A life without worms

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Worms have co-evolved with humans over millions of years. To survive, they manipulate host systems by modulating immune responses so that they cause (in the majority of hosts) relatively subtle harm. Anthelminthic treatment has been promoted as a measure for averting worm specific pathology and to mitigate subtle morbidities which may include effects on anaemia, growth, cognitive function and economic activity. With our changing environment marked by rapid population growth, urbanisation, better hygiene practices and anthelminthic treatment, there has been a decline in worm infections and other infectious diseases and a rise in non-communicable diseases such as allergy, diabetes and cardiovascular disease. This review reflects upon our age-old interaction with worms, and the broader ramifications of life without worms for vaccine responses and susceptibility to other infections, and for allergy-related and metabolic disease. We touch upon the controversy around the benefits of mass drug administration for the more-subtle morbidities that have been associated with worm infections and then focus our attention on broader, additional aspects of life without worms, which may be either beneficial or detrimental.

Keywords: Allergy, Anthelminthic, Helminths, Infectious diseases, Metabolic disease, Vaccines

Introduction

Over a billion people are estimated to be infected with helminths, most living in areas of poverty.[1,2] Helminths have co-existed with mammals for millions of years. Their lifecycles have evolved to ensure their survival while minimising harm to the mammalian host. Soil transmitted helminths (STH) such as hookworm, *Ascaris lumbricoides, Trichuris trichiura* and *Strongyloides stercoralis* spend part of their lifecycle in soil and gain access to their human host through skin penetration or ingestion. For the filarial nematodes, an insect vector takes up microfilariae during a blood meal and, after development in the insect, the parasite is injected into the next host during another blood meal. For water borne helminths such as *Schistosoma*, cercariae shed by the snail intermediate host access the definitive human host by skin penetration during contact with infested water. After migratory and development stages, adult worms lodge in body tissues such as the gut, blood vessels and lymphatics. In most cases, helminths do not replicate in the mammalian host.[3]

Helminths induce short and long term morbidity, and pathology in some body systems: gastrointestinal tract (malabsorption, diarrhoea, macro and micronutrient deficiencies, bleeding, intestinal obstruction, rectal prolapse), liver (peri-portal fibrosis, cholangitis, cholangiocarcinoma, hepatocellular carcinoma), cardiovascular system (anaemia), lymphatic system (lymphoedema), central nervous system (blindness, epilepsy), genitourinary tract (haematuria, hydronephrosis, bladder cancer), lungs (Loeffler's syndrome).[4] These effects depend on the type and number of helminths in the host. Treatment is deserved to avert these harmful effects.

Societies in developing countries are experiencing remarkable population growth, urbanisation and lifestyle changes. With better hygiene and 'deworming' interventions, helminth infections are declining. Concurrently, there is a rise in non-communicable diseases (NCDs) such as diabetes[5] and cardiovascular diseases,[6] contributing significantly to global mortality and attributed largely to changes in diet and lifestyle. Could the decline in helminth infections be playing a role in this epidemiological transition? With helminth elimination the ultimate goal of mass drug administration (MDA) programmes,[7] it is of interest to reflect on the prospect of a worm-free life. Do we clearly understand, are we ready for, the consequences of life divorced from the partnership established over millions of years? In this narrative review we discuss current evidence regarding the benefits of MDA, ways in which worms manipulate us, and the possible

effects of helminth infection on responses to vaccines and unrelated infectious diseases, and on allergy and metabolic disease.

How much do we benefit from MDA?

MDA entails administration of anthelminthic medicines without reference to an individual's infection status, or test of cure. The World Health Assembly endorsed MDA for school children as a schistosomiasis and STH control strategy for high transmission settings[8] and this has been widely adopted.

MDA policy is premised on anticipated benefits for helminth-specific pathology, maternal anaemia, birth weight, childhood growth, anaemia, cognitive function, school performance and long term economic returns. We do not question the benefit of MDA for controlling pathologies such as schistosome-induced fibrosis, hookworm-induced anaemia, elephantiasis and river blindness. However, the impact of MDA on more subtle morbidities associated with helminths has been difficult to demonstrate.

