Allergic Disorders in Africa and Africans: Is It Primarily a Priority?

Erasto Vitus Mbugi, PhD,[1] and Jaffu Othniel Chilongola, PhD[2]

Abstract: In Africa, the burden of some diseases has been a problem for centuries. The spectrum of African diseases includes allergies, infections, nutritional deficiencies, and natural disasters. Efforts made by scientists to search for possible means of disease control have been outstanding; however, in some infections, solutions are still out of reach. In disease control programs, it might be worthwhile to pay attention to the most striking diseases than merely follow a holistic approach. This short review tackles the problems of allergy and allergens in Africa as compared with other disease burdens that may suggest the need for a more balanced approach based on priority.

Key Words: allergy, allergens, Africa

(*WAO Journal* 2010; 3:175–181)

INTRODUCTION

Available reports with amalgamative approach have given precise arguments and valuable attention on allergy and allergens in Africans.[1] These reports have shown concern on what might be an added problem to already existing disease calamities that face and possibly contribute to undermine the economic development in Africa.

Despite recent efforts and proposal for natural mechanisms for control of allergic conditions such as allergic inflammation,[2] the prevalence of allergic diseases that has dramatically increased globally over decades[3,4] remains to be among major challenges to developing countries whose economy relies mainly on agriculture. Studies on allergy and allergens have pointed out interesting areas of concern such as 1) increase in allergic symptoms with increasing gross national income of the country, 2) an 'urban diet' component on increased skin reactivity to allergens, 3) lower incidence of allergies in rural Africa compared with urban, and 4) higher prevalence of and greater severity of allergies in people of African ancestry in affluent countries than the natives of the host countries.[1] From these propositions, the authors address the issue of genetic component in African population playing a role in the control of the development of allergies, indicating the possible existence of a complex mechanism. With both genetic and environmental factors being involved, the authors[1] propose possible solutions to lower the incidence. Several mechanisms might be involved in regulating the occurrence of allergy apart from genetic and environmental factors. In developing countries for example, prolonged breast-feeding has been reported to be protective against development of allergic disorders, particularly hay fever, in children born to nonallergic parents.[5] However, previous studies by Obihara et al[5] have indicated the protection to be restricted only to children without allergic predisposition but not those born to allergic parents. Other reports have put more emphasis on 'the hygiene hypothesis' and the role of parasites,[6–15] and microbial infections like tuberculosis[16,17] in potentially regulating the development of allergic disorders. In principle, the idea reflects that, future development of mycobacterial-based[18] and parasite-based vaccines against allergic diseases at least in children could be ideal and rewarding.

Prevalence of Allergy and Allergens

The global prevalence of allergy is reported to be in the range of 20–30% of the world's population including different forms of allergic diseases.[19] This global prevalence seems to have increased with time particularly in the last 3 decades.[20] The symptoms of asthma, allergic rhinitis, and atopic eczema in adolescents, for example, have been increasing over years in Africa.[21] Severe allergic reactions with systemic effects involving the whole body (anaphylaxis) may occur depending on etiology such as food allergy.[22] Mathematically, the prevalence of allergy is higher than even commonly reported diseases like tuberculosis (TB) and HIV/AIDS (Table 1). The consequences of allergic disorders particularly in southern Africa are so great that they can result into significant morbidity, employment absenteeism, loss of quality of life and in some instances, fatal outcomes. In addition, allergies remain to pose a huge health costs in affected regions, affecting all ages, from the poorest to the richest.[23] Similar

From the [1]Muhimbili University of Health and Allied Sciences, Biochemistry Department, School of Medicine, Dar es Salaam, Tanzania; and [2]Kilimanjaro Clinical Research Institute, Kilimanjaro Christian Medical College, Moshi, Tanzania.

Dr Jessy Pax Masimba Mboro is acknowledged for material support during preparation of this manuscript. The Departments of Animal Sciences (Cell Biology and Immunology Group), Wageningen University in The Netherlands, and The Department of Biochemistry, School of Medicine, Muhimbili University of Health, and Allied Sciences in Tanzania are acknowledged for their moral support during preparation of this review.

Correspondence to: Erasto Vitus Mbugi, PhD, Muhimbili University of Health and Allied Sciences, Biochemistry Department, School of Medicine, P.O. Box 65001, Dar es Salaam, Tanzania.

Telephone: +255-784-586-869. Fax: +255-222-150-465. E-mail: rerasto@yahoo.com.

TABLE 1. Prevalence of Allergy in Africa as Compared to Other Selected Infections

Disease	Prevalence (%)	Reference
Malaria	40	WHO,[31] Breman,[32] Moore, and Ewart[33]
Tuberculosis	29	Chaisson and Martinson[34]
HIV/AIDS	0.1–26.1	UNAIDS[35,36]
Schistosomiasis	75–100*	Estmbale[37,38]
Other intestinal worms	1–43	Modjarrad et al[39]
Allergy	20–30	Pawankar et al[19]

*Estimates varies among African countries and the data presented here comes mainly from the coast.

effects could be expected elsewhere across Africa necessitating dedicated efforts by scientists to study the disease and propose viable control strategies.

