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PERSPECTIVE

PEOPLE AND NATURE
BRITISH ECOLOGICAL SOCIETY

# Three reasons why expanded use of natural enemy solutions may offer sustainable control of human infections

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## Abstract

1. Many infectious pathogens spend a significant portion of their life cycles in the environment or in animal hosts, where ecological interactions with natural enemies may influence pathogen transmission to people. Yet, our understanding of natural enemy opportunities for human disease control is lacking, despite widespread uptake and success of natural enemy solutions for pest and parasite management in agriculture.
2. Here we explore three reasons why conserving, restoring or augmenting specific natural enemies in the environment could offer a promising complement to conventional clinical strategies to fight environmentally mediated pathogens and parasites. (a) Natural enemies of human infections abound in nature, largely understudied and undiscovered; (b) natural enemy solutions could provide ecological options for infectious disease control where conventional interventions are lacking; and, (c) many natural enemy solutions could provide important co-benefits for conservation and human well-being.
3. We illustrate these three arguments with a broad set of examples whereby natural enemies of human infections have been used or proposed to curb human disease burden, with some clear successes. However, the evidence base for most proposed solutions is sparse, and many opportunities likely remain undiscovered, highlighting opportunities for future research.

KEYWORDS

biological control, disease control, disease ecology, infectious disease, natural enemies, sustainability, sustainable development

Susanne H. Sokolow and Giulio A. De Leo are Senior Authors.

[Correction added on 23 October 2021, after first online publication: The author's name Guilio has been corrected to Giulio.]

## 1 | INTRODUCTION

The war against citrus pests in ancient Chinese orchards was not won by eliminating insect life, but by cultivating it. A strategy still in use today, farmers introduced yellow citrus ants, voracious predators of beetles, flies and hymenopteran crop pests, to orchards to protect fruit from pest damage (Huang & Yang, 1987). This is the earliest documented example of biological control, or pest control using natural enemies. Active management of these natural 'enemies of our enemies' is a key component of integrated pest management in agriculture, around which ecosystem services evaluations and commercial industries worth billions of dollars have emerged (Losey & Vaughan, 2006; Naranjo et al., 2015; Naylor & Ehrlich, 1997; Power, 2010). Like agricultural pests, many parasites and pathogens that cause disease in humans spend a considerable amount of their life cycle in the environment or in animal hosts where natural enemy interactions can influence their abundance and, subsequently, transmission to humans (Figure 1). Here, we argue that broadening our understanding of interactions between environmentally mediated infectious organisms and their natural enemies could help to identify novel ecological interventions for human health. Effective ecological interventions, or actions that leverage ecological mechanisms to protect human health (Sokolow et al., 2019), may also offer co-benefits in other sectors like biodiversity conservation and sustainable development.

Human health benefits from natural enemies all the time. On the skin, mucosa and in the gut, healthy communities of beneficial microbes can suppress the proliferation of harmful bacteria through resource competition and the production of antimicrobial compounds (Dethlefsen et al., 2007; Ng et al., 2013). Applying an ecosystem perspective to the microbial infections we host has led to clinical trials and commercialization of some natural enemy-based therapeutics, including probiotics for use against *Salmonella enterica* serovar Typhimurium, *Clostridium difficile* and upper respiratory infections (Bernaola Aponte et al., 2013; Goldenberg et al., 2017; Hao et al., 2015; Kassam et al., 2013; Koretz & Rotblatt, 2004). More recently, bacteriophages (naturally occurring viruses that infect and kill bacteria and archaea) have received increased attention as a promising alternative to antibiotics for multidrug-resistant infections (Dedrick et al., 2019; Nobrega et al., 2015).

In the environment, where the focus of this Perspective lies, natural regulation of infectious organisms and disease hosts is an ongoing process that may benefit human health by limiting populations of disease-causing organisms. Free-living stages of parasites and pathogens, and their non-human hosts are embedded in ecological communities, where they are used as resources by consumers