Mass treatment for hookworm in the American south at the turn of 20th century was associated with greater school enrolment, attendance and literacy and long-term gain in income.[9] Further, in 2004, Miguel and Kremmer published a highly influential report showing an association between school-based MDA and reduced school absenteeism among Kenyan children.[10] Ten years later, these children who were dewormed at school had more years of school enrolment, more time in employment and longer work hours each week.[11] However, recent reanalyses of the original data have highlighted the challenges of evaluating such interventions.[12,13]

A large cluster-randomised trial in India with one million pre-school children showed little effect of regular deworming on mortality in pre-school children.[14] A Cochrane review[15] concluded that treating children known to have STH may improve weight gain but evidence of benefits on haemoglobin, school attendance and cognitive function is limited; also that community based treatment programmes had little or no effect on these outcomes. Similarly, a systematic review found the evidence insufficient to link helminths to cognitive performance[16] and a further meta-analysis concluded that mass deworming of children had little or no effect on weight, height, cognition, school attendance or mortality.[17]

WHO recommends anthelminthic treatment during pregnancy, hoping that it will reduce maternal anaemia, increase birth weight and reduce mortality. The benefits are not yet clear.[18] We, and others, have found limited overall effects[19] of anthelminthic use during pregnancy on maternal anaemia, and none on birth weight, perinatal mortality or congenital abnormalities.[20–23] Anthelminthic treatment during pregnancy did not affect infectious disease incidence or response to immunisation.[24,25] A Cochrane review notes that evidence is insufficient to recommend use of anthelminthic medication for pregnant women in the first trimester and administration of a single dose anthelminthic was not associated with any impact on maternal anaemia.[26]

There has been debate on the policy of MDA[27] and systematic review methodology has been questioned in its application to helminths.[28,29] However, it brings to light the need for more evidence to support MDA and to understand fully its benefits.

How do worms manipulate us?

The age-old colonisation of mammals by helminths has been successful mainly because of the latter's shrewd manipulation of host systems (Figure 1).

Helminths employ enzymes and other excretory/secretory proteins to disrupt and alter host tissues, thus successfully migrating, feeding, establishing niches and developing strategies to exit the host to complete their life-cycles. For example, *Schistosoma* cercariae contain proteases that aid in skin penetration[30] while the major excretory/secretory protein of *Trichuris trichiura* induces pore formation to facilitate helminth entrenchment in the gut.[31]

Loss of mucosal and epithelial integrity as helminths take root in the host is often accompanied by release of inflammatory mediators, such as alarmins and damage associated molecular patterns,[32] normally detrimental to the helminth and its host. However, helminth excretory/secretory products also work to offset this. For example, secreted products of *Heligmosomoides polygyrus* block production of the alarmin IL-33, a key inducer of Th2-type inflammation.[33] Besides, to curb host morbidity from helminth-inflicted tissue injury, helminth-induced mediators spearhead tissue healing and remodelling.[34]

But perhaps the helminth's most potent survival weapon is the wide array of mechanisms developed to evade or regulate a vigilant host immune system. At the helm are helminth-induced Th2-type and regulatory immune responses. Helminth-induced Th2 cytokines interleukin (IL)-4 and IL-13 promote alternative activation of macrophages, resulting in production of large amounts of immunomodulatory IL-10 and transforming growth factor (TGF)-β,[35] and T cell hypo-responsiveness involving regulatory T cells.[36] Helminth-induced, IL-10-producing 'regulatory B cells' have also been demonstrated.[37] A notable consequence of helminth-induced immunomodulation is the attenuation of responses to 'bystander' antigens,[38] widely implicated in the helminth-associated modulation of immune responses to a number of non-communicable and communicable diseases.

Helminth-allergy interactions are a good example of the bystander effect. Although antigenic targets for allergen- and helminth-specific immune responses are similar,[39] helminth infections seem to be protective against allergy-related conditions in both humans and mice. Current evidence[32,40] points to an extensive array of immunomodulatory mechanisms underlying inverse helminth-allergy associations. They range from induction of IL-10-producing regulatory T cells, regulatory B cells and alternatively activated antigen presenting cells, promotion of polyclonal IgE synthesis and immunoglobulin class switching to IgG4, to suppression of release of alarmins (such as IL-33) and inhibition of type 2 innate lymphoid cell activity.

