Helminth therapy or elimination: epidemiological, immunological, and clinical considerations

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Deworming is rightly advocated to prevent helminth-induced morbidity. Nevertheless, in affluent countries, the deliberate infection of patients with worms is being explored as a possible treatment for inflammatory diseases. Several clinical trials are currently registered, for example, to assess the safety or efficacy of *Trichuris suis* ova in allergies, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, psoriasis, and autism, and the *Necator americanus* larvae for allergic rhinitis, asthma, coeliac disease, and multiple sclerosis. Studies in animals provide strong evidence that helminths can not only downregulate parasite-specific immune responses, but also modulate autoimmune and allergic inflammatory responses and improve metabolic homoeostasis. This finding suggests that deworming could lead to the emergence of inflammatory and metabolic conditions in countries that are not prepared for these new epidemics. Further studies in endemic countries are needed to assess this risk and to enhance understanding of how helminths modulate inflammatory and metabolic pathways. Studies are similarly needed in non-endemic countries to move helminth-related interventions that show promise in animals, and in phase 1 and 2 studies in human beings, into the therapeutic development pipeline.

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Introduction

Parasitic worms have accompanied man throughout history.[1] Infections with helminths such as roundworms, hookworms, whipworms, and schistosomes are often asymptomatic; only a few hosts carry high worm burdens and have overt clinical pathology.[2] Moreover, mortality due to helminths is rare. These features suggest a long evolutionary coadaptation between these parasites and man. Key to this partnership is the immunological interaction between helminths and their mammalian hosts. Helminths polarise immune responses and modulate regulatory processes, which might account for their long-term survival within a host.[3] In the course of the evolutionary relationship, helminths seem to have fundamentally affected the genetic composition of the host.[4] In heavily exposed human populations, helminths seem to have particularly promoted selection for genes that control the expression levels of cytokines. This adaptation might represent an effort to overcome the regulatory responses induced by helminths. In the absence of worms, such an adaptation could be detrimental and predispose individuals to immune-mediated diseases including allergies and autoimmunity.[3]

In the 20th century, great effort was put into the worldwide control of infectious diseases. However, the decrease in parasitic and other infectious diseases was associated with a substantial increase in prevalence of chronic inflammatory disorders such as asthma, autoimmune diseases (type 1 diabetes, multiple sclerosis), and inflammatory bowel disease.[5] Although the prevalence of asthma and allergic disorders seems to have stabilised in developed countries, the prevalence has increased in developing countries.[6] These epidemiological results accord with the hygiene hypothesis or derivatives, such as the so-called old friends hypothesis[7] and the biodiversity hypothesis,[8] which suggest that the removal of the regulatory effects of microorganisms and parasites—from populations genetically adapted to live with them—tends to lead to an imbalance in the immune system and an increase in immune-mediated diseases.[9]

Consequently, the question arises of whether helminths should be regarded as harmful pathogens or as beneficial commensals. In low-resource settings deworming is advocated to prevent worm-associated morbidity,[10] whereas several research groups in high-income countries are investigating the therapeutic potential of worms and their secreted products in the treatment of inflammatory diseases. This paradox needs to be carefully considered because the practical implications are manifold.

In this Review we summarise present knowledge about immunological and metabolic changes associated with chronic helminth infections, the possible consequences of deworming with respect to inflammatory diseases, and the evidence as to whether a controlled use of worms to treat patients is beneficial, with a view to use helminth-derived molecules as new therapeutics.

Polarisation of immune responses: a double-edged sword

The immune system is equipped with different cell types that recognise and eliminate pathogens. Innate lymphoid cells,[11] dendritic cells, and T cells seem key to the control of different classes of incoming pathogens (figure 1). Type-1 immune responses protect against intracellular pathogens, type-2 responses combat helminths and ectoparasites, and type-17 cells seem to be important against extracellular bacteria and fungi.[12] These responses, spearheaded by T-helper cells, can inflict damage to tissues and organs if uncontrolled. Th1 and Th17 cells release pro-inflammatory cytokines that recruit and activate macrophages and neutrophils, which can attack pathogens. However, their inappropriate activation is associated with autoimmune and inflammatory diseases. Th2 cells trigger responses that disable, degrade, and dislodge parasites,[3] but an overactivated Th2 immune response can lead to allergic disorders. Therefore, an

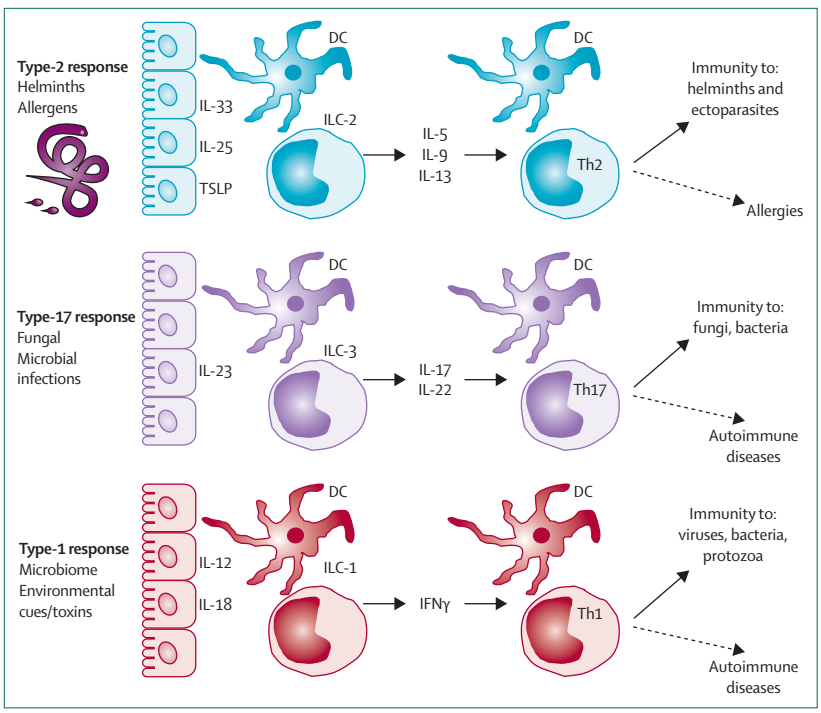

Figure 1: **Polarisation of T-cell responses to incoming pathogens and environmental factors**
At mucosal surfaces, epithelial and immune cells detect changes or danger in the environment. Dependent on the nature of the insult, cytokines are produced, which can drive the expansion of group 1, 2, or 3 innate lymphoid cells (ILC-1, ILC-2, and ILC-3) that in turn are associated with the induction of T-helper cells (ILC-1 is associated with Th1, ILC-2 with Th2, and ILC-3 with Th17). The different T-helper cells combat invading microorganisms. However, when uncontrolled, similar T-cell responses can lead to pathological conditions (shown by broken arrows). DC=dendritic cell. IL=interleukin. TSLP=thymic stromal lymphopoietin. IFN γ=interferon gamma.