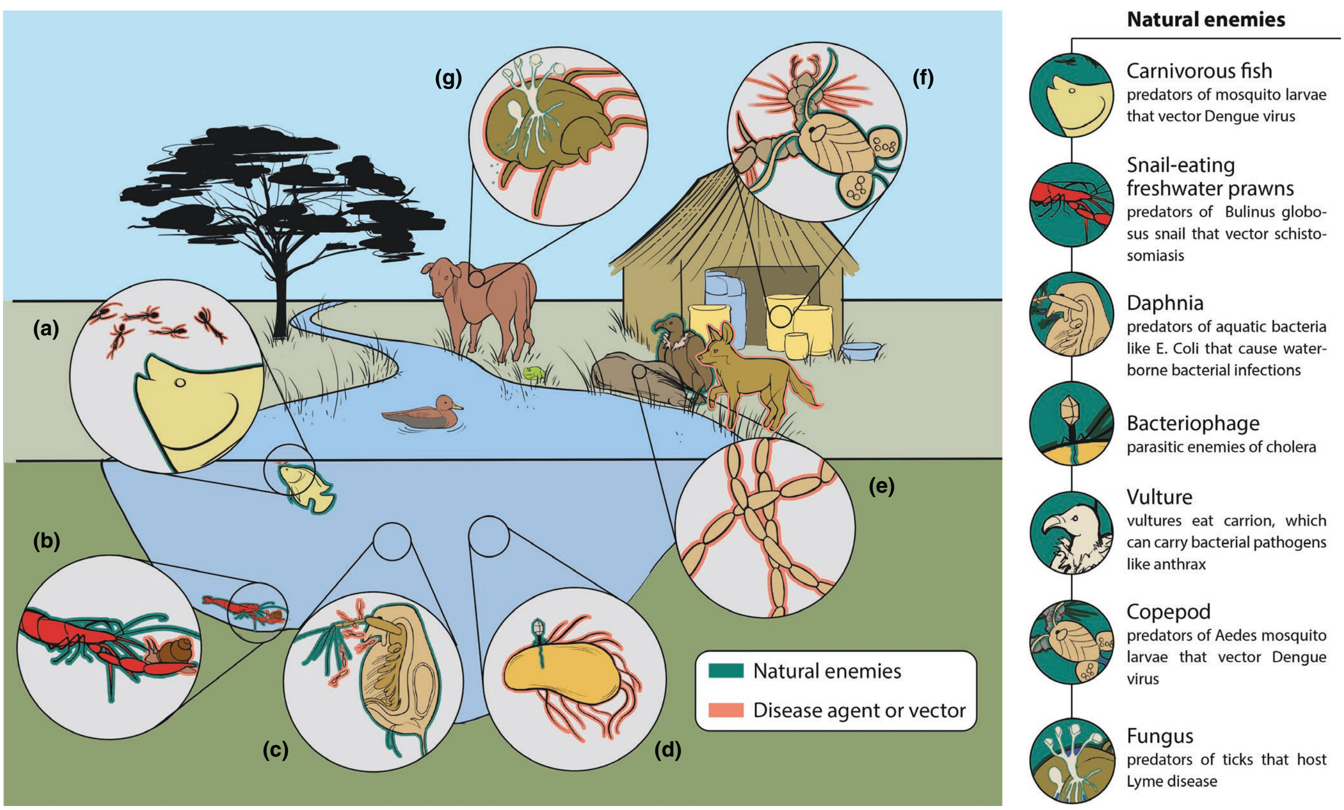


**FIGURE 1** Natural enemies (outlined in green) of human infections in the environment (outlined in orange). (a) Larvivorous fish predators of mosquito vectors. (b) *Macrobrachium* spp. crustacean predators of schistosomiasis intermediate host snails. (c) *Daphnia* spp. crustacean predators of aquatic bacteria, including *Escherichia coli* and *Campylobacter jejuni*. (d) Phage predation on *Vibrio cholerae*. (e) Vulture consumers of disease-carrying carcasses, and competitors of wild dogs that can carry rabies. (f) Copepod predators of larval *Aedes* mosquito vectors of dengue virus. (g) Fungal pathogen, *Beauveria bassiana*, of tick disease vectors

and compete with other organisms for their own resources. Some of the natural enemies of important disease vectors, including mosquitoes, ticks, flies and snails, have been identified, revealing a wide range of naturally occurring enemies (Erlanger et al., 2008; Jenkins, 1964; Kamareddine, 2012; Keiser et al., 2005; Lacey & Lacey, 1990; Lardans & Dissous, 1998; Pointier et al., 2011; Samish et al., 2004). However, very little is known about the true breadth of natural enemy interactions that could potentially be used for human infection control through natural enemy protection (i.e. species or habitat conservation) or implementation (i.e. population augmentation or introduction). Of those interactions that have been identified as potential ecological interventions, quantitative evidence on their epidemiological impact and cost-effectiveness is severely lacking (Lugassy et al., 2021; McKinnon et al., 2016). Subsequently, there is limited knowledge and little operational use of specific natural enemy tools for human infection control in the environment, leading to an under-appreciation of the ecosystem services that they may provide to people. This is in contrast to a rich history of natural enemy research and implementation for pest and pathogen control in agriculture, including through classical (inoculative) and conservation biological control strategies (Barratt et al., 2018).