Host metabolic responses may also be influenced by helminth infections. For example, *S. mansoni* egg antigen-treated obese mice have increased levels of white adipose tissue Th2-type cells, modified macrophage activation and reduced adipose tissue mass and improved insulin sensitivity.[41] Non-obese diabetic mice infected with *H. polygyrus* and *Trichinella spiralis* are protected against type-1 diabetes through the Th2-associated reduction of inflammatory autoimmune responses.[42] There is also recent evidence in humans and mice that helminths may protect against inflammatory
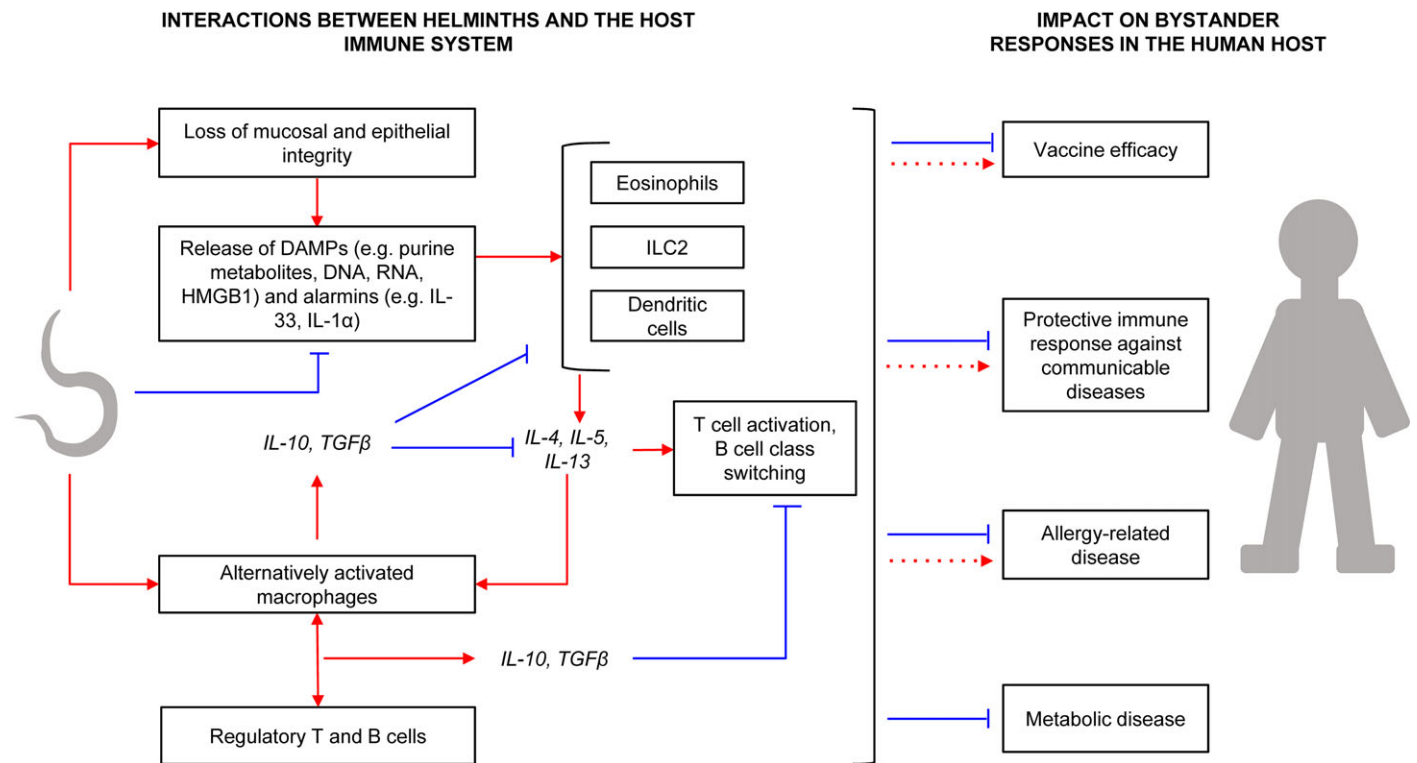
Figure 1. Interactions between helminths and the host immune system, and the impact on bystander responses. Red arrows and blue lines denote positive and suppressive effects, respectively. Helminth migration in the host results in tissue injury, resulting in release of Damage Associated Molecular Patterns (DAMPs) and alarmins. DAMPs and alarmins are involved in the initial activation of eosinophils, type 2 innate lymphoid cells (ILC2) and antigen presenting cells (APCs) such as dendritic cells (DCs), which then mediate further inflammation in the host. However, some helminth secretory products can suppress alarmin release and DC maturation, and some helminth enzymes degrade DAMPs. Helminths also interfere with APC activities, promoting an alternative activation phenotype, which results in production of large amounts of IL-10 and TGFβ. These cytokines downmodulate eosinophil, ILC2 and DC responses, and promote lymphocyte hyporesponsiveness involving regulatory lymphocytes. Helminth interaction with host immunity has spillover effects on responses to bystander antigens. For instance, helminth infections may result in impaired immune responses to vaccines and communicable diseases, although specific helminth molecules may actually have enhancing effects. Likewise, there is evidence for both inverse and positive helminth-allergy associations, although any notable effects on metabolic conditions have been beneficial. DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; HMGB1: High Mobility Group Box 1.

