

Review article

Allergic disorders in African countries: linking immunology to accurate phenotype

Identification and characterization of risk and protective factors for allergy is important for developing strategies for prevention or treatment. The prevalence of allergy is clearly higher in affluent countries than in developing countries like, e.g. Africa. Especially in urban areas of developing countries, allergy is however on the increase. In Africa, we have the unique opportunity to investigate risk and protective factors and the influence of urbanization and westernization, i.e. almost to take a look at Europe, Australia or the USA as they were before their allergy epidemics. Moreover, migrants from developing to affluent countries experiencing an increased burden of allergy provide new insights into risk and protective factors. Allergen exposure, diet and infections are the major exogenous influences playing a role as risk and protective factors. Depending on the nature, timing, chronicity and level of exposure, each of them can promote or inhibit allergy. Perhaps with the exception of infections, availability of data from Africa on their role in the development of allergy is limited. Detailed epidemiological studies in rural and urban Africa combined with basic immunological research are needed to unravel mechanisms of increase in allergy and of protection. The maturation of the immune system at young age under influence of exogenous factors results in differences in T-cell-skewing (Th1/Th2/Treg) and humoral responses. It is essential to perform studies from a 'non-Eurocentric' angle (e.g. local allergens, locally validated questionnaires and diagnostic procedures). Such studies will provide the affluent countries with new leads to combat the allergy epidemic and more importantly help prevent it in Africa.

R. van Ree¹, M. Yazdanbakhsh²

¹Department of Experimental Immunology, Academic Medical Center, Amsterdam, the Netherlands; ²Department of Parasitology, Leiden University Medical Center, Leiden, the Netherlands

Dr Ronald van Ree
Department of Experimental Immunology
Academic Medical Center
Amsterdam
the Netherlands

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A steady increase over the past decades has resulted in an estimated 40% of the population in high-income countries being allergic. The prevalence of allergic disorders is not uniform across the globe as indicated by the International Study of Asthma and Allergies in Childhood (ISAAC), which started to investigate the scale of the allergic problem worldwide and the factors affecting it (1). By using uniform questionnaires, dispensed in 56 countries, it was concluded that prevalence of allergies is high in high-income countries but lower in many of the so-called developing countries (2). Among these, African countries such as Kenya (13.9%), Morocco (7.8%), Nigeria (10.7%), South Africa (16.1%) and Algeria (5.9%) have self-reported asthma in the past 12 months, which was consistently lower than prevalences obtained from countries such as the UK (18.4%), New Zealand (29.7%), Ireland (31%) or USA (22.9%). From the most recent ISAAC reports, the time trends in the prevalence of allergic symptoms, indicate an increase for most of these African centres (3). Interestingly, in countries in Latin America, particularly those in the Eastern regions, which in phase I ISAAC study showed relatively high prevalences of allergic disorders, the time trends indicate either no change

or even a decrease in prevalence of asthma symptoms (3). That the situation is complex is indicated from the data on developing countries in Asia-Pacific where despite relatively low prevalences of asthma in phase I, there are not only increases but also decreases in prevalence of asthma symptoms in phase III studies of ISAAC. The main aim of such worldwide studies is to determine the burden of the disease to allow appropriate allocation of national funds towards prevention and cure of allergic disorders. These studies can also help to clarify risk and protective factors that lead to variation in development and expression of allergic disorders. A complete understanding of the factors that lead to the lower prevalence of allergies in some geographical areas and to the time trends observed will help us design strategies to prevent any future increase in allergic disorders worldwide.

Risk and protective factors

The major exogenous risk and protective factors are allergens, pollution, diet and infections (Fig. 1).

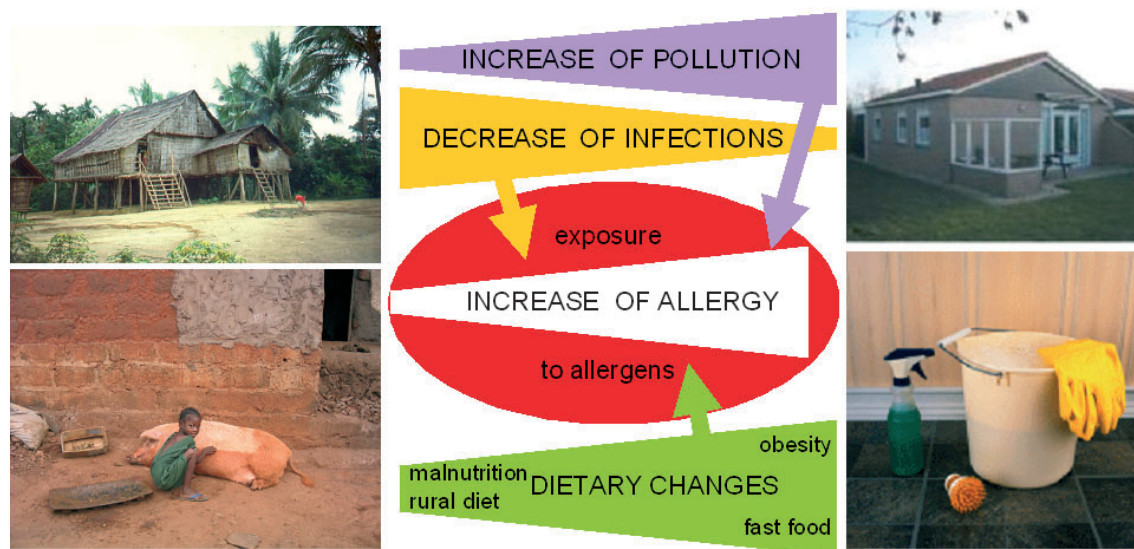


Figure 1. Exogenous factors involved in development of allergy. Exposure to allergen is the prime risk factor for the development of allergy occurring in rural Africa, urban Africa and affluent countries. This exposure however occurs in the context of different levels of pollution, of infections and of significant dietary changes.

