chapter 7

Parasitic worms and allergies in childhood: insights from population studies 2008-2013

Abena S. Amoah[1, 2], Daniel A. Boakye[2], Ronald van Ree[3] and Maria Yazdanbakhsh[1]

Affiliations:

[1] Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands;
[2] Department of Parasitology, Noguchi Memorial Institute for Medical Research, Accra, Ghana;
[3] Department of Experimental Immunology and Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands

- Pediatric Allergy and Immunology 2014 May;25(3):208-17 -

Abstract

The last few decades have seen a marked increase in the global prevalence of allergic diseases particularly among children. Among the factors attributed to this rise has been reduced exposure to pathogens during childhood leading to insufficient maturation of the regulatory arm of developing immune systems. Over the years, a number of epidemiological studies have observed an inverse relationship between parasitic worm (helminth) infections and allergies. The purpose of this review is to highlight insights from population studies conducted among children published between 2008 and 2013 that explore the complex dynamics between helminth infections and allergies. These insights include the effect of anthelmintic treatment on allergic responses, an elucidation of immune mechanisms and an examination of helminth-induced immunoglobulin E cross-reactivity.

A better understanding of the relationship between helminths and allergies is imperative as research directions move towards harnessing the therapeutic potential of helminths and their products in the treatment of allergic disorders.

Keywords

Anthelmintic treatment; asthma; atopy; eczema; helminths; immune mechanisms; immunoglobulin E cross-reactivity; rhinoconjunctivitis; skin prick testing; urbanization

Introduction

Over the past few decades, there has been a sharp increase worldwide in the prevalence of allergic disorders such as asthma, rhinitis, eczema and food allergies particularly among children [1]. The hygiene hypothesis provides an explanation for these observations in terms of how over the course of time in Western countries, improved hygiene, smaller family sizes and fewer childhood infections may have driven an increase in allergies [2]. In immunological terms, reduced pathogenic exposure during childhood leads to inadequate maturation of the immune system's regulatory arm thus resulting in uninhibited inflammatory responses towards harmless antigens [3, 4].

A rise in allergic diseases is also being observed in rapidly urbanizing developing countries where a reduction in infectious diseases, improved hygiene and the adoption of a so-called "western lifestyle" are factors driving this increase [5]. For example, studies from Asian economic hubs dating back to the 1970s illustrate how a higher prevalence of asthma among urban populations was associated with wealth and lifestyle in contrast with a lower prevalence of asthma in rural environments [6]. These investigations emphasize the importance of environmental exposures in the pathogenesis of allergic disorders in general. Key among such exposures is infections with parasitic worms (helminths).

Helminths are metazoan parasites that have evolved the ability to down-regulate their host's immune responses and thus protect against their own elimination as well as reduce severe pathology in the host [7, 8]. Over 1 billion people worldwide are infected with one or more helminth species [9]. Most of these individuals are currently found in tropical regions of the world where such infections are linked to poverty and poor sanitation [10].

Helminth infections are of particular interest to studies of allergic disorders as they induce strong T-helper-2 (Th2) responses leading to high levels of immunoglobulin E (IgE) antibodies. Despite the common immunological profiles associated with both helminths and allergies, there is little overlap in the geographical distribution of these two health problems. This suggests that not all Th2 responses lead to allergic outcomes and that strong Th2 profiles seen in helminth-infected subjects do not translate into allergic disease. In fact, studies show that helminth infections could even be inversely associated with allergic disorders [11, 12]. However, the interactions are indeed complex as some investigations find an inverse association but others show no effect or even a positive association.

In recent years, studies among children from helminth-endemic areas at various stages of urbanization have provided new and interesting insights. The purpose of this review is to highlight research findings from population studies focused on children aged 0 to 18 years and published between 1 January 2008 and 31 July 2013. To identify relevant publications, searches were conducted in PubMed using key words related to 'allergy' or 'hypersensitivity' in combination with 'helminths', 'parasites' or 'worms'. These were restricted to human studies in children (birth – 18 years). Studies focusing on helminths that have not evolved to infect humans but where humans acquire infections by accident such as *Toxocara* species [13-16], *Echinococcus granulosus* [17] and *Ascaris suum* [18] were excluded.

Helminths and allergy: associations in population studies

Recent cross-sectional studies conducted in Brazil by the Social Changes, Asthma and Allergy in Latin America (SCAALA) group [19] have shown that among urban poor children aged 4-11 years living in Salvador, heavy infection with the helminth *Trichuris trichiura* in early childhood (on average at age 2 years) is associated with reduced odds of skin prick test (SPT) reactivity later in childhood [20]. Apart from demonstrating the importance of timing and early-life infections in the pathogenesis of childhood allergy, this study illustrates how heavy helminth infections (compared to light infections) may have a protective effect against allergies. Similarly, an investigation from South Africa comparing allergy outcomes among rural children of the Xhosa ethnicity to urban Xhosa children of low socioeconomic status found that after adjusting for area and detectable allergen-specific IgE, current *Ascaris lumbricoides* infection was associated with reduced odds of SPT reactivity [21].

However, other investigations have observed no effect of helminths on SPT reactivity. For example, among Cuban children aged 4-14 years living in helminth-endemic areas, current intestinal helminth infection was not associated with SPT reactivity [22]. However, it is important to note that among this study population, given the well-organized health provision in Cuba, it is very likely that the children were regularly dewormed and indeed the intensity of helminth infections was relatively low. Some studies have even observed a positive association between *Ascaris*-specific IgE (sIgE) and SPT reactivity for example, among urban black adolescents (median age 18 years) living in Cape Town, South Africa [23]. However, a limitation of the latter study is that *Ascaris*-sIgE may not be a useful marker for current ascariasis infection since elevated levels may indicate past infection or cross-reactivity due to other helminth antigens or environmental allergens.

Aside from SPT reactivity, the effects of helminths on other allergy outcomes have also been examined. Among a cohort of 3960 Afro-Ecuadorian children aged 6-16 years living in Ecuador, heavy *T. trichiura* infection was inversely associated with atopic wheeze but not with non-atopic wheeze [24]. On the other hand, a case-control study among 219 5 year old rural Bangladeshi children reported that current *A. lumbricoides* infection was not significantly associated with reported wheeze [25].

With regards to airway hyperresponsiveness, Calvert and Burney examined urban and rural Xhosa children and observed that current *A. lumbricoides* infection was associated with increased odds of exercise-induced bronchoconstriction (EIB) [21]. Since they had also found an inverse association between *A. lumbricoides* and SPT reactivity, they concluded that in areas with a heavy burden of *A. lumbricoides* infection, this helminth may induce an inflammatory response in the lungs that is independent of the parasite's effect on SPT reactivity [21]. In line with this, in a case-control study design, children with heavy *A. lumbricoides* infection (>100 eggs / grams) in Brazil, were found to be five times more likely to have bronchial hyperresponsiveness (BHR) measured by bronchial provocation tests compared to children with low loads or no infection [26].

When it comes to reported allergic disease, current infection with *A. lumbricoides* was linked to a more than 4 times reduced odds of atopic eczema in rural Cuban children aged 4-14 years [27]. Conversely, a history of *Enterobius vermicularis* infection in the same children was associated with an increased risk of reported allergic rhinoconjunctivitis and atopic eczema, emphasizing the importance of taking into consideration species of helminth. A history of hookworm infection was also associated with reported allergic rhinoconjunctivitis [27]. However, given that reported history of helminth infection can be an unreliable parameter, these findings should be considered with caution.

