

Human allergy and geohelminth infections: a review of the literature and a proposed conceptual model to guide the investigation of possible causal associations

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Geohelminth infections and allergic disease are major public health problems and there is evidence in developing countries that they are associated. Although there is an extensive literature of the relationship between geohelminth infections and allergy, there is little consensus on whether the association is causal and if so, whether geohelminth infections may increase or decrease the risk of allergy. An explanation for the conflicting findings of epidemiological studies is that geohelminths decrease the risk of allergy in areas of high infection prevalence and increase the risk of allergy in areas of low prevalence. Chronic geohelminth infections are inversely associated with allergy and anthelmintic treatment may increase the prevalence of allergy. In this paper, we review studies that have investigated the relationship between geohelminths and allergy; discuss the relevance of prevalence and timing of geohelminth infections and propose a conceptual model to define relevant scientific questions in future human and animal studies.

Introduction

Geohelminth (also known as intestinal helminth or soil-transmitted helminth) infections and allergic disease both cause significant morbidity worldwide. Geohelminths are primarily a health problem of resource-poor developing countries, whereas allergic diseases are recognized as increasingly important in resource-rich developed countries. However, the epidemiology of allergic diseases appears to be changing in developing countries—particularly in populations undergoing urbanization—where the frequency of allergy may be increasing very fast.^{1,2} In rural areas of developing countries, allergic disease is relatively rare,^{1,2} and in

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such areas, it appears to be inversely associated with the prevalence of geohelminth infections, particularly in highly endemic communities.^{3,4} This latter observation has led to the suggestion that geohelminth infections may be an important environmental exposure that is keeping the frequency of allergy low in such areas.³ The relationship between helminth infections and allergy has been the focus of a large body of research in basic and population-based sciences, but remains unclear.

Geohelminths

Geohelminth infections include *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Ancylostoma duodenale* and *Necator americanus*). These infections have a worldwide distribution being present in almost all geographic and climatic regions, except for those with extremes of cold or heat where survival of infectious stages in the environment is impossible. Prevalences tend to be highest in warm, moist climates and are closely correlated with poor environmental hygiene (in particular, a lack of adequate excreta disposal) and lack of access to health services. The estimated global prevalences of *A. lumbricoides*, *T. trichiura* and hookworm are 1.5 billion, 1.3 billion and 900 millions, respectively, and greater than 2 billion humans are infected with at least one of these parasites.⁵

Hookworm is transmitted through skin contact with free-living larvae in the soil, whereas ascariasis and trichuriasis are transmitted through ingestion of embryonated eggs from the environment. Ascariasis and hookworm undergo a phase of larval migration through the lungs, whereas trichuriasis has a purely enteric life cycle. Infections with ascariasis and trichuriasis peak in prevalence and intensity between 5 and 15 years of age in endemic areas and there is a decline in both epidemiological parameters in adulthood.⁵ Infections with hookworm tend to be delayed until infants are able to walk, and prevalence and intensity increase into adulthood.⁵

Geohelminths cause chronic infections in areas where the parasites are endemic, and individual adult parasites may survive for between 1 and 15 years.⁵ Because the morbidity caused by geohelminth infections is strongly associated with infection intensity,⁵ morbidity—including important effects on growth, nutrition and mental development in childhood—tends to be greatest in heavily infected children and vulnerable adults (e.g. women of child-bearing age) with long exposure histories. Epidemiological observations have provided evidence that geohelminth infections and another important helminth infection, schistosomiasis, may affect the risk of the development of allergy.^{3,4,6}

Allergy and the causes of its increase

Allergic diseases that include asthma, eczema and rhinitis are inflammatory diseases associated with allergic sensitization to environmental allergens. Allergic diseases are an important cause of morbidity in developed countries where they are the commonest cause of chronic disease in childhood.⁷ They are becoming an increasingly important cause of morbidity in urbanizing populations in developing countries.^{1,2} The prevalence of allergic diseases is relatively low in rural areas of Europe^{8,9} and also may be low in rural areas in developing countries,^{1,10,11} although the available epidemiological data on allergy prevalence from such areas are limited.