The modern era of clinical disease intervention, which dominates public health strategies to control environmentally mediated diseases (Remais & Eisenberg, 2012), has vastly improved the health and wellbeing of billions of people worldwide (Bloom & Cadarette, 2019). At the same time, billions of people remain at-risk for long-standing, re-emerging and emerging infectious diseases, many with important environmental reservoirs that clinical interventions alone may not adequately address (Bloom & Cadarette, 2019; Garchitorena et al., 2017). Therefore, we argue three key reasons why the human health impacts of natural enemy interactions with disease-causing organisms in the environment deserve more attention. (a) Natural enemies of disease-causing organisms abound in nature, largely undiscovered; (b) natural enemy solutions could provide ecological options for infectious disease control where conventional (chemical-based) approaches are limited or insufficient; and, (c) natural enemy solutions could offer a wide range of co-benefits in other sectors like conservation and food security. First, we explore these three reasons with relevant examples. Next, we discuss challenges that have hindered research on and implementation of natural enemy solutions, and how we might overcome some of those challenges in the near future.

## 2 | THREE REASONS WHY NATURAL ENEMY SOLUTIONS FOR SUSTAINABLE CONTROL OF HUMAN INFECTIONS DESERVE MORE ATTENTION

### 2.1 | Reason 1: Natural enemies of disease-causing organisms abound in nature

Growing interest in understanding the ecological contexts of infectious disease transmission may help incentivize research to better understand the diversity and health impacts of natural enemies. Parasites and pathogens are increasingly well-recognized as components of complex ecosystems (Horwitz & Wilcox, 2005). Several prominent research movements embrace this perspective as critical to better prevent infections and protect human health. These include EcoHealth, One Health and Planetary Health (Charron, 2012; Evans & Leighton, 2014; Whitmee et al., 2015). Each movement has its own distinct flavour (Lerner & Berg, 2017), but all recognize the importance of understanding how ecological interactions influence human health outcomes (Lerner & Berg, 2017). However, empirical evidence that links knowledge to actionable solutions to leverage ecological interactions for infection control is sparse (Lugassy et al., 2021; McKinnon et al., 2016). This is especially true for natural enemies: in a recent systematic evidence map linking ecosystem functions to 14 vector-borne and zoonotic diseases, the epidemiological impact of predation and competition was identified as a major knowledge gap (Lugassy et al., 2021).

Despite the evidence gaps, opportunities to identify novel natural enemy solutions for health abound, because natural enemies abound in nature. We focus on three distinct types of natural enemies that nearly all living organisms contend with—predators, parasites and ecological competitors. In agriculture, natural enemy solutions typically exploit consumer–resource (or enemy–victim) interactions (i.e. interactions with predators, parasitoids and pathogenic micro-organisms; van Lenteren et al., 2018). We include ecological competitors in our broad definition of natural enemies because the negative outcomes of competition on population sizes of infectious organisms can, in certain contexts, have substantial impacts on infectious disease transmission, and could be leveraged as natural enemy solutions for human health.

#### 2.1.1 | Predators

Virtually all organisms serve as food for other organisms. Predation is a form of consumer–resource relationship in which a predator attacks, kills and ingests prey (Lafferty et al., 2015). Predators can influence the transmission of environmentally mediated disease by consuming free-living infectious organisms or non-human hosts (Figure 2a). Predators can be grouped according to their diet breadth. Generalists consume a wide variety of prey, while specialists have a narrow prey breadth. In the 20th century, agricultural biocontrol activities tended to focus on specialist predators and parasitoids, as diet specificity was considered a key attribute for natural enemies that were to be introduced to exotic habitats (Symondson et al., 2002). However, high prey specificity also means that specialists can become scarce when prey is limited (Symondson et al., 2002), thus leading to periods of increased human disease risk when specialist predator density declines and prey density increases (Ostfeld & Holt, 2004). The role of generalist predators in providing a chronic, background level of pest suppression in agriculture has been appreciated more recently, evidenced by a growing movement towards conservation biological control. Under this scheme, efforts

