interactions, alternative treatment options, vector control, model organisms

Introduction

Vertebrate-parasitic nematodes (VPN) infect millions of people worldwide (James et al., 2018; WHO, 2007). These nematode infections are usually chronic and target a variety of organ systems – from the skin to the gastrointestinal tract (Blaxter 1998). Some of the most deleterious are the filarial nematodes that damage the lymphatic system – known as lymphatic filariasis – causing debilitating limb oedema (elephantiasis) and even renal damage (Bockarie et al., 2009; Taylor et al., 2010).

From a public health perspective, the main treatment strategy for filariasis is preventative chemotherapy in the form of Mass Drug Administration (MDA) (CDC, 1993; Molyneux & Zagaria, 2002; WHO, 2019a). Mass Drug Administration programmes administer antiparasitic medication to all members of a community at risk without first testing individuals for an infection. Mathematical models predicted that these regimens are not sufficient to keep the disease controlled in areas with high prevalence (Michael et al., 2004). Among the challenges to MDA is compliance as successful elimination requires at least five doses of anti-filarial drugs and one or more doses are often missed (Burgert-Brucker et al., 2020; De Souza et al., 2020). Only two combinations of three different drugs are available to treat filariasis and all three target the larval stage of the nematodes only, leaving adult worms unaffected (Ottesen et al., 1997; WHO, 2011).

The wide-spread use of a limited number of anti-filarial medications also carry the risk of drug resistance developing in these nematodes (Michael et al., 2004; Schwab et al., 2005). With antimicrobial resistance on the WHO's list of top ten threats to global health, it is crucial to optimise additional/alternative treatment options (Friedrich, 2019; WHO, 2019b). The interactions between nematodes, insects and bacteria – concerning both nematodes responsible for human disease and insect-parasitic nematodes – provide opportunities to explore such alternatives.

Nematode-insect-bacterial interactions

Nematodes capable of infecting and killing insects are known as entomopathogenic nematodes (EPN) (Lewis & Clarke, 2012; Torres-Barragan et al., 2011; Zhang et al., 2008). Entomopathogenic nematodes are used as beneficial biological control agents of insect pests, providing an alternative to expensive, broad-spectrum, chemical insecticides (Benseddik et al., 2021; Coppel & Mertins, 1977; Vega et al., 2012). Nematodes from the *Heterorhabditis* and *Steinernema* genera are frequently used in biocontrol and are therefore the EPN most commonly studied (Dillman & Sternberg, 2012; Kaya & Gaugler, 1993). In addition to playing host to nematodes, insects are often involved in the nematode life cycle as intermediate hosts or vectors (Katiyar & Singh, 2011; Ryss et al., 2005). Dispersal by an insect vector is a characteristic of many animal and some plant-parasitic nematodes.

Bacteria often play a role in nematode-insect interactions. *Heterorhabditis* and *Steinernema* coevolved with bacteria in the genera *Photorhabdus* and *Xenorhabdus* to become virulent insect pathogens (Adams et al., 2006; Boemare, 2002). The bacteria contribute to a suitable environment for nematode development and multiplication by killing and digesting the insect host and preventing other micro-organisms from colonising the carcass (Brivio et al., 2005). In the case of parasitic nematodes causing human diseases such as filariasis, an intracellular endosymbiont, *Wolbachia*, is involved in the nematode's survival and reproduction (Taylor et al., 2005, 2010). Furthermore, *Wolbachia* also influences many insects' biology, either as mutualist or as pathogen (Hughes & Rasgon, 2012; Werren et al., 1995).

The relative ease with which insects and nematodes can be cultured and manipulated – with or without their bacterial symbionts – make them useful models for observing interspecies relationships (Hallem et al., 2007; Stock, 2005). Host-parasite interactions such as the insect's immune response to invasion and how the nematode overcomes the immune response can be investigated through studying parasitic nematodes and their insect hosts and vectors (Brivio & Mastore, 2018; Cooper & Eleftherianos, 2016). Parasitic nematodes and symbiotic bacteria also provide opportunities to study factors influencing mutualism, such as the evolution of

biochemical communication between host and symbiont (Ciche & Sternberg, 2007; Ruby, 2008).