Allergic diseases are caused by a complex interaction between host genetics and environmental factors.¹² It is important to note that most studies investigating allergy prevalence have not distinguished between symptoms associated with allergic sensitization and those that are not. Because the prevalence of allergy appears to have increased dramatically over the previous four decades,¹³ it is likely that changes in environmental exposures underlie such temporal trends. Important environmental exposures that have been associated with the risk of allergy include high-level exposure to allergens,¹⁴ exposure to pets¹⁵ and farm animals,¹⁴ socio-economic level,¹⁶ nutritional status¹⁴ and life-style factors such as diet¹⁴ and smoking.¹⁴

The observations that children with older siblings, those who live in large families¹⁶ or those who attend day care¹⁴ have a reduced risk of allergy have led to the development of the hygiene hypothesis. This hypothesis proposes that reduced exposures to childhood infections increase the risk of allergy.^{16,17} Some infectious agents are inversely associated with allergy risk, including measles,¹⁶ malaria¹⁸ and gastrointestinal infections such as hepatitis A virus and *Helicobacter pylori*.¹⁶ There has been considerable interest also in the potential role of geohelminth infections in modulating allergy risk in areas that are endemic for these parasites.⁴

Allergy and helminths

Helminth parasites including geohelminths can induce strong allergic responses in humans.¹⁹ There are close similarities between the allergic inflammation caused by the host immune responses to environmental allergens and to parasite antigens—both are associated with high levels of IgE, tissue eosinophilia and mastocytosis, mucus hypersecretion and T cells that preferentially secrete type 2 cytokines (e.g. IL-4, IL-5 and IL-13).^{3,4}

The human response to infections with helminth parasites is distinct between first (acute) infections and chronic infections.¹⁹ Although the distinction between acute and chronic infections is somewhat arbitrary, it does provide a useful framework for understanding differences in the host responses to these parasites. Acute infections include primary infections and repeated or intermittent infections without a period of continuous infection between infection episodes and may result from infrequent or short exposures and affect generally visitors and expatriates in endemic areas.¹⁹ Acute infections are associated with several allergic syndromes.¹⁹ For example, an asthma-like illness (Loeffler's syndrome) is associated with the passage of *A. lumbricoides* larvae through the lungs. Clinical allergic reactions appear to be rare among individuals with chronic infections (i.e. infections lasting for years)²⁰ or in endemic areas and suggest that either host or parasite or both can down-regulate the allergic inflammatory response to the presence of the parasite to avoid host pathology and/or parasite elimination.

Consistent with the acute and chronic clinical phenotypes observed in helminth-infected individuals, observations from epidemiological studies that have examined the relationship between helminth infections and allergy have provided evidence for both allergy-enhancing and allergy-suppressant effects of geohelminths in different populations.²¹ These inconsistencies could be explained by geohelminths enhancing allergic reactivity in populations with low prevalence of infection (e.g. <10%) and suppressing allergy in populations where the infections are highly prevalent (e.g. >50%), although the findings of some studies are not consistent with such simple categorization. For example, a nested case-control study in a highly endemic area in Ethiopia provided evidence that hookworm infection was inversely associated with symptoms of wheeze, but that trichuriasis was positively associated with allergen skin test reactivity.²²

Allergic disease could be caused directly by the host immune response to the parasite—parasite antigen as the allergen that causes allergic inflammation—or could be affected by the presence of the parasite modulating an ongoing allergic inflammatory response to an allergen (not the parasite). The latter possibility has significant public health implications that concurrent geohelminth infections may affect the development or clinical course of allergic diseases such as asthma.

Epidemiological evidence for an association between allergy and geohelminth infection

Allergic or atopic diseases are associated with significant levels of allergen-specific IgE, evidence of skin sensitization to the same

allergens and clinical symptoms affecting the skin (eczema/atopic dermatitis), upper airways (allergic rhinitis) and lower airways (atopic asthma). The major part of the evidence for an association between geohelminths and allergy, presented below, has been generated by epidemiological cross-sectional studies that have recognized weakness for the inference of causality (i.e. the lack of chronological sequence between cause and effect and uncontrolled confounding).