important component of the immune system is the regulatory network, with regulatory T cells (Tregs), which are capable of controlling activated effector T cells through expression of inhibitory molecules, at the frontline.[13] Moreover, there is evidence for subtypes of antigen-presenting cells—including monocytes, macrophages, dendritic cells, and B cells—that contribute to suppression of the immune system, resolution of inflammation, and tissue repair, and act as rheostats for homoeostasis.[14]

Helminth-induced immune regulatory network

Studies in the 1970s established that, in individuals infected with helminths, the proliferative response of lymphocytes to parasite antigens was lower than in those exposed but not infected.[15,16] These investigations led to the concept that cellular immune hyporesponsiveness, induced by helminths to evade the host immune system,[17] is part of a sophisticated immune regulatory network that operates during helminth infections.[18] Non-lymphocytic adherent cells can suppress antifilarial responses in patients with *Brugia malayi* microfilariae.[19] These cells were probably representatives of regulatory antigen-presenting cells: alternatively activated macrophages, suppressory monocytes, or regulatory dendritic cells.[20–22] Subsequently, focus shifted to suppressory CD8+ T cells and then to regulatory CD4+ T cells.[23] Findings from animal models and several cross-sectional studies in human helminthiases have provided supportive evidence for the enhanced number and expanded functional capacity of Tregs during helminth infections.[24,25] Importantly, helminth-derived molecules have been identified that can drive Treg induction in mice.[26,27] Regulatory B cells, defined as B10 cells producing interleukin 10, were also identified during human helminth infections and are associated with the suppression of T-cell responses.[28,29] Thus, helminths and their excretory-secretory molecules are endowed with the ability to act through a broad array of cellular mediators to temper host immune responses (figure 2).

On the basis of the ability of helminth infections to induce a regulatory network, helminths might protect against inflammatory diseases.[33] To investigate this hypothesis, human studies have so far included cross-sectional association studies, anthelmintic trials, and trials of helminth therapy.

Associations between helminth infections and inflammatory diseases

Atopy and allergy-related diseases

Animal models show that helminths might protect against allergic airway inflammation.[34] However, results for the association between worms and allergy-related conditions from cross-sectional studies of people are inconclusive (reviewed by Leonardi-Bee and colleagues,[35] and Flohr and colleagues,[36] and updated in table 1, which does not contain literature previously reviewed). For atopy, assessed as a positive skin-prick test to a panel of allergens, an inverse association with worms has been noted, with occasional exceptions.[36] Results have been inconsistent for allergy-related clinical syndromes, such as eczema, wheezing, and asthma. Factors that might affect this relationship are complex and include the timing, burden, or chronicity of helminth infections, helminth species, and host genetics.[52]

Multiple sclerosis

A 1966 case-control study highlighted the contribution of environmental factors in multiple sclerosis; the presence of piped water, a flush toilet, and sharing a room with one person or more were recorded as environmental factors associated with patients with multiple sclerosis compared with healthy controls.[53] Moreover, in an ecological study, country prevalences of multiple sclerosis and *Trichuris trichiura* infections were almost mutually exclusive.[54] Correale and Farez[55] compared helminth-infected and helminth-uninfected patients with multiple sclerosis and showed that new MRI lesions appeared less frequently in infected individuals during 5 years of follow-up. This difference seemed to be associated with an increased production of interleukin 10 and transforming growth factor-β by peripheral blood mononuclear cells and the suppressive activity of Tregs.[55] Furthermore, when a few patients infected with helminths were treated with anthelmintics because of their intestinal symptoms, the number of clinical relapses and MRI lesions increased,

and regulatory immune responses decreased in parallel.[56] The murine model for multiple sclerosis (experimental autoimmune encephalomyelitis) provided further evidence for a protective effect of helminths or their products[57–60] on the clinical course and inflammation in the CNS.

Rheumatoid arthritis

Epidemiological studies in 1975 in South Africa showed that the prevalence of rheumatoid arthritis in urban areas was similar between black Africans and white populations, whereas in rural areas the prevalence was much lower for black Africans.[61] An association with parasitic infections was not proven, but several rodent studies have shown that helminth infections or helminth extracts can suppress or prevent arthritis.[62] A case-control study in India showed that no patient with rheumatoid arthritis harboured circulating microfilariae or filarial antigens, by contrast with 40% of healthy controls.[63]

Inflammatory bowel disease

The finding that the prevalence of inflammatory bowel disease was higher in northern than in southern parts of Europe and the USA led to formulation of the inflammatory bowel disease hygiene hypothesis.[64] The few studies of the association between helminths and inflammatory bowel disease have shown conflicting results.[65–67] However, these studies used self-reported helminth infection in early life or immunological markers of exposure to helminths, which are very uncertain measurements, to define helminth exposure. Studies in murine models have consistently shown that infection with worms protects against several forms of experimentally induced colitis.[68]

Diabetes

Type 1 diabetes is another autoimmune condition linked to the immune modulatory properties of helminths. In the non-obese diabetes mouse model, infection with several helminth species prevented type 1 diabetes.[69] Data from the Chennai Urban Rural Epidemiology Study (CURES) in India showed that antifilarial IgG4 antibody concentration, as proxy for current filarial infection, was greater in non-diabetics, which suggests that active filarial infection might protect against type 1 diabetes.[70]

Type 2 diabetes is regarded as an inflammatory disease,[71] but has a different pathogenesis and is affected by genetic, nutritional, and other lifestyle factors. In another CURES report, patients with type 2 diabetes had a lower prevalence of lymphatic filariasis than patients without diabetes.[72] Moreover, patients with type 2 diabetes and lymphatic filariasis had lower serum concentrations of pro-inflammatory cytokines than did patients without lymphatic filariasis. This finding suggests that filarial infections in type 2 diabetes can have regulatory functions, although the effect on disease severity was not investigated.

