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Make New Friends and Keep the Old? Parasite Coinfection and Comorbidity in *Homo sapiens*

Melanie Martin, Aaron D. Blackwell, Michael Gurven, and Hillard Kaplan

Introduction

Across species, the fitness costs of parasitic infection have been a major force shaping host adaptations to avoid infection (Hart 2009; Schmid-Hempel 2003; Sheldon and Verhulst 1996), diminish the cost of infection (Minchella 1985; Råberg et al. 2009), and even advertise resistance to infection to possible mates (Hamilton and Zuk 1982; Moller 1990). These adaptations, in turn, have shaped selection on parasite transmission and virulence, leading to coevolved host–parasite systems. Host–parasite interactions are further shaped by local environments and proximate host factors that influence transmission risk and infectious outcomes, including age, sex, and nutritional and immune status (Anderson and May 1981; Anderson 1991; Quinnell et al. 1995; Schad and Anderson 1985; Woolhouse 1992).

Host–parasite interactions are often observed and modeled as hosts interacting with a single parasite species. Yet as is increasingly observed in animal populations, including humans, coinfection with two or more species (alternately termed "multiple-species" or "polyparasitic" infection) may be the rule in nature (Howard et al. 2001; Booth et al. 1998; Bordes and Morand 2009; Pullan and Brooker 2008). Coinfecting species may include any number of "typical parasites" (e.g., helminths, flukes, tapeworms) and/or pathogens (e.g., bacteria, viruses, protozoa), each with different associated exposure risks, infectious sites, reproductive strategies, virulence,

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Tsimane Health and Life History Project

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and associated immune responses (Alizon 2008; May et al. 2009; Rigaud et al. 2010; de Roode et al. 2005; Van Baalen and Sabelis 1995). Of particular interest is the role of immune responses in mediating coinfection risk, as an immune response generated by one species may either increase or decrease a host's susceptibility to infection with another (Christensen et. al. 1987; Cox 2001; Supali et al. 2010). At the same time, infecting species may competitively inhibit establishment or replication by other species (Lim and Heyneman 1972; Fredensborg and Poulin 2005). As such, coinfection may increase, decrease, or have no effect on host fitness, depending on the individual species involved (Fellous and Koella 2009).

For humans—whose habitats span from hot, humid jungles to dry deserts, frozen tundras, and sterile office buildings—infection risk may be especially varied. Differences in parasitic and pathogenic exposure appear to have been a major force shaping genetic variation across human populations (Fumagalli et al. 2011). Given its ubiquity in nature and among nonindustrialized populations (Howard et al. 2001), multiple-species infection was likely equally common and varied among human and hominin ancestral populations. Along with more transient infections, hominin ancestors would have harbored multiple symbiotic organisms common to other mammals: commensal bacteria, pseudo-commensals, ectoparasites, and helminths (Armelagos and Harper 2005; Rook 2008). As proposed by the "hygiene hypothesis," continuous exposure to these organisms during mammalian evolution may have favored the evolution of immunoregulatory systems that required their antigenic input to develop appropriately (Jackson et al. 2008). In modern industrialized, hygienic environments, infection with many of these "old friends" (particularly helminths) is exceedingly rare, and consequently, disorders of immunoregulation (i.e., allergy, asthma, chronic inflammatory conditions) have become increasingly common (Rook 2008).

However, these old friends are also not without costs. First, helminth-induced immunoregulation, which downregulates proinflammatory responses, may decrease resistance to other parasites and more virulent pathogens, resulting in increased infection intensity or exacerbated immunopathology (Graham et al. 2005; Pullan and Brooker 2008). Second, exposure to helminth coinfection may increase investment in immune function (Bordes and Morand 2009), which may divert energy away from other fitness-enhancing allocations, such as growth and reproduction (Sheldon and Verhulst 1996; Adamo 2001; Uller et al. 2006; Blackwell et al. 2010; Muehlenbein et al. 2010). Given the risk of helminth coinfection in ancestral environments, potentially divergent immune responses, and the costs of increased investment in immune function, several questions arise. How does helminth coinfection risk and associated morbidity vary across environments and with different interacting species? How costly are multiple-species infections involving helminths in humans? What multiple-species infections would have been typical for ancestral populations? Finally, how have recent environmental changes altered helminth coinfection risk in modern populations, and what are the consequences for human health?

In this chapter, we review known aspects of immune responses to helminths and other parasitic and pathogenic threats and consider how coinfections involving

helminths may affect human immune function and health, both past and present. We first review host, environmental, and parasitic characteristics that influence the likelihood of helminth coinfection. We then examine helminth-protozoa coinfection and helminth-associated morbidity among the Tsimane of lowland Bolivia. The Tsimane are a subsistence-scale, forager-horticulturalist population afflicted with a high burden of both parasites and pathogens. We examine coinfection involving helminths and protozoa and interactions between helminths and the risk of other infections and inflammatory conditions. Although many aspects of the Tsimane environment are unlikely to match those of ancestral hunter-gatherer populations, the Tsimane disease ecology is likely more representative of ancestral conditions than that of a contemporary industrialized or transitioning population. Our intent is to provide an example of the complex interactions between infecting species that would likely have been present through much of human history.

Multiple-Species Infections in Humans

Across human populations, associations between coinfecting species and infectious outcomes vary widely (Hagel et al. 2011; Howard et al. 2001; Walson and John-Stewart 2007). This variation may result from (1) individual host and parasite factors influencing transmission and infection risk and (2) direct and indirect interactions between coinfecting species (Cox 2001; Karvonen et al. 2009; Lello and Hussell 2008). First, factors that mediate the risk of single-species transmission influence the likelihood of multiple-species infection. Host factors influencing susceptibility to infection include age, sex, socioeconomic status, physical condition, nutritional status, sanitation and hygiene, work and labor demands, access to medical care, prior exposure or immunization to infecting species, water supply, and interactions with infected or reservoir hosts (Esrey et al. 1991; Haswell-Elkins et al. 1987; Sayasone et al. 2011). Local ecological features (e.g., seasonality, soil, streams, ponds, etc.) and the life cycles, growth requirements, and density and distribution of parasites in a given environment further influence transmission risk (Anderson 1991; Hall and Holland 2000; Holland 2009). Parasites with similar transmission routes (e.g., soil transmitted or waterborne) and microclimatic requirements for growth and replication are more likely to coinfect hosts (Ellis et al. 2007; Fleming et al. 2006; Haswell-Elkins et al. 1987; Supali et al. 2010).