Aside from just helminths, some investigations have looked at multiple infections with other childhood pathogens. For example, among the SCAALA cohort in Salvador, Brazil, a cross-sectional study investigated whether helminth, viral and bacterial infections were associated with reported wheeze, SPT reactivity and specific IgE to locally important allergens. The study observed that in addition to the protective effect of *A. lumbricoides* infection, past exposure to *Toxoplasma gondii*, Epstein - Barr virus and herpes simplex virus (assessed by seropositivity) were each associated with a lower prevalence of SPT reactivity but not reported wheeze [28]. This finding highlights the important role of diverse childhood pathogens in reducing the risk of SPT reactivity. Furthermore, a birth cohort of children from Ethiopia observed that at 3 years, *Helicobacter pylori* infection was linked to borderline reduced odds of reported eczema as well as SPT reactivity to house dust mite [29].

Taken together, although there is strong evidence for protective effects of helminths on allergic outcomes in animal models [8], the results of cross-sectional studies in humans vary. Though it is generally agreed that helminth infections are often negatively associated with SPT, no or positive associations are reported with lung function or reported clinical symptoms of allergy. It is important to bear in mind that species of helminth as well as timing and burden of infection can all contribute to inconsistent findings in population studies particularly when the study outcome is as complex and multifactorial as clinical allergy.

Effect of anthelmintic treatment on allergy markers

Cross-sectional studies examining associations between helminths and allergy outcomes are prone to the problem of temporality [30] since these parameters are determined at the same time. Therefore, prospective studies are needed to fully investigate causality.

Some early longitudinal studies on the effect of repeated anthelmintic treatment among children in helminth-endemic areas observed an increase in SPT reactivity to aeroallergens in treated compared to placebo groups [31, 32] while another investigation found no effect [33]. Among studies published in the last 5 years, a randomized double-blind placebo-controlled trial on the effect of anthelmintic treatment among 1566 Vietnamese schoolchildren aged 6-17 years observed that after 12 months of anthelmintics at 0, 3, 6 and 9 months, treatment was associated

with an increased risk of SPT reactivity to any allergen [34]. However, the trial did not observe an effect of anthelmintic treatment on EIB, wheeze, rhinitis or flexural eczema. Also in Southeast Asia, a household-based cluster-randomized, double-blind place-controlled trial in a helminth-endemic area on Flores Island, Indonesia, assessed the effect of anthelmintic treatment (albendazole) every 3 months for 21 months on SPT reactivity among 1364 children aged 5-15 years [35]. At 21 months, treatment was associated with a statistically significant increase in the risk of SPT reactivity to cockroach allergen but not to 'any allergen' [35]. Similar to the trial in Vietnam, anthelmintic treatment had no effect on reported symptoms of asthma and atopic eczema in this study population [35].

Among 108 intestinal helminth positive Cuban schoolchildren aged 5-13 years, van der Werff *et al.* investigated the effect of anthelmintic treatment every 6 months for 24 months on SPT reactivity and reported allergic disease outcomes [36]. During the follow-up period, four groups of infected children from randomly selected primary schools in the same municipality as the treated cohort were used as reference groups to assess general trends over time in the outcomes of interest. The prevalence of SPT reactivity increased significantly following 1st and 2nd anthelmintic treatment but returned to the baseline prevalence subsequently [36]. The study observed that deworming was associated with a significant reduction in the proportion of children reporting asthma but not allergic rhinoconjunctivitis or atopic eczema [36].

Altogether, the majority of recent studies appear to suggest that anthelmintic treatment of at least one year increases SPT reactivity (Figure 1) but has no effect on reported allergic symptoms. As the prevalence of clinical symptoms is generally low, the question remains whether studies are sufficiently powered for these outcomes.

In terms of long-term anthelmintic treatment, a study in Ecuador in rural communities examined the impact of 15-17 years of community treatment with the anthelmintic drug ivermectin on the prevalence of SPT reactivity and allergic symptoms among schoolchildren aged 6-16 years [37]. The study found that the prevalence of SPT reactivity was two times greater among children living in treated communities compared to children living in adjacent untreated areas. Treatment was also associated with more than 2 times the odds of reported eczema but not symptoms of asthma and rhinoconjunctivitis [37].

The fact that most studies on the effect of anthelmintic treatment focus on school-age children has led to speculation that the lack of an effect of treatment on clinical allergy outcomes may be due to the age of children enrolled in these studies. By school-age, these children may have passed through the key windows in early life during which their immune systems are primed towards phenotypes that are more susceptible to or protected against allergies later in childhood. Therefore, studies among younger children in helminth-endemic countries are essential in furthering our understanding of how the developing immune system is protected against allergies at a young age.

One such study was a large randomized, double-blind, placebo-controlled trial carried out in Uganda that examined the effects of anthelmintic treatment among

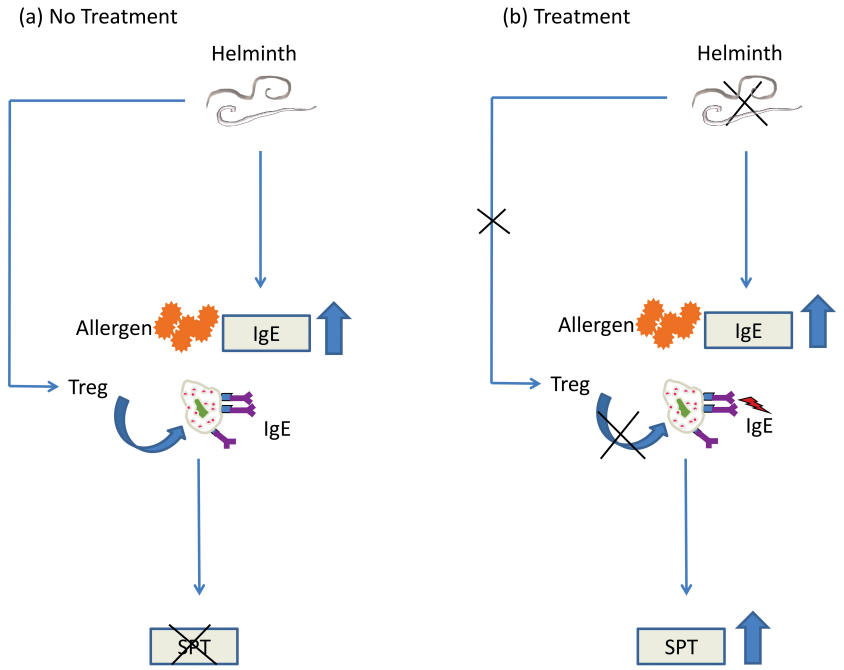

Figure 1: The effect of anthelmintic treatment on IgE sensitization and SPT reactivity

(a) During a chronic helminth infection, elevated levels of allergen-specific IgE are observed but helminth-induced regulatory mechanisms suppress SPT reactivity. (b) Following anthelmintic treatment and the removal of helminths, IgE memory remains largely unaffected but regulatory mechanisms decrease allowing increased SPT reactivity.

pregnant women on allergy outcomes in their offspring. In this trial, 2507 women in an area endemic for soil-transmitted helminths as well as the water-borne helminth *Schistosoma mansoni* were recruited and allocated to receive either albendazole (for soil-transmitted helminths) versus placebo or praziquantel (for *S. mansoni*) versus placebo. The trial found that treatment with albendazole (compared to placebo) among pregnant women was strongly linked to an increased risk of doctor-diagnosed infantile eczema in their offspring [38]. Praziquantel treatment had no overall effect but among infants whose mothers were *S. mansoni* positive at baseline, praziquantel treatment was associated with an increased risk of doctor-diagnosed infantile eczema but had no effect among infants whose mothers were *S. mansoni* negative [38]. The trial also found that albendazole treatment was positively associated with reported recurrent wheeze.