Geohelminths and allergen skin test reactivity

Epidemiological studies have shown an inverse relationship between geohelminth infection and allergen skin test reactivity,^{4,23} with evidence of a dose–response relationship and reduced risk of atopy for greater geohelminth parasite burdens.⁴ Not all studies, however, have shown this inverse association and studies in China²⁴ and South Africa,²⁵ in areas of low geohelminth prevalence, have provided evidence for positive associations between geohelminth infection and allergen skin test reactivity.

Geohelminths and asthma

Several studies have investigated the relationship between asthma symptoms and geohelminth infections and results are inconsistent.⁴ Recent studies have provided evidence for an inverse relationship between wheeze symptoms and geohelminth infections detected by stool examinations,^{22,26} whereas other studies have shown no statistically significant relationship^{11,23} or even a positive association between asthma symptoms and geohelminth infections^{4,24} or the presence of IgE to *Ascaris*.^{4,25,27} The clinical course of asthma may be altered in individuals infected with helminth parasites causing a milder form of illness⁶ in areas where infections are highly endemic, although in areas of lower prevalence, the converse may be true.²⁵

Geohelminths and atopic dermatitis

There is little epidemiological data on the prevalence of atopic dermatitis in rural areas of the tropics. The prevalence of atopic dermatitis was found to be lower in rural areas when compared with urban areas of Ethiopia,²⁸ but risk was unrelated to geohelminth infection.²⁹ A cross-sectional study of schoolchildren in Ecuador provided no evidence for an association between atopic dermatitis and geohelminth parasites.¹¹ A small intervention study in Uganda provided evidence that the infants of mothers with helminth infection at the time of delivery had a reduced risk of eczema when compared with those born of uninfected mothers (9 versus 39%, respectively).³⁰

Geohelminths and allergic rhinitis

A study in Ecuador showed no relationship between reported symptoms of allergic rhinitis and geohelminth parasites,¹¹ a study in urban Taiwan provided evidence for an inverse association between enterobiasis and a previous diagnosis of allergic rhinitis³¹ and a study in South Africa provided evidence for a positive association between rhinitis symptoms and the presence of IgE to *Ascaris*.²⁵

Effect of anthelmintic treatment on allergy

Although cross-sectional epidemiological studies conducted in areas that are highly endemic for geohelminth parasites have provided some evidence of an inverse association between geohelminths and atopy or asthma that is consistent with geohelminths providing protection against the development of allergic disease, alternative explanations are that allergy protects against worm infections or that the same genetic factors may be associated with both a higher risk of allergy and protection against helminths.³²

Several intervention studies of the effect of removal of helminths by anthelmintic treatment on allergy/atopy have been conducted to shed light on this conundrum, but these also have provided inconsistent findings. Two studies have shown an increase in allergen skin test reactivity after anthelmintic treatment. (i) A non-randomized intervention study in Venezuela showed that monthly anthelmintic treatment with oxantel–pyrantel over a period of 18 months caused an increase in the prevalence of atopy (i.e. an increase in skin test reactivity to house dust mite from 17 to 68%) among 94 children with a high prevalence of infection before treatment.³³ (ii) An open-label placebo-controlled randomized intervention study in Gabon treated children with a combination of praziquantel and mebendazole every 3 months and examined skin test reactivity to house dust mite at 6-month intervals in skin test negative individuals.³⁴ The study provided evidence that anthelmintic treatment resulted in a significant increase in the rate of developing skin sensitivity to house dust mite compared with placebo (hazard ratio 2.51, 95% CI 1.85–3.41) in 165 children followed-up over 30 months, an effect that appeared to be mediated partly by reductions in geohelminth infections.³⁴ Both these studies were relatively small and the validity of study in Venezuela is unclear because of large potential biases and uncontrolled confounding. The study in Gabon measured the incidence of atopy in non-atopic children, and although the study showed a treatment effect on the incidence of atopy, it did not show a statistically significant effect of treatment on the prevalence of atopy and

some children who converted to skin test positivity reverted to negative skin tests over the course of the study.³⁴