The value of studying the interactions between insects and their parasites extends beyond gaining insight into the particular pest or biocontrol management system. These investigations may also reveal novel treatment strategies for challenging human conditions. For instance, the insect vectors and bacterial symbionts of parasitic nematodes present promising targets for combatting these infections in humans. Additionally, the systems that insect parasitic nematodes use to evade and even suppress the host immune response are increasingly well studied (Angeles et al., 2020; White et al., 2020). This not only enables the nematodes to survive and cause disease within the host, but to influence co-existing infections as well as non-infectious conditions of the host. The close phylogenetic relatedness amongst human and insect infecting nematodes, as well as the presence of orthologous genes involved in virulence and defence, mean the organisms involved in entomopathogenic nematode parasitism (nematode parasite, insect host, bacterial symbiont), can be used as simpler models to study nematode infections in humans.

Insect and bacterial options to manage nematode infections

Target the insects

Filarial nematodes are transmitted to their vertebrate hosts by mosquitoes of different genera (Bockarie et al., 2009). Consequently, transmission can be interrupted by targeting the insect vector. Vector control usually consists of spraying insecticides inside homes and distributing netting material impregnated with long-lasting insecticides (Pedersen & Mukoko, 2002; WHO, 1984). Other vector control strategies target the source of mosquitoes, for instance, polystyrene beads that form floating layers on potential breeding sites such as pit latrines and water tanks suffocate mosquito larvae, leading to a drastic decline in the adult mosquito population (Curtis et al., 2002; Maxwell et al., 1990, 1999). Combined vector control and MDA suppress the transmission of filariasis more effectively and with less resurgence than MDA alone. A focus on integrated vector management in addition to MDA was therefore

included in the strategic plan for 2010-2020 of the Global Programme to Eliminate Lymphatic Filariasis (WHO, 2010).

Effective vector control also impacts diseases that co-exist with filariasis, for instance malaria and Dengue fever which are transmitted by the same mosquitoes (Manga, 2002). Unfortunately, wherever chemicals are used, the risk of resistance developing exists and resistance to a number of insecticides have been documented (Rodriguez et al., 1993; WHO, 1984). Similarly, the use of polystyrene beads is not fool-proof as all the potential mosquito breeding sites in a community have to be identified and treated, its use is limited to smaller bodies of still-standing water, and it is not effective for all mosquito species. Flooding of pits containing these polystyrene beads leads to unsightly pollution and loss of larvicidal function (Curtis et al., 2002).

With an increasing number of insect genomes being sequenced and made available in public databases, together with the development of advanced gene-editing tools, gene modification provides an alternative to traditional chemical or environmental vector control measures (Kim & Kim, 2014; Yin et al., 2016). Genetically-modified mosquitoes are already being released to control mosquito populations responsible for the spread of Dengue fever, for example (Carvalho et al., 2015; Lacroix et al., 2012). Releasing transgenic organisms is of course not without risks. Modified genes might be transmitted to the wild-type population and changes in the wild-type population could affect the virulence of the vector-borne pathogen. Molecular insight into the interactions between parasite, vector and bacterial symbiont are therefore important, not only to discover additional treatment targets, but also to ensure the safety of existing and developing control measures (Castillo et al., 2011).

Target the bacteria

The nematode species responsible for the majority of filariasis all rely on an intracellular bacterium for development and reproduction (Taylor, Bandi, et al., 2005; Taylor et al., 2010). The bacterial symbiont, *Wolbachia*, belongs to the order Rickettsiales – the same order containing *Rickettsia* species associated with tick-bite fever and other spotted fevers. The drugs used to treat rickettsia infections, especially

doxycycline, successfully suppress filarial infections (Mand et al., 2012; Taylor, Makunde, et al., 2005). Unfortunately, a course of treatment with doxycycline lasts six to eight weeks and cannot be used in pregnant women or children.

By targeting the bacteria and its molecular pathways, instead of the eukaryotic pathways of nematodes, drugs with potentially fewer adverse reactions on humans can be developed. The combination of high-throughput assays and bioinformatics tools facilitate the screening of millions of compounds for desirable properties (Clare et al. 2015). One such study identified five compounds with potential fast-acting anti-*Wolbachia* activity (Clare 2019). These compounds can now be tested in animal and clinical trials.