Within the same Ugandan birth cohort, the offspring of the enrolled pregnant women were randomized to receive quarterly single-doses of albendazole or placebo from the age of 15 months to 5 years [39]. By 5 years, no effect of quarterly albendazole treatment on eczema was observed. However, this may not be surprising given that the prevalence of helminth infections was extremely low in this cohort.

Aside from helminth infections in endemic areas, a Danish study examined whether enterobiasis infection, common in Western Europe and North America [40], protects against chronic inflammatory diseases [41]. The study examined prescriptions for the anthelmintic medication mebendazole as a proxy for enterobiasis infection among 924,749 children. Mebendazole prescription information was linked to diagnoses of asthma from the age of 5 years onwards through the national patient registry. Filling a prescription for mebendazole was associated with a very small but significant increased risk of asthma [41].

Taken together, these studies suggest that worms in early life are able to lower the risk of developing clinical allergy, the most common in this time window being eczema, while this does not seem to apply to airway allergy, which often develops later in life (Figure 2).

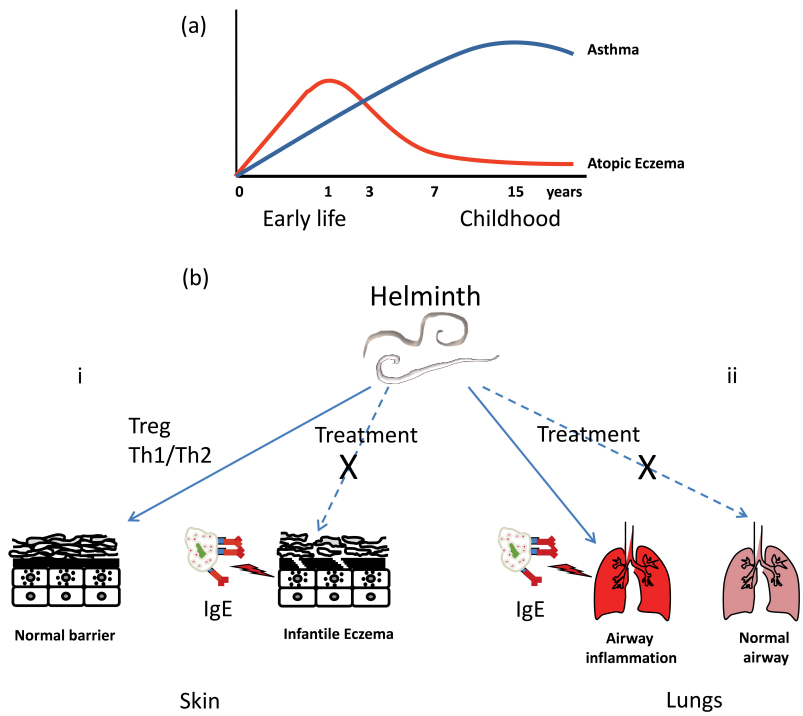

Figure 2: The effects of anthelmintic treatment on allergy-related symptoms in early life and later childhood.

Theoretical framework for the effects of anthelmintic treatment on allergy-related symptoms in early life and later childhood. (a) The current model of the Allergic March with atopic eczema peaking in the first years of life while asthma peaks later in childhood. (b-i) In pregnant women with helminth infections, *in utero* signals alter the immune system of the foetus resulting in a lack of early symptoms of allergy such as infantile eczema. However, treatment of pregnant women removes this immune modulatory activity and leads to increased manifestation of infantile eczema (b-ii) In later childhood, helminth infections either have no effect on allergy-related symptoms or in the case of *Ascaris lumbricoides* which has a lung stage, there is airway inflammation and symptoms of asthma. Anthelmintic treatment in *A. lumbricoides*-infected individuals would lead to the restoration of normal airway activity and fewer reports of asthma symptoms.

Immune mechanisms

Type 2 immune responses induced by helminths are characterized by the expansion of innate lymphoid cells-2 [42] as well as Th2 cells that lead to increased production of cytokines such as interleukin 4 (IL-4), IL-5, IL-9 and IL-13 [43]. During a helminth infection, these factors are all key to the control of inflammation, enhancement of tissue repair and can result in worm expulsion [44]. Moreover, chronic helminth infections can induce an immune regulatory network in the host characterized by regulatory T cells, regulatory B cells and alternatively activated macrophages [43]. The result is an anti-inflammatory environment typified by elevated levels of IL-10 and TGF-β as well as general T-cell hyporesponsiveness [8] which is thought to enhance survival of the worms within their immunocompetent host.

A number of studies in humans have provided evidence that IL-10 plays a key role in the helminth-induced immune regulation of allergic responses [8]. A study conducted in Gabon, Central Africa had established that children infected with the helminth *Schistosoma haematobium* had lower SPT reactivity to house dust mite compared to uninfected children in the same area [45]. The study showed that IL-10 production by parasite-antigen stimulated peripheral blood mononuclear cells (PBMCs) was higher in *S. haematobium* infected children compared to uninfected and elevated IL-10 levels were negatively associated with SPT reactivity [45]. In line with this, the recent anthelmintic trial conducted among Vietnamese children [34] found that SPT reactivity was inversely associated with higher IL-10 in response to hookworm antigen [34] and that after 12 months of deworming, there was a trend towards lower IL-10 responses in the treatment group although this was not statistically significant [34]. In contrast however, a study among Ecuadorian children living in a helminth-endemic area, observed no relationship between *A. lumbricoides* antigen induced IL-10 (or the frequency of IL10+ T cells) and SPT reactivity [46].

In another study in Ecuador, at the end of 12 months of deworming with albendazole (cluster-randomized study design), Cooper and colleagues examined whole blood cytokine responses of 214 children from 42 schools selected from a total of 1,632 children [47]. Results indicated that anthelmintic treatment was associated with enhanced Th2 cytokine responses to *A. lumbricoides* adult worm antigen (but lower IL-10 responses) as determined by whole blood cultures. Although this profile would support the notion that allergic responses increase with deworming, the investigators did not see differences in these cytokines in SPT positive versus negative subjects [47]. In addition, as one of the few studies using cytokine responses to aeroallergens (*Dermatophagoides pteronyssinus* and *Periplaneta americana*) the group found no differences between treated and untreated subjects. However, like studies conducted in affluent countries [48], the induction of cytokine production by these allergens was altogether very low.

Regarding the development of Th2 immune responses from infancy, a birth cohort study performed in a helminth-endemic area near Jakarta, Indonesia followed Th2 immune responses from 2 to 48 months among 240 children whose mothers were

recruited during pregnancy [49]. In this study, whole blood cultures were used to assess Th2 cytokine responses by measuring IL-5 response to a mitogen as well as to helminth antigens at 5 time-points between 2 and 48 months. The study found that substantial Th2 responses were seen from 5 months onwards and increased over time. Concurrently, total IgE levels were shown to gradually increase over time peaking at 48 months. Remarkably, when SPT reactivity was assessed at 48 months, strong Th2 immune responses did not translate into SPT reactivity [49]. Rather, low maternal education was associated with reduced odds of SPT reactivity while maternal infection with the filarial worm *Wuchereria bancrofti* during pregnancy tended to reduce the odds of SPT reactivity but this was not statistically significant. This longitudinal study demonstrates how children born into helminth-endemic areas develop strong Th2 responses that increase with age but do not translate into allergic response.