bowel diseases through Th2-type immunity-mediated expansion of a protective microbiota.[43]

Helminth-induced bystander response suppression is a double-edged sword. We may benefit from helminth-driven regulation of non-communicable diseases, as elaborated above. However, helminth excretory/secretory products and Th2 cytokines have been shown to suppress anti-microbial functions of innate immune cells (dendritic cells and macrophages), leading to increased differentiation of regulatory T cells and Th2 cells while impeding the development of protective Th1-type responses and potentially compromising immunity to several communicable diseases.

Worms and vaccines

Following recognition of the Th1/Th2 hypothesis,[44] the contrasting ability of mycobacterial and helminth antigens to elicit Th1 and Th2 responses, respectively, and mutual inhibition between these opposing effects,[45] it was proposed that helminth co-infection might account for the poor efficacy of vaccines such

as BCG in tropical settings and the high prevalence of TB and HIV in Africa.[46] As helminth prevalence declines, will vaccines become more effective, and susceptibility to other infectious diseases decrease?

Studies in animal models largely suggest that this will be the case. In the mouse, infection with *H. polygyrus* (a nematode with a life-cycle confined to the gut) modified the response to a malaria protein vaccine, resulting in reduced antibody and Th1 responses, increased Th2 and regulatory responses and impaired protection against malaria challenge.[47] Treatment of the helminth before, but not after, immunisation abrogated these effects, emphasising the importance of co-infection at the time of immunisation. Similar effects of *H. polygyrus* have been reported for a DNA malaria vaccine, but not for live, irradiated sporozoites,[48] or for live BCG,[49] indicating that the impact of a particular helminth differs by vaccine type: protein, DNA or live attenuated organisms. Mice infected with *Schistosoma* species (which cause systemic infections) show impaired induction of protective immunity both to malaria[50] and to TB challenge (following BCG),[51] indicating that different helminth infections have different effects. *Schistosoma* infections also resulted in

impaired antibody responses to toxoid and protein vaccines—but a study on hepatitis B immunisation showed a gradual recovery of the response when the infection was treated after immunisation.[52] The life-cycle of *Trichinella spiralis* involves an intestinal phase, followed by encystment in skeletal muscle; suppression of the IgA response to cholera toxin[53] and to hepatitis B immunisation[54] has been demonstrated during the intestinal, but not the muscle, stages of the life-cycle. While these experiments demonstrate suppressive effects, intraperitoneal injection of *Ascaris* extract concurrently with BCG has been shown to enhance macrophage activation and suppress BCG replication[55] and a protein from the filarial worm *Onchocerca volvulus* shows promise as an adjuvant for influenza vaccine.[56] Together, studies in mice show that helminth infections have important potential to supress vaccine responses, but that helminth species, stage of life-cycle, timing of helminth exposure and treatment, and characteristics of the vaccine may be important determinants of the outcome and that specific helminth molecules may actually have enhancing effects. As well, differences between murine models are likely to result from genetics of the host and intensity of helminth infection used.