Wolbachia bacteria also colonise many insect species and other arthropods, either as mutualists or pathogens (Hughes & Rasgon, 2012; Jeyaprakash & Hoy, 2000; Werren et al., 1995). *Wolbachia* endosymbionts influence the host insect's reproductive fitness and can increase the fertility of infected females or cause sterility in males (Miller et al., 2010). Artificial infection of previously uninfected insects can be lethal or reduce the capability to vector certain pathogens (Moreira, Iturbe-Ormaetxe, et al., 2009; Moreira, Saig, et al., 2009; Suh et al., 2009). The ability of *Wolbachia* to alter insect reproduction, earns them a place in vector control and these bacteria are already being investigated for use against malaria, dengue fever and lymphatic filariasis (Brelsfoard et al., 2008; Hughes et al., 2011; Turley et al., 2009). As in the case of insect vectors and nematode parasites, the molecular mechanisms underlying these interspecific interactions are in need of further investigation (Hughes & Rasgon, 2012).

The use of nematodes and insects as mini-host models

Models for nematode infections in humans

Nematode infections of humans are regarded as "neglected tropical diseases" (WHO, 2019a). Especially poorer socio-economic communities carry the burden of the filarial diseases (Brelsfoard et al., 2008; O'lorcain & Holland, 2000; WHO, 2007). In order to "Ensure healthy lives and promote well-being for all at all ages", the eradication of

neglected tropical diseases forms part of the 2030 Agenda for Sustainable Development (UN, 2015). Research into filariasis is, however, hampered by the cost and complexity of studying infections in their vertebrate hosts.

The use of simpler organisms to study complex biological and pathological processes is not new. The free-living nematode, *Caenorhabditis elegans* has since the 1960s been put to use in the investigation of human conditions ranging from neurological degeneration and aging to metabolic diseases and cancer (Markaki & Tavernarakis, 2010; Tissenbaum, 2015). Genes involved in the pathogenicity of medically important fungi, including *Candida* spp. and *Cryptococcus* spp., play similar roles when infecting and killing model invertebrates such as *Drosophila melanogaster* and *C. elegans* (Chamilos et al., 2007). Subsequently, susceptible invertebrates present the opportunity to study fungal virulence mechanisms and even test antifungal treatment without exposing patients to added risks.

Both VPN and EPN suppress the immune responses of their host (McSorley et al., 2013; Navarro et al., 2013). As VPN and EPN are closely related phylogenetically (Bai et al., 2013; Blaxter & Koutsovoulos, 2015), orthologues of genes associated with host immunosuppression can be found in both types of nematodes (Lu et al., 2017). Insect-pathogenic *Heterorhabditis bacteriophora* shares ancestral traits with free-living *C. elegans* but is phylogenetically positioned closer to the mammal-parasitic nematodes. *H. bacteriophora*, therefore, represents a “bridge” species to translate existing knowledge of molecular pathways in *C. elegans* and other EPN, to VPN (Bai et al., 2013). Compared to mammalian parasites, EPN culturing requires fewer resources in terms of laboratory equipment and personal protection, as well as host animals. As a result, entomopathogenic nematodes and their insect hosts offer an alternative option to study nematode infections of humans and other mammals.

Models for bacterial infections in humans

Knowledge on interspecies interactions gained from studying EPN systems is not limited to the field of nematode infections. The symbiotic bacteria of EPN represent as important models to study bacteria-host interactions, as nematode-host interactions

(Lewis & Clarke, 2012). Bacteria from the genera *Photorhabdus* and *Xenorhabdus* (the symbionts of *Heterorhabditis* and *Steinernema*, respectively) form part of the Enterobacteriaceae (Tailliez et al., 2010). Other members of this family include the common human pathogens, *Escherichia coli*, *Salmonella* spp., *Yersinia* spp. and *Proteus* spp. In fact, *Proteus mirabilis* – one of the most common causative agents of urinary tract and hospital-acquired infections (Armbruster and Mobley 2012; Chen et al. 2012) – is the closest phylogenetic relative to *Photorhabdus* and *Xenorhabdus*. Therefore, an understanding of pathogenicity in the entomopathogenic bacteria can contribute to a search for similarities in the human pathogen. The discovery of such orthologous virulence pathways could reveal strategies for the prevention and treatment of *P. mirabilis* infection in humans.