Once transmitted, infecting species must also establish and replicate. Typical parasites such as helminths do not replicate inside hosts; eggs are excreted and larval life stages occur in soil or animal vectors. Consequently, infection intensity and pathogenicity depend on the infectious dose of initial and secondary infections (Anderson and May 1979; May and Anderson 1979; Lafferty and Kuris 2002). In contrast, pathogens replicate asexually in hosts and effects on hosts are independent of the initial infectious dose (Lafferty and Kuris 2002).

For coinfecting species, the sequential order of establishment, infectious dose, and density of established parasites influence infectious outcomes of secondarily invading species (Fellous and Koella 2009). Coinfecting species may inhibit the establishment of new parasites through direct competition or competitive inhibition (e.g., monopolizing host resources), ultimately reducing infection intensity or pathogenesis of one or more species (Lafferty et al. 1994; Fredensborg and Poulin 2005). Direct competition is more likely when species inhabit similar locales in the host (e.g., skin, lung, gut, blood, or lymphatic system) (Karvonen et al. 2009). Finally, individual species can indirectly influence establishment and clearance of coinfecting species across locales through antagonistic or synergistic immune responses.

Immune Responses to Parasites and Pathogens

Mammalian, and indeed all vertebrate, immune systems have evolved to counter invasions from diverse parasites and pathogens. Responses may be optimized to clear infection and/or minimize damage from infection, depending on the infectious agent's own evolved strategy to evade or exploit host immune pathways (Allen and Maizels 2011). The immune system makes strong phenotypic commitments in response to infection, which may lead to biased immune responses that in turn influence coinfection outcomes (Bradley and Jackson 2008). Each of the several different types of immune defense, therefore, has its own costs and benefits, and organisms must allocate resources appropriately to invest in defenses that are useful for local pathogens (Long and Nanthakumar 2004; McDade 2005).

The vertebrate immune system is generally divided into two levels of response: innate and adaptive immunity. Innate immunity is the first line of defense, found in all plants and animals; it recognizes and responds to generic signals of invasion (e.g., unchanging structures on bacteria cell walls) with nonspecific responses including inflammation, induction of acute-phase proteins (e.g., C-reactive protein), activation of the complement system (a cascade of proteins that assist antibodies and phagocytic cells in pathogen clearance), and activation and recruitment of white blood cells, or leukocytes, to target and clear infected host cells and extracellular viruses, bacteria, and protozoa.

Adaptive immunity is found only in vertebrates and, compared to innate immunity, is highly specific, highly flexible in its recognition capabilities, and capable of antigen-specific memory. Importantly, helminth diversity—a proxy for coinfection risk—may have selected for increased investment in adaptive immunity during mammalian evolution (Bordes and Morand 2009). Adaptive immunity is activated when particles from invading organisms (antigens) are engulfed and processed by phagocytic cells of the innate immune system. These cells present the antigens to effector cells of the adaptive system (T and B cells), which are then activated and clonally expanded. Activated B cells release antibodies, which bind to antigen and

facilitate pathogen clearance. Activated B cells may also develop into memory B cells, which are the basis of acquired immunity.

Activated T cells undergo further differentiation into various subgroups of T cells that direct different immune responses. These subgroups include cytotoxic T cells, helper T cells (T_H), and regulatory T cells (T_{reg} cells). Helper T cells are further differentiated into T_H1, T_H2, and T_H17 cells based on the cytokines they are associated with. In brief, T_H1 cells and associated cytokines such as IFN-γ stimulate inflammatory and cell-killing activity important in clearance of pathogens (e.g., protozoa, trypanosomes, bacteria, viruses). T_H2-associated cytokines (primarily IL-4, IL-5, IL-13) stimulate antibodies including immunoglobulin E (IgE), IgG1, and (in humans) IgG4 production, as well as basophils, eosinophils, and mast cells, which are important in mediating clearance and tissue repair associated with typical parasites (e.g., helminths, flatworms) (Allen and Maizels 2011). T_H1 and T_H2 responses are directly antagonistic, with IL-4 inhibiting IFN-γ production and vice versa (Maizels and Yazdanbakhsh 2003).

Clearance of coinfecting species that provoke similar immune responses may be enhanced through cross-immunity (Lello and Hussell 2008; Supali et al. 2010), which can also diminish the likelihood of future coinfection with other commonly associated species (Karvonen et al. 2009). Conversely, immune responses directed against one species may suppress responses against other species if the coinfecting species invoke antagonistic immune responses. As is discussed below, increasing evidence suggests that helminths may bias immune function in a manner that increases susceptibility to viral and bacterial infections.

Helminth-Induced Immune Responses and Coinfection in Humans

Helminths are a large category of parasite known to have significant effects on host fitness. The term “helminth” refers collectively to wormlike parasites and encompasses two phyla of major human parasites: Platyhelminthes (flatworms), which include tapeworms (e.g., *Taenia* spp. and *Hymenolepis* spp.) and flukes (e.g., *Schistosoma mansoni* and *Schistosoma japonicum*), and Nematoda (roundworms), which include ascarids (e.g., *Ascaris lumbricoides*), filarial worms (e.g., *Wuchereria bancrofti*), pinworm (e.g., *Enterobius vermicularis*), whipworm (*Trichuris trichiura*), threadworm (*Strongyloides stercoralis*), and hookworm (referring to *Ancylostoma duodenale* and *Necator americanus*, which are often undifferentiated in microscopic identification). Helminths—which are long lived, grow to sexual maturity in hosts, but do not replicate in hosts—evoke relatively gentle immune responses in mammals, quite distinct from the strong inflammatory responses evoked by transient microbial pathogens that present imminent threats to host fitness (Jackson et al. 2008; Allen and Maizels 2011).

Helminths shift T cell populations towards a T_H2 immune response, with corresponding decreases in T_H1 and proinflammatory responses (Cooper et al. 2000; Fallon and Mangan 2007; Fox et al. 2000; Hewitson et al. 2009; Maizels and Yazdanbakhsh 2003; Yazdanbakhsh et al. 2002). T_H2 cells activated by helminths in mucosal tissues induce production of IL-13 and IL-4 cytokines that drive mucosal and muscular responses to dislodge the parasites. In non-mucosal tissues, T_H2-induced pathways and innate immune cells such as eosinophils, basophils, and mast cells help drive parasite killing. IgE secreted from B cells is important in protecting hosts from extraintestinal and encysted stages of helminths and may facilitate antibody-induced larval killing following concomitant or secondary infections (Allen and Maizels 2011).