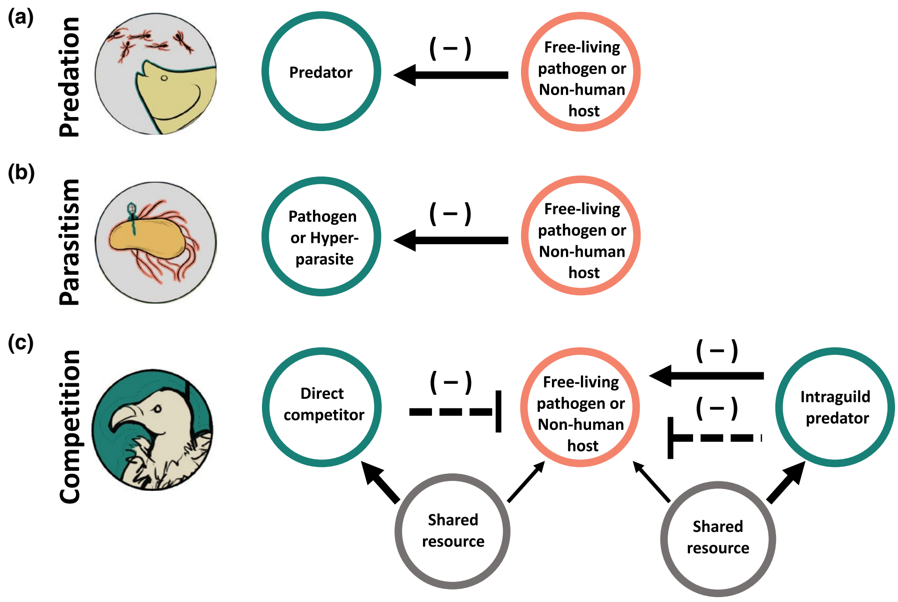


FIGURE 2 General categories of natural enemy interactions with disease-causing organisms: (a) predation; (b) parasitism and (c) competition, including intra-guild predation, a special case of competition when an organism is both a competitor and a predator of another organism

are made to enhance the abundance of native generalist predators (individual species or guilds of multiple species) for sustained pest suppression (Symondson et al., 2002).

The beneficial role that predators play in human infection control has often been appreciated only retrospectively, after their depletion was found to correlate with disease outbreaks (Ostfeld & Holt, 2004). For example, overfishing in Lake Malawi resulted in population losses of cichlid fish, some of which predated on freshwater snails that serve as the intermediate host for human schistosomiasis (snail fever). The schistosomiasis outbreak that followed the depletion of fish stocks suggested that the fish had been performing an important ecosystem service for human health (Stauffer & Madsen, 2012; Stauffer et al., 2006). Field studies to better quantify the ecosystem services that predators provide for human health are badly needed, because efforts to conserve, restore or augment natural predator populations could potentially yield benefits for both health and the environment. Currently, evidence that natural predators can be proactively harnessed to improve disease control is poor.

### 2.1.2 | Parasites

Parasitism is another type of consumer–resource relationship in which one organism, the parasite, lives on or inside a host, benefitting at the host's expense (Figure 2b; Lafferty & Kuris, 2002). Parasites and pathogens (including hyperparasites, or parasites of parasites) are commonly used for pest control in agriculture and have to a lesser extent been investigated as tools for human disease control. Leveraging natural enemy research for biopesticide development in agriculture, some insect pathogens or their chemical derivatives were commercialized for use against human disease vectors. For example, *Bacillus thuringiensis* subsp. *israelensis* (Bti) and *Lysinibacillus sphaericus* (formerly *Bacillus sphaericus*) are widely available biopesticides effective against several major disease vectors, including mosquitoes and blackflies (vectors of onchocerciasis; Regis et al., 2001). More recently, *Metarhizium brunneum* and *Beauveria bassiana*—entomopathogenic fungi that induce high mortality in adult *Anopheles* spp. mosquitoes (malaria vectors), *Ixodes* spp. black-legged ticks (Lyme disease vectors) and larval *Phlebotomus* sand flies (leishmaniasis vectors)—have been developed for commercial use (Figure 1; Amora et al., 2009; Farenhorst et al., 2011; Fernandes & Elias Pinheiro Bittencourt, 2008; George et al., 2013; Hornbostel et al., 2005; Kaaya, 2000; Scholte et al., 2006).

Bacteriophages, or highly specific viruses of bacteria, are some of the most abundant and diverse microbes on earth. In food sciences, bacteriophages are currently being investigated as a type of preservative that kills food-borne pathogens like *Salmonella*, *Campylobacter*, *Listeria*, *Staphylococcus* and *Vibrio* spp. (Bai et al., 2016). Bacteriophages have also been considered as a potential control agent against *Vibrio cholerae*, both as a disease therapy and as an environmental intervention (Yen et al., 2017; Figure 1). However, limited evidence for both of these cholera control strategies is mixed (Faruque et al., 2005; Nelson et al., 2009; Silva-Valenzuela & Camilli, 2019). Even so, bacteriophages continue to generate attention as an important potential alternative to antibiotics, as concern over antibiotic-resistant pathogens in the environment and in people grows.

### 2.1.3 | Ecological competitors

Competition for resources can limit populations of free-living parasites and pathogens, or their non-human hosts (Figure 2c). For example, there is some (marginally significant) evidence that biologically diverse rodent communities in the western United States support a lower Sin Nombre hantavirus abundance, potentially because resource competition limits the relative abundance of an important reservoir host, *Peromyscus maniculatus* (Clay et al., 2009). In Caribbean countries such as Antigua, Guadeloupe, Martinique, Montserrat, Puerto Rico and St. Lucia, snail-borne schistosomiasis disease has been dramatically reduced in low-transmission settings, thanks in part to the accidental or intentional introduction of competitor snail species. These snail competitors included *Pomacea glauca*, *Marisa cornuarietis*, *Melanoides tuberculata* or *Tarebia granifera*, presence of which reduced, displaced or prevented colonization of specific schistosome-transmitting snails species (Pointier & Jourdane, 2000).