Results from epidemiological studies combined with the knowledge on pollen and latex cross-reactivity, and systemic reactions to contact allergens and celiac disease have shown a prevalence of food allergy in the adult European population to be ~5%.[24] Additionally, contact allergens in foods resulting into dermatitis in patients allergic to some allergens such as nickel and fragrances have been proposed.[25,26] While most data for allergy and allergens comes from developed European countries, experience shows that few patients or even none may report allergies to medical personnel particularly in rural Africa unless the consequences are enormous. Some studies have suggested differences in reporting of allergic disorders to be related to language, culture, and access to medical care rather than real differences in prevalence.[27] Most of the allergy cases in rural Africa are contact allergies that may lead to mild dermatitis and pruritus.[28] Among signs and symptoms include minor inflammation of visible mucosa, which is frequently itchy. The adverse consequences of food allergy for example are mostly associated with the immune system involvement despite the lack of sufficient evidence for the supposition.[24] The hygiene hypothesis, however, has been used in some instances to explain the differences in susceptibility between people from developed countries and those living in developing Africa.[11] The most probable reason for intolerance like what is observed in milk intolerance is genetic lactose deficiency involvement that is reported to account for milk intolerance worldwide despite varying prevalence.[29] As it is well experienced elsewhere, self-reported food allergies, for example, vary from individual to individual. Reports by Brugman et al[30] in the late 1990s indicated that 7.2% of school children self-reported food hypersensitivity in The Netherlands, something that can rarely happen in rural Africa. While awareness to allergy and allergens is high in developed countries the vice versa applies to developing countries, where attention is directed toward striking and poverty-related diseases namely, TB, HIV/AIDS, and malaria. Although the prevalence of allergy and some other diseases in Africa are often extrapolated from European data, there are data available to show the prevalence of allergy as compared with other selected infections and infestations in Africans and elsewhere across the world (Table 1).

Despite the limited information on allergy and allergens in Africa, it is likely that predisposition to allergens will increase especially in urban areas. Comparatively, allergic disorders have been relatively extensively studied in South Africa than in other African countries. Potter et al reported all types of allergies to have been frequently diagnosed in peri-urban and urban dwelling black South Africans.[40] Because of the diverse of ancestry of populations in South Africa, there is a notable diversity in exposure to allergens varying between rural and urban. This diversity is attributed to the rapid migration of people to peri-urban informal settlements leading to dramatic change in lifestyle and allergen exposure.[41] In 1979, van Nierkerk et al[42] reported a nearly nonexistent prevalence of sensitization to allergens and asthma in rural Xhosa children over the past 2 decades. However, a report of dramatic increase of atopy in the same rural Xhosa children of South Africa 24 years later[43] is a reflection of a double increase in prevalence more than 2 decades after the previous report. With growing cities and increased predisposition to allergens in urban areas, it is apparent that the prevalence of allergy will gradually rise elsewhere in Africa. Available reports[44] point out children to have more allergic reactions to both outdoor and indoor allergens. The fuels used and higher volumes of road traffic in cities are thought to contribute to this increase[45–47] marked by the increase in the prevalence of asthma and allergic rhinoconjuctivitis. Poor outdoor air quality, exposure to indoor allergens and a stressful lifestyle have been shown to be the major determinants of allergic disorders.[48] Exposure of rural children to agricultural pesticides and irritants and the adoption to a more Westernized lifestyle such as the use of beds with mattresses, pillows, and blankets are among factors that are proposed to influence the development of asthma in susceptible African children.[49] This is critical because it reflects that the inherently low prevalence of allergies in African population may be damaged by adoption to new lifestyles. Reports on latex allergy in South African children from population of low socioeconomic status and poor hygiene have shown a low prevalence of latex sensitization as compared with their counter children.[50] However, inadequate information on the prevalence of allergic disorders worldwide and Africa in particular[51] necessitates a much more dedicated involvement for the scientific community to uncover the global allergy epidemic and its epidemiology. This is also one of the recommendations by the World Allergy Organization.[19]

POTENTIAL ALLERGENS

Potential allergens include grass pollens that are mostly seasonal,[52] but weeds such as plantain in southern Africa are said to contribute in induction of allergic reactions.[53,54] In coastal regions however, grass pollens may induce hypersensitivity reactions almost throughout the year particularly in southern Africa with spring type of climate.[52] Reports on allergy and allergens in Africa have absolutely focused on the current and prospective situation worldwide that may not be