The largest study to date, a cluster-randomized study that followed 68 schools and 1632 children in Ecuador, examined the effect of albendazole treatment every 2 months for a year, compared with no intervention.³⁵ The study showed no effect of anthelmintic treatment on allergen skin test reactivity or allergic symptoms. Four reasons could have lead to this. First, 12 months of suppressive chemotherapy may be insufficient time to reverse an established immunological effect—the previous studies in Venezuela³³ and Gabon³⁴ provided anthelmintic treatment for 18 and 30 months, respectively—although there is evidence that the anti-inflammatory and immune suppressive effects of helminths can be reversed rapidly after chemotherapy.²¹ Secondly, different geohelminth parasites may have differing effects. Hookworm may have greater modulating effects than ascariasis and trichuriasis, and the prevalence of infections with this parasite was relatively low (14.5% prevalence) in the area studied in Ecuador.³⁵ Thirdly, previous intervention studies may have been subject to uncontrolled confounding (for example, by socio-economic status and overcrowding³⁵). Fourth, protection against allergy is likely to be multifactorial and may not be dependent on any single environmental exposure. A protective association of geohelminths in one population may not necessarily be observed in another population in which different combinations of environmental factors are present.

Some evidence from Venezuela has suggested that providing anthelmintic treatment may reduce (rather than increase) asthma symptoms. (i) In the same group of children in Venezuela that showed an increase in the prevalence of allergen skin test reactivity after 18 months of anthelmintic treatment, peak flow responses following inhaled bronchodilator decreased in the anthelmintic-treated group and increased in the untreated group.³⁶ (ii) A separate open-label randomized intervention study in Venezuela showed that monthly anthelmintic treatments with albendazole over the period of a year reduced symptoms of wheeze and the need for asthma medications.³⁷ However, the much larger Ecuadorian study described earlier was unable to show an effect of anthelmintic treatment on either allergic symptoms or exercise-induced bronchospasm.

The effect of geohelminths in suppressing atopy may be more important in the first years of life and the temporary elimination of infections later in childhood or adulthood may not affect a phenotype that is 'programmed' in infancy. Consistent with such a hypothesis, a small randomized double-blind placebo-controlled study of a single dose of anthelmintic treatment (praziquantel and albendazole) given to a group of 103 pregnant women in Uganda provided evidence for a

non-significant trend of a reduced risk of subsequent atopic dermatitis in the offspring of the treated mothers.³⁰

Immunological mechanisms of geohelminth-mediated suppression of allergy

There is strong evidence from experimental murine models of allergy that geohelminths can modulate allergic reactivity³⁸ in the airways resulting in enhanced or suppressed allergic inflammation depending on the model used. However, the immune system of the mouse is very different from ours and it is not clear how relevant these findings are to human populations. This is also a problem for the large volume of literature that reviews the potential immunological mechanisms by which helminth infections may modulate allergic disease,^{3,21,38} almost all of which are derived from observations in experimental animal models. Data from human populations are extremely scarce. Geohelminth infections in humans may modulate allergic sensitization or allergic effector responses. Current evidence has provided more evidence for the latter, because allergic sensitization measured by elevated levels of polyclonal or allergen-specific IgE is enhanced in populations that are endemic for geohelminth infections.^{18,39}

Pathways that could be modulated by geohelminth infections include effector components of immediate hypersensitivity and the late phase response and could be achieved through inhibition of mast cell activation (for example, IL-10 has inhibitory effects on mast cells⁴⁰) and inhibition of effector cell recruitment and function at inflammatory sites. Particular prominence has been given to the roles of immunosuppressive cytokines, such as IL-10,⁴¹ and regulatory T cell populations.⁴² There are no published human data to support a protective role of helminth infection-induced regulatory T cell populations against allergic inflammation but some evidence for a modulatory role for IL-10: among children living in an area endemic for schistosomiasis in Gabon, individuals with higher levels of parasite antigen-induced IL-10 *in vitro* had a reduced risk of allergen skin test reactivity.⁴³

The importance of the timing of exposures to geohelminths

Timing in relation to immune maturation

The time of first exposures to geohelminth infections could determine the regulatory effects. The protective effect of farming against allergy in rural European populations may be dependent on exposure occurring

in the first⁴⁴ to the fifth⁴⁵ year of life and exposures occurring later may have weak or negligible effects. Similar observations have been made for the protection mediated against allergy of household pets⁴⁶ and could be explained in terms of critical time windows in early life for certain gene–environment protective interactions to be effective. Early immune ‘programming’ (for more specific effects) and/or early immune maturation (for non-specific effects) may be important for the protective effects of geohelminth infections against allergy to be manifest.