In certain contexts, competition may drive a 'dilution effect'. The dilution effect hypothesis posits that disease transmission rates tend to be lower in more diverse ecological communities. In theory, this occurs because (a) biodiversity decreases the relative abundance of suitable hosts, or (b) biodiversity decreases encounter rates between disease-causing organisms and suitable hosts, and increase that between disease-causing organisms and unsuitable hosts (Rohr et al., 2020; Wood et al., 2014). For example, some experimental evidence suggests that human risk for schistosomiasis is inversely related to local diversity of trematodes (the class of parasites to which schistosomes belong). Laboratory and field studies suggest that, where trematode diversity is high, competition between larval stages of human and non-human trematodes to infect snail hosts reduces the relative abundance of schistosome infections in snails (Johnson et al., 2009; Laidemitt et al., 2019; Sulieman & Pengsakul, 2013; Tang et al., 2009). Even though the indirect effect of specific competitors on human disease risk is difficult to quantify, diverse guilds of competitors might be helping to mitigate human disease risk, outside our notice, all the time.

## 2.2 | Reason 2: Natural enemy solutions could provide ecological options for infectious disease control where conventional interventions are limited

Major advances in medicine and global health have vastly reduced infectious disease mortality (Dye, 2014). Even so, environmentally mediated diseases including malaria, diarrhoea and most of the neglected tropical diseases (NTDs) remain some of the most significant causes of morbidity and mortality world-wide (Bloom & Cadarette, 2019; Dye, 2014; WHO, 2016). NTDs alone infect over a billion people, predominantly the world's poorest and most vulnerable populations. Meanwhile, other infectious diseases have emerged or re-emerged in recent decades, including West Nile virus, Zika, plague, avian influenza and Lyme disease, among others (Kilpatrick & Randolph, 2012; Morens et al., 2004). Conventional intervention strategies, like vaccines, drug treatment and insecticide-based vector control, are crucial tools in the fight against environmentally mediated diseases. However, there are currently no licensed vaccines to prevent malaria or any neglected tropical disease, apart from dengue (Hotez, 2019). Mass drug administration (the primary strategy to reduce global NTD morbidity and mortality) can be highly effective, but does not prevent infections. Consequently, a survey conducted between 2007 and 2011 of more than 400 NTD experts concluded that elimination of several major NTDs, including soil-transmitted helminths and schistosomiasis, will not be feasible with mass drug administration alone (Keenan et al., 2013). Finally,

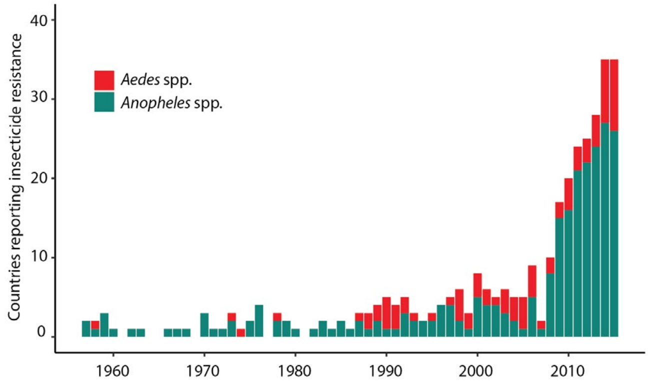


**FIGURE 3** The number of countries reporting mosquito vector resistance to one or more major classes of insecticide used globally in the fight against mosquito-borne diseases. Data were obtained from the Vectorbase database (Giraldo-Calderón et al., 2015); resistance data were filtered to include resistance reported as per cent mortality, and resistance was conservatively defined as mosquito mortality less than 95%

insecticide resistance is a growing problem challenging long-term control of many important insect vectors of disease (Nauen, 2007; Figure 3). To enhance sustainable control of environmentally mediated diseases, complementary strategies that target the environmental reservoirs of diseases are badly needed (Evan Secor, 2014; Garchitorena et al., 2017; Remais & Eisenberg, 2012).

Promisingly, modelling studies on Buruli ulcer and schistosomiasis control strategies showed that integrated MDA and environmental intervention, including through use of natural enemies, may control disease faster and more cost-effectively than either approach alone (Garchitorena et al., 2017; Hoover et al., 2019; Lo et al., 2018; Sokolow et al., 2015). For example, Sokolow et al. (2015) modelled empirical evidence to show that MDA plus restoration of snail predators (freshwater *Macrobrachium* prawns) in water bodies where humans were acquiring schistosome infections reduced disease burden in people more than MDA alone. The prawn predators are also a valued food product, and could provide nutrition and income in addition to snail control.