Many helminths (as well as commensal bacteria) also induce T_{reg} activity in order to enhance their own survival in the host (Maizels et al. 2009). T_{reg} cells release cytokines that suppress T_H1 and T_H2 responses in order to minimize immunopathology and epithelial damage caused by immune activation (Rook 2008; Round and Mazmanian 2009). T_{reg} activity may also promote production of IgG4 over IgE and reduce expulsion of worms from the host (Mingomataj et al. 2006). Enhanced and spontaneous production of T_{reg} cytokines has also been observed in children with chronic *A. lumbricoides* or *T. trichiura* infection and *A. lumbricoides/T. trichiura* coinfection, suggesting endemic exposure to multiple helminths promotes stronger immunoregulation (Turner et al. 2008; Figueiredo et al. 2010).

As such, the prototypical T_H2/T_{reg} response induced by helminths may be better characterized as a "tolerance" response that contains the extent of helminth infection while limiting damage to the host (Jackson et al. 2008). In this case, the interests of host and parasite may align. Chronic exposure to helminths, which present low or intermediate threats to host fitness compared to pathogens, would favor a continual tolerance response over successive, highly inflammatory responses that would be energetically costly and highly immunopathogenic to hosts. A tolerance response would also be favored by helminths, as the T_{reg} response enhances their own long-term survival in the host, while T_H2 responses may limit establishment and competition by secondary invaders, allowing established parasites to monopolize host resources (Jackson et al. 2008).

The tolerance response suggests that mammals share a deep coevolutionary legacy with helminths. The IgE antibody, which is integral to antihelminth responses, is a derived innovation in the mammalian lineage (Jackson et al. 2008). However, more recent coevolution is also apparent: in humans, helminths appear to have played a major role in genetic population divergence since the appearance of anatomically modern humans within the last 200,000 years (Fumagalli et al. 2010). More recent evidence of helminth infection in human history comes from mummified remains dating to approximately 30,000 BP in the Old World (*A. lumbricoides*) and 7,837 BP in the New World (*E. vermicularis*) (Gonçalves et al. 2003), as well as historical writings from classical Egyptian and Greek physicians (Cox 2002).

Today, however, helminth exposure and associated immune phenotypes are varied across human populations. Hygiene, medicine, and socioeconomic development

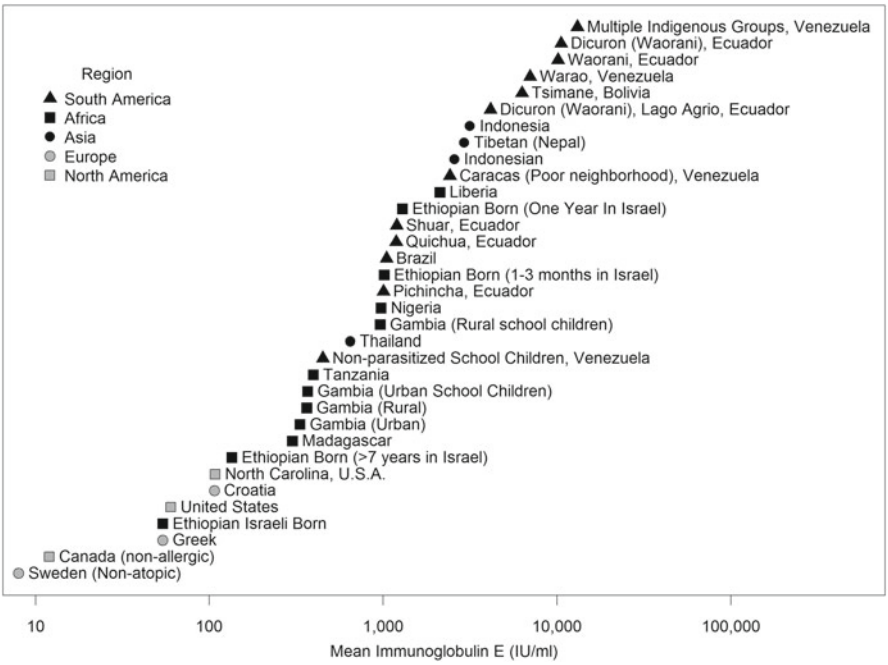

Fig. 1 Variation in human IgE by population. Values are geometric means for each published population (Adapted from Blackwell et al. (2010), which contains the complete references for each population)

have drastically reduced early helminth exposure in many industrialized populations. Average IgE levels in North America and Europe are as much as 200 times lower than those observed in subsistence-scale populations (Fig. 1). The highest IgE levels are found among lowland indigenous groups in Ecuador (Buckley et al. 1985; Kaplan et al. 1980; Kron et al. 2000) and Venezuela (Hagel et al. 2006; Lynch et al. 1983), which have reported geometric mean IgE in excess of 10,000 IU/ml. In contrast, geometric mean IgE in the USA is 52 IU/ml (Blackwell et al. 2011). Although genetic factors have been shown to influence IgE levels (Weidinger et al. 2008) and IgE levels show relatively high heritability when parents and offspring experience similar environments (Grant et al. 2008), differences between populations appear to be influenced largely by exposure to helminths (Cooper et al. 2008) and other parasites and pathogens, including malaria (Perlmann et al. 1994, 1999). Immigrants who move from areas with endemic helminth infections to those with low endemicity show an eventual drop in IgE levels, although it may take a decade or more for levels to fall significantly (Iancovici Kidon et al. 2005; Kalyoncu and Stålenheim 1992).

While the low IgE levels observed in North America and Europe are consistent with low levels of helminth exposure, individuals in these populations with allergic

diseases such as asthma *do* show elevated IgE levels (e.g., Bergmann et al. 1995; Holford-Strevens et al. 1984; Lindberg and Arroyave 1986). Variations on the "hygiene" and "old friends" hypotheses posit that a major factor in the rise of allergic, autoimmune, and inflammatory disorders in industrialized populations today is a mismatch between a human immune system that coevolved with "old friends" (e.g., helminths and commensals) and a modern hygienic environment in which these "old friends" are largely absent (Rook 2008). Without early and regular antigenic input from helminths, immune system development is altered, resulting in "inappropriate" T_H2 immune responses to harmless environmental antigens. When induced by helminths, those same immune responses may depress allergic reactions (Maizels 2005; Wilson and Maizels 2004), to the extent that prescribed low-dose infections may be effective clinical treatments (Blount et al. 2009; Feary et al. 2010). The downregulation of inflammatory pathways induced by low-grade helminth infections may also protect against diabetes (Maizels et al. 2009), obesity (Wu et al. 2011), and immunopathology associated with opportunistic bacterial infections (Anthony et al. 2008).