Conclusion

Insight into the interactions at play within one multi-species system will benefit the improvement or control of the system in question, but could also prove applicable in other settings. The current treatment strategies that only target the nematodes responsible for human infection are unlikely to relieve the burden of chronic, debilitating disease in areas with high prevalence (Stolk et al., 2018). However, a combination of approaches that also control or manipulate the interaction with insect vectors and bacterial symbionts, has a better chance of being effective and well-tolerated.

Insect- and vertebrate-parasitic nematodes both suppress the host immune response, but EPN are much easier, safer, and cheaper to culture than human pathogens. Although nematode-insect models may not mimic human diseases in every respect, simpler systems do make the application of genetic and molecular techniques easier in order to dissect pathogen-host interactions (Markaki & Tavernarakis, 2010).

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References

Adams, B. J., Fodor, A., Koppenhöfer, H. S., Stackebrandt, E., Stock, S. P., & Klein, M. G. (2006). Biodiversity and systematics of nematode–bacterium entomopathogens. *Biological Control*, *38*(1), 4–21.

Angeles, J. M. M., Mercado, V. J. P., & Rivera, P. T. (2020). Behind enemy lines: Immunomodulatory armamentarium of the schistosome parasite. *Frontiers in Immunology*, *11*.

Armbruster, C. E., & Mobley, H. L. T. (2012). Merging mythology and morphology: The multifaceted lifestyle of *Proteus mirabilis*. *Nature Reviews Microbiology*, *10*(11), 743–754.

Bai, X., Adams, B. J., Ciche, T. A., Clifton, S., Gaugler, R., Kim, K., Spieth, J., Sternberg, P. W., Wilson, R. K., & Grewal, P. S. (2013). A lover and a fighter: The genome sequence of an entomopathogenic nematode *Heterorhabditis bacteriophora*. *PLOS One*, *8*(7), e69618.

Benseddik, Y., Joutei, A. B., Laghfiri, M., Blenzar, A., Amiri, S., Ezrari, S., Saleh, A., Mokrini, F., Tahiri, A., Dababat, A. A., & Lahlali, R. (2021). Efficacy assessment of entomopathogenic nematodes native to Morocco against the white grubs *Rhizotrogus obesus* Lucas and *Geotrogus olcesii* Fairmaire (Coleoptera: Scarabaeidae). *Crop Protection*, *143*, 105534.

Blaxter, M. L. (1998). *Caenorhabditis elegans* is a nematode. *Science*, *282*(5396), 2041–2046.

Blaxter, M. L., & Koutsovoulos, G. (2015). The evolution of parasitism in Nematoda. *Parasitology*, *142*(S1), S26–S39.

Bockarie, M. J., Pedersen, E. M., White, G. B., & Michael, E. (2009). Role of vector control in the global program to eliminate lymphatic filariasis. *Annual Review of Entomology*, *54*(1), 469–487.

Boemare, N. (2002). Interactions between the partners of the entomopathogenic bacterium nematode complexes, *Steinernema-Xenorhabdus* and *Heterorhabditis-Photorhabdus*. *Nematology*, *4*(5), 601–603.

Brelsfoard, C. L., Séchan, Y., & Dobson, S. L. (2008). Interspecific hybridization yields strategy for South Pacific filariasis vector elimination. *PLOS Neglected Tropical Diseases*, *2*(1), e129.

Brivio, M. F., & Mastore, M. (2018). Nematobacterial complexes and insect hosts: Different weapons for the same war. *Insects*, *9*(3), 117.

Brivio, M. F., Mastore, M., & Pagani, M. (2005). Parasite-host relationship: A lesson from a professional killer. *Invertebrate Survival Journal*, *2*, 41–53.