For many important vector-borne diseases, chemical-based vector control is the main strategy to prevent disease transmission. However, extensive use of insecticides for vector control has led to a worrying rise in insecticide resistance (Figure 3). Currently, there is evidence for vector (e.g. mosquito, blackfly, sandfly, tick) resistance against all major classes of insecticides (Nauen, 2007), resulting in an increasingly urgent need for alternative methods to control vectors of public health importance. Notably, when faced with widespread insecticide resistance in blackfly populations, the Onchocerciasis Control Programme (OCP) of West Africa turned to commercially available Bti to enhance the control of *Simulium* spp. blackfly larvae. The program ultimately reduced onchocerciasis in 16 participating countries through a combination of vector control and drug distribution (Regis et al., 2001). However, potential non-target impacts of Bti, while generally understood to be minimal, are still being unravelled (Poulin et al., 2010).

Given the immense impact of mosquito-borne diseases on people, communities and economies, finding alternative options to insecticide-based control, as insecticide resistance mounts, has been elevated in priority. Two very different natural enemy strategies have received the most attention as insecticide alternatives—biopesticides and the use of larvivorous mosquito predators (Figure 4). Like chemical insecticides, biopesticides can be mass produced and spread across large areas. As discussed already, Bti is one of the most widely used mosquito larvicides, and entomopathogenic fungi show promise against adult mosquitoes. It is possible that mosquitoes will develop resistance to biopesticides (Lacey, 2007), but so far, no evidence suggests widespread Bti resistance in field populations of mosquitoes, even after decades of application (Tetreau et al., 2013). And, because entomopathogenic fungi produce several toxins that kill adult mosquitoes, it is likely that mosquito populations develop resistance over a much longer time-scale than they do for chemical insecticides (Benelli et al., 2016).

More recently, *Wolbachia pipientis*, a rickettsia-like bacterium that naturally infects a wide range of insects, has been leveraged as a new biopesticide against mosquitoes (Figure 4). Theoretically, *Wolbachia* might reduce disease transmission via two mechanisms: (a) population suppression via release of *Wolbachia*-infected males that produce sterile offspring when mated with wild-type females, thus reducing the vector population over many generations (akin to sterile insect techniques (Benedict & Robinson, 2003)), and (b) population replacement via release of male and female mosquitoes infected with a vertically transmissible *Wolbachia* strain that confers resistance to specific pathogens (Figure 4; Flores & O'Neill, 2018; Hughes et al., 2011). However, *Wolbachia* infection in some *Anopheles* mosquitoes may increase vector competence, which would severely challenge the dissemination of this solution into natural environments where mosquito-borne disease transmission occurs (Weiss & Aksoy, 2011).

As for predators, the World Health Organization (WHO) has promoted larvivorous fish as an insecticide alternative for malaria control since the 1970s (Figure 1; Walshe et al., 2017). In the light of negative environmental consequences following fish introductions, discussed in more detail in the next section, the WHO has scaled back their pitch (Walshe et al., 2017). And, evidence for the scheme is lacking. A recent review assessing larvivorous fish for mosquito vector control found no studies that reported human malaria transmission as an outcome, thus limiting impact and cost-effectiveness studies (Walshe et al., 2017). For *Aedes* spp. mosquitoes (vectors of dengue, Zika and chikungunya, and other arboviruses), copepods are included alongside larvivorous fish in WHO documentation for dengue control strategies (WHO, 2011) and have proven efficient larval predators in specific environments. For example, a series of studies carried out over several years in Vietnam showed that *Mesocyclops* copepods introduced to mosquito breeding containers can reduce larval and adult mosquito density and dengue seroprevalence in humans (Figure 4; Lazaro et al., 2015). Such a large-scale intervention has not been replicated in other locations, and success in the Vietnamese communities may be attributable to a key combination of several factors including environmental conditions conducive to copepod survival, significant community involvement and larval habitat clean-up campaigns. Copepod studies in other regions have had mixed outcomes, and while considered relatively cheap and low maintenance (Soumare & Cilek, 2011), human transmission and cost-effectiveness studies have not yet been undertaken.

## 2.3 | Reason 3: Natural enemy solutions could offer co-benefits for conservation, food security and human well-being

Recognizing the ecosystem services that natural enemies provide beyond human health could help align natural enemy solutions