At the same time, chronic helminth infection can be costly to hosts. Presently, the most common human helminth infections involve intestinal nematodes, especially the soil-transmitted helminths (STH) *A. lumbricoides, T. trichiura,* and hookworm. Adult STH reside and replicate in the host's gut and pass eggs through host feces. *A. lumbricoides* and *T. trichiura* eggs are ingested by hosts, whereas hookworm eggs penetrate the skin, generally the bottom of the feet (Hotez et al. 2008; Jackson et al. 2008). STH are widespread but are most prevalent in tropic and subtropic regions (Chan et al. 1994; Silva et al. 2003). In many nonindustrialized nations, STH infections are endemic and—despite increased efforts to improve sanitary conditions, access to health care, and implement large-scale control programs—remain a significant cause of morbidity, particularly among children (Bethony et al. 2006). Complications ensuing from STH infections in children and adults (e.g., anemia, growth faltering, reduced work output, and impaired cognitive ability), compounded with poor nutrition and poverty, likely contribute to poor economic growth in these areas (Guyatt 2000).

Coinfections involving multiple STH, or at least one STH and another parasite or pathogen, are exceedingly common in nonindustrialized populations (Hotez et al. 2008). Multiple STH infections are often associated with increased infection intensity, egg output, and morbidity (Booth et al. 1998; Brooker et al. 2000; Ellis et al. 2007; Pullan and Brooker 2008). It is also increasingly documented that helminth infection and helminth-typical immune biasing may diminish immune responses to vaccines, viruses, and bacteria, resulting in increased susceptibility to other infectious diseases (e.g., HIV/AIDS (Bentwich et al. 1995); BCG, typhoid, measles, and polio vaccines (Labeaud et al. 2009); tuberculosis (Lienhardt et al. 2002)). In sum, helminths may interact with human immune function and other host factors in a myriad of complex ways that have varying implications for human health. The risks and effects of helminth coinfection therefore, while of clear clinical and epidemiological significance, are also of relevance to researchers working across evolutionary and ecological fields.

Helminth Coinfection and Morbidity in the Tsimane of Bolivia

Human immune pathways may have been selected to counter the disease ecologies of our predecessors, which included constant exposure to multiple parasites and pathogens. Unfortunately, much of our understanding of human immune function and health has derived from populations living under evolutionarily novel conditions in which common parasites and pathogens are largely absent. Wider surveying of the patterns of helminth coinfection and comorbidity across a range of environments are needed to better understand the varying consequences of endemic helminth exposure—and lack thereof—in both nonindustrialized and industrialized populations.

In this section we present and review data on helminth coinfection and comorbidity patterns in an Amazonian, small-scale subsistence population, the Tsimane of lowland Bolivia. We focus specifically on the risk of coinfection involving helminths and *Giardia lamblia* (aka *Giardia intestinalis, Giardia duodenalis*), a common Tsimane intestinal protozoan. We then examine the links between helminth infection and other medical diagnoses. This research provides an example of the interactions that may occur when multiple species and conditions afflict a single population (Table 1).

Overview of the Tsimane

The Tsimane are a subsistence-level Amerindian population (pop. ~10,000) scattered across approximately 120 villages along the Maniquí River and surrounding forest areas. Most Tsimane have minimal access to medical care, market foods, or wage labor opportunities and subsist primarily on locally cultivated plantains, rice, manioc, and corn, hunted game, and wild fish (Gurven et al. 2007). Tsimane live in large family clusters in open-air huts with thatched-palm roofs. Few villages have wells or other clean water sources; water is generally obtained from nearby rivers and streams and rarely boiled. As of yet, no village has electricity or sewage. The Tsimane do not maintain outhouses but urinate and defecate privately in surrounding foliage. Domestic animals (dogs, cats, pigs, and chickens) are owned by individual families but are rarely penned and roam freely around villages and familial spaces. Despite economic impoverishment, the Tsimane are food secure. Nearly 70 % of the average adult diet is comprised of locally cultivated rice, plantain, manioc, and maize, with the remaining 30 % of the diet comprised of hunted game, river fish, and cultivated or foraged fruits and nuts. There is little wasting indicative of protein malnutrition in children (Foster et al. 2005), and the prevalence of underweight (body mass index < 18.5) among reproductive aged females is <2 %.

Table 1 Characteristics of common Tsimane intestinal parasites

Parasite/type	% infected Latin Am/Caribbean	Transmission route	Infection site	Immune response	Age peak	Associated morbidity
Hookworm (helminth)[a]	9 %	Skin penetration Oral	Small intestine	T_H2/T_{reg}	Adulthood	Intestinal blood loss; iron-deficiency anemia; protein malnutrition
Ascaris lumbricoides (helminth)	15 %	Fecal–oral	Small intestine	T_H2/T_{reg}	5–10 year	Lactose intolerance; vitamin A deficiency; intestinal obstruction; hepatopancreatic ascariasis
Trichuris trichiura (helminth)	18 %	Fecal–oral	Cecum Colon	T_H2/T_{reg}	5–10 year	Colitis; Trichuris dysentery syndrome; rectal prolapse; impaired nutrition
Giardia lamblia (protozoan)	Unknown	Contaminated water Fecal–oral	Small intestine	T_H1/T_H2	Weaning infants, children	Diarrhea, flatulence, vomiting, intestinal mucosal damage; fat, sugar, and vitamin malabsorption; lactose, vitamin A deficiency

References: Bethony et al. (2006), Brooker et al. (2004), Hotez et al. (2008), Ortega and Adam (1997), Wolfe (1992)

[a]Hookworm = *Ancylostoma duodenale/Necator americanus*

Methods of Tsimane Data Collection

Since 2002, the Tsimane have been participants in the ongoing Tsimane Health and Life History Project (THLHP). THLHP researchers have worked extensively in Tsimane villages, collecting demographic, anthropological, and biomedical data while also providing primary medical care. The data presented in this chapter was collected from participants seen by a mobile team of THLHP physicians, who traveled annually through Tsimane villages from 2007 to 2010.

Patients seen by THLHP physicians were given routine physical exams (patient history, symptom investigation, blood pressure and temperature, height and weight). Physicians administered vitamins, antibiotics, and antihelmintics as warranted, following on-site analysis of participant blood and fecal samples. Ethnographic and epidemiological information on the Tsimane, methods for age estimation, subject sampling, biomarker collection, and physician diagnostics have been described elsewhere (Gurven et al. 2007, 2008, 2009).