A number of recent reports from the SCAALA cohort of urban children aged 4-11 living in Salvador, Brazil where past and current infections (helminth, viral and bacterial) were associated with reduced SPT reactivity, have provided further insight into the immunological control of allergies in an emerging economy [50-53]. First, the effect of environmental exposures on cytokine production in unstimulated whole blood from 1376 children was examined [50]. It was observed that the proportion of children spontaneously producing IL-10 was significantly greater among those without access to drinking water [50]. It was also found that intestinal helminth infection was associated with the induction of immune hyporesponsiveness that was stronger in children producing spontaneous IL-10 [51]. Later, cytokine responses from whole blood cultures stimulated with mitogen were measured in 1127 children and different immunological phenotypes were defined: 'responsive' (characterized by generalized cytokine production above cytokine detection limits), 'under-responsive' (characterized by few responses above the detection limit) and 'intermediate' [52]. The responsive phenotype was strongly associated with higher maternal education, adequate street paving and light infection burden. Furthermore, the responsive phenotype was also linked to increased odds of SPT reactivity as well as allergen-specific IgE sensitization. Thus, enhanced immune responsiveness seemed to be linked to environmental factors and atopic outcomes. However, the study found no evidence of a significant association between the different immune phenotypes and reported wheezing or asthma. This is consistent with other epidemiological study findings where effects are observed for allergic sensitization but less for wheeze or asthma [54].

Aside from immune profiles based on cytokine responses, other mechanisms have also been investigated [55-57]. One of particular interest is a study determining whether basophil suppression occurs in humans infected with helminths. Larson *et al.* examined histamine release by whole blood cells of a subset of 28 helminth-infected children from Ecuador aged 8-14 years before and two weeks after anthelmintic treatment [58]. Stimulation of blood with anti-IgE showed a considerable increase in basophil activation post helminth treatment. This indicates that the ability of basophils

to respond to both IgE-dependent and IgE-independent activation is suppressed during intestinal helminth infection in humans [58]. Given the role of basophils as effector cells in the allergic immune response, suppression of basophil functionality may be an additional mechanism by which helminths protect against allergies [58].

Helminth-induced IgE cross-reactivity

Cross-reactivity reflects the phylogenetic relations between organisms that results in a large degree of homology in the primary structure of proteins eventually leading to homologous three dimensional structures and potential cross-reactivity [59]. Since the 1980s, two types of IgE cross-reactivity related to allergy have been recognized: cross-reactivity due to proteins and cross-reactivity due to glycans on glycoproteins known as cross-reactive carbohydrate determinants (CCDs) [59].

The first indications of possible helminth involvement in IgE cross-reactivity came from observations in population studies of elevated levels of allergen specific IgE without skin reactivity or symptoms among helminth-infected children [3].

A. Protein cross-reactivity and helminths

Although there has been extensive characterization of cross-reactivity between plant-derived proteins for example between birch and apple allergens, cross-reactivity between allergens from invertebrates such as mites, shrimp, cockroach and schistosomes is a growing area of interest [59]. A number of proteins such as tropomyosin [60], paramyosin [61] and glutathione-S-transferase (GST) [62] have recently been studied in some detail. In Brazil, among children aged 3 to 6 years from a helminth-endemic area as well as patients with cockroach allergy from an allergy clinic, a strong correlation was observed between IgE against *Ascaris* tropomyosin and IgE against *P. americana* tropomyosin [60]. Notably, 75.6% of the children from the helminth-endemic area had IgE antibodies against cockroach tropomyosin yet had no symptoms of cockroach allergy [60].

IgE cross-reactivity between house dust mite tropomyosin (Der p 10) and the filarial nematode *Onchocerca volvulus* has also been demonstrated and may account for elevated levels of mite-specific IgE seen in helminth exposed individuals [63]. With respect to GST protein, GST from cockroach (Bla g 5) and from the filarial worm *W. bancrofti* (WbGST) were found to be 30% identical at the amino acid level and IgE against Blag 5 strongly correlated with IgE against WbGST [62].

An analysis of cross-reactivity between extracts of *A. lumbricoides* and dust mite allergens was conducted in the Philippines in subjects with high levels of IgE to extracts of *Ascaris* and mite allergens [61]. Absorption assays demonstrated that *A. lumbricoides* antigens could inhibit up to 92% of mite-specific IgE among allergic subjects while mite allergens inhibited up to 54% of *Ascaris*-sIgE among *Ascaris*-infected subjects. IgE responses to the recombinant form of the paramyosin *Blomia* allergen (Blo t 11)

were also assessed and positive rBlot t 11-fD –specific IgE reactivity was seen in 80% of allergic subjects and 46% of *A. lumbricoides* positive subjects thus indicating cross-reactivity between paramyosin from *Blomia* and paramyosin from *A. lumbricoides* [61].

In view of helminth-associated IgE cross-reactivity, Carvalho and colleagues evaluated the use of IgE responses to recombinant *Blomia* allergens (rBlo t 5 and rBlo t 21) to improve specificity in determining allergy to mite in a population from the tropics [64]. To this end, sera from a subset of children (N=35) enrolled in the SCAALA study in Brazil all of whom had elevated allergen-specific IgE was assessed for IgE reactivity to recombinant *Blomia* allergens. The study found that 82.9% of the children who had elevated IgE against *B. tropicalis* extract had IgE to rBlo t 5 and rBlo t 21 [64]. Absorption assay results showed that pre-incubation with *Ascaris* antigens affected IgE reactivity to *B. tropicalis* extract but not to rBlo t 5 and to rBlo t 21. This study demonstrates the value of using recombinant mite allergens rather than crude mite extract for serodiagnostic purposes in a population from a helminth-endemic area.

B. Carbohydrate cross-reactivity and helminths

One of the earliest investigations into carbohydrate cross-reactivity observed that one third of grass pollen-sensitized individuals in an outpatient population in the Netherlands had elevated levels of IgE against peanut extract without peanut SPT reactivity or peanut allergy symptoms [65]. Further analysis revealed that in 91% of cases, IgE directed against N-linked carbohydrates of glycoproteins known as cross-reactive carbohydrate determinants (CCDs) could be detected [65]. Cross-reactive IgE directed against CCDs in this population was also demonstrated to have poor biological activity [65]. It is estimated that between 15% and 30% of allergic patients generate IgE directed against glycans [66]. The two major N-glycan motifs involved in cross-reactivity are xylose and core-3-linked fucose which are found in plants and invertebrates including helminths [67].

A prominent feature of helminth infections is elevated levels of IgE directed against allergens without SPT reactivity [68]. A recent study in Africa has demonstrated that carbohydrate cross-reactivity might play a role in this phenomenon [69]. In schoolchildren aged 5-16 years in Ghana, 17.5% of subjects were IgE sensitized to peanut (≥0.35 kU/L) yet 92.4% of those sensitized were peanut SPT negative [69]. In addition, current infection with *S. haematobium* was strongly associated with peanut IgE sensitization and a strong correlation was observed between IgE against whole peanut extract and IgE against CCDs. Notably, inhibition assays demonstrated that not only could this IgE against whole peanut extract be almost completely inhibited by the CCD marker bromelain, but also by *S. haematobium* soluble egg antigen which is enriched with N-glycans [69]. Furthermore, basophil histamine release assays demonstrated that the IgE directed against peanut in this population had low biological activity [69]. This study provides a model which proposes that in helminth infections, primary sensitization may occur to carbohydrate moieties present in helminths which

are also present in some well-characterized allergens such as peanut and that such IgE antibodies have low biological activity (Figure 3).