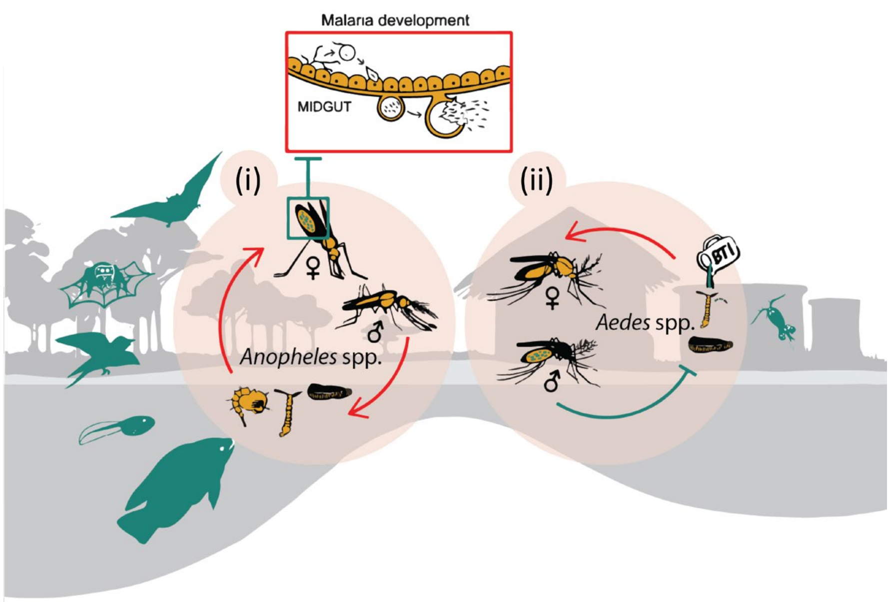


**FIGURE 4** Natural predators (green) of adult and larval mosquitoes are widespread, and include various species of bats, arthropods, birds, amphibians, fish and crustaceans. Naturally occurring strains of *Wolbachia* bacteria may (i) inhibit development of arboviruses in *Aedes* spp. and, potentially, malaria in *Anopheles* spp., or (ii) lead to sterility when artificially infected male mosquitoes mate with wild, uninfected females

with other Sustainable Development Goals, including biodiversity conservation and food production to fight poverty and hunger. In specific contexts where conservation of natural enemies confers a health benefit, conservation biological control could yield win-wins for health and nature. In North America and Europe, observational evidence suggests that functionally diverse predator communities are associated with lower tick infection prevalence of Lyme disease, caused by the bacterium *Borrelia burgdorferi* (Ostfeld et al., 2018). Some have suggested that landscape-level protection or restoration of predators (e.g. foxes and wolves) could protect people against tick-borne disease. Protection of smaller predators, like the red fox, could enhance rodent predation and, consequently, tick infection probability (e.g. Hofmeester et al., 2017; Levi et al., 2012). Restoration of larger wolf predators could indirectly reduce rodent populations by limiting coyote abundance (which are inversely associated with fox abundance) and by decreasing deer abundance (which are important reproductive hosts for ticks; Kilpatrick et al., 2017; Levi et al., 2012). As this example shows, protecting some natural enemies could align goals for conservation and protecting human health.

Some natural enemy solutions may have important co-benefits for food security. In Vietnam, snail-eating fish have been stocked in aquaculture facilities for both biological control against fish-borne zoonotic trematodes (e.g. *Clonorchis sinensis* and *Opisthorchis viverrini*) and food consumption (Hung et al., 2013). Reducing trematode infection in fish protects human health and local economies, because trematode infection can reduce fish survival and marketability (Hung et al., 2013). Evidence from a field study in Northern Vietnam suggests that stocking exotic juvenile black carp *Mylopharyngodon piceus* in aquaculture ponds reduces trematode prevalence in fish (Hung et al., 2013). Black carp have also been experimentally stocked in rice paddies for mosquito biological control. Studies in southern India and China showed that the nutrient input from fish increased rice yields, and in China, malaria transmission was reduced after many years of stocking fish (Victor et al., 1994; Wu et al., 1991). In settings where mosquito-borne disease and snail-borne schistosomiasis are co-endemic, the scheme could theoretically limit mosquito and snail populations in rice fields simultaneously. A downside of approaches using black carp in particular is that invasive carp can devastate ecosystems (Ferber, 2001; Naylor et al., 2001). Therefore, carp introductions would ideally take advantage of sterile stocks or be strictly contained to specific areas to eliminate undue damage to native biodiversity. Looking ahead, use of native fish or non-native fish natural enemies under strict management schemes could provide important dual benefits of hunger alleviation or food security and infection control.

In some cases, natural enemy solutions may emerge from decision-making in other sectors. In India, vulture populations have dramatically declined because of a bio-accumulative drug used in livestock (diclofenac) that kills vultures when they eat treated carcasses. In response, a ban on the drug diclofenac was instituted in India in 2006 (Cuthbert et al., 2011). The diclofenac ban may indirectly benefit human health and well-being. Vulture declines have coincided with a rise in the number of feral dogs (which compete with vultures for carrion) and, subsequently, human rabies risk (Figure 1; Swan et al., 2006). Vulture declines might also coincide with increased risk for bacterial pathogens, including anthrax, that can proliferate in carcasses that would otherwise be cleared by vultures (Figure 1; Markandya et al., 2008). This is a unique form of intra-guild predation (Figure 2c) where a predator (the vulture) and pathogen (anthrax) compete for a shared resource (the prey), while the predator also consumes the pathogen. It remains to be seen if the diclofenac ban in India and in surrounding nations will restore vultures and the ecosystem services that they provide. If so, the ban might additionally benefit food security via reduced livestock predation by wild dogs and sanitation services via clearing of carcasses that can contaminate water sources (Hopkins et al., 2020). As this example demonstrates, some natural enemy solutions may emerge from decision-making in other sectors, and could be one link in a network of positive outcomes for health, conservation and well-being.