of primary relevance to the African population that is still lagging behind technologically. We all understand that in poor African communities, floods of diseases coexist such that attention on allergy and allergens may possibly be overlooked and given low priority. Epidemiological reports in Africa have indicated higher prevalence of allergic sensitization in urban than in rural communities.[40,42,55–57] This idea could seem contradicting as most of people would associate rural communities with greater risk of allergens and allergies because of the nature of people's activities in rural areas. For example, the higher levels of mites in stored items and humidity may be associated with agricultural activities in rural areas.[58] Nevertheless, low prevalence of allergy is reported contrary to what most scientists would expect in terms of causal-effect relationships! In South Africa for example, the prevalence of allergic rhinitis in children aged 13–14 years old is said to be in the range of 13–17%. The common allergens, accounting for more than 80% of allergies in allergic rhinitis patients in South Africa include but not limited to house-dust mites, bermuda grass, rye grass, pets (cats, dogs, rabbits, horses), cockroaches (especially in the Durban area), and fungal spores.[59] However, it is possible that the prevalence varies across Africa because of different lifestyles and environment[10] particularly the interaction with geohelminths infestations.[60] A relevant and timely epidemiological study coupled with appropriate interpretation of results will be useful to establish the prevalence of allergy in Africa and the possible interaction with other prevailing infections. It has been proposed that despite IgE sensitization to environmental allergens in Africans, helminths-infested individuals are somehow protected from mast cell degranulation and inflammatory responses.[10] Susceptibility to allergens differs among individuals in different populations. Food allergy for example, is said to be uncommon in the general population but more frequently occurring in children (up to 8%) compared with adults (2%). About 35% of children with severe eczema experience food allergy involving IgE antibodies, and 6% of children with asthma experience food-induced wheezing.[22,61] Food sensitivity can be so severe that a systemic reaction involving the whole body (anaphylaxis), can occur after breathing airborne particles of the food allergen to which the subject is allergic.[22]

Expression of Allergic Disorders in Concurrent Infections

Coexisting infections positively or negatively influence each other, thus influencing the outcome of either of the diseases or infections. In African populations, concurrent diseases are inevitable because of the prevailing favorable tropical environment for microbial growth and multiplication. In addition, poverty, poor diagnostic facilities, and poor health systems in some areas have posed difficulties in disease control strategies. In allergic disorders, different views have been proposed to determine the development and fate of allergic disorders including infection and infestations. A study by Adams et al[16] revealed a down-regulation in total serum IgE concentration after successful treatment for TB; the decline that is ascribed to enhanced type-1 response. From the hygiene hypothesis it is argued that the stimulation of the immune system by microbes or microbial products could protect from development of inflammatory diseases. This means that a reduced exposure to infectious agents may explain the rise in allergic and autoimmune diseases in industrialized countries.[11] In addition, several studies have revealed that parasites such as *Toxoplasma gondii*,[62–64] schistosomes,[9,65–68] and intestinal helminths[69–74] are negatively associated with allergic disorders. Suppression of immune responses is a probable mechanism that *T. gondii*, for example, confers reduced allergic reactivity.[11] Similarly, intestinal heminths and schistosomes are said to carry immunomodulatory molecules that upon interaction with the immune system may result into a protective suppressor responses[75,76] limiting the development of allergic disorders.[11] Despite the proposed benefits of parasitic infections on reduction of the risk for development of allergic disorders, the definite association is still uncertain.[60,74] In particular, the modulation of host inflammatory response against the parasite during helminths infection and causal association with atopic diseases is still obscured. However, attention to some proposed mechanisms (discussed in next sections) by induction of interleukin (IL)-10 and TGF-β[9] with genetic variations[7] remain valuable albeit the need for properly designed studies to find out the real causal associations.[60] The benefit of the protective role of immunosuppression in reducing risks of development of allergic disorders in helminths and other infections is critical. However, it remains to be an opportunity cost to leave patients to live with infections that potentially reduce the risks of developing allergic disorders. In other words, the challenge is whether we should not treat parasitic infections in favor of their protective role to allergic disorders. Available reports have further revealed light helminths infections to be associated with the amplification of allergen-specific IgE responses and high skin reactivity, whereas heavy parasite burden[66,72] protects from atopic skin reactivity despite a high degree of sensitization to mite.[70] Priority setting for dealing with diseases in such circumstances is crucial although none of the diseases can be neglected, particularly in Africa.

Proposed Mechanisms Through Which Infections Influence Development and Fate of Allergic Disorders[6]

Potential mechanisms by which infection with pathogens might influence the development of allergic disorders include but not limited to: 1) Induction of T_h1 responses by viruses or bacteria in the sense that the IFN-γ produced by CD4 T_h1 cells, NK cells, or cytotoxic CD8 T lymphocytes (CTLs) directly interferes with the development of T_h2 cells. Viral and bacterial infections also induce the production of the T_h2 response inhibiting cytokines IL-12, IL-18, IL-23, TNF-α, IFN-α, and IFN-β by dentritic cells (DCs) and macrophages. 2) Macrophages, particularly DCs, also express certain costimulatory molecules known to be associated with enhanced T_h1 and decreased T_h2 responses, further reducing T_h2-cell development. Infections with helminths and bacteria induce the production of IL-10 and TGF-β;[7,9] both directly suppressing the development of allergic responses. Regulatory T-cells (Tr-cells) numbers are also increased by infec-