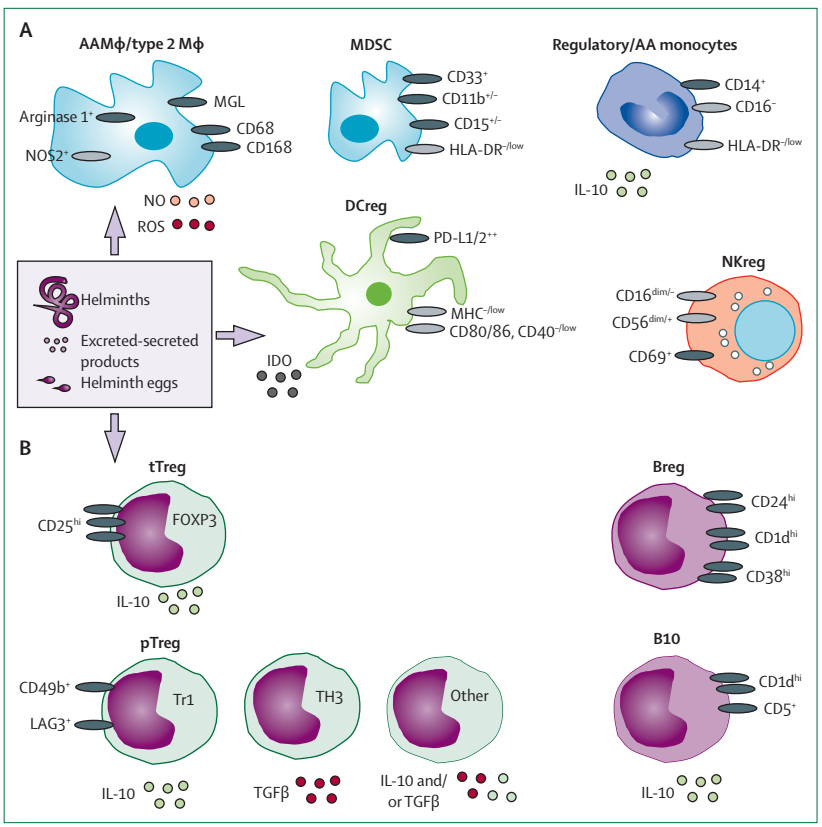

Figure 2: **Helminth-induced regulatory cell network**
Helminths or their excreted or secreted products are able to drive a regulatory network of (A) innate and (B) adaptive immune compartments. Several surface markers and intracellular molecules characterise these different cell subsets. Among the innate regulatory cells (A) are alternatively activated macrophages (AAMϕ), myeloid-derived suppressor cells (MDSC),[30] regulatory dendritic cells (DCreg), and regulatory natural killer cells (NKreg).[31] The adaptive regulatory network (B) consists of regulatory T and B cell subsets; some of their phenotypic characteristics are indicated.[32] The molecules are fully established (dark grey) or not fully established (light grey) markers. AA=alternatively activated. Mϕ=macrophage. MGL=macrophage galactose type C lectin. NOS=nitric oxide synthase. NO=nitric oxide. ROS=reactive oxygen species. IDO=indoleamine 2,3-dioxygenase. PD-L=programmed death ligand. CD=cluster of differentiation. IL=interleukin. tTreg=thymus-derived T-regulatory cell. pTreg=peripherally induced T-regulatory cell. Breg=B-regulatory cell. TGFβ=transforming growth factor beta.

Longitudinal studies of the consequences of deworming

Atopy and allergy-related diseases

The effect of worms on allergic conditions has been studied in children from worm-endemic areas with different anthelmintic drugs for various periods of follow-up. Table 2 shows an overview of placebo-controlled randomised trials and the appendix provides additional details about study populations, interventions, and effect sizes. A cluster-randomised trial in 1632 children from Ecuador that assessed albendazole versus placebo once every 2 months for 1 year showed no effect on skin-prick test responses.[75] A randomised trial in 1566 rural children from Vietnam of benzimidazoles versus placebo every 2 months for 12 months showed an increased risk of positive skin-prick test responses to allergens for those receiving benzimidazoles.[76] A trial in Indonesia assessed albendazole treatment given every 3 months compared