In humans, studies of the impact of helminth co-infection on vaccine responses are important in their own right, and also offer an important surrogate for studies on susceptibility to infections, which are much more difficult to undertake. The bystander modulatory effects of chronic helminth infections are of potential direct significance in adolescents and adults when primary or recall immunisation occurs in this age group. For example, for human papilloma virus immunisation, tetanus and other boosters, and during outbreaks, such as the recent Yellow Fever and Ebola epidemics; also when novel vaccines are undergoing initial evaluations in older populations. Observational studies among children and adults have shown associations between helminth infection and suppression of antibody and Th1 responses, particularly during systemic filarial infections and schistosomiasis: vaccines affected include BCG, tetanus, typhoid and a candidate malaria vaccine.[57–65] Hepatitis B immunisation may also be impaired in the context of schistosomiasis[66] but effects may be limited to those with hepatosplenic disease, calling into question the causal mechanisms involved.[67] Clinical trials may help us to test whether helminth induced immunomodulation is causal in suppression of vaccine responses and, so far, these have been confined to effects of geohelminths. Treatment of geohelminths with albendazole has been shown to improve the Th1 response to BCG,[68,69] and the antibody and Th1 response to oral cholera vaccine.[70,71] No studies have yet investigated the effects of treating schistosomiasis or filariases but, on balance, the data so far suggest that vaccine responses will improve with the elimination of worms.

However, the majority of vaccines in current use target pathogens that cause substantial disease and death in early life. They are administered to the very youngest age groups in whom chronic helminth infections have yet to establish themselves. In these age groups, it is maternal infection status that is potentially of greatest importance in terms of impacting on a newborn's capacity for induction of vaccine-specific responses. Evidence that the human fetus could be sensitised in utero to helminths and mycobacterial antigen[72] suggested that prenatal exposure might influence infant vaccine responses. Indeed, initial studies by Malhotra and colleagues showed an association between sensitisation to *Schistosoma* or filarial antigens in utero and a Th2 bias to the infant response to BCG immunisation.[73] Malhotra and colleagues also described adverse associations between prenatal exposure to hookworm and other helminths and the response to diphtheria toxoid and *Haemophilus influenzae* type B (HiB) immunisation in infancy,[74] but this has not been confirmed by results from Uganda where the only association observed was a possible enhancement of IgG responses to pertussis toxin, HiB and hepatitis B among infants of mothers with *Strongyloides*.[25,75,76] A study in Ecuador also showed no association between exposure to maternal geohelminths and infant responses to diphtheria toxoid, tetanus, pertussis, measles, Rubella or HiB, but enhanced IgA responses to polio and rotavirus.[77] An important consideration is that the infant outcome may vary depending on the nature and timing of the exposure to parasite antigens: Malhotra and colleagues showed that infant DT responses were enhanced if the infant was sensitised to malaria antigens, but suppressed if the infant was 'tolerised'.[74] Only one substantive trial has investigated the effects of treating helminths during pregnancy on infant vaccine responses: this did not confirm findings from an earlier pilot[78] and gave only weak evidence of an effect of treating maternal hookworm on the infant response to tetanus or BCG immunisation.[24,25] Further work is needed to understand whether helminth elimination among pregnant women will alter the infant response to key vaccines.