tions with bacteria and helminths. Tr-cells suppress allergic responses by inhibiting T_h2 effector functions, by cell-cell contact or by secreting IL-10 and TGF-β 3) T_h1 responses induced by viruses or bacteria directly exacerbate allergic diseases by generally increasing the inflammation in the affected tissue. Respiratory viruses can directly induce 4) airway eosinophilia, 5) goblet cell metaplasia and mucus production, 6) airway neutrophilia, or 7) smooth muscle contraction, directly causing wheezing or enhancing the already existing allergic inflammation. 8) Viral- or bacterial-specific IgE mediates mast cell degranulation during infection or re-exposure to the pathogen, enhancing a pre-existing allergic response or directly causing it. All these mechanisms potentially induce profound T_h2 responses that can enhance allergic responses. Infections also cause damage to the natural protective barriers, which normally limit the access of allergens to the body, leading to the development of allergen-specific T_h2 cells or enhance allergic responses, for example, through increased mast cell degranulation.[6] Consequently, the fate of an allergic disorder may be limited to less severe outcome or exacerbated to more severe outcome by influencing the pre-existing allergic responses. A recent study by Pacifico et al[77] has shown *Schistosoma mansoni* antigens to modulate experimental allergic asthma in a murine model by $CD4^+$ $CD25^+$ $Foxp3^+$ T cells (Tr-cells, Tregs) independent of interleukin-10. Thus, there might be several factors beyond our current knowledge that influence the development of allergy and related outcomes that may also vary worldwide and possibly with prevailing lifestyles.

Potential Susceptibility to Allergy and Allergens With Gross National Income

Presumptive association between gross national income and development of allergies is to be considered when studying allergic disorders despite the need for scientific exploration. In Africa, for example, a substantial number of allergic disorders have been studied ranging from food to contact allergies. Compared with other African countries, South Africa is relatively more developed further endorsing the idea that allergic disorders are associated with development and an increase in income. The association is mediated by possible source of allergens available in artificial foods (termed 'urban diets'[1]) that are mostly accessible by individuals with high income. This is evident through the link between people of African ancestry (genetic component), 'urban diets,' and higher prevalence of allergies such as asthma in urban than rural people.[78] Existing evidence indicates a rapid increase in the prevalence of allergy with increase in urbanization.[13,49,79] There is high possibility that Africans may have the genetic component,[13,80] which is associated with the development of allergies but the occurrence of disease is limited. The idea is that for the disease to occur there must be presence of allergens in artificial foods to favor the occurrence of the disorder. There is evidence that susceptibility to asthma and atopy among certain populations of African descent is influenced by a functional polymorphism in the gene encoding Duffy antigen/receptor for chemokines.[81] This is a genetic variant, which confers resistance to malarial parasitic infection, but may also partially explain ethnic differences in morbidity associated with asthma. A recent study[82] has revealed the susceptibility to asthma to be associated with polymorphisms in the sialic acid-binding immunoglobulin-like lectin-8 (Siglec-8) gene. Interestingly, it is also thought that even in the urban, the incidence of allergic disorders is higher in high income people than in those with low income.[1] This is attributed to the fact that the rich and high income earning people get access, and consume urban diets. It is also possible that, the allergens in non urban diets (common foods) are favored by unknown urban diet component only accessible by people who are financially well-off to access these diets. Currently, there is increasing amount of processed foods available in supermarkets available only in urban areas at costs that are only affordable by rich or high income families. This signifies the difference in exposure to allergens or possibly allergen-containing foods between rich and poor but also between urban and rural people despite the supposed genetic component. These are the 'urban diets.'

The low prevalence of allergies in rural people may first be attributed to type of food that we may call 'rural diets.' These foods contain variety of natural components that supposedly may have therapeutic values. Some of green vegetables, fruits, and roots consumed by rural people grow naturally in the field. These apparently contain medicinal components (probably anti-IgE) that naturally limit expression of allergic syndromes inadvertently neutralizing the sensitization to development of allergy. Albeit, the mechanisms still needs to be researched in African situation to quantify this supposition. For instance, early consumption of peanuts in infancy has been found to be associated with a low prevalence of peanut allergy.[83] Further reports[40] have revealed that rural Africans living in grasslands, in a traditional accommodation, with traditional dietary practices rarely suffer from allergic diseases. In particular, the shift to healthier food eating habit from traditional foods is said to have increased exposure to food allergens, hence the frequency of reported food allergies.[84–86] For instance, data indicating the prevalence of IgE-mediated allergies and the disease-eliciting allergens in Africa are still insufficient.[87] Most of the information comes from developed countries; even those relating developing countries are too few to reflect the real African situation. There could be other factors such as genetic resistance to allergy in African despite coexistence with allergens, something that necessitates further studies. Secondly, the nature of agricultural activities in rural areas may not contribute to exposure of the population to allergens. Different communities have different storage procedures for their agricultural products. Palyvos et al,[58] for example, reported mites in stored products in Greece. However, it is uncertain whether or not the storage situations in Greece differ with those found in Africa, furthermore, the environment may have impact on disease progression. In addition, the fact that most of infestations (65.3%)[58] is from records of samples in stores of agricultural cooperative unions, further supports the idea of 'urban diets.'[1] This has an implication in that, modification of these products more likely favor perpetuation of allergy-causing allergens. Storage of foods in rural areas at individual level differs with those at co-operative unions and

most likely, local (natural) antimite materials that may be in use by rural farmers might have a protective role toward thriving of allergens. All these factors are still presumptive and are potential areas to be further researched.