See Online for appendix

	Helminth species	Number of participants	Age (years)	Outcome	Effect size (CI)	Effect direction
Atopy						
Alcântara-Neves et al 2010, Brazil[37]	*Trichuris trichiura*; *Ascaris lumbricoides*; anti-ascaris IgE	283	1–4·2	asIgE	1·52 (0·66–3·50); 0·64 (1·30–1·39); 7·29 (3·90–13·64)	NS; NS; ↑
Calvert et al 2010, South Africa[38]	*Ascaris* spp	3322	8–12	Skin-prick test	0·63 (0·42–0·94)	↓
Choi et al 2011, Korea[39]	*Clonorchis sinensis*	1116	30–86	Skin-prick test	1·86 (1·20–2·87)	↑
Djuardi et al 2013, Indonesia[40]	*Wuchereria bancrofti* (mother in pregnancy)	126	4	Skin-prick test; asIgE	0·35 (0·07–1·70); 0·43 (0·16–1·15)	NS; NS
Hamid et al 2013, Indonesia[41]	Hookworm	315	5–15	Skin-prick test	0·46 (0·21–1·00)	↓
Mendonça et al 2012, Brazil[42]	Toxocara seropositivity	1148	4–11	Skin-prick test	0·74 (0·57–0·97)	↓
Moncayo et al 2012, Ecuador[43]	*T trichiura*; *A lumbricoides*; anti-ascaris IgE	149 wheezers, 227 controls*	7–19	Skin-prick test; Skin-prick test; asIgE	0·42 (0·17–0·99); 0·82 (0·41–1·64); 5·34 (2·49–11·45)	↓; NS; ↑
Rodrigues et al 2008, Brazil[44]	Ascaris (early childhood); trichuris (early childhood); any worm (early childhood); any worm† (late childhood)	1055	4·4–11·3	Skin-prick test	0·63 (0·44–0·90); 0·58 (0·37–0·92); 0·63 (0·45–0·87); 0·78 (0·57–1·06)	↓; ↓; ↓; NS
Supali et al 2010, Indonesia[45]	*T trichiura*; *Brugia malayi*	422; 574	2–90; 2–90	Skin-prick test	1·48 (0·79–2·76); 0·56 (0·35–0·88)	NS; ↓
Wördemann et al 2008, Cuba[46]	*A lumbricoides*; hookworm; *T trichiura*; *Enterobius vermicularis*	1320	4–14	Skin-prick test	No statistically significant associations	NS
Asthma-related symptoms						
Alcântara-Neves et al 2010, Brazil[37]	*T trichiura*; *A lumbricoides*	682	1–4·2	Wheeze	2·60 (1·54–4·38); 1·09 (0·71–1·66)	↑; NS
Amberbir et al 2011, Ethiopia[47]	Any worm (hookworm, *Ascaris* spp, *Trichuris* spp)	876	3	Wheeze	0·74 (0·29–1·90)	NS
Bager et al 2012, Denmark[48]	History of treatment for *E vermicularis* with mebendazole	924 749	0–14	Asthma	IRR 1·07 (1·00–1·13)	↑
Mendonça et al 2012, Brazil[42]	Toxocara seropositivity	1148	4–11	Wheeze and asthma	1·21 (0·92–1·60)	NS
Cobzaru et al 2012[49]	Toxocara seropositivity	76 asthmatics, 88 controls*	5–16	Asthma	13·7 (6·31–29·86)	↑
Choi et al 2011, Korea[39]	*C sinensis*	1116	30–86	Wheeze; EIB	0·94 (0·54–1·62); 1·30 (0·87–1·92)	NS; NS
Kanobana et al 2013, Cuba[50]	Toxocara antibodies; hookworm; *A lumbricoides*	958	5–14	Asthma	1·51 (1·01–2·26); 0·53 (0·32–0·87); 1·29 (0·73–2·28)	↑; ↓; NS
Moncayo et al 2012, Ecuador[43]	*T trichiura*; *A lumbricoides*; anti-ascaris IgE	149 wheezers, 227 controls*	7–19	Wheeze	0·72 (0·44–1·18); 0·90 (0·55–1·48); 2·24 (1·33–3·78)	NS; NS; ↑
Walsh 2011, USA[51]	Toxocara antibodies	12 174	17–65	FEV_1	Adjusted mean difference; −73 mL (−128·1 to −17·9; ie, reduced FEV_1, increased bronchoconstriction)	↑
Wördemann et al 2008, Cuba[46]	*A lumbricoides*; hookworm; *T trichiura*; *E vermicularis*	1320	4–14	Skin-prick test	No statistically significant associations	NS
Eczema						
Amberbir et al 2011, Ethiopia[47]	Any worm (hookworm, *Ascaris* spp, *Trichuris* spp)	876	3	Eczema	0·39 (0·09–1·63)	NS
Wördemann et al 2008, Cuba[46]	*A lumbricoides*; hookworm; *T trichiura*; *E vermicularis*	1320	4–14	Atopic dermatitis	0·23 (0·08–0·68); no statistically significant associations‡	↓; NS; NS; NS
Rhinoconjunctivitis						
Amberbir et al 2011, Ethiopia[47]	Any worm (hookworm, *Ascaris* spp, *Trichuris* spp)	876	3	Rhinitis	0·49 (0·12–2·09)	NS
Wördemann et al 2008, Cuba[46]	*A lumbricoides*; hookworm; *T trichiura*; *E vermicularis*	1320	4–14	Rhinoconjunctivitis	No statistically significant associations‡	NS

If not indicated, effect size is odds ratio. asIgE=allergen-specific immunoglobulin E. EIB=exercise-induced bronchospasm. FEV_1=forced expiratory volume in one s. IRR=incidence rate ratio. NS=not significant. *Case-control study. †*Ascaris* spp (current infections) showed a significant inverse association with infection intensity (p=0·008) whereas the inverse trend for *T trichiura* was not significant (p=0·078). ‡Wördemann and colleagues, in their final model, also showed positive associations between rhinoconjunctivitis and history of hookworm (odds ratio 2·81 [95% CI 1·23–6·42]) or *E vermicularis* (odd ratio 1·34 [1·00–1·79]), and between atopic dermatitis and history of *E vermicularis* (1·86 [1·34–2·58]).

Table 1: **Completed studies that show associations between atopy or allergy-related diseases and helminths**

with placebo in 1364 children. A significant increase in cockroach reactivity (reactivity to skin-prick tests with cockroach allergens) was noted after 21 months but, overall, skin-prick test responses were not changed.[79] None of these three trials showed any effects of anthelmintic treatment on clinical allergy outcomes. Since clinical allergy is quite rare in these areas, the power of the studies might have been insufficient to detect significant effects. Moreover, differences in species of prevalent helminths, in coprevalence of additional immunomodulating infec-

	Study design and intervention	Outcomes
Effects of anthelmintic treatment in healthy populations		
Van den Biggelaar et al 2004, Gabon[73]	A placebo-controlled trial of every 3 months praziquantel and mebendazole in school children (aged 5–14 years)	Increased rate of skin-prick test conversion in treated children and a greater decrease in total IgE
Elliott et al 2005, Uganda[74]	A double-blind, placebo-controlled trial; single-dose albendazole in pregnancy, eczema events in the offspring	A weak effect on infantile eczema* but not statistically significant
Cooper et al 2006, Ecuador (ISRCTN61195515)[75]	A non-blinded, cluster-randomised trial of albendazole twice every month for 1 year	No statistically significant effect on skin-prick test†, wheeze, rhinoconjunctivitis, eczema, VFD, or EIB
Flohr et al 2010, Vietnam[76]	A double-blind, placebo-controlled trial among school children; single-dose mebendazole given once then albendazole given daily for 3 consecutive days once every 3 months	Increase in skin-prick test positivity; no statistically significant effect on changes in EIB†, flexural eczema, wheeze, or rhinitis
Mpairwe et al 2011, Uganda (ISRCTN32849447, EMaBS)[77]	A double-blind, placebo-controlled trial; 2x2 factorial design; single dose albendazole and praziquantel in pregnancy, eczema events in the offspring	Increased rate of eczema among infants of mothers who received albendazole, and among infants of *Schistosoma mansoni*-infected mothers who received praziquantel
Ndibazza et al 2012, Uganda (ISRCTN32849447, EmaBS)[78]	Double-blind, placebo-controlled trial of a single dose of albendazole given once every 3 months to pre-school children (age 15 months to 5 years)	No statistically significant effect on clinical eczema events‡
Wiria et al 2013, Indonesia, (ISRCTN83830814, ImmunoSPIN)[79]	Household-based cluster-randomised, double-blind, placebo-controlled trial	Some evidence of an increase in skin-prick test response to cockroach at 21 months but no overall statistically significant effect on skin-prick test†, specific IgE, wheeze, or atopic dermatitis
Effects of anthelminthics in asthmatics		
Lynch et al 1997, Venezuela[80]	A non-blinded, controlled trial of albendazole once a month for 1 year among asthmatics	Statistically significant reduction in asthmatic crises, number of months on maintenance treatment, and salbutamol use in albendazole-treated group compared with previous year. No change in control group
Almeida et al 2012, Brazil[81]	Double-blind, placebo-controlled trial, single treatment with albendazole and praziquantel among asthmatics	No statistically significant change in asthma severity scores, FEV_1, or cytokine responses to house dust mites