Although the lack of clinical relevance of IgE antibodies against CCDs has been demonstrated [70], in recent years, IgE directed against the carbohydrate epitope galactose-α-1,3-galactose (α-gal) has been linked to two forms of anaphylaxis [71]. The first being immediate onset anaphylaxis following the first infusion of the monoclonal antibody cetuximab among patients from the Southeastern United States receiving therapy for cancer [72]. Further analysis determined that reactions occurred in patients with pre-existing IgE against α-gal [71] possibly induced by the lone star tick *Amblyomma americanum* [73]. The second form of anaphylaxis associated with α-gal is delayed onset reactions 3-6 hours following ingestion of mammalian meat products (Figure 3) [71]. Although the reasons behind the delay in the onset of reactions are

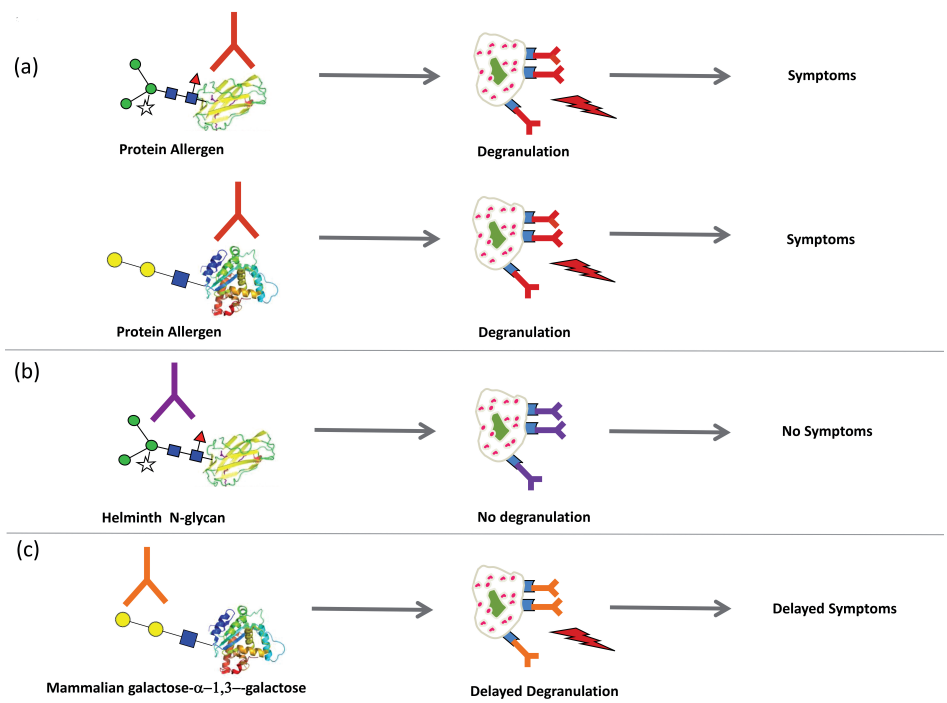

Figure 3: Immunoglobulin E antibody binding to different allergen epitopes

A simplified illustration of IgE antibody binding to different allergen epitopes. (a) IgE directed against protein epitopes of an allergen has strong biological activity and can lead to mast cell degranulation and allergy-related symptoms. (b) IgE directed against the N-glycan xylose or core-3-linked fucose carbohydrate epitopes has low biological activity and does not result in strong mast cell degranulation and related symptoms (c) IgE directed against the galactose-α-1,3-galactose (α-gal) carbohydrate epitope can result in mast cell degranulation and delayed symptoms. However, in some cases where α-gal is intravenously infused, symptoms can be immediate. The different colours of IgE antibodies are used to suggest strong (red), weak (purple) or intermediate (orange) biological activity.

yet to be fully understand, it is believed that it represents the time for red meat to be digested and for associated lipids to be absorbed [71].

Interestingly, in serum samples from children living in rural helminth-endemic communities in Kenya and Ecuador, positive IgE responses to α-gal have been observed which could be tick-related but could also indicate the involvement of helminths or other ectoparasites [71]. In addition, a study conducted in Zimbabwe examined IgE responses against α-gal in rural helminth-infected subjects as well as urban doctor-diagnosed cat allergic patients [74]. In the parasite-infected group, 85% had IgE against α-gal and 66% had IgE against the cat allergen Fel d 5 found in cat dander extract (CDE) [74]. The IgE to α-gal and IgE to Fel d 5 were highly correlated which is in line with recent studies that have demonstrated that α-gal is present on Fel d 5 [75]. Furthermore, only 2 out of 47 of the parasite-infected had IgE to the recombinant form of the cat allergen Fel d 1 which does not carry α-gal. By contrast, among the cat allergic patients, only a few had IgE responses to Fel d 5 and α-gal while 74% had responses to recombinant Fel d 1 [74]. These observations imply that in helminth-endemic areas, the IgE to α-gal is not clinically relevant. However, given that no information was collected on reactions to mammalian meat in the helminth-endemic areas [76], more in-depth studies are needed to assess the prevalence of sensitization to α-gal in populations in different geographical areas and the relationship between sensitization and clinical outcomes.

Future directions

Recombinant allergen technology

IgE cross-reactivity between helminth antigens and environmental as well as food allergen extracts has demonstrated the potential limits in diagnostic value of testing IgE responses against whole allergen extracts in helminth-endemic populations. Therefore, the use of recombinant allergen technology for the evaluation of IgE responses to allergens is much needed for better specificity and to improve diagnostic accuracy.

Helminth products as therapies

Given the abundant evidence from epidemiological and experimental studies of the immunomodulatory properties of helminths, in the past few years, steps have been taken towards harnessing the potential of helminths and their products in the treatment of allergies as well as autoimmune conditions. One such therapeutic possibility is the use of eggs from the pig nematode *Trichuris suis* which was first used in clinical trials to treat inflammatory bowel disease [77]. Since then, a double-blind, placebo-controlled, parallel group trial among adults in Denmark has examined the efficacy of *T. suis* ova therapy in the treatment of grass pollen-induced allergic rhinitis and has shown no therapeutic effect [78]. There are currently 13 active or completed clinical trials with *T. suis* eggs [79] and their results will establish whether treatment later in life (as opposed to in early life) with relatively low exposure to helminths might be effective.

In addition, hookworm larvae have also been used to infect human volunteers with the view towards a potential therapy for inflammatory diseases [80]. For helminthic therapy research in general, much effort is being put into the characterization of helminth-derived molecules with modulatory activity to be able to treat patients with well-defined products rather than full infections [81].

Novel allergens relevant in the tropics

The recent study on peanut allergy among schoolchildren in Ghana found that in a subset of those with elevated IgE responses to whole peanut extract, a few had elevated IgE to the recombinant form of the peanut allergen Ara h 9 [69]. Furthermore, IgE antibodies against Ara h 9 were biologically active at low allergen concentrations as determined by basophil histamine assays. Ara h 9 is a member of the nonspecific lipid transfer protein (LTP) family of allergens and appears to play a role in peanut allergy among patients in the Mediterranean region [82]. It is believed that the peach LTP allergen Pru p 3 may act as primary sensitizer among peanut allergic subjects in Spain [83]. The origin of sensitization to LTPs in areas of the tropics such as Ghana and the role of helminths remain unknown but provide future directions for further research. Aside from the case of Ara h 9, other novel allergens found in the tropics exist that require better characterization [84].