## 3 | CHALLENGES TO RESEARCH AND OPERATIONALIZE NATURAL ENEMY SOLUTIONS HAVE LIMITED THEIR UPTAKE, BUT OVERCOMING THESE CHALLENGES MAY BE ON THE HORIZON

Experimental studies that simultaneously quantify human health outcomes and co-benefits of natural enemies are exceedingly rare. The lack of scientific focus on natural enemies for human disease control has likely been influenced by several high-profile examples of classical biological control gone wrong (i.e. the accidental or intentional introduction of exotic enemies in a new habitat). Mismanagement of mosquitofish (*Gambusia affinis* and *Gambusia holbrooki*) in freshwater ecosystems is one such example related to infectious disease control. Mosquitofish can establish self-sustaining populations and consume large numbers of mosquito larvae, though a causal relationship linking mosquitofish introductions to reduced human malaria incidence is lacking (Walshe et al., 2017). Even so, they have been transported globally for more than 100 years to control mosquitoes, and are now considered one of the most invasive fish species world-wide. Established populations can significantly impact native fauna, as they consume a wide range of insect, fish and amphibian eggs (Nico et al., 2017). To overcome this barrier to natural enemy solutions, several established risk assessment frameworks could be used to screen and test candidate species for biological control via species introductions (Pyšek & Richardson, 2010). And, novel technological developments in aquaculture could minimize the impacts of invasive aquaculture species used as natural enemies of human pathogens or their animal hosts. Some aquaculture products, including *Macrobrachium* freshwater prawns (predators of schistosomiasis intermediate host snails; Figure 1), can be produced as monosex populations so that they are unable to establish self-sustaining populations in schistosome-endemic areas where the prawn is not native (Savaya et al., 2020). While this requires repeated deployment in order to maintain effective densities for disease control, thus adding cost to their initial investment, it helps to address fears of uncontrollable invasive species damage to ecosystems and it also aligns goals of food production with that of improved health and well-being.

Another related hindrance to the wide application of natural enemies for human disease control is the lack of investment in this area of research and development. As opposed to investment in pharmaceuticals and chemical control agents, conservation biological control approaches cannot be patented or commercialized. And, many conservation biological control approaches may offer long-term benefits that are more difficult to predict, quantify and fund than short-term 'silver bullet' therapeutics and chemical environmental controls (Lewis et al., 1997). Even though many of the proposed solutions discussed in this Perspective piece are not amenable to fast return on investment, or even to commercialization or patenting, they could offer strong long-term impacts which makes their discovery and implementation a valuable contribution towards a sustainable future.

A result of the lack of investment in natural enemy research may be a lack of existing evidence on natural enemy impacts, especially regarding studies that trace the interlinkages among species interactions in the environment to outcomes for human diseases. To foster more attention to natural enemy research, evidence on links between the ecological outcomes of natural enemy solutions (i.e. population changes in natural enemy targets) and epidemiological outcomes (i.e. changes in human disease outcomes) is badly needed. Randomized controlled trials (RCTs) have been used to test biomedical, engineering and behavioural interventions for many infectious diseases, and could be adapted for natural enemy strategies, too. Moving forward, confidence in natural enemy solutions may grow if we apply the same standards and investments in these tools as we do for biomedical and behavioural ones. And, testing natural enemy solutions through RCT-like frameworks may allow them to be evaluated on par with other existing or potential interventions, to determine if further research and investment is warranted.

## 4 | CONCLUSIONS

Natural enemies of disease-causing organisms abound in nature, and their potential impact on human health may become more apparent as research on the ecological context of parasite and pathogen transmission grows. Looking ahead, some natural enemy solutions could complement conventional (chemical drug or insecticide-based) strategies to curb disease transmission by targeting environmental sources of infection. This could be especially important where conventional interventions are lacking. Some natural enemy solutions might simultaneously offer important co-benefits for nature conservation and food security, aligning natural enemy solutions with Sustainable Development Goals. Currently, however, evidence on the epidemiological impacts, cost-effectiveness and feasibility of harnessing natural enemy solutions through natural enemy protection (i.e. species or habitat conservation) or implementation (i.e. population augmentation or introduction) is sparse, and more research is badly needed to assess the full potential of natural enemy solutions for infectious disease control.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHORS' CONTRIBUTIONS

G.A.D.L. conceived the idea; I.J.J. conducted the literature review and I.J.J. and S.H.S. wrote the manuscript. All authors provided substantial input into ideas, figures, and revisions.

### DATA AVAILABILITY STATEMENT

This manuscript does not include any data.

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