Burgert-Brucker, C. R., Zoerhoff, K. L., Headland, M., Shoemaker, E. A., Stelmach, R., Karim, M. J., Batcho, W., Bougouma, C., Bougma, R., Didier, B. B., Georges, N., Marfo, B., Lemoine, J. F., Pangaribuan, H. U., Wijayanti, E., Coulibaly, Y. I., Doumbia, S. S., Rimal, P., Salissou, A. B., … Brady, M. (2020). Risk factors associated with failing pre-transmission assessment surveys

(pre-TAS) in lymphatic filariasis elimination programs: Results of a multi-country analysis. *PLOS Neglected Tropical Diseases*, *14*(6), e0008301.

Carvalho, D. O., McKemey, A. R., Garziera, L., Lacroix, R., Donnelly, C. A., Alphey, L., Malavasi, A., & Capurro, M. L. (2015). Suppression of a field population of *Aedes aegypti* in Brazil by sustained release of transgenic male mosquitoes. *PLOS Neglected Tropical Diseases*, *9*(7), e0003864.

Castillo, J. C., Reynolds, S. E., & Eleftherianos, I. (2011). Insect immune responses to nematode parasites. *Trends in Parasitology*, *27*(12), 537–547.

CDC. (1993). Recommendations of the international task force for disease eradication. *Morbidity and Mortality Weekly Report*, *42*(16), 1–38.

Chamilos, G., Lionakis, M. S., Lewis, R. E., & Kontoyiannis, D. P. (2007). Role of mini-host models in the study of medically important fungi. *The Lancet Infectious Diseases*, *7*(1), 42–55.

Chen, C., Chen, Y., Lu, P., Lin, W., Chen, T., & Lin, C. (2012). *Proteus mirabilis* urinary tract infection and bacteremia: Risk factors, clinical presentation, and outcomes. *Journal of Microbiology, Immunology and Infection*, *45*(3), 228–236.

Ciche, T. A., & Sternberg, P. W. (2007). Postembryonic RNAi in *Heterorhabditis bacteriophora*: A nematode insect parasite and host for insect pathogenic symbionts. *BMC Developmental Biology*, *7*(1), 101.

Clare, R. (2019). *Anti-filarial drug discovery: Targeting the* Wolbachia *endosymbiont* [PhD Thesis]. University of Liverpool.

Clare, R. H., Cook, D. A. N., Johnston, K. L., Ford, L., Ward, S. A., & Taylor, M. J. (2015). Development and validation of a high-throughput anti-*Wolbachia* whole-cell screen: A route to macrofilaricidal drugs against onchocerciasis and lymphatic filariasis. *Journal of Biomolecular Screening*, *20*(1), 64–69.

Cooper, D., & Eleftherianos, I. (2016). Parasitic nematode immunomodulatory strategies: Recent advances and perspectives. *Pathogens*, *5*(3), 58.

Coppel, H. C., & Mertins, J. W. (1977). Examples of insect pest suppression utilizing nematodes. In *Biological insect pest suppression* (pp. 98–105). Springer-Verlag.

Curtis, C. F., Malecela-Lazaro, M., Reuben, R., & Maxwell, C. A. (2002). Use of floating layers of polystyrene beads to control populations of the filaria vector *Culex quinquefasciatus*. *Annals of Tropical Medicine & Parasitology*, *96*(8), 97.

De Souza, D. K., Gass, K., Otchere, J., Htet, Y. M., Asiedu, O., Marfo, B., Biritwum, N.-K., Boakye, D. A., & Ahorlu, C. S. (2020). Review of MDA registers for lymphatic filariasis: Findings, and potential uses in addressing the endgame elimination challenges. *PLOS Neglected Tropical Diseases*, *14*(5), e0008306.

Dillman, A. R., & Sternberg, P. W. (2012). Entomopathogenic nematodes. *Current Biology*, *22*(11), R430–R431.

Friedrich, M. J. (2019). WHO's top health threats for 2019. *JAMA*, *321*(11), 1041–1041.

Hallem, E. A., Rengarajan, M., Ciche, T. A., & Sternberg, P. W. (2007). Nematodes, bacteria, and flies: A tripartite model for nematode parasitism. *Current Biology*, *17*(10), 898–904.

Hughes, G. L., Koga, A. R., Xue, P., Fukatsu, T., & Rasgon, J. L. (2011). *Wolbachia* infections are virulent and inhibit the human malaria parasite *Plasmodium falciparum* in *Anopheles gambiae*. *PLOS Pathogens*, *7*(5), e1002043.