Concluding remarks

The intersection between helminths and allergies has been an interesting area of research which has shed light on immunological pathways, on allergen structure and on cross-reactivity as well as on differences in allergic phenotypes / outcomes in different geographical locations. Future studies have to build on these findings in order to generate the tools to diagnose, treat and prevent allergic disorders not only in affluent countries where they are rampant but also in areas where allergies are emerging as chronic diseases of public health importance.

References

1. World Allergy Organization, WAO White Book on Allergy 2011-2012: Executive Summary: World Allergy Organization, 2011.
2. Strachan D, Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55: S1-S10.
3. Yazdanbakhsh M, Kremsner PG, van Ree R, Allergy, Parasites, and the Hygiene Hypothesis. Science 2002;296: 490-94.
4. McSorley HJ, Hewitson JP, Maizels RM, Immunomodulation by helminth parasites: defining mechanisms and mediators. International Journal for Parasitology 2013;43: 301-10.
5. Linneberg A, The increase in allergy and extended challenges. Allergy 2011;66 Suppl 95: 1-3.
6. Asher MI, Urbanisation, asthma and allergies. Thorax 2011;66: 1025-6.
7. Maizels RM, Yazdanbakhsh M, Immune regulation by helminth parasites: cellular and molecular mechanisms. Nature Reviews Immunology 2003;3: 733-44.

8. Smits HH, Everts B, Hartgers FC, Yazdanbakhsh M, Chronic Helminth Infections Protect Against Allergic Diseases by Active Regulatory Processes. Current Allergy and Asthma Reports 2010;10: 3-12.
9. Boatin BA, Basanez MG, Prichard RK, Awadzi K, Barakat RM, Garcia HH, Gazzinelli A, Grant WN, McCarthy JS, N'Goran EK, Osei-Atweneboana MY, Sripa B, Yang GJ, Lustigman S, A research agenda for helminth diseases of humans: towards control and elimination. PLOS Neglected Tropical Diseases 2012;6: e1547.
10. WHO, Soil-transmitted helminth infections. Geneva: World Health Organization, 2014.
11. Feary J, Britton J, Leonardi-Bee J, Atopy and current intestinal parasite infection: a systematic review and meta-analysis. Allergy 2011;66: 569-78.
12. Flohr C, Quinnell RJ, Britton J, Do helminth parasites protect against atopy and allergic disease? Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2009;39: 20-32.
13. Fernando D, Wickramasinghe P, Kapilananda G, Dewasurendra RL, Amarasooriya M, Dayaratne A, Toxocara seropositivity in Sri Lankan children with asthma. Pediatrics international : official journal of the Japan Pediatric Society 2009;51: 241-5.
14. Cobzaru RG, Ripa C, Leon MM, Luca MC, Ivan A, Luca M, Correlation between asthma and Toxocara canis infection. Revista Medico-chirurgicala a Societatii de Medici si Naturalisti din Lasi 2012;116: 727-30.
15. Mendonca LR, Veiga RV, Dattoli VC, Figueiredo CA, Fiaccone R, Santos J, Cruz AA, Rodrigues LC, Cooper PJ, Pontes-de-Carvalho LC, Barreto ML, Alcantara-Neves NM, Toxocara seropositivity, atopy and wheezing in children living in poor neighbourhoods in urban Latin American. PLOS Neglected Tropical Diseases 2012;6: e1886.
16. Kanobana K, Vereecken K, Junco Diaz R, Sariego I, Rojas L, Bonet Gorbea M, Polman K, Toxocara seropositivity, atopy and asthma: a study in Cuban schoolchildren. Tropical Medicine & International Health : TM & IH 2013;18: 403-6.
17. Garcia-Ara MC, Bobolea I, Caballero T, Quirce S, Boyano-Martinez MT, Specific immunoglobulin E to Echinococcus granulosus in children allergic to cow's milk proteins. Journal of Investigational Allergology and Clinical Immunology 2012;22: 374-5.
18. Pinelli E, Willers SM, Hoek D, Smit HA, Kortbeek LM, Hoekstra M, de Jongste J, van Knapen F, Postma D, Kerkhof M, Aalberse R, van der Giessen JW, Brunekreef B, Prevalence of antibodies against Ascaris suum and its association with allergic manifestations in 4-year-old children in The Netherlands: the PIAMA birth cohort study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2009;28: 1327-34.
19. Barreto ML, Cunha SS, Alcantara-Neves N, Carvalho LP, Cruz AA, Stein RT, Genser B, Cooper PJ, Rodrigues LC, Risk factors and immunological pathways for asthma and other allergic diseases in children: background and methodology of a longitudinal study in a large urban center in Northeastern Brazil (Salvador-SCAALA study). BMC Pulmonary Medicine 2006;6: 15.
20. Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA, Simoes SM, Fiaccone R, Amorim L, Cooper PJ, Barreto ML, Early infection with Trichuris trichiura and allergen skin test reactivity in later childhood. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2008;38: 1769-77.
21. Calvert J, Burney P, Ascaris, atopy, and exercise-induced bronchoconstriction in rural and urban South African children. The Journal of Allergy and Clinical Immunology 2010;125: 100-5 e1-5.
22. Vereecken K, Kanobana K, Wordemann M, Junco Diaz R, Menocal Heredia L, Ruiz Espinosa A, Nunez FA, Rojas Rivero L, Bonet Gorbea M, Polman K, Associations between atopic markers in asthma and intestinal helminth infections in Cuban schoolchildren. Pediatric Allergy and Immunology : official publication of the European Society of Pediatric Allergy and Immunology 2012;23: 332-8.
23. Levin M, Muloiwa R, Le Souef P, Motala C, Ascaris sensitization is associated with aeroallergen sensitization and airway hyperresponsiveness but not allergic disease in urban Africa. The Journal of Allergy and Clinical Immunology 2012;130: 265-7.