Studies were individually randomised controlled trials, unless otherwise specified. VFD=visible flexural dermatitis. EIB=exercise-induced bronchospasm. FEV_1=forced expiratory volume in 1 s. *Exploratory outcome. †Primary outcome. ‡Planned secondary outcome.

Table 2: **Trials of anthelmintic treatment that examine the effects on atopy and allergy-related disease outcomes**

tions,[33,82,83] in exposure to environmental pollutants, or in duration and timing of treatment, could have had a major effect on trial outcomes.

Early-life exposures affect the development of physiological and immunological processes,[84] and therefore the timing of an intervention might be an important element to determine trial outcomes. In support of this notion, a study in Cuba showed that infants growing up in the economic crisis in the 1990s had a reduced risk of developing asthma and rhinoconjunctivitis later in life.[85] Moreover, a trial in 2507 pregnant women in Uganda that compared single doses of albendazole and praziquantel versus matching controls (in a 2×2 factorial design) showed that albendazole during pregnancy was associated with an increased risk of eczema in infancy[77] and in the first 5 years of life.[78] Praziquantel during pregnancy was also associated with an increased risk of eczema in infancy, but only in children whose mothers were infected with *Schistosoma mansoni*.[77] However, albendazole treatment given every 3 months to children was not associated with an increased risk of eczema in early childhood.[78] These results suggest that in-utero events might be more important in priming or programming the child's immune system than events in early childhood. Surprisingly, the Ugandan study showed no beneficial effects of anthelmintic treatment during pregnancy on the immune responses to early childhood vaccines, and on none of the anticipated benefits for birthweight, resistance to infections, or improved child development[86,87] that would have compensated for the noted adverse effect on eczema.[77,78]

The time needed before an intervention has an effect could be important. A study in Ecuador compared skin-prick test reactivity and allergy-related symptoms in children (aged 6–16 years) from communities that had received 15–17 years of periodic ivermectin treatment with those from adjacent untreated communities.[88] The prevalence of skin reactivity to allergens in children from long-term treated communities was double that of children from untreated communities. Children from the treated communities also had a higher prevalence of recent eczema symptoms.[88] Although the study was limited by the fact that the communities were not randomised, the results suggest that long-term interventions against helminths might be needed not only to change responsiveness to allergens or allergy-related clinical outcomes but also to affect other inflammatory disorders.

The studies described so far investigated cohorts representing the general population. Another approach has been to examine effects of anthelmintic treatment in people who already have an allergy-related disease. In a small trial of individuals aged 5–50 years with a history of asthma in the last 12 months from a schistosomiasis-endemic area in Brazil,[81] study participants received a

single dose of albendazole and praziquantel, or placebo. Investigators recorded no differences in asthma severity between the treatment groups during the 3 month follow-up period. All participants were then treated with both drugs and worsening of asthma symptoms was recorded at 15 months, but there was no comparison group for this part of the study.[81] Larger trials investigating the effect of the treatment of worms in people with established allergy-related diseases are warranted.

Effect on other inflammatory diseases

The effect of deworming on other chronic inflammatory diseases has not been extensively studied, partly because (and inherent to the hypothesis) the prevalence of helminth infections and these conditions show little overlap. Bager and colleagues[48] assessed the effect of anthelmintic treatment retrospectively on chronic inflammatory diseases, in a population cohort in Denmark.[48] In this study 14% of more than 900 000 children were prescribed mebendazole, for probable *Enterobius vermicularis* infection (pinworm), a disease that is still endemic in the USA and Europe.[89] Incidence for asthma, type 1 diabetes, juvenile arthritis, and inflammatory bowel disease was not significantly higher in treated children.[48] However, the authors suggest that mebendazole was usually prescribed on the basis of symptoms rather than parasitological diagnosis of pinworm infection. Moreover, enterobiasis in these children might not have been sufficiently chronic to induce immune regulation, and the treatment prescribed might have abrogated the possible benefits.

Immunological consequences

Several studies have assessed immune responses after anthelmintic treatment. Within clinical trials, Th1 and Th2 cytokine production to helminth antigens was enhanced after albendazole treatment in children (average age of 9 years) in Ecuador,[90] and after praziquantel treatment of pregnant women in Uganda.[91] However, the effect of deworming on regulatory responses was not consistent. A decrease in interleukin 10 might be expected after clearance of immunoregulatory helminth infections, but production of *S mansoni*-specific interleukin 10 was higher in women treated with praziquantel than in those given placebo in the Ugandan study[91] (in line with earlier studies, which were not placebo-controlled[92,93]). By contrast, other studies have shown a decrease in interleukin-10 concentrations after anthelmintic treatment,[76,90] which paralleled an increase in allergic reactivity measured by a skin-prick test.[76] More advanced statistical methods, such as latent class analysis, might help to understand how complex immune response patterns are associated with disease outcomes; defined immune phenotypes can be incorporated into regression models with other important factors included in these associations, such as environmental conditions.[94] A complicating factor in the study of immune responses after anthelmintic treatment is that dead worms, or products released by dying worms, can stimulate immune reactivity too; thus treatment might boost responses by the release of parasite antigens into the host circulation and removal of parasite-induced immunosuppression.

Helminth treatment might result in an increased T-cell response to some non-helminth antigens,[95,96] but very few studies have investigated allergen-specific cellular immune responses after anthelmintic treatment. The trial in Ecuador recorded no differences in cytokine production in response to cockroach and housemite (*Dermatophagoides pteronyssinus*) antigens after repeated treatment with albendazole.[90] Additional trials are therefore needed to explore this issue.