Hughes, G. L., & Rasgon, J. L. (2012). *Wolbachia* infections in arthropod hosts. In F. E. Vega & H. K. Kaya (Eds.), *Insect pathology* (Second, pp. 351–366). Elsevier Inc.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858.

Jeyaprakash, A., & Hoy, M. A. (2000). Long PCR improves *Wolbachia* DNA amplification: *Wsp* sequences found in 76% of sixty-three arthropod species. *Insect Molecular Biology*, *9*(4), 393–405.

Katiyar, D., & Singh, L. (2011). Filariasis: Current status, treatment and recent advances in drug development. *Current Medicinal Chemistry*, *18*(14), 2174–2185.

Kaya, H. K., & Gaugler, R. (1993). Entomopathogenic nematodes. *Annual Review of Entomology*, *38*(1), 181–206.

Kim, H., & Kim, J. (2014). A guide to genome engineering with programmable nucleases. *Nature Reviews. Genetics*, *15*(5), 321.

Lacroix, R., McKemey, A. R., Raduan, N., Wee, L. K., Ming, W. H., Ney, T. G., AA, S. R., Salman, S., Subramaniam, S., & Nordin, O. (2012). Open field release of genetically engineered sterile male *Aedes aegypti* in Malaysia. *PLOS One*, *7*(8), e42771.

Lewis, E. E., & Clarke, D. J. (2012). Nematode parasites and entomopathogens. In F. E. Vega & H. K. Kaya (Eds.), *Insect pathology* (2nd ed., pp. 395–424). Academic Press.

Lu, D., Macchietto, M., Chang, D., Barros, M. M., Baldwin, J., Mortazavi, A., & Dillman, A. R. (2017). Activated entomopathogenic nematode infective juveniles release lethal venom proteins. *PLOS Pathogens*, *13*(4), e1006302.

Mand, S., Debrah, A. Y., Klarmann, U., Batsa, L., Marfo-Debrekyei, Y., Kwarteng, A., Specht, S., Belda-Domene, A., Fimmers, R., & Taylor, M. J. (2012). Doxycycline improves filarial lymphedema independent of active filarial infection: A randomized controlled trial. *Clinical Infectious Diseases*, *55*(5), 621–630.

Manga, L. (2002). Vector-control synergies, between 'Roll Back Malaria' and the Global Programme to Eliminate Lymphatic Filariasis, in the African region. *Annals of Tropical Medicine & Parasitology*, *96*(8), 129.

Markaki, M., & Tavernarakis, N. (2010). Modeling human diseases in *Caenorhabditis elegans*. *Biotechnology Journal*, *5*(12), 1261–1276.

Maxwell, C. A., Curtis, C. F., Haji, H., Kisumku, S., Thalib, A. I., & Yahya, S. A. (1990). Control of Bancroftian filariasis by integrating therapy with vector control using polystyrene beads in wet

pit latrines. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *84*(5), 709–714.

Maxwell, C. A., Mohammed, K., Kisumku, U., & Curtis, C. F. (1999). Can vector control play a useful supplementary role against bancroftian filariasis? *Bulletin of the World Health Organization*, *77*(2), 138–143.

McSorley, H. J., Hewitson, J. P., & Maizels, R. M. (2013). Immunomodulation by helminth parasites: Defining mechanisms and mediators. *International Journal for Parasitology*, *43*(3–4), 301–310.

Michael, E., Malecela-Lazaro, M. N., Simonsen, P. E., Pedersen, E. M., Barker, G., Kumar, A., & Kazura, J. W. (2004). Mathematical modelling and the control of lymphatic filariasis. *The Lancet Infectious Diseases*, *4*(4), 223–234.

Miller, W. J., Ehrman, L., & Schneider, D. (2010). Infectious speciation revisited: Impact of symbiont-depletion on female fitness and mating behavior of *Drosophila paulistorum*. *PLOS Pathogens*, *6*(12), e1001214.

Molyneux, D. H., & Zagaria, N. (2002). Lymphatic filariasis elimination: Progress in global programme development. *Annals of Tropical Medicine & Parasitology*, *96*(8), 15.