24. Moncayo AL, Vaca M, Oviedo G, Erazo S, Quinzo I, Fiaccone RL, Chico ME, Barreto ML, Cooper PJ, Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. Thorax 2010;65: 409-16.
25. Takeuchi H, Zaman K, Takahashi J, Yunus M, Chowdhury HR, Arifeen SE, Baqui A, Wakai S, Iwata T, High titre of anti-Ascaris immunoglobulin E associated with bronchial asthma symptoms in 5-year-old rural Bangladeshi children. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2008;38: 276-82.
26. da Silva ER, Sly PD, de Pereira MU, Pinto LA, Jones MH, Pitrez PM, Stein RT, Intestinal helminth infestation is associated with increased bronchial responsiveness in children. Pediatric Pulmonology 2008;43: 662-5.
27. Wordemann M, Diaz RJ, Heredia LM, Collado Madurga AM, Ruiz Espinosa A, Prado RC, Millan IA, Escobedo A, Rojas Rivero L, Gryseels B, Gorbea MB, Polman K, Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. Tropical Medicine & International Health : TM & IH 2008;13: 180-6.
28. Alcantara-Neves NM, Veiga RV, Dattoli VCC, Fiaccone RL, Esquivel R, Cruz ÁA, Cooper PJ, Rodrigues LC, Barreto ML, The effect of single and multiple infections on atopy and wheezing in children. The Journal of Allergy and Clinical Immunology 2012;129: 359-67.e3.
29. Amberbir A, Medhin G, Erku W, Alem A, Simms R, Robinson K, Fogarty A, Britton J, Venn A, Davey G, Effects of Helicobacter pylori, geohelminth infection and selected commensal bacteria on the risk of allergic disease and sensitization in 3-year-old Ethiopian children. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2011;41: 1422-30.
30. Hennekens C, Buring J, Epidemiology in Medicine. First Edition Edn: Lippincott, Williams & Wilkins, 1987.
31. Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N, Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. The Journal of Allergy and Clinical Immunology 1993;92: 404-11.
32. van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, Missinou MA, Borrmann S, Kremsner PG, Yazdanbakhsh M, Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. The Journal of Infectious Diseases 2004;189: 892-900.
33. Cooper PJ, Chico ME, Vaca MG, Moncayo AL, Bland JM, Mafla E, Sanchez F, Rodrigues LC, Strachan DP, Griffin GE, Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geohelminth parasites: a cluster-randomised trial.The Lancet 2006;367: 1598-603.
34. Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, Simmons C, Telford G, Brown A, Hien TT, Farrar J, Williams H, Pritchard DI, Britton J, Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2010;40: 131-42.
35. Wiria AE, Hamid F, Wammes LJ, Kaisar MM, May L, Prasetyani MA, Wahyuni S, Djuardi Y, Ariawan I, Wibowo H, Lell B, Sauerwein R, Brice GT, Sutanto I, van Lieshout L, de Craen AJ, van Ree R, Verweij JJ, Tsonaka R, Houwing-Duistermaat JJ, Luty AJ, Sartono E, Supali T, Yazdanbakhsh M, The effect of three-monthly albendazole treatment on malarial parasitemia and allergy: a household-based cluster-randomized, double-blind, placebo-controlled trial. PLOS ONE 2013;8: e57899.
36. van der Werff SD, Polman K, Ponce MC, Twisk JW, Junco Diaz R, Gorbea MB, Van der Stuyft P, Childhood atopic diseases and early life circumstances: an ecological study in Cuba. PLOS ONE 2012;7: e39892.
37. Endara P, Vaca M, Chico ME, Erazo S, Oviedo G, Quinzo I, Rodriguez A, Lovato R, Moncayo AL, Barreto ML, Rodrigues LC, Cooper PJ, Long-term periodic anthelmintic treatments are associated with increased allergen skin reactivity. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2010;40: 1669-77.
38. Mpairwe H, Webb EL, Muhangi L, Ndibazza J, Akishule D, Nampijja M, Ngom-wegi S,

Tumusime J, Jones FM, Fitzsimmons C, Dunne DW, Muwanga M, Rodrigues LC, Elliott AM, Anthelminthic treatment during pregnancy is associated with increased risk of infantile eczema: randomised-controlled trial results. Pediatric Allergy and Immunology : official publication of the European Society of Pediatric Allergy and Immunology 2011;22: 305-12.

39. Ndibazza J, Mpairwe H, Webb EL, Mawa PA, Nampijja M, Muhangi L, Kihembo M, Lule SA, Rutebarika D, Apule B, Akello F, Akurut H, Oduru G, Naniima P, Kizito D, Kizza M, Kizindo R, Tweyongere R, Alcock KJ, Muwanga M, Elliott AM, Impact of anthelminthic treatment in pregnancy and childhood on immunisations, infections and eczema in childhood: a randomised controlled trial. PLOS ONE 2012;7: e50325.
40. Ferrero MR, Roser D, Nielsen HV, Olsen A, Nejsum P, Genetic variation in mitochondrial DNA among Enterobius vermicularis in Denmark. Parasitology 2013;140: 109-14.
41. Bager P, Vinkel Hansen A, Wohlfahrt J, Melbye M, Helminth infection does not reduce risk for chronic inflammatory disease in a population-based cohort study. Gastroenterology 2012;142: 55-62.
42. Licona-Limon P, Kim LK, Palm NW, Flavell RA, TH2, allergy and group 2 innate lymphoid cells. Nature Immunology 2013;14: 536-42.
43. Girgis NM, Gundra UM, Loke P, Immune regulation during helminth infections. PLOS Pathogens 2013;9: e1003250.
44. Gause WC, Wynn TA, Allen JE, Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. Nature Reviews Immunology 2013;13: 607-14.
45. van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, Yazdanbakhsh M, Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. The Lancet 2000;356: 1723-7.
46. Cooper PJ, Mitre E, Moncayo AL, Chico ME, Vaca MG, Nutman TB, Ascaris lumbricoides-induced interleukin-10 is not associated with atopy in schoolchildren in a rural area of the tropics. The Journal of Infectious Diseases 2008;197: 1333-40.
47. Cooper PJ, Moncayo AL, Guadalupe I, Benitez S, Vaca M, Chico M, Griffin GE, Repeated treatments with albendazole enhance Th2 responses to Ascaris Lumbricoides, but not to aeroallergens, in children from rural communities in the Tropics. The Journal of Infectious Diseases 2008;198: 1237-42.
48. Bullens DM, De Swerdt A, Dilissen E, Kasran A, Kroczek RA, Cadot P, Casaer P, Ceuppens JL, House dust mite-specific T cells in healthy non-atopic children. Clinical and Experimental Allergy : journal of the British Society for Allergy and Clinical Immunology 2005;35: 1535-41.
49. Djuardi Y, Supali T, Wibowo H, Kruize YC, Versteeg SA, van Ree R, Sartono E, Yazdanbakhsh M, The development of TH2 responses from infancy to 4 years of age and atopic sensitization in areas endemic for helminth infections. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 2013;9: 13.
50. Figueiredo CA, Alcantara-Neves NM, Veiga R, Amorim LD, Dattoli V, Mendonca LR, Junqueira S, Genser B, Santos M, de Carvalho LC, Cooper PJ, Rodrigues L, Barreto ML, Spontaneous cytokine production in children according to biological characteristics and environmental exposures. Environmental Health Perspectives 2009;117: 845-9.
51. Figueiredo CA, Barreto ML, Rodrigues LC, Cooper PJ, Silva NB, Amorim LD, Alcantara-Neves NM, Chronic intestinal helminth infections are associated with immune hyporesponsiveness and induction of a regulatory network. Infection and Immunity 2010;78: 3160-7.
52. Figueiredo CA, Amorim LD, Alcantara-Neves NM, Matos SM, Cooper PJ, Rodrigues LC, Barreto ML, Environmental conditions, immunologic phenotypes, atopy, and asthma: new evidence of how the hygiene hypothesis operates in Latin America. The Journal of Allergy and Clinical Immunology 2013;131: 1064-8, 68 e1.
53. Figueiredo CA, Barreto ML, Alcantara-Neves NM, Rodrigues LC, Cooper PJ, Cruz AA, Pontes-de-Carvalho LC, Lemaire DC, dos Santos Costa R, Amorim LD, Vergara C, Rafaels N, Gao L, Foster C, Campbell M, Mathias RA, Barnes KC, Coassociations between IL10 polymorphisms, IL-10 production, helminth infection, and asthma/wheeze in an urban tropical population in