Considerations for anthelmintic treatment

In conclusion, although anthelmintic trials are the design of choice to establish cause and effect, or to minimise confounding and the problem of reverse causation, they are based on several assumptions whose validity is unknown. First, the studies assume that the effect of worms is immediately removed after treatment and that development of allergy symptoms follows soon thereafter; however, the protective effects of worms might persist long after anthelmintic treatment. Second, any recorded effect might be due to the anthelmintic drug itself, or from the broader range of effects of the drug, and not because of the elimination of worms. Albendazole binds to tubulin and thereby interferes with the formation of microtubules in the cytoskeleton.[97] As a result, albendazole can affect protozoa,[98,99] fungi,[100] and mammalian cells.[101] In the trial in Uganda, maternal treatment with albendazole was associated with an increased incidence of infantile eczema, even in the children of mothers with no evidence of helminth infection.[77] Therefore, results from anthelmintic trials should be interpreted with caution and it might be helpful to examine effects of a variety of anthelmintic drugs in additional trials.

Helminth therapy in human beings

A more direct approach, which avoids the pitfalls described, is to study the effects of helminths with live infective stages, or to mimic the effects through helminth-derived molecules. Helminth therapy began in the 1990s with use of *Trichuris suis* ova and later *Necator americanus* larvae.

Trichuris infections

T suis is a pig whipworm that colonises the human gut for a short period. *T suis* ova have been particularly studied as a therapy in inflammatory bowel disease.[68] After two open-label trials assessing the safety of *T suis* infection in patients with inflammatory bowel disease showed promising results (about 70% remission in Crohn's disease[102,103]), Summers and colleagues[104] set out to study the effect of *T suis* ova in a first placebo-controlled, double-blind, randomised trial including 54 patients with

ulcerative colitis.[104] The ulcerative colitis disease activity index in the *T suis* ova group improved significantly compared with the placebo group; however, the number of remissions was not significantly different. Another group characterised the local immune responses surrounding trichuris worms, by studying a patient who self-medicated with *T trichiura*, the human whipworm.[105] In this patient, during colitis, the T cells producing only interleukin 17 were abundant, whereas after trichuris infection more multifunctional T cells were induced, producing cytokines including interleukin 22.[105] In a murine asthma model, treatment with interleukin 22 improved airway constriction and limited airway inflammation.[106] In addition to the induction of regulatory cells, trichuris worms seem to modify the cytokine signature of local inflammatory cells. Interleukin 22, together with type-2 cytokines, might contribute to tissue repair and restore gut homoeostasis.[107] However, an accumulation of interleukin 17 and interleukin 22 coexpressing cells was associated with colorectal cancer, a result that warrants careful consideration of this molecule.[108] In October, 2013, the outcome of a trial undertaken in 250 patients with inflammatory bowel disease showed no strong beneficial effect of *T suis* ova.[109] The full details of the results are yet to be published.

A safety trial of *T suis* ova in patients with multiple sclerosis was a starting point for a planned phase 2 trial. The trial followed up five patients with relapsing–remitting multiple sclerosis after inoculation with *T suis* ova.[110] Although most patients had mild gastrointestinal symptoms, the number of new lesions shown by MRI was lower during *T suis* ova treatment than before treatment, or after treatment was discontinued. This result was not accompanied by a change in circulating Tregs or alternatively activated monocytes, which suggests that such cells might be recruited in affected tissues and absent in peripheral blood.

A randomised controlled trial of *T suis* ova in 100 patients with allergic rhinitis showed that the therapy induced gastrointestinal symptoms and *T suis*-specific antibody responses without any effect on rhinitis symptom scores, medication use, or skin-prick test reactivity.[111] However, this trial has been criticised because the time between infection with *T suis* ova and the start of the hay fever season might have been too short for sufficient regulatory responses to develop.[112]

As of June, 2014, 18 clinical trials are registered to assess the safety or efficacy of *T suis* ova in allergies, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, psoriasis, and autism (table 3).

	Sponsor	Phase	Status	Condition
Interventions involving *Trichuris suis* ova				
EUCTR2007–006099–12-DK	Statens Serum Institut, Denmark	2	Completed	Allergic rhinitis
NCT01070498	Beth Israel, Boston, USA	1	Completed	Food allergy
NCT01279577/EUCTR2006–000720–13-DE	Dr Falk Pharma, Frankfurt, Germany	2	Ongoing	Crohn's disease
ACTRN12608000241336	Asphelia Pharaceuticals, San Diego, USA	1	Not yet recruiting	Crohn's disease
NCT01434693	Coronado Biosciences, USA	1	Completed	Crohn's disease
NCT01576471	Coronado Biosciences, USA	2	Ongoing	Crohn's disease
NCT01433471	New York University, New York, USA	2	Recruiting	Ulcerative colitis
NCT01953354	NIAID, Bethesda, Maryland, USA	2	Recruiting	Ulcerative colitis
NCT01413243/EUCTR2009–015319–41-DE	Charité, Berlin, Germany	2	Recruiting	Multiple sclerosis
NCT00645749	University of Wisconsin, Madison, USA	2	Ongoing	Multiple sclerosis
NCT01006941	Rigshospitalet, Copenhagen, Denmark	2	Completed	Multiple sclerosis
EUCTR2011–006344–71-DE	Immanuel Hospital, Berlin, Germany	2	Unknown	Rheumatoid arthritis
NCT01836939	Mount Sinai School of Medicine, New York, USA	2	Ongoing	Psoriasis
NCT01948271	Tufts Medical Center, Boston, USA	1	Recruiting	Psoriasis
NCT02011269	Coronado Biosciences, USA	2	Not yet recruiting	Psoriasis
NCT01040221	Montefiore, New York, USA	1	Recruiting	Autism
NCT01734941	Hadassah Medical Organization, Jerusalem, Israel	2	Recruiting	Autism
NCT02140112	Coronado Biosciences, USA	2	Recruiting	Autism
Hookworm larvae intervention				
NCT00232518	University of Nottingham, UK	2	Completed	Allergic rhinoconjunctivitis
NCT00469989	University of Nottingham, UK	2	Completed	Asthma
NCT00671138	Princess Alexandra Hospital, Brisbane, Australia	2	Unknown	Coeliac disease
NCT01661933	Princess Alexandra Hospital, Brisbane, Australia	1&2	Recruiting	Coeliac disease
NCT01470521/EUCTR2008–005008–24-GB	University of Nottingham, UK	2	Recruiting	Multiple sclerosis

NIAID=National Institute of Allergy and Infectious Diseases.