Moreira, L. A., Iturbe-Ormaetxe, I., Jeffery, J. A., Lu, G., Pyke, A. T., Hedges, L. M., Rocha, B. C., Hall-Mendelin, S., Day, A., Riegler, M., Hugo, L. E., Johnson, K. N., Kay, B. H., McGraw, E. A., van den Hurk, A. F., Ryan, P. A., & O'Neill, S. L. (2009). A *Wolbachia* symbiont in *Aedes aegypti* limits infection with dengue, Chikungunya, and Plasmodium. *Cell*, *139*(7), 1268–1278.

Moreira, L. A., Saig, E., Turley, A. P., Ribeiro, J. M. C., O'Neill, S. L., & McGraw, E. A. (2009). Human probing behavior of *Aedes aegypti* when infected with a life-shortening strain of *Wolbachia*. *PLOS Neglected Tropical Diseases*, *3*(12), e568.

Navarro, S., Ferreira, I., & Loukas, A. (2013). The hookworm pharmacopoeia for inflammatory diseases. *International Journal for Parasitology*, *43*(3), 225–231.

O'lorcain, P., & Holland, C. V. (2000). The public health importance of *Ascaris lumbricoides*. *Parasitology*, *121*(S1), S51–S71.

Ottesen, E. A., Duke, B. O. L., Karam, M., & Behbehani, K. (1997). Strategies and tools for the control/elimination of lymphatic filariasis. *Bulletin of the World Health Organization*, *75*(6), 491–503.

Pedersen, E. M., & Mukoko, D. A. (2002). Impact of insecticide-treated materials on filaria transmission by the various species of vector mosquito in Africa. *Annals of Tropical Medicine and Parasitology*, *96*(Supplement 2), S91-95.

Rodriguez, M., Ortiz, E., Bisset, J. A., Hemingway, J., & Saledo, E. (1993). Changes in malathion and pyrethroid resistance after cypermethrin selection of *Culex quinquefasciatus* field populations of Cuba. *Medical and Veterinary Entomology*, *7*(2), 117–121.

Ruby, E. G. (2008). Symbiotic conversations are revealed under genetic interrogation. *Nature Reviews. Microbiology*, *6*(10), 752–762.

Ryss, A., Vieira, P., Mota, M. M., & Kulinich, O. (2005). A synopsis of the genus *Bursaphelenchus* Fuchs, 1937 (Aphelenchida: Parasitaphelenchidae) with keys to species. *Nematology*, *7*(3), 393–458.

Schwab, A. E., Boakye, D. A., Kyelem, D., & Prichard, R. K. (2005). Detection of benzimidazole resistance–associated mutations in the filarial nematode *Wuchereria bancrofti* and evidence for selection by albendazole and ivermectin combination treatment. *The American Journal of Tropical Medicine and Hygiene*, *73*(2), 234–238.

Stock, S. P. (2005). Insect-parasitic nematodes: From lab curiosities to model organisms. *Journal of Invertebrate Pathology*, *89*(1), 57–66.

Stolk, W., Prada, J. M., Smith, M. E., Kontoroupis, P., De Vos, A. S., Touloupou, P., Irvine, M. A., Brown, P., Subramanian, S. V., Kloek, M., Michael, E., Hollingsworth, T. D., & de Vlas, S. (2018). Are alternative strategies required to accelerate the global elimination of lymphatic filariasis? Insights from mathematical models. *Clinical Infectious Diseases*, *66*(Supl 4), S260–S266.

Suh, E., Mercer, D. R., Fu, Y., & Dobson, S. L. (2009). Pathogenicity of life-shortening *Wolbachia* in *Aedes albopictus* after transfer from *Drosophila melanogaster*. *Applied and Environmental Microbiology*, *75*(24), 7783–7788.

Tailliez, P., Laroui, C., Ginibre, N., Paule, A., Pagès, S., & Boemare, N. (2010). Phylogeny of *Photorhabdus* and *Xenorhabdus* based on universally conserved protein-coding sequences and implications for the taxonomy of these two genera. Proposal of new taxa: *X. vietnamensis* sp. Nov., *P. luminescens* subsp. *Caribbeanensis* subsp. Nov., *P. luminescens* subsp. *Hainanensis* subsp. Nov., *P. temperata* subsp. *Khanii* subsp. Nov., *P. temperata* subsp. *Tasmaniensis* subsp. Nov., and the reclassification of *P. luminescens* subsp. *Thracensis* as *P. temperata* subsp. *Thracensis* comb. Nov. *International Journal of Systematic and Evolutionary Microbiology*, *60*(8), 1921–1937.