Results of parasitic infection presented and reviewed in this chapter were obtained through community sampling and patient diagnostics conducted from 2004 to 2010. Fecal samples collected by THLHP researchers were analyzed using two methods. From 2004 to 2008, fecal samples were analyzed for the presence of helminth eggs, larvae, and protozoa by direct identification on wet mounts. Beginning in 2007, fecal samples were also preserved in 10 % formalin solution following direct identification and later quantitatively analyzed using a modified Percoll (Amersham Pharmacia) technique (Eberl et al. 2002). Methods of fecal sample collection and parasite identification using both methods have been described in greater detail elsewhere (Vasunilashorn et al. 2010; Blackwell et al. 2011). Data presented here were aggregated from the two methods, with individuals coded as either infected or not infected if helminths were detected by either method ($n = 3{,}628$).

Helminth and Protozoan Infections Among the Tsimane

Tsimane exposure to multiple gastrointestinal parasites and pathogens is endemic and lifelong. From fecal samples collected from 2004 to 2010, we estimate that 77 % of Tsimane are infected with at least one intestinal parasite (Table 2). The most common infections are hookworm, *G. lamblia*, and *A. lumbricoides*, infecting 51 %, 37 %, and 15 % of Tsimane, respectively. Females are more likely to be infected with *A. lumbricoides* than males (OR = 1.33, $\chi^2 = 9.30$, $p = 0.002$) and less likely to be infected with *S. stercoralis* (OR = 0.70, $\chi^2 = 4.57$, $p = 0.03$), while other infections do not vary significantly by sex. *T. trichiura* and *S. stercoralis* are relatively uncommon, infecting only 3.6 % and 3.7 % of subjects. Hookworm infections are less common in children 10 and younger than in Tsimane over age 10 (37 % vs. 55 %) and show a steady increase with age (Fig. 2). Nearly 1/3 of the Tsimane

Table 2 Prevalence of Tsimane single- and multiple-species infections

	All ages (n=3,628)		≤10 (n=893)		≥10 (n=2,735)	
	N	%	*N*	%	*N*	%
Infection						
Hookworm	1,842	50.8	328	36.7	1,514	55.4
G. lamblia	1,336	36.8	308	34.5	1,028	37.6
A. lumbricoides	544	15.0	132	14.8	412	15.1
T. trichiura	129	3.6	16	1.8	113	4.1
S. stercoralis	135	3.7	18	2.0	117	4.3
Any infection	**2,801**	**77.2**	**581**	**65.1**	**2,220**	**81.2**
Hookworm only	956	26.4	176	19.7	780	28.5
G. lamblia only	680	18.7	186	20.8	494	18.1
A. lumbricoides only	133	3.7	32	3.6	101	3.7
T. trichiura only	14	0.4	2	0.2	12	0.4
S. stercoralis only	12	0.3	2	0.2	10	0.4
Total single-species infections	**1,795**	**49.5**	**398**	**44.5**	**1,397**	**51.1**
Hookworm and *G. lamblia*	422	11.6	61	6.8	361	13.2
Hookworm and *A. lumbricoides*	194	5.3	47	5.3	147	5.4
Hookworm and *S. stercoralis*	67	1.8	5	0.6	62	2.3
A. lumbricoides and *G. lamblia*	65	1.8	17	1.9	48	1.8
Hookworm and *T. trichiura*	29	0.8	3	0.3	26	1.0
T. trichiura and *G. lamblia*	14	0.4	2	0.2	12	0.4
S. stercoralis and *G. lamblia*	12	0.3	7	0.8	5	0.2
A. lumbricoides and *T. trichiura*	12	0.3	1	0.1	11	0.4
A. lumbricoides and *S. stercoralis*	6	0.2	1	0.1	5	0.2
Total 2-species infections	**821**	**22.5**	**144**	**16.1**	**677**	**24.8**
Hookworm, *A. lumbricoides, G. lamblia*	79	2.2	26	2.9	53	1.9
Hookworm, *S. stercoralis, G. lamblia*	25	0.7	2	0.2	23	0.8
Hookworm, *A. lumbricoides, T. trichiura*	21	0.6	2	0.2	19	0.7
Hookworm, *T. trichiura, G. lamblia,*	20	0.6	3	0.3	17	0.6
Hookworm, *A. lumbricoides, S. stercoralis*	15	0.4	2	0.2	13	0.5
Hookworm, *S. stercoralis, T. trichiura*	5	0.1	0	0.0	5	0.2
A. lumbricoides, T. trichiura, G. lamblia	8	0.2	2	0.2	6	0.2
A. lumbricoides, S. stercoralis, G. lamblia	3	0.1	1	0.1	2	0.1
Total 3-species infections	**176**	**4.9**	**38**	**4.1**	**138**	**5.0**
Hookworm, *A lumbricoides, T. trichiura, G. lamblia*	4	0.1	1	0.1	3	0.1
Hookworm, *A. lumbricoides, S. stercoralis, G. lamblia*	3	0.1	0	0.0	3	0.1
Hookworm, *S. stercoralis, T. trichiura, G. lamblia*	1	0.0	0	0.0	1	0.0
Hookworm, *A. lumbricoides, S. stercoralis, T. trichiura*	1	0.0	0	0.0	1	0.0
Total 4-species infections	**9**	**0.2**	**1**	**0.1**	**8**	**0.3**
Total 2+ species infections	**1,006**	**27.6**	**183**	**20.2**	**823**	**30.1**

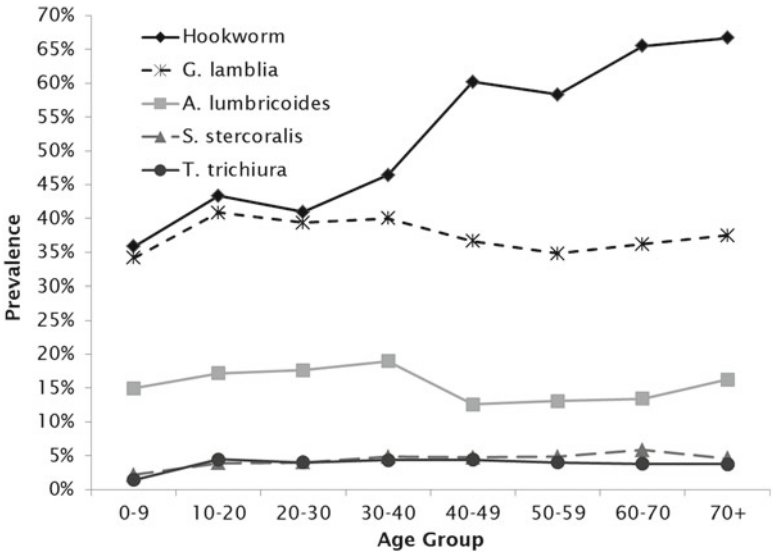

Fig. 2 Total prevalence of Tsimane intestinal parasites by age

population harbors a multiple-species infection, though prevalence rates of different coinfectious combinations are varied (Table 2). Hookworm is present in 85 % and *G. lamblia* present in 65 % of all coinfections, while 55 % of coinfections involve both hookworm and *G. lamblia.*