Studies by Riedler et al,[88] however, have revealed early exposure to the farming environment and intake of farm milk to have a strong protective effect on allergic manifestation, in particular, the development of asthma, hay fever, and atopic sensitization. The only question is how frequent exposure to farming environment and milk intake should be considered protective? An increased production of IL-10 because of chronic parasitic infection is said to prevent allergic reaction[9] and that genetic variation in IL-10 production is associated with atopic reactivity.[7] This could also explain the low prevalence of allergies in the African population that are also subjected to parasitic diseases, such as helminths and malaria. IL-10 has been shown to be a switching factor that enhances IgG_4 production while inhibiting IgE production, thus reduced incidence of allergy.[89] In our recent study (not related to allergy) that assessed the effect of zinc deficiency on IgG subclasses in malaria infection (Erasto V Mbugi, Gerco den Hartog, Jacobien Veenemans, Raimos M Olomi, John F Shao, Hans Verhoef, Huub FJ Savelkoul, manuscript submitted for publication), high IgG_4 levels were found to be associated with chronic asymptomatic malaria in Tanzanian children of less than 5 years of age. The question is whether zinc deficiency or chronic malaria could be protective against allergic disorders that could mean that asymptomatic malaria is of benefit in Africa and other endemic areas! Experiments from animal models have demonstrated some infections to modulate the expression of the immune system, resulting in the suppression of allergic inflammation.[90] This modulation has been proposed to be through priming of the Tr-cells activity. These cells may be responsible for the protection of populations with chronic infections against atopic diseases.[90] Basing on the 'hygiene hypothesis,' African countries, having a high burden of chronic and persistent infections, could be at merit. Nevertheless, this supposedly an advantage could be abrogated by what seems to be a modern lifestyle from 'the western countries' resulting into increased burden of atopic disorders, thus complicating the situation. Studies should target populations with both a high burden of chronic infections and a high prevalence of environmental allergens, probably involving multiple centers, effectively studying the urban-rural, genetic, and interregional differences[13,90] on allergy susceptibility. A lot still needs to be done on allergy research in Africans since the 'hygiene hypothesis' cannot stand as the only explanation for differences in allergen susceptibility after reports by Steinman et al[43] of dramatic worldwide increases in allergic diseases in both rural and urban Africans.

Advanced Immunologic Research Facilities

Most of limiting factors for research in Africa is the lack of own facilities targeting variety of diseases; both infectious and non infectious, including advanced allergological researches.[87] As a result, relatively few data on allergology in Africa are available. Analysis of allergens sensitization profile have revealed remarkable differences as regards grass pollen and mite allergens between African and European patients, necessitating a component-resolved allergy testing to optimize allergy prevention and therapy in different populations.[91] It is not surprising that cases of allergy may not be reported frequently as reporting of such cases depends on seriousness like any other disease (from experience in Africa). The necessity to educate the general population to understand the importance of allergy and allergens to public health and provision of advanced immunologic facilities in Africa are of critical priority. This idea is however, challenged by the fact that in Africa, we have few immunologists, predominantly studying the immunology of relatively highly infectious diseases namely, HIV/AIDS, malaria, and TB. The host country funding constraints have limited African researchers to deal with genotypes and cytokine secretion patterns studies in international collaboration programs that mainly provide short-term solutions.[87] Training and retaining scientists who will produce research and sound diagnostic tests suited to the African environment will therefore, be a key for sustainable research development in African countries providing ways of solving problems of allergic disorders apart from other striking diseases. Findings from a study by Sibanda[51] have revealed inhalant allergy and general allergies to be common in some African populations. These findings might reflect that more improved immunologic research and diagnostic tools could contribute in increasing awareness of people toward allergic disorders and its health and socioeconomical impacts.

CONCLUSION

The under-reporting of allergic disorders in Africa, has given priority to other highly morbid conditions such as malaria, HIV, and TB. It is probably crucial to search for specific environmental and genetic factors that impact the phenotypes of allergy in African settings. The question remains as to whether research on allergy and allergens should be the current priority in Africa that is flooded with other endemic diseases with higher morbidity and mortality rates. The estimated prevalence of allergic disorders in Africa (Table 1) seems to be almost similar to these diseases although the awareness to its economic burden is not as clear as it is for malaria, TB, and HIV/AIDS. A balanced approach in tackling disease calamities in Africa should be of primary consideration under limited resources.