Taylor, M. J., Bandi, C., & Hoerauf, A. (2005). *Wolbachia* bacterial endosymbionts of filarial nematodes. *Advances in Parasitology*, *60*, 245–284. https://doi.org/10.1016/S0065-308X(05)60004-8

Taylor, M. J., Hoerauf, A., & Bockarie, M. (2010). Lymphatic filariasis and onchocerciasis. *The Lancet*, *376*(9747), 1175–1185.

Taylor, M. J., Makunde, W. H., McGarry, H. F., Turner, J. D., Mand, S., & Hoerauf, A. (2005). Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: A double-blind, randomised placebo-controlled trial. *The Lancet*, *365*(9477), 2116–2121.

Tissenbaum, H. A. (2015). Using *C. elegans* for aging research. *Invertebrate Reproduction & Development*, *59*(S1), 59–63.

Torres-Barragan, A., Suazo, A., Buhler, W. G., & Cardoza, Y. J. (2011). Studies on the entomopathogenicity and bacterial associates of the nematode *Oscheius carolinensis*. *Biological Control*, *59*(2), 123–129.

Turley, A. P., Moreira, L. A., O'Neill, S. L., & McGraw, E. A. (2009). *Wolbachia* infection reduces blood-feeding success in the dengue fever mosquito, *Aedes aegypti*. *PLOS Neglected Tropical Diseases*, *3*(9), e516.

UN. (2015). *Transforming our world: The 2030 agenda for sustainable development*. General Assembly 70 Session.

Vega, F. E., Kaya, H. K., & Tanada, Y. (Eds.). (2012). *Insect pathology* (2nd ed.). Elsevier/Academic Press.

Werren, J. H., Windsor, A., D. O., & Guo, H., L. M. (1995). Distribution of *Wolbachia* among neotropical arthropods. *Proceedings: Biological Sciences*, *262*(1364), 197–204. JSTOR.

White, M. P. J., McManus, C. M., & Maizels, R. M. (2020). Regulatory T-cells in helminth infection: Induction, function and therapeutic potential. *Immunology*, *160*(3), 248–260.

WHO. (1984). *Lymphatic filariasis: Fourth report of the WHO Expert Committee on Filariasis*. World Health Organization.

WHO. (2007). *Global Programme to Eliminate Lymphatic Filariasis: Progress report on mass drug administration in 2006* (ISSN 0049-8114). World Health Organization.

WHO. (2010). *Progress report 2000-2009 and strategic plan 2010-2020 of the Global Programme to Eliminate Lymphatic Filariasis: Halfway towards eliminating lymphatic filariasis*. World Health Organization.

WHO. (2011). Global Programme to Eliminate Lymphatic Filariasis: Progress report on mass drug administration, 2010. *Weekly Epidemiological Record = Relevé Épidémiologique Hebdomadaire*, *86*(35), 377–387.

WHO. (2019a). Global update on implementation of preventive chemotherapy against neglected tropical diseases in 2018. *Weekly Epidemiological Record*, *94*(38), 425–438.

WHO. (2019b). *Ten threats to global health in 2019*. World Health Organisation. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

Yin, C., Shen, G., Guo, D., Wang, S., Ma, X., Xiao, H., Liu, J., Zhang, Z., Liu, Y., Zhang, Y., Yu, K., Huang, S., & Li, F. (2016). InsectBase: A resource for insect genomes and transcriptomes. *Nucleic Acids Research*, *44*(D1), D801–D807.

Zhang, C., Liu, J., Xu, M., Sun, J., Yang, S., An, X., Gao, G., Lin, M., Lai, R., He, Z., Wu, Y., & Zhang, K. (2008). *Heterorhabditidoides chongmingensis* gen. Nov., sp. Nov. (Rhabditida: Rhabditidae), a novel member of the entomopathogenic nematodes. *Journal of Invertebrate Pathology*, *98*(2), 153–168.