Time-dependent effects of geohelminth infections and other environmental exposures on the development of allergic disease are illustrated in Figure 1. This hypothetical model speculates that the effects of geohelminths on allergy risk occur through modification of the interaction between genetic predisposition and environmental exposures to aeroallergens. The effects on the immature immune system may be both quantitative (e.g. the ‘intensity’ of exposure being relevant in inducing early immune maturation) and qualitative (the type of exposure may be

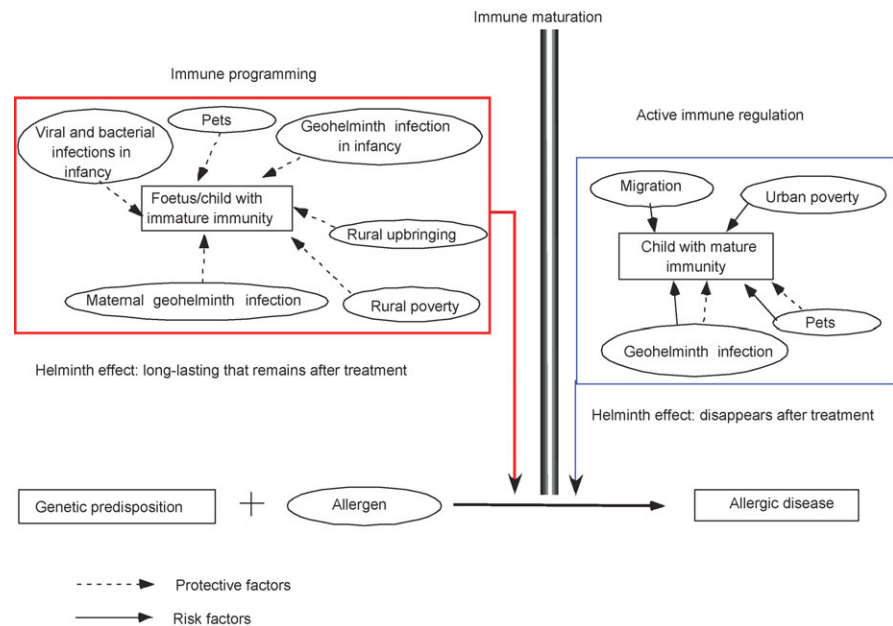


Fig. 1 Two proposed mechanisms for the effect of geohelminth infections on allergy. These two mechanisms are proposed to act by modification of the interaction of genetic traits with allergens that leads to the development of allergic disease. In early life, geohelminth exposures could affect allergy risk through programming of the immune system before the process of immune maturation is complete. Other environmental exposures occurring at the same time could interact with geohelminth infections to reduce subsequent allergy risk. Environmental exposures including geohelminth infections occurring after immune maturation in later childhood could affect allergy risk by a process of active regulation, but maintenance of regulation may require the persistence of the exposure.

important for providing 'protective' signals to the maturing immune system).

Early exposures of the foetus to maternally derived geohelminth antigens via the placenta or of the infant through early infections could induce host tolerance to the parasite.

Qualitative effects

The early development of allergic inflammatory responses to aeroallergens could be suppressed through cross-reactivity of tolerogenic epitopes shared by parasites and aeroallergens or through the bystander effects of parasite-mediated suppression of inflammation. Helminths could provide specific early signals to the developing immune system, which protect against the subsequent development of allergy.