REFERENCES

1. Obeng BB, Hartgers F, Boakye D, Yazdanbakhsh M. Out of Africa: what can be learned from the studies of allergic disorders in Africa and Africans? *Curr Opin Allergy Clin Immunol.* 2008;8:391–397.
2. Rauter I, Krauth M-T, Westritschnig K, et al. Mast cell-derived proteases control allergic inflammation through cleavage of IgE. *J Allergy Clin Immunol.* 2008;121:197–202.
3. Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss study on air pollution and lung diseases in adults. *Int Arch Allergy Immunol.* 1995;106:149.
4. Linneberg A. Increase in allergy: a global challenge. *Drugs Today (Barc).* 2008;44(Suppl B):5–10.
5. Obihara CC, Marais BJ, Gie RP, et al. The association of prolonged breastfeeding and allergic disease in poor urban children. *Eur Respir J.* 2005;25:970–977.

6. Kamradt T, Goggel R, Erb KJ. Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection. *Trends Immunol.* 2005; 26:260–267.
7. van den Biggelaar AHJ, Hua T-D, Rodrigues LC, Kremsner PG, Yazdanbakhsh M, Kube D. Genetic variation in IL-10 is associated with atopic reactivity in Gabonese schoolchildren. *J Allergy Clin Immunol.* 2007;120:973–975.
8. van den Biggelaar AHJ, Lopuhaa C, van Ree R, et al. The prevalence of parasite infestation and house dust mite sensitization in Gabonese schoolchildren. *Int Arch Allergy Immunol.* 2001;126:231–238.
9. van den Biggelaar AHJ, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. *Lancet.* 2000;356:1723–1727.
10. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science.* 2002;296:490–494.
11. Yazdanbakhsh M, Matricardi PM. Parasites and the Hygiene Hypothesis. *Clin Rev Allergy Immunol.* 2004;26:15–23.
12. Yazdanbakhsh M, van den Biggelaar A, Maizels RM. Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. *Trends Immunol.* 2001;22:372–377.
13. Ndiaye M, Bousquet J. Allergies and parasitoses in sub-Saharan Africa. *Clin Rev Allergy Immunol.* 2004;26:105–114.
14. Obihara CC, Bardin PG. Hygiene hypothesis, allergy and BCG: a dirty mix? *Clin Exp Allergy.* 2008;38:388–392.
15. Obihara CC, Beyers N, Gie RP, et al. Respiratory atopic disease, Ascaris-immunoglobulin E and tuberculin testing in urban South African children. *Clin Exp Allergy.* 2006;36:640–648.
16. Adams JFA, Schölvinck EH, Gie RP, Potter PC, Beyers N, Beyers AD. Decline in total serum IgE after treatment for tuberculosis. *Lancet.* 1999;353:2030–2032.
17. Obihara CC, Beyers N, Gie RP, et al. Inverse association between Mycobacterium tuberculosis infection and atopic rhinitis in children. *Allergy.* 2005;60:1121–1125.
18. Obihara CC, Bollen CW, Beyers N, Kimpen JL. Mycobacterial infection and atopy in childhood: a systematic review. *Pediatr Allergy Immunol.* 2007;18:551–559.
19. Pawankar R, Baena-Cagnani CE, Bousquet J, et al. State of World Allergy Report 2008: allergy and chronic respiratory diseases. *World Allergy Org J.* 2008;1(Suppl):S4–S17.
20. Potter PC, Warner JO, Pawankar R, et al. Recommendations for competency in allergy training for undergraduates qualifying as medical practitioners: a position paper of the World Allergy Organization. *World Allergy Org J.* 2009;2:150–154.
21. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol.* 2007;18:560–565.
22. Motala C. Food Allergy: World Allergy Organization. Available at: http://www.worldallergy.org/public/allergic diseases center/foodallergy/. Accessed March 25, 2010.
23. Potter PC. Inaugural lecture: allergy in southern Africa. *Curr Allergy Clin Immunol.* 2009;22(4):156–161.
24. Madsen C. Prevalence of food allergy/intolerance in Europe. *Environ Toxicol Pharmacol.* 1997;4:163–167.
25. Veien NK, Hattel T, Laurberg G. Low nickel diet: an open prospective trial. *J Am Acad Dermatol.* 1993;29:1002.
26. Veien NK, Hattel T, Laurberg G. Can oral challenge with balsam of Peru predict possible benefit from a low-balsam diet? *Am J Contact Dermat.* 1996;7:84.
27. Mercer MJ, Joubert G, Ehrlich RI, et al. Socioeconomic status and prevalence of allergic rhinitis and atopic eczema symptoms in young adolescents. *Pediatr Allergy Immunol.* 2004;15:234–241.
28. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population: prevalence and main findings. *Cont Dermatitis.* 2010;62:75–87.