Table 3: **Overview of registered clinical trials on helminthic therapy**

Necator americanus larvae

Live *N americanus* larvae (human hookworm) can establish long-term infections in man (with longevity of several years). The safety of *N americanus* larvae was assessed in a dose-ranging study in the UK. Inoculation with 50 larvae or more resulted in substantial gastrointestinal symptoms.[113,114] However, inoculation with ten larvae was sufficient to achieve an infection intensity equivalent to 50 eggs per gram of faeces in healthy volunteers and induced a modest immunological response, as measured by eosinophil counts, IgE concentrations, and hookworm-specific IgG concentrations.[114]

Further safety studies showed that in patients with allergic rhinitis, the lung passage of hookworm larvae did not cause deterioration in airway reactivity[115] and that hookworm-induced type-2 responses did not potentiate an allergen-specific IgE response.[116] The randomised controlled trial of *N americanus* infection in patients with asthma, with ten larvae, did not show any beneficial effects against asthma symptoms.[117] A randomised controlled trial of *N americanus* infection in patients with coeliac disease showed no effect on the clinical response to wheat challenge.[118] However, these trials were undertaken with a maximum of only 16 volunteers in each group. The immunological responses in peripheral blood and the mucosal tissue were investigated after hookworm therapy. In participants infected with hookworm, unstimulated mucosal cells produced less interferon-γ and interleukin 17 than in uninfected participants, whereas cells stimulated with the wheat protein gliadin showed a greater production of Th2 cytokine.[119] When hookworm-specific responses were assessed, peripheral blood mononuclear cells and mucosal cells produced higher concentrations of Th2 cytokines in hookworm-infected participants.[120] In parallel, a strong downregulation of interleukin 23, thought to originate from an innate cell source, was reported that could account for the suppression of Th17 responses noted in the earlier study.[119] These data show that helminth therapy might be able to change local and systemic immune responses. However, many more and larger studies are needed, and to be completed in a standardised manner, to firmly establish the extent of immune modulation that is achievable and its potential to change clinical outcomes. Five clinical trials are registered to use *N americanus* larvae for allergic rhinitis, asthma, coeliac disease, and multiple sclerosis (table 3).

Challenges in helminth immunotherapy

Helminthic therapy has some drawbacks. *N americanus*, and possibly *T suis*, could have pathogenic effects in people, particularly at high doses. Patients undergoing helminth infection should be monitored closely for infection intensity and for possible extraintestinal manifestations of the infection.[121] The long-term results of helminth immunotherapy have not yet been assessed; 24 weeks has been the longest follow-up time for clinical, parasitological, and immunological outcomes. The question remains whether these parameters would change after a longer period of time. The advantage of the introduction of hookworm infections is that only occasional inoculations would be needed, whereas *T suis* ova would need to be given every 2–3 weeks because it is not a natural human infection. However, this implies that hookworm infections are less controllable because they lead to chronic infestations. The timing of infection is another issue since evidence suggests that the protective immune modulatory effects might be most effectively established in early life.[78,84] Moreover, the full development of immunomodulatory effects might take years. In this respect, introduction of parasites as a preventive measure in early life would be the most effective way to control inflammatory diseases.

Although immune regulatory responses are desired to counteract inflammatory disorders, they could be detrimental for other immune-associated conditions; defence against incoming pathogens might be impaired, and anti-tumour immune responses could be compromised. Efforts by the scientific community are being made to inhibit Tregs in cancer by immunotherapy.[122] Moreover, immunosuppressive agents, such as glucocorticoids, and the increasingly prescribed tumour necrosis factor (TNF) inhibitors for inflammatory bowel disease and rheumatoid arthritis, are associated with an increased risk of (myco)bacterial and some viral infections, such as herpes zoster.[123,124] However, helminth-induced immunoregulation might be more selective than present forms of immunotherapy. For example, evidence shows that B cells can escape Treg control when toll-like receptors (TLR) 4 and TLR 9 are triggered, which happens during viral and bacterial infections.[125] Further studies of the effect of helminth co-infection on susceptibility to other infections and to cancer, which can be undertaken in endemic settings, will be helpful, alongside helminth therapy trials in non-endemic settings, to assess these aspects of the safety of helminth therapy.

Helminth-derived molecules

Because helminth infections have clinical and pathological results, focus is shifting towards helminth-derived molecules to substitute treatment using whole parasites.[126] Several helminthic products with immune-modulating properties have been defined.[127] Although studies in animal models have shown promise, no helminth-derived molecule has been given to human beings. The filarial-derived glycoprotein ES-62 is the best characterised candidate molecule for therapeutic trials. This phosphorylcholine-coupled glycoprotein (first described in 1989[128]) has beneficial effects in a mouse model of arthritis,[129] and reduces the production of pro-inflammatory cytokines in synovial cells from patients with rheumatoid arthritis.[129] Additionally, filarial-derived glycoprotein ES-62 inhibits mast cell histamine release, which shows that it might protect against allergic diseases.[130]

Heligmosomoides polygyrus excreted-secreted products suppress murine allergic airway inflammation.[131] AvCystatin, a molecule secreted by *Acanthocheilonema viteae*, inhibits the development of allergic airway inflammation and acute colitis in mice.[132] In-vitro Th2 responses of peripheral blood mononuclear cells in patients allergic to grass pollen are substantially reduced by the addition of AvCystatin to cultures.[133] Furthermore, although less well characterised, soluble products from *S mansoni*, *T suis*, and *Trichinella spiralis* can suppress clinical signs of murine experimental autoimmune encephalomyelitis by modulation of dendritic cells.[134]

Extracts from *S mansoni* adult worms and excreted-secreted products of the canine hookworm *Ankylostoma caninum* have shown beneficial effects in murine models of colitis.[135] Although treatment with *S mansoni* extracts did not improve the clinical score of colitis, it diminished local inflammation and myeloid cell infiltration in colon tissue. In parallel, lower Th1 and Th17 responses and enhanced expressions of interleukin 10 and transforming growth factor-β in T cells were recorded in local tissues.[135] These results show that changed immune responses do not always lead to clinical improvements, and a longer follow-up might be needed for a clinical improvement to be detectable. Finally, lacto-N-fucopentaose III (LNFPIII; a LewisX-containing glycan that is found in *S mansoni* eggs) suppresses experimental autoimmune encephalomyelitis by enhancement of interleukin 10 and Th2 cytokines,[136] and improves psoriasis by reducing interferon-γ production in the skin.[137] Taken together, these encouraging results from animal models warrant further studies and possible clinical trials, to assess their beneficial effects.