Quantitative effects

Early geohelminth infections in conjunction with other early infectious exposures (e.g. mycobacteria, hepatitis A virus, etc.) could provide important maturational signals for the immune system and stimulate the development of a 'robust anti-inflammatory network'.¹⁷

Before a state of 'immune maturation' has been reached, early exposures to geohelminths might programme the immune response irreversibly such that the later removal of infections through anthelmintic treatment would have no effect on the programmed response.³⁵

The model speculates that later exposures after a state of immune maturation has been reached may be capable of regulating the immune response, but that immune regulation may be dependent on the continuous presence of the exposure. Removal of the exposure could reverse the regulatory effects. Most of the exposures in this model (Fig. 1) are considered to be socio-environmental risk factors (e.g. migration, urban poverty and pets), although this is not necessarily the case. Geohelminths (and pets) could either protect against allergy (heavy parasite burdens and chronic infections acquired later in childhood) or increase the risk of allergy (light or intermittent infections acquired in later childhood), and removal of geohelminths through anthelmintic treatment could reverse these active regulatory effects causing increased^{36,37} or decreased^{33,34} allergic inflammation, respectively.

A conceptual framework for the study of the potential effects of helminth infections on allergic disease is provided in Figure 2. In this model, we discuss four types of exposures, the first of which, exposure A (early geohelminth exposures affecting the development of the 'immune regulatory network'), is time-dependent in relation to immune maturation and is discussed earlier.

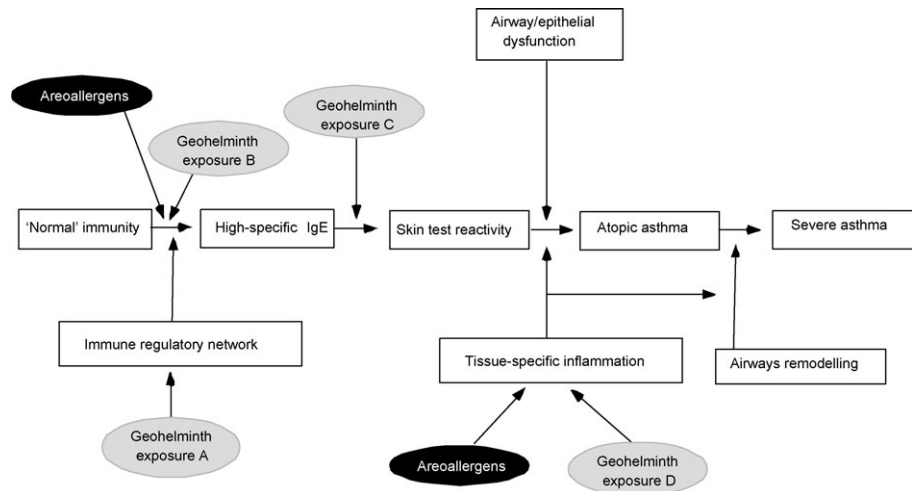


Fig. 2 Conceptual model illustrating the stages in the evolution of the allergic process when geohelminth exposures could affect the development of allergic sensitization and allergic disease. Four exposures are shown: A—early exposures affecting the development of the ‘immune regulatory network’; B—geohelminth infection that precedes early IgE sensitization to aeroallergen; C—geohelminth infections after sensitization modulate skin test reactivity to aeroallergens and D—gehelminths modulate allergic inflammation by direct action on the lungs.

Timing in relation to allergic sensitization

Exposure B (*geohelminth infection that precedes early IgE sensitization to aeroallergens*) in Figure 2 could affect IgE sensitization to aeroallergens directly. Under some circumstances, infections could enhance allergic sensitization through Th2 adjuvant effects.^{4,21} In other circumstances, such as when first exposures to helminths precede sensitization to aeroallergens, sensitization of a specific IgE response could be inhibited.^{47,48}

Helminth infections acquired after the development of sensitization to aeroallergens could affect directly skin test reactivity to aeroallergens (exposure C—Geohelminth infections after sensitization modulate skin test reactivity to aeroallergens), such that for the same level of specific IgE to allergens, there is reduced skin test reactivity.¹⁸ Interestingly, in populations living in areas endemic for helminth parasites, there is not a clear and simple relationship between high levels of specific IgE and skin test reactivity to the same allergen.^{18,40} Explanations for this include immune regulatory effects of chronic helminth infections, polyclonal IgE activation by helminth parasites and cross-reactivity between allergens of helminth infections and aeroallergens.⁴⁰ It is possible that ‘acute’ helminth infections could enhance allergen skin test reactivity.^{24,25}