29. Auricchio S, Semenza G. *Introduction. Common Food Intolerances 2: Milk in Human Nutrition and Adult-Type Hypolactasia*. Karger: Basel; 1993.
30. Brugman E, Meulmeester JF, Spee-van der Wekke A, Beuker RJ, Radder JJ, Verloove-Vanhorick SP. Prevalence of self-reported food hypersensitivity among school children in The Netherlands. *Eur J Clin Nutr.* 1998;52:577–581.
31. World Health Organization (WHO). *Reducing Risks, Promoting Healthy Life.* Geneva, Switzerland; 2002.
32. Breman JG. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *Am J Trop Med Hyg.* 2001;64:1–11.
33. Moore M, Ewart S. Policy challenges in malaria vaccine introduction. *Am J Trop Med Hyg.* 2004;71(Suppl 2):248–252.
34. Chaisson RE, Martinson NA. Tuberculosis in Africa: combating an HIV-driven crisis. *N Eng J Med.* 2008;358:11.
35. UNAIDS. AIDS Epidemic Update. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArc/2009.
36. UNAIDS. Report on the Global AIDS Epidemic. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2.
37. Estmbale BBA. Parasitic infestation in children. *E Afr Med J.* 2001:277–278.
38. Tohon ZB, Mainassara HB, Garba A, et al. Controlling schistosomiasis: significant decrease of anaemia prevalence one year after a single dose of praziquantel in Nigerien schoolchildren. *PLoS Negl Trop Dis.* 2008; 2:e241.
39. Modjarrad K, Zulu I, Redden DT, Njobvu L, Freedman DO, Vermund SH. Prevalence and predictors of intestinal helminth infections among human immunodeficiency virus type 1-infected adults in an urban African setting. *Am J Trop Med Hyg.* 2005;73:777–782.
40. Potter PC, Davis G, Manjra A, Luyt D. House dust mite allergy in Southern Africa: historical perspective and current status. *Clin Exp Allergy.* 1996;26:132–137.
41. Potter PC. Overview of the indigenous allergens of South Africa. *Curr Allergy Clin Immunol.* 2007;20:174–176.
42. van Niekerk CH, Weinberg EG, Shore SC, Heese HV, van Schalkwyk JD. Prevalence of asthma: a comparative study of urban and rural Xhosa children. *Clin Exp Allergy.* 1979;9:319–324.
43. Steinman HA, Donson H, Kawalski M, Toerien A, Potter PC. Bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children. *Pediatr Allergy Immunol.* 2003;14:383–393.
44. ISAAC. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema. *Lancet.* 1998;351:1225–1232.
45. Nicolaou N, Siddique N, Custovic A. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy.* 2005;60:1357–1360.
46. Report WHO. WHO European Centre for Environment and Health. Effects of air pollution on children's health and development: a review of the evidence. Copenhagen, WHO Regional Office for Europe. Available at: http://www.euro.who.int/document/E86575.pdf. Accessed January 8, 2010.
47. Report WHO. WHO Regional Office for Europe. Health aspects of air pollution: results from the WHO project "systematic review of health aspects of air pollution in Europe." Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark 2004.
48. Marshall GD. Internal and external environmental influences in allergic diseases. *J Am Osteopath Assoc.* 2004;104(Suppl):S1–S6.
49. Weinberg EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol.* 2000;105:224–231.
50. Asmah J, Dawn LL, Siti Arija Mad A, et al. Low prevalence of latex sensitivity in South African spina bifida children in Cape Town. *Pediatr Allergy Immunol.* 2005;16:165–170.
51. Sibanda EN. Inhalant allergies in Zimbabwe: a common problem. *Int Arch Allergy Immunol.* 2003;130:2–9.
52. SAARWG. Allergic rhinitis in South Africa: diagnosis and management. Consensus document: South African Allergic Rhinitis Working Group (SAARWG). *SA Med J.* 1996;86:1315–1328.
53. SAAS. South African Allergy Society. Available at: http://www.allergysa.org/. Accessed March 24, 2010.
54. Gadermaier G, Dedic A, Obermeyer G, Frank S, Himly M, Ferreira F. Biology of weed pollen allergens. *Curr Allergy Asthma Rep.* 2004;4: 391–400.
55. Dagoye D, Bekele Z, Woldemichael K, et al. Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. *Am J Respir Crit Care Med.* 2003;167:1369–1373.
56. Dagoye D, Bekele Z, Woldemichael K, et al. Domestic risk factors for wheeze in urban and rural Ethiopian children. *QJM.* 2004;97:489–498.
57. Van Niekerk CH, Weinberg EG, Shore SC, et al. Prevalence of childhood asthma in Africa. *Lancet.* 1977;309:96–97.