An emerging frontier: immunometabolism and helminth infections

Immunometabolism is an emerging specialty, which investigates the interaction between nutrients, metabolism, and the immune system.[138] Macrophages might have a central role in the crosstalk between the immune system and organs controlling whole-body energy metabolism. Classically activated macrophages in adipose tissue can produce pro-inflammatory cytokines, such as TNF, which interfere with the insulin-signalling pathway and lead to the development of insulin resistance, whereas alternatively activated macrophages improve insulin sensitivity.[139] Interleukin 4, a key Th2 cytokine implicated in helminth immunity, plays an important part in the development and maintenance of alternatively activated macrophages in adipose tissue[140] and in the control of peripheral insulin sensitivity.[141] Helminth infections might therefore have beneficial effects on metabolic disorders. First, worms, as multicellular complex organisms, use host nutrients for their survival; and second, they are the strongest natural stimuli for type-2 immune responses, which was confirmed by the identification of several helminth-derived molecules that can skew immune responses towards Th2 cells.[142,143] A study in mice by Wu and colleagues[140] showed that eosinophils were a key source of alternatively activated macrophage-inducing interleukin 4 in adipose tissue, and that helminth-induced eosinophilia resulted in alternatively activated macrophage induction and a sustained improvement in glucose tolerance.[140] Further, LNFPIII, an immunomodulatory glycan[144] present in human milk[145] and on *S mansoni* eggs, improves whole-body glucose tolerance in high fat diet-induced obese mice through the restoration of insulin sensitivity in white adipose tissue, partly through increased interleukin-10 production by macrophages and dendritic cells.[146] These studies emphasise the possible metabolic advantages of harbouring helminths that, if supported in people, would open new possibilities for helminths and helminth-derived molecules as therapeutics to control a group of diseases that are major causes of morbidity worldwide.

Conclusions and future perspectives

In summary, a paradox exists between efforts to deworm populations with helminth-associated morbidities, and initiatives to test helminthic therapy on patients with hyperinflammatory diseases (figure 3). Large-scale deworming activities are mainly implemented in the tropics and subtropics, whereas helminthic therapy trials in patients with hyperinflammatory diseases are done in affluent countries.

Murine models support the hypothesis that helminths or their products could be beneficial for inflammatory conditions. Human studies in poor-resource settings have been less consistent, which could be accounted for

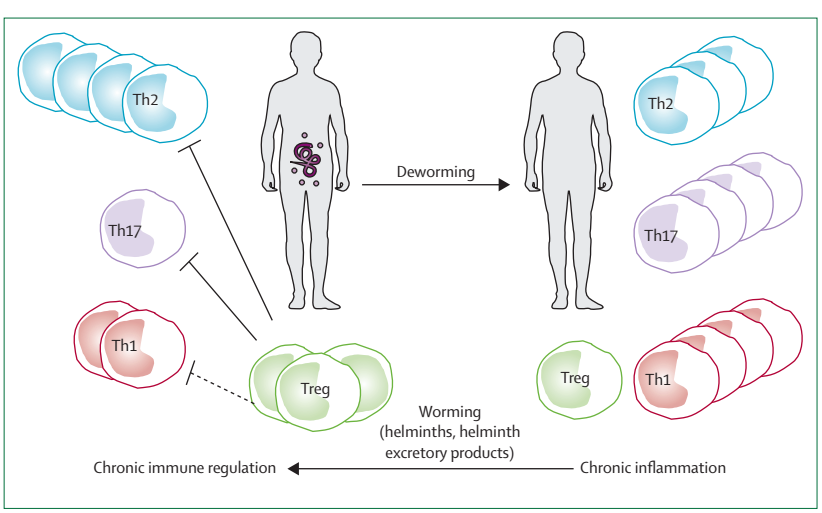

Figure 3: **Immunological effects of deworming and worming**
Helminth-infected individuals (left panel) express enhanced Th2 responses but these are kept under control by the increased number or functional capacity of Tregs. After deworming (right panel), removal of immune suppression could lead to overt inflammation, which is characteristic of several inflammatory diseases; Th1, Th2, or Th17 responses are more active as Tregs decrease in number or function. Treatment with experimental helminth infection or with helminth-derived immunomodulatory molecules could restore the immune regulation noted during natural chronic helminth infections. Th=T-helper cells. Tregs=T-regulatory cells.

Search strategy and selection criteria

We searched PubMed for articles in English published from Jan 1, 1950, to Feb 20, 2014, with the search terms: "helminth", "worm", "immunology", "allergy", "asthma", "atopy", "inflammatory diseases", "multiple sclerosis", "inflammatory bowel diseases", "rheumatoid arthritis", "diabetes", "randomised clinical trial", and "helminthic therapy". Animal studies were excluded, except for those that were in-vivo studies of helminth infections or helminth-derived molecules and inflammatory diseases. We included all helminth therapy trials but excluded deworming trials that were not placebo-controlled.

by the presence of other modulating infections and because the clinical effects of deworming might take time to establish. Further deworming trials should take these issues into account and plan for longer follow-up periods. Mass deworming programmes are advocated,[147] which creates opportunities to investigate prospectively whether deworming leads to an increased prevalence of allergic and other inflammatory diseases. Well designed trials, in the context of large-scale deworming programmes, would allow the (as-yet uncertain) benefits of this intervention in human populations to be assessed,[148,149] and weighed against potential adverse effects on inflammatory and metabolic disease risks. Human trials of the therapeutic use of helminths in resource-rich settings might elucidate the role of helminths in human physiology, metabolism, and immunology. Although some positive results have so far been reported in inflammatory bowel disease and multiple sclerosis, not much benefit has been seen in the treatment of asthma and allergies. Further trials need to be less modest in the number of patients included, the duration of helminth infection, and, if safety data allow, the dose of infection used, while accounting for the possibility of accumulating low-dose infections.

Contributors

LJW did the literature searches, and drafted and finalised the manuscript and the figures; HM assisted with the literature search and drafting of the manuscript and tables; and AME and MY developed the concept, inputted into the literature search, and reviewed the content.

Declaration of interests

AME reports grants from Wellcome Trust and from the European Union. LJW, HM, and MY declare no competing interests.

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