Helminth Coinfection and Infection Intensity Risk Among the Tsimane

Half of all multiple-species infections observed involved infection with at least two helminth species. As has been shown elsewhere (e.g., Howard et al. 2001), we found that individual helminth infection increases the risk of coinfection with other helminths. The strongest positive association we observed was between *A. lumbricoides* and *T. trichiura,* with *T. trichiura*-infected subjects nearly six times as likely to be coinfected with *A. lumbricoides* (Table 3). Each helminth infection was associated with higher odds of infection with another helminth. *A. lumbricoides* (OR = 1.40, $p < 0.001$), *T. trichiura* (OR = 1.47, $p = 0.05$), and *S. stercoralis* (OR = 3.28, $p < 0.001$) were all predictive of hookworm infection, while hookworm was associated with *A. lumbricoides* (OR = 2.32, $p < 0.001$), and *A. lumbricoide*s was associated with *T. trichiura* (OR = 2.54, $p < 0.001$). Howard et al. (2001), in a survey of 60 international studies of helminth coinfection, found that in ~70 % of cases, the risk of coinfection with *A. lumbricoides* and *T. trichiura* was significantly higher than would be expected by independent transmission. In the same study, increased risks

Table 3 Odds ratios for infection with one parasite given infection with another

	Dependent				
Independent	*G. lamblia*	Hookworm	*A. lumbricoides*	*T. trichiura*	*S. stercoralis*
G. lamblia		0.54***	0.64*	0.89^{ns}	0.51^{t}
Hookworm	0.54***		2.32***	1.14^{ns}	1.77^{ns}
A. lumbricoides	0.72**	1.40***		2.54**	0.97^{ns}
T. trichiura	1.13^{ns}	1.47*	2.03^{t}		1.11^{ns}
S. stercoralis	0.83^{ns}	3.28***	1.08^{ns}	1.10^{ns}	
Age (decades)	1.04*	2.22***	0.87*	1.05^{ns}	1.06^{ns}
Sex (male)	1.03^{ns}	1.10^{ns}	0.44**	0.77^{ns}	0.91^{ns}

Odds ratios were calculated in binomial logistic mixed models with all independent variables in one model, controlling for age, sex, and repeat observations

Parameter significance: $^{t}p \leq 0.10$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$; ^{ns}nonsignificant

for hookworm-A. *lumbricoides* and hookworm-*T. trichiura* coinfections were also widely documented (Howard et al. 2001).

Significantly higher infection intensity associated with helminth coinfection has been widely reported (Brooker et al. 2000; Howard et al. 2002); we observed a similar relationship in the Tsimane. Among infected Tsimane patients, hookworm egg count was significantly higher in the presence of *S. stercoralis* ($\beta = 170.7$ eggs/g, $p < 0.001$). *A. lumbricoides* intensity was significantly increased by hookworm coinfection ($\beta = 416.2$ eggs/g, $p = 0.004$). *S. stercoralis* intensity was higher with *A. lumbricoides* ($\beta = 397.4$ eggs/g, $p < 0.001$), but not if an individual was infected by both *A. lumbricoides* and hookworm ($\beta = -417.4$, $p < 0.001$). There were no significant effects of coinfection on *T. trichiura* intensity. As a caution, the relationship between coinfection and infection intensity is somewhat difficult to parse. In many studies, high-intensity infection with one species is associated with increased coinfection risk, but it is unclear if high-intensity infections predispose hosts to coinfection or vice versa (Raso et al. 2004; Fleming et al. 2006). Host factors such as age or nutritional status may also predispose hosts to coinfection and higher infection intensity (Pullan and Brooker 2008).

Given the high prevalence of helminth infection among the Tsimane (77 %), the prevalence of helminth coinfection (14 %) in the Tsimane is much lower than rates reported for many other tropical, underdeveloped populations (e.g., 58 % Tanzania, Booth et al. 1998; 49 % Kenya, Brooker et al. 2000; 68 % Rwanda, Mupfasoni et al. 2009). The lower helminth coinfection rates in the Tsimane may be due to the relatively lower prevalence of helminths other than hookworm. As compared to the referred African populations, the Tsimane may also be less negatively impacted by recent environmental and socioeconomic changes (e.g., food insecurity, malnutrition, increased population density, environmental degradation) that may increase host susceptibility to coinfection and/or exposure to multiple parasites—including more virulent parasites and pathogens such as *Schistosoma* and *Plasmodium* spp. It is also worth nothing that even in the absence of malnutrition and more virulent coinfecting species, coinfection in the Tsimane was associated with increased infection intensity.

Table 4 Odds of infection based on receipt of antihelmintic or antiprotozoal drugs at the previous medical visit

	Any helminth	Hookworm	*A. lumbricoides*	*G. lamblia*
(Intercept)	0.41***	0.33***	0.05***	0.77**
Received antihelmintic	1.15	1.12	0.41***	1.29*
Received antiprotozoal	1.46**	1.61***	0.83	0.93
Age (years)	1.02***	1.02***	1.00	1.00
Sex (male)	1.06	1.13^{t}	0.72*	1.05
Dist. to San Borja (10 km)	1.14***	1.09***	1.19***	0.92***

Parameter values are odds ratios estimated in separate generalized logistic mixed model for each parasite or pathogen.
Parameter significance: $^{t}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

Previously, we have also shown that early and chronic elevated IgE—characteristic of endemic helminth exposure—is also associated with growth deficits (Blackwell et al. 2010). Thus, endemic exposure to multiple helminths may be a significant cause of morbidity in the Tsimane. Future research with the Tsimane will investigate host factors that increase susceptibility to helminth coinfection and infection intensity and will evaluate if certain helminth coinfections and higher infection intensity are associated with increased morbidity.