Brazil. The Journal of Allergy and Clinical Immunology 2013;131: 1683-90.
54. Eder W, Ege MJ, von Mutius E, The asthma epidemic. The New England Journal of Medicine 2006;355: 2226-35.
55. Rujeni N, Nausch N, Bourke CD, Midzi N, Mduluza T, Taylor DW, Mutapi F, Atopy is inversely related to schistosome infection intensity: a comparative study in Zimbabwean villages with distinct levels of Schistosoma haematobium infection. International Archives of Allergy and Immunology 2012;158: 288-98.
56. Rujeni N, Nausch N, Midzi N, Mduluza T, Taylor DW, Mutapi F, Schistosoma haematobium infection levels determine the effect of praziquantel treatment on anti-schistosome and anti-mite antibodies. Parasite Immunology 2012;34: 330-40.
57. Rujeni N, Nausch N, Midzi N, Gwisai R, Mduluza T, Taylor DW, Mutapi F, Soluble CD23 levels are inversely associated with atopy and parasite-specific IgE levels but not with polyclonal IgE levels in people exposed to helminth infection. International Archives of Allergy and Immunology 2013;161: 333-41.
58. Larson D, Cooper PJ, Hubner MP, Reyes J, Vaca M, Chico M, Kong HH, Mitre E, Helminth infection is associated with decreased basophil responsiveness in human beings. The Journal of Allergy and Clinical Immunology 2012;130: 270-2.
59. Aalberse RC, Akkerdaas J, van Ree R, Cross-reactivity of IgE antibodies to allergens. Allergy 2001;56: 478-90.
60. Santos AB, Rocha GM, Oliver C, Ferriani VP, Lima RC, Palma MS, Sales VS, Aalberse RC, Chapman MD, Arruda LK, Cross-reactive IgE antibody responses to tropomyosins from Ascaris lumbricoides and cockroach. The Journal of Allergy and Clinical Immunology 2008;121: 1040-6 e1.
61. Valmonte GR, Cauyan GA, Ramos JD, IgE cross-reactivity between house dust mite allergens and Ascaris lumbricoides antigens. Asia Pacific Allergy 2012;2: 35-44.
62. Santiago HC, LeeVan E, Bennuru S, Ribeiro-Gomes F, Mueller E, Wilson M, Wynn T, Garboczi D, Urban J, Mitre E, Nutman TB, Molecular mimicry between cockroach and helminth glutathione S-transferases promotes cross-reactivity and cross-sensitization. The Journal of Allergy and Clinical Immunology 2012;130: 248-56 e9.
63. Santiago HC, Bennuru S, Boyd A, Eberhard M, Nutman TB, Structural and immunologic cross-reactivity among filarial and mite tropomyosin: implications for the hygiene hypothesis. The Journal of Allergy and Clinical Immunology 2011;127: 479-86.
64. Carvalho Kdos A, de Melo-Neto OP, Magalhaes FB, Ponte JC, Felipe FA, dos Santos MC, dos Santos Lima G, Cruz AA, Pinheiro CS, Pontes-de-Carvalho LC, Alcantara-Neves NM, Blomia tropicalis Blo t 5 and Blo t 21 recombinant allergens might confer higher specificity to serodiagnostic assays than whole mite extract. BMC Immunology 2013;14: 11.
65. van der Veen MJ, van Ree R, Aalberse RC, Akkerdaas J, Koppelman SJ, Jansen HM, van der Zee JS, Poor biologic activity of cross-reactive IgE directed to carbohydrate determinants of glycoproteins. The Journal of Allergy and Clinical Immunology 1997;100: 327-34.
66. Commins SP, Platts-Mills TA, Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. The Journal of Allergy and Clinical Immunology 2009;124: 652-7.
67. Altmann F, The role of protein glycosylation in allergy. International Archives of Allergy and Immunology 2007;142 99-115
68. Ponte JC, Junqueira SB, Veiga RV, Barreto ML, Pontes-de-Carvalho LC, Alcantara-Neves NM, A study on the immunological basis of the dissociation between type I-hypersensitivity skin reactions to Blomia tropicalis antigens and serum anti-B. tropicalis IgE antibodies. BMC Immunology 2011;12: 34.
69. Amoah AS, Obeng BB, Larbi IA, Versteeg SA, Aryeetey Y, Akkerdaas JH, Zuidmeer L, Lidholm J, Fernandez-Rivas M, Hartgers FC, Boakye DA, van Ree R, Yazdanbakhsh M, Peanut-specific IgE antibodies in asymptomatic Ghanaian children possibly caused by carbohydrate determinant cross-reactivity. The Journal of Allergy and Clinical Immunology 2013.
70. Mari A, Ooievaar-de Heer P, Scala E, Giani M, Pirrotta L, Zuidmeer L, Bethell D, Van Ree R, Evaluation by double-blind placebo-controlled oral challenge of the

clinical relevance of IgE antibodies against plant glycans. Allergy 2008;63: 891-96.

71. Commins SP, Platts-Mills TA, Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). Current Allergy and Asthma Reports 2013;13: 72-7.
72. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA, Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. The New England Journal of Medicine 2008;358: 1109-17.
73. Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, Kocan KM, Fahy JV, Nganga LW, Ronmark E, Cooper PJ, Platts-Mills TAE, The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α1,3 galactose The Journal of Allergy and Clinical Immunology 2011;127: 1286-93.e6.
74. Arkestål K, Sibanda E, Thors C, Troye-Blomberg M, Mduluza T, Valenta R, Grönlund H, van Hage M, Impaired allergy diagnostics among parasite-infected patients caused by IgE antibodies to the carbohydrate epitope galactose-α1,3 galactose The Journal of Allergy and Clinical Immunology 2011;127: 1024-28.
75. Gronlund H, Adedoyin J, Commins SP, Platts-Mills TA, van Hage M, The carbohydrate galactose-alpha-1,3-galactose is a major IgE-binding epitope on cat IgA. The Journal of Allergy and Clinical Immunology 2009;123: 1189-91.
76. Commins SP, Platts-Mills TA, Tick bites and red meat allergy. Current Opinion in Allergy and Clinical Immunology 2013;13: 354-9.
77. Summers RW, Elliott DE, Qadir K, Urban JF, Jr., Thompson R, Weinstock JV, Trichuris suis seems to be safe and possibly effective in the treatment of inflammatory bowel disease. The American Journal of Gastroenterology 2003;98: 2034-41.
78. Bager P, Arnved J, Ronborg S, Wohlfahrt J, Poulsen LK, Westergaard T, Petersen HW, Kristensen B, Thamsborg S, Roepstorff A, Kapel C, Melbye M, Trichuris suis ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial. The Journal of Allergy and Clinical Immunology 2010;125: 123-30 e1-3.
79. Clinical Trials with Trichuris suis. In: ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (USA) [Accessed 18 October 2013]
80. Daveson AJ, Jones DM, Gaze S, McSorley H, Clouston A, Pascoe A, Cooke S, Speare R, Macdonald GA, Anderson R, McCarthy JS, Loukas A, Croese J, Effect of hookworm infection on wheat challenge in celiac disease--a randomised double-blinded placebo controlled trial. PLOS ONE 2011;6: e17366.
81. Cooke A, Parasitic worms and inflammatory disease. Current Opinion in Rheumatology 2012;24: 394-400.
82. Krause S, Reese G, Randow S, Zennaro D, Quaratino D, Palazzo P, Ciardiello MA, Petersen A, Becker W-M, Mari A, Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population. The Journal of Allergy and Clinical Immunology 2009;124: 771-78.e5.
83. Javaloyes G, Goikoetxea MJ, Garcia Nunez I, Aranda A, Sanz ML, Blanca M, Diaz Perales A, da Souza J, Esparza I, del Pozo V, Blazquez AB, Scheurer S, Vieths S, Ferrer M, Pru p 3 acts as a strong sensitizer for peanut allergy in Spain. The Journal of Allergy and Clinical Immunology 2012;130: 1432-4 e3.
84. Kung SJ, Steenhoff AP, Gray C, Food Allergy in Africa: Myth or Reality? Clinical Reviews in Allergy and Immunologyl 2012.


Background Information