Timing in relation to triggering clinical disease and severity

Atopy, whether measured by the presence of allergen-specific IgE in sera or skin test reactivity to allergen extracts, is a strong risk factor for asthma in developed countries,⁴⁹ but the proportion of atopics with clinical asthma (or the proportion of asthmatics with atopy) appears to be much smaller in some rural areas of Europe⁹ and in many developing countries.^{11,23} Co-factors specific for the lung environment may be necessary for the translation of allergic sensitization into allergic inflammation in the lungs. Helminths with a pulmonary phase of larval migration could affect asthma development through effects on the respiratory epithelium, airways dysfunction (increase or decrease) and airways remodelling (Exposure D—geohelminths modulate allergic inflammation by direct action on the lungs). Such effects could be achieved by modulation of the inflammatory environment in the lungs. Migration of helminth larvae through the lungs during early ‘acute’ infections could enhance allergic inflammation,^{24,25} whereas chronic helminth infections during which larvae ‘trickle’ through the lungs continuously may suppress inflammatory activity^{22,26} and reduce the long-term risk of irreversible changes to the airways associated with remodelling.

A model for the causal association between helminth infections and asthma

Figure 2 is provided as a conceptual framework for the formulation of research questions and to guide the choice of study design to investigate causal associations between helminth infections and allergy in human populations and to identify mechanistic studies in experimental animal models that are likely to be relevant to human populations. Intervention studies of anthelmintics provided during pregnancy and/or in the first 2 years of life would investigate the effects of exposures A, B and C. Similarly, birth cohort studies could examine the natural effects of early helminth exposures in the development of asthma. Intervention studies of the effects of anthelmintic treatment on allergen skin test reactivity in schoolchildren would examine the effects of exposure C. Finally, exposure D could be investigated prospectively in infants or through cross-sectional and case–control studies of children (with and without asthma symptoms) or through intervention studies of asthmatic children living in areas endemic for helminth parasites. Therapeutic studies that expose allergic subjects to geohelminth infections⁵⁰ address the role of exposure D.

Conclusion

Geohelminth infections and allergy are major public health problems and may be causally associated. Numerous epidemiological studies have provided substantive but conflicting evidence of the relationship between geohelminths and allergy, with different studies providing evidence of a positive association, a negative association or no association. The lack of consensus in the literature could be explained by design issues in individual studies (e.g. cross-sectional and uncontrolled confounding); or it may reflect real variation, if the modulatory effects of geohelminth infections on allergic reactivity are markedly different for different geohelminths, are modified by prevalence of geohelminth infections or are due to timing of exposure in relation to immune maturation or sensitization.

This review has focused on the relationship between geohelminth parasites and allergy and has referred to other helminth infections (i.e. schistosomiasis) where relevant. However, observations for geohelminths are not necessarily generalizable to other helminth parasites, particularly helminth parasites that parasitize the vascular (e.g. schistosome and some filarial parasites) and lymphatic (e.g. some filarial parasites) ducts and that may have different modulatory effects on host immunity.

The timing of exposure to geohelminth infections may be of particular importance in determining the effect of geohelminths on allergy. Early exposures (*in utero*, if the mother is infected or in early infancy) could have important qualitative or quantitative effects on immune maturation and the development of appropriate immune regulation. Inadequate or delayed signals (e.g. microbial and parasite exposures) for immune programming and maturation may limit the ability to develop a regulated immune response that may be critical for the avoidance of inappropriate inflammatory responses that lead to allergic disease. Early exposures to geohelminths that affect immune programming/maturation may not be reversible by later treatment of geohelminth infections. Later exposures to geohelminths after the establishment of immune programming/maturation could regulate actively the immune response (either by increasing or by decreasing allergic reactivity) and the removal of these infections by anthelmintic treatment could reverse the modulatory effects.

The existing evidence for an association between geohelminths and allergy may appear contradictory, but it is possible that we have not been asking the right questions within the right context. We propose a conceptual framework that identifies four different times at which exposures to geohelminth parasites may affect allergy risk and suggest

that these exposures could have different effects on the development of allergic sensitization and asthma. The model may assist in formulating relevant research questions in future epidemiological and mechanistic studies and may also be useful in informing the choice of appropriate study design and in the interpretation of study results.

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