Evidence of Hookworm and Giardia lamblia *Antagonism Among the Tsimane*

In contrast to the higher odds of helminth coinfection, we have found that the risk of helminth-giardia coinfection among the Tsimane is significantly less common than would be predicted by independent transmission. *G. lamblia* infection was associated with significantly lower odds of infection with both hookworm (OR = 0.54, $p < 0.001$) and *A. lumbricoides* (OR = 0.64, $p < 0.001$), while hookworm and *A. lumbricoides* were conversely associated with lower odds of *G. lamblia* infection (OR = 0.54, $p < 0.001$; OR = 0.72, $p < 0.001$). To put the size of this effect into perspective, 31 % of those infected with any helminth were also infected with *G. lamblia*, compared to 45 % of those without helminth infection. Of those with *G. lamblia* infection, 49 % were infected with at least one helminth, compared to 64 % of those without *G. lamblia.*

Given the apparent antagonism between helminth and *G. lamblia* infection, we examined how treatment for helminths affected later risk of infection with *G. lamblia,* and vice versa (Table 4). Receiving an antihelmintic had no effect on the odds of being infected with any helminth (OR = 1.15, $p = 0.28$) or with hookworm (OR = 1.12, $p = 0.34$) but did reduce the odds of *A. lumbricoides* infection (OR = 0.41, $p < 0.001$). However, receipt of antihelmintics was also associated with increased odds for *G. lamblia* infection (OR = 1.29, $p = 0.03$). Antiprotozoal agents had no effect on the odds of *G. lamblia* infection 1 year later (OR = 0.93, $p = 0.55$) but were

associated with increased odds of hookworm infection at the subsequent visit (OR = 1.60, $p < 0.001$).

Our results are consistent with those reported by Rousham (1994), who observed an increase in *G. lamblia* prevalence following mebendazole treatment for *A. lumbricoides* and *T. trichiura* infection. The apparent antagonism may reflect competitive inhibition or cross-immunity. In a murine model, *G. lamblia*, which reside on microvilli in the small intestine, were inhibited by *Trichinella spiralis* when these helminths inhabited the small intestine but not at later stages when they moved to muscular tissue, suggesting a physical rather than immune interaction between the two species (Chunge et al. 1992). In our study, only *A. lumbricoides* and hookworm, both of which inhabit the small intestine, were negatively associated with *G. lamblia*, whereas *T. trichiura* (located further down in the large intestine) was not, supporting these earlier observations.

Studies have also shown that *G. lamblia* clearance and protective immunity are mediated by mixed T_H1 and T_H2 cytokine production (characterized by both INF-γ and IL-4), as well as T_H2 antibody responses (IgA, IgG, IgE) (Abdul-Wahid and Faubert 2008; Jiménez et al. 2009; Matowicka-Karna et al. 2009). Therefore, it is possible that helminth-induced T_H2 activity may provide some cross-immunity against *G. lamblia*. However, Hagel et al. (2011) found a higher prevalence of *G. lamblia* in association with *A. lumbricoides* infection—but only at moderate intensity and in conjunction with increased T_{reg} cytokine activity—suggesting helminth-giardia coinfection risk may only be increased with helminth-induced T_{reg} activity. Future studies with the Tsimane will examine the range of immune parameters alternately associated with helminth and protozoan infection and may shed further light on the role of immune responses in helminth-giardia antagonism.

Helminth Infection Is Associated with Altered Odds for Respiratory and Inflammatory Diagnoses

It has been suggested that the immunomodulatory properties of helminths may protect against allergies, autoimmune, and inflammatory disorders. However, helminth-induced immune biasing may increase susceptibility to other infectious diseases. To examine potential interactions between helminths, *G. lamblia*, and other medical conditions, we grouped THLHP patient disease diagnoses into broad categories representing the most common types of complaint. Excluding diagnoses of helminthiasis and giardiasis, these included gastrointestinal problems (43 % of 3,391 patient examinations), muscle or back pain (34 %), upper respiratory illnesses (28 %), urinary tract infections (13 % cases), fungal infections (8 %), arthritis (6 %), skin infections (3 % cases), and traumatic burns or injuries (2 %). For analysis, we divided the sample by age into children ≤ 16 years of age and adults over age 16 since many diagnoses were not equally prevalent in children and adults (Table 5). Controlling for age, sex, and village location, helminth infections were associated with greater odds of upper respiratory infection in children (OR = 1.33, $p = 0.04$).

Table 5 Association between current helminth and giardia infection and likelihood of medical diagnosis during medical visit

			Odds ratios				
Sample	Medical diagnosis (cases)	Cases (%)	Helminth infected	Giardia infected	Age (years)	Sex (male)	Dist. to town (per 10 km)
Children ≤ 16 years	Gastrointestinal problems	454 (42 %)	1.09	0.88	0.97^{t}	1.01	0.91**
n = 894	Fungal infections	70 (6 %)	1.17	0.88	1.00	1.23	1.06
obs = 1,086	Upper respiratory infections	474 (44 %)	1.33*	0.99	0.93***	0.73*	1.11***
	Urinary tract infections	19 (2 %)	0.58	0.75	1.24	0.46	0.62
	Skin infections	57 (5 %)	0.84	0.37	0.79^{t}	0.46	1.13
	Trauma	17 (2 %)	0.54	0.68	1.13	0.51	0.65
	Muscle or back pain	10 (1 %)	0.50	0.28	1.54	1.45	1.33
Adults > 16	Gastrointestinal problems	989 (43 %)	1.31**	1.01	1.00	1.02	0.97
n = 1,439	Fungal infections	186 (8 %)	1.00	0.49*	0.99	1.09	1.02
obs = 2,305	Upper respiratory infections	474 (21 %)	1.09	0.84	0.99***	0.97	0.99
	Urinary tract infections	423 (18 %)	1.03	0.96	1.00	0.35***	0.88***
	Skin infections	35 (2 %)	0.20	0.53	0.99	1.01	1.07
	Trauma	55 (2 %)	1.75	1.07	0.95	1.35	0.81
	Arthritis[a]	198 (9 %)	0.68*	1.13	1.06***	0.48***	1.13**
	Muscle or back pain	1,143 (50 %)	0.72***	1.32**	1.00	2.01***	1.07***

Parameter values are odds ratios estimated in separate generalized logistic mixed model for each medical diagnosis
Parameter significance: $^{t}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$
[a]There were no children with arthritis

In adults, helminths were associated with greater odds of non-giardia gastrointestinal problems (OR = 1.31, $p < 0.01$) and with reduced odds of both arthritis (OR = 0.68, $p = 0.04$) and muscle or back pain (OR = 0.72, $p < 0.001$). *G. lamblia* was associated with reduced odds of adult fungal infection (OR = 0.49, $p = 0.02$) and greater odds of adult muscle or back pain (OR = 1.32, $p < 0.01$). Neither was significantly associated with trauma, skin infection, or urinary tract infection.