Given the complex effects of helminths on vaccine responses it is not surprising that effects on infectious disease susceptibility are complex too (reviewed elsewhere).[79–81] A possible unifying hypothesis, supported by recent evidence from mouse models,[82] is that chronic helminth co-infection has little effect on the innate response to incident infections (and may even enhance it) but does impair adaptive responses that control replication of established infections. For example, in the case of TB, a recent trial on effects of anthelminthic treatment on bovine TB among wild buffalo in South Africa's Kruger National Park found that regular anthelminthic treatment had no impact on *Mycobacterium bovis* infection incidence, but resulted in lower mortality among *M. bovis* infected animals.[83] Similarly, we found little evidence that helminth co-infection affects susceptibility to TB infection in humans,[84] but recent results suggest that treatment of helminths may abrogate regulatory T cells-mediated suppression of Th1 cell frequency and function in helminth-TB co-infection[85] and hints at improved clinical outcome.[86]

Worms and allergy-related disease

Results from epidemiological studies on the relationship between helminths and allergy have been inconsistent. As for vaccine studies, different helminth species interact with the host's immune system differently, resulting in different clinical outcomes. An earlier review and meta-analysis[87] found that hookworm had an inverse association with asthma (summary odds ratio [OR] 0.50, 95% CI 0.28–0.90), with a 'dose-response' by infection intensity, *A. lumbricoides* showed a positive association and *T. trichiura* showed no relationship. Another meta-analysis[88] showed an inverse association between helminthic

infections and allergen skin sensitisation (summary OR 0.69, 95% CI 0.6–0.79).

Exposure to helminth infections in-utero and in early childhood is negatively associated with allergy risk in childhood. Our birth cohort in Uganda showed that maternal hookworm during pregnancy was associated with a reduced incidence of eczema in childhood (adjusted hazard ration [aHR] 0.71, 95% CI 0.51–0.99), with a dose-response, and that early childhood infections with *T. trichiura* and hookworm were associated with a reduced incidence of childhood eczema.[89] Treatment of maternal helminths during pregnancy increased the incidence of eczema in childhood.[24,90] A study in Brazil also showed that early childhood infections with *T. trichiura* and *A. lumbricoides* were associated with a lower prevalence of allergen skin reactivity in later childhood.[91] In Gabon, a lower prevalence of skin reactivity to house dust mite was reported among children infected with *Schistosoma haematobium* compared to those without the infection.[92] Most studies have considered helminths as an independent variable in regression models, but there is increasing evidence that helminths are effect-modifiers of the relationship between atopy and clinical allergy. We found that maternal hookworm during pregnancy attenuated the association between *Dermatophagoides*-specific IgE and eczema in childhood, as well as the effects of other known risk-factors for eczema such as mother's history of eczema and female gender.[89] This effect-modification has also been reported in studies in Ecuador.[93, 94] A study conducted in Uganda found a positive association between *Dermatophagoides*-specific IgE and histamine release among children without hookworm but not amongst children with hookworm.[95]

Despite the inconsistencies outlined, epidemiological studies have consistently shown a lower prevalence of clinical allergy (and sometimes atopy) in rural compared to urban areas in low and middle income countries.[96–98] This is consistent with the observed low prevalence of asthma/allergy among children raised on farms compared to city dwellers in high income countries.[97] In the high income countries, this farm effect has been attributed to exposure to diverse microbiome on the farm and to the consumption of unpasteurised dairy products.[98] For low and middle income countries, the protective effect had been attributed partly to geohelminths,[93] but the possible role of the microbiome has not yet been extensively explored. Animal studies have demonstrated interactions between helminths and microbiota.[99] Could the microbiome in rural settings explain why, in Ugandan island communities, we found a very low prevalence of clinical allergies, despite positive associations between helminths and reported wheeze (and atopy)?[100]

Additionally, there is increasing evidence of attenuation of the relationship between atopy and allergy among children in rural compared to urban areas in low and middle income countries.[93,101,102] This has been attributed partly to geohelminths, but the role of other infections and microbiome deserves investigation.

Studies on immigrants from rural to urban setting represent natural experiments. One such study[103] found that immigrants from rural Ethiopia to Israel had a low prevalence of atopy and allergy, and a negative association between helminth infection and atopy on arrival, which was quickly reversed after a year of living in Israel. This was attributed to the treatment of

helminths, a decline in helminths among the untreated, and exposure to a novel environment.