58. Palyvos N, Emmanouel N, Saitanis C. Mites associated with stored products in Greece. *Exp Appl Acarol.* 2008;44:213–226.
59. Butler N. National Guidelines at a glance: allergic rhinitis. *SA Pharmaceutical J.* 2009;76:25–27.
60. Cooper PJ, Barreto ML, Rodrigues LC. Human allergy and geohelminth infections: a review of the literature and a proposed conceptual model to guide the investigation of possible causal associations. *Br Med Bull.* 2006;79–80:203–218.
61. Motala C. New perspectives in the diagnosis of food allergy. *Curr Allergy Clin Immunol.* 2002;15:96–100.
62. Matricardi PM, Rosmini F, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ.* 2000;320:412–417.
63. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol.* 2002;110:381–387.
64. Linneberg A, Østergaard C, Tvede M, et al. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol.* 2003;111:847–853.
65. Araujo MI, de Carvalho EM. Human schistosomiasis decreases immune responses to allergens and clinical manifestations of asthma. *Chem Immunol Allergy.* 2006;90:29–44.
66. Carvalho EM, Bastos LS, Araujo MI. Worms and allergy. *Parasite Immunol.* 2006;28:525–534.
67. Cardoso LS, Oliveira SC, Góes AM, et al. Schistosoma mansoni antigens modulate the allergic response in a murine model of ovalbumin-induced airway inflammation. *Clin Exp Immunol.* 2010. [Epub ahead of print]
68. Araujo MI, Lopes AA, Medeiros M, et al. Inverse association between skin response to aeroallergens and Schistosoma mansoni infection. *Int Arch Allergy Immunol.* 2000;123:145–148.
69. Cooper PJ, Chico ME, Rodrigues LC, et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol.* 2003;111(Suppl 1):995–1000.
70. Lynch NR, Lopez RI, Di Prisco-Fuenmayor MC, et al. Allergic reactivity and socio-economic level in a tropical environment. *Clin Allergy.* 1987;17:199–207.
71. 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. *J Allergy Clin Immunol.* 1993;92:404–411.
72. Scrivener S, Yemaneberhan H, Zebenigus M, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet.* 2001;358:1493–1499.
73. Nyan OA, Walraven GEL, Banya WAS, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. *Clin Exp Allergy.* 2001;31:1672–1678.
74. Cooper PJ. Interactions between helminth parasites and allergy. *Curr Opin Allergy Clin Immunol.* 2009;9:29–37.
75. van der Kleij D, Latz E, Brouwers JFHM, et al. A novel host-parasite lipid cross-talk. Schistosomal lyso-phosphatidylserine activates toll-like receptor 2 and affects immune polarization. *J Biol Chem.* 2002;277:48122–48129.
76. Okano M, Satoskar AR, Nishizaki K, Harn DA Jr. Lacto-N-fucopentaose III found on schitosoma mansoni egg antigens functions as adjuvant for proteins by inducing Th2-type response. *J Immunol.* 2001;167:442–450.
77. Pacifico LGG, Marinho FAV, Fonseca CT, et al. Schistosoma mansoni antigens modulate experimental allergic asthma in a murine model: a major role for CD4+ CD25+ Foxp3+ T cells independent of interleukin-10. *Infect Immun.* 2009;77:98–107.
78. Platts-Mills TAE, Cooper PJ. Differences in asthma between rural and urban communities in South Africa and other developing countries. *J Allergy Clin Immunol.* 2010;125:106–107.
79. Cullinan P. Asthma in African cities. *Thorax.* 1998;53:909–910.
80. Grant AV, Araujo MI, Ponte EV, et al. High heritability but uncertain mode of inheritance for total serum IgE level and schistosoma mansoni infection intensity in a Schistosomiasis-endemic Brazilian population. *J Infect Dis.* 2008;198:1227–1236.
81. Vergara C, Tsai YJ, Grant AV, et al. Gene encoding Duffy antigen/receptor for chemokines is associated with asthma and IgE in three populations. *Am J Respir Crit Care Med.* 2008;178:1017–1022.
82. Gao P-S, Shimizu K, Grant AV, et al. Polymorphisms in the sialic acid-binding immunoglobulin-like lectin-8 (Siglec-8) gene are associated with susceptibility to asthma. *Eur J Hum Genet.* 2010. [Epub ahead of print].
83. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol.* 2008;122:984–991.
84. Jeebhay MF. Occupational allergy and asthma among food processing workers in South Africa. *African Newsletter.* 2002;12:59–62.
85. Jeebhay MF, Robins TG, Lehrer SB, Lopata AL. Occupational seafood allergy: a review. *Occup Environ Med.* 2001;58:553–562.
86. Lopata AL, Jeebhay MF. Allergy and asthma to indigenous seafood species in South Africa. *Curr Allergy Clin Immunol.* 2007;20:196–200.
87. Sibanda EN. Research and clinical aspects of immunology in Africa. *Curr Opin Immunol.* 2001;13:528–532.
88. Riedler J, Braun-Fahrländer C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet.* 2001;358:1129–1133.
89. Jeannin P, Lecoanet S, Delneste Y, Gauchat J-F, Bonnefoy J-Y. IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol.* 1998;160:3555–3561.
90. Obihara CC. Infection and atopic disease burden in African countries: key to solving the 'hygiene hypothesis'? *Curr Allergy Clin Immunol.* 2007;20:178–183.
91. Westritschnig K, Sibanda E, Thomas W, et al. Analysis of the sensitization profile towards allergens in central Africa. *Clin Exp Allergy.* 2003;33:22–27.