The observation of increased odds of respiratory infection in children but reduced odds of arthritis and muscle or back pain in older adults is consistent with predictions based on the immunomodulatory effects of helminths and elaborated on in the hygiene hypothesis. In the absence of helminth and commensal-induced immunoregulation, inflammation may be excessive, leading to autoimmune disorders such as arthritis. Previously we have shown that IgE, a marker of past and current helminth infection, is associated with lower inflammatory markers, such as CRP (Blackwell et al. 2010), and lower total cholesterol (Vasunilashorn et al. 2010). However, as observed in the Tsimane, helminth infection may have varying effects on comorbidity during different life stages, with different clinical implications. Helminths may be protective in preventing inflammatory disorders during adulthood, but their immunoregulatory effects may increase susceptibility to infectious disease at younger ages.

Limitations and Future Directions

There are several limitations of our analysis that limit wider extrapolation of our results and interpretations. First, infectious status among the Tsimane is diagnosed on the basis of a single fecal sample only, which may underestimate the true prevalence of both single- and multiple-species infections in this population. Second, THLHP community sampling does not permit us to conclusively discriminate between acute, chronic, or resolving infections, which may influence our interpretations of parasite associations in hosts. We also as yet do not have data on the possible risk of coinfection involving helminths and more virulent diseases known to afflict the Tsimane, including leishmaniasis, dengue fever, tuberculosis, leptospirosis, and other common viral and bacterial infections. While we have shown that endemic helminth infection in the Tsimane may be protective against a common intestinal protozoan, helminth-induced T_H2/T_{reg} biasing may increase susceptibility to coinfection with these more virulent pathogens.

Finally, although we have shown that the prevalence of helminth coinfection among the Tsimane is lower than that of several African populations, Tsimane coinfection rates may have increased in recent decades and may continue to increase in coming years. The Tsimane have only been permanently settled in their current territory since the mid-twentieth century (Gurven et al. 2007; Huanca 2006). Increased sedentism, population growth and density, interactions with domesticates, fecal contamination of local water sources, and emerging social threats (e.g., prostitution and alcohol abuse) have likely increased the rate of exposure to existing and

novel parasites and other infectious diseases. Meanwhile, hygienic conditions, access to medical care, vaccine coverage, and antibiotic usage—though improving—remain poor. Novel patterns of coinfection, and their effects on Tsimane health and immune function, may yet be emerging. Moreover, while the Tsimane environment may be more similar to a recent ancestral environment than that of a contemporary industrialized population, it is by no means identical to the disease ecology of our hominin ancestors.

Future research with the Tsimane will examine the role of additional host and environmental factors on coinfection susceptibility, such as regional and seasonal risks, and additional variation in immune and morbidity markers associated with different coinfectious combinations and infection intensities. In particular, more sensitive surveys of pathogen prevalence and helminth-pathogen risk are needed in this population. Such research may help to identify current risk factors associated with a wider range of multiple-species infections and may help predict how emerging infectious threats are likely to interact with current endemic intestinal parasites and associated immune responses.

Conclusions

In humans, the prevalence and distribution of a range of multiple-species infections has been increasingly well documented in epidemiological research but remains understudied from an evolutionary or ecological perspective. Researchers interested in human-pathogen coevolution should consider the additional challenges posed by parasitic coinfection. There are many factors that influence parasite coinfection risk and coinfectious outcomes in hosts. In this chapter, we focused on coinfections involving STH, which are the most widespread human intestinal parasite and induce characteristic immunoregulatory responses suspected to influence a range of coinfectious outcomes.

Chronic helminth infection, which may have been the norm during human ancestry, is associated with varying risks and benefits in modern human populations. While the prevalence of multiple helminth infection among the Tsimane is lower than that reported for several African populations, infection with a single helminth species in the Tsimane was associated with helminth coinfection risk, and multiple helminth infections were associated with increased infection intensity.

Our results suggest that helminth infection during childhood increases risk of respiratory illness, which may indicate increased susceptibility to bacterial and viral infection due to helminth-induced immune biasing. These results have implications for vaccination programs and the spread of epidemic diseases among the Tsimane and require further investigation. Other work has suggested that early and chronic elevated IgE, characteristic of endemic helminth exposure, is also associated with growth deficits (Blackwell et al. 2010). Therefore, helminth infection may still pose a substantial threat to health and well-being in the Tsimane and other nonindustrialized populations.

At the same time, helminth-giardia coinfection in the Tsimane occurs less frequently than would be predicted by independent transmission. The lower risk of helminth-giardia coinfection may be mediated by direct competition or controlled by strong T_H2 mechanisms invoked by chronic helminth challenge. Future research is needed to elucidate the mechanisms of helminth-giardia antagonism, particularly given the clinical implications of increased infection risk following antihelmintic or antiprotozoal administration. The results reviewed here also suggest that helminth infection and elevated IgE in adulthood is associated with lower incidence of inflammatory-associated morbidity (Blackwell et al. 2010; Vasunilashorn et al. 2010). These findings are all consistent with the proposal that some inflammation-linked "diseases of modernity," such as obesity and heart disease, may be due to the absence of "old friends" with which our immune systems coevolved.

We intend this discussion of the costs, benefits, and altered risks of coinfection associated with helminths to illustrate the importance of considering multiple-species infections and the role of infectious communities in affecting the evolution of immune responses in hosts, the virulence of pathogens, and implications for health and treatment. In sum, we have presented evidence of a complex trade-off in the risks and benefits of helminth infection in humans. These trade-offs are likely to vary by life stage, environment, and host factors influencing coinfection and morbidity risk, which are constantly changing across the human landscape. These factors may influence differences in patterns of coinfection prevalence and associated morbidity observed today and must be considered in models of ancestral parasite and pathogen coinfection risk. Identifying and understanding both the ancestral and emerging risks of coinfection pose an important challenge for researchers working across varied human populations, which will be best met by an integrated cultural, epidemiological, ecological, and evolutionary approach.

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