The helminth-allergy relationship is complicated by the many inter-related factors at play. To obtain a conclusive stand, we need to conduct comprehensive studies that take into account the various helminth-related variables, and the potential interaction and confounding with the microbiome, other infections (such as malaria) and interaction and other environmental exposures. This will require extensive data collection and advanced statistical analyses. But the potential benefits are worth it, for we will be able to understand better how to harness the beneficial effects of worms or the rural environment for the primary, secondary and tertiary prevention of asthma, allergies and other chronic inflammatory conditions that may be associated with a life without worms.

Worms and metabolic disease

A recent systematic review showed that individuals with a previous or current helminth infection were 50% less likely to have metabolic dysfunction.[104]

In diet induced obese mice, chronic infection with *Schistosoma mansoni* lowered whole body insulin resistance and glucose intolerance and improved peripheral glucose uptake and insulin sensitivity. Injection of schistosome antigens induced a similar effect[41] and, in a separate study, reduced atherosclerosis in mice.[105] Mice infected with *H. polygyrus* had lower blood glucose, insulin resistance, fat accumulation than uninfected mice[106] and benefits were sustained even after clearance of the helminth.[107] *Nippostrongylus brasiliensis* infection was associated with decreased weight gain and improved glucose metabolism.[108] Similarly, diet induced obese mice infected with *Litomosoides sigmodontis* or exposed to its antigen had improved glucose tolerance.[109]

In humans, a cross-sectional study in rural China showed that individuals with a history of schistosomiasis infection exhibited lower fasting blood glucose levels compared to controls who had never had schistosomiasis.[110] A study in India[111] reported a lower prevalence of filarial infections in patients with type 2 diabetes than in non-diabetic controls. Patients with type 2 diabetes and lymphatic filariasis had lower concentrations of pro-inflammatory cytokines—IL-6 and GM-CSF—than patients without lymphatic filariasis. Among aboriginal adults in Australia, prior *Strongyloides stercoralis* infection was associated with reduced type 2 diabetes risk.[112] Infection with STH has also been associated with decreased insulin resistance and lower body mass index, abdominal obesity, and lipid levels.[113,114]

Together, these recent findings indicate that helminth infections may convey important benefits for metabolic disease in humans. If so, understanding the mechanisms with a view to harnessing this knowledge for prevention and therapy of metabolic disease is important.

Conclusions

Helminths can be damaging, especially when there are intense infections: therefore, control is good. Some authors have also argued that MDA is a cost-effective health investment for
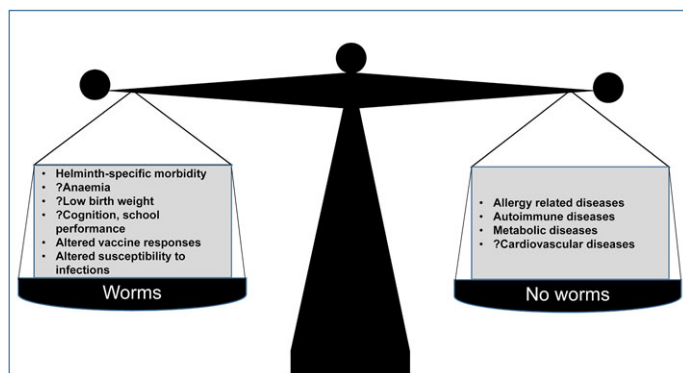
Figure 2. Is 'de-worming' good for us?

governments[115] although, as we have discussed, controlled trials to date have struggled to confirm a major impact of MDA on the subtle morbidities and mortality associated with worm infections in observational studies. As the debate on MDA continues, we need to note that removal of helminths leaves the immune system out of balance. We postulate that helminth elimination will result in a broad array of additional effects, both beneficial and detrimental to human health. The consequences may include altered responses to vaccines and to infectious diseases, and increased susceptibility to inflammatory conditions such as allergy-related disease and metabolic disease (Figure 2). Further work is needed to understand helminth-human interactions and their mechanisms, so that we can mitigate adverse consequences in the event that helminth infections in humans are eliminated.

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