Allergens

Exposure to allergens is the prime risk factor for the development of allergic diseases (4). The original concept, however, of a straightforward positive correlation between the level of exposure and the risk of developing allergy has (partly) been refuted. As regards cat allergy for example, a bell-shaped relationship between exposure levels and the development of sensitization and allergy was found. Increasing levels of Fel d 1 were linked to an increased risk of sensitization, but above a certain threshold, exposure to Fel d 1 turned into a protective factor (5). For house dust mite and pollen such a relationship has not (yet) been demonstrated. Possibly, house dust mite and pollen allergens simply do not reach levels of exposure that protect. Alternatively, exposure to other factors, e.g. endotoxin accompanying pet allergen exposure, forms the basis for the protective effect (6). Despite the fact that certain levels of allergens may prove to be protective, allergen exposure is still a major risk factor for the development of allergy. In the absence of allergens, no allergy develops (7–9), and above an allergen-specific threshold, the risk of sensitization increases in parallel with exposure. It therefore remains important to measure allergens in the environment. This will allow establishing dose–response relationships between exposures on the one hand and sensitization and clinical allergy on the other hand. Moreover, in Africa, where allergen-specific serum IgE levels are frequently poor predictors for clinical allergy, it is important to establish whether there is a correlation between allergen exposure and sensitization. In other words, ‘does environmental exposure to common aero-allergens explain sensitization?’ or ‘do we need to search for alternative

explanations, e.g. IgE antibodies against parasite antigens that cross-react with allergens?’ Data regarding indoor allergen exposure were reported in a very limited number of studies in Africa. A study in Tanzania, on the relationship between perinatal exposure to Der p 1 and Fel d 1, found no association between exposure levels and wheezing (10). This study was performed among newborns that were followed up to 4 years of age. A survey in Ghana among schoolchildren (9–16 years) with and without asthma reported indoor levels of Der p 1, Der f 1, Can f 1, Fel d 1 and Bla g 2 (11). Combined Der p 1 and Der f 1 levels were higher in homes of asthmatics than of healthy children. Sensitization to mite (and to a lesser extent to cockroach) was a strong risk factor for asthma (10.4 for mite and 4.9 for cockroach). Pet allergens (Fel d 1 and Can f 1) were much lower than observed in British homes although pet ownership is equally common (12). This was explained by the fact that cats and dogs live much more outdoors in Ghana. Finally, in Ethiopia, Der p 1 levels were studied in relationship to wheeze (13). Again a significant association was found. All these studies were performed with allergens that were originally identified as risk factors in developed countries. *Dermatophagoides pteronyssinus* and *D. farinae* are also part of the indoor environment of African homes, and Fel d 1 and Can f 1 are allergens of cats and dogs independent of whether they live in Europe, USA or Africa. Very limited information is available about the local mite species. Two smaller Egyptian studies provided evidence that it is worthwhile exploring local differences (14, 15). In some environments, non-pyroglyphid mites were shown to be the dominant species (15). Assays to specifically address exposure to local mite species are therefore needed. Pollen flight data are not as

easily accessible for Africa as for Europe, although studies on sensitization to grass pollen from South Africa have clearly demonstrated that local grasses play an important role (16–18). Overall, more attention is needed to identify local sources of allergen exposure and to the development of assays for measurement of these allergens.

Pollution

Outdoor air pollution has been studied extensively as a potential risk factor for (exacerbations of) asthma and to a lesser extent of rhino-conjunctivitis. High levels of traffic-related emissions have indeed been correlated to increased prevalence of respiratory allergies (19, 20). Various factors like NO_x, CO, SO₂, O₃, and PM₁₀, PM_{2.5} or more general diesel exhaust have been implicated. Diesel particles have been shown to interact with pollen allergens and increase their allergenicity (20). Hardly any study has looked at the role of outdoor air pollution in the development of allergic diseases in Africa. To the best of our knowledge, in the past 5 years only one report from Africa was published that specifically focused on air pollution, i.e. on the proximity of homes to roads and the risk of wheeze in an Ethiopian population (21). Although the effects were minimal (OR 1.17; 95% CI: 1.01–1.36), living within 150 m of the nearest road was a risk factor for the development of wheeze. The intensity of traffic also contributed, with a slightly higher risk of wheeze (OR 1.26; 95% CI: 1.03–1.53) when traffic was above median flow. Various forms of indoor air pollution, like (passive) smoking and domestic fuel use, have also been implicated as risk factors for respiratory allergies. Although exposure to tobacco smoke is generally accepted as a risk factor (22), results from studies among African populations are limited and inconclusive (23–26). A report from Ethiopia has revealed that changing to more modern sources of domestic fuel (cooking on kerosene) increases the risk of sensitization and allergic symptoms (27).

Diet

There is no doubt that diet plays a role in the development of atopy, allergy and asthma, sometimes as a risk factor, sometimes as a protective factor. Prolonged breast feeding (at least 4–6 months) is generally accepted as a protective factor, although there are conflicting reports (28, 29). Two excellent recent reviews have focused on the role of diet in the development of allergy and asthma (30, 31). Risk factors essentially fall into two categories, i.e. decreased intake of antioxidants (such as vitamin C, vitamin E, selenium, α -carotene, β -carotene and β -cryptoxanthin) as a result of decreased intake of fresh fruit and vegetables (32), and an increased ratio in the diet of omega-6 (margarine/vegetable oils)/omega-3 (oily fish) polyunsaturated fatty acids (n-6 PUFA/n-3 PUFA). A more general diet-related risk factor for the development of asthma is obesity (33).

Obviously, most of these factors potentially play a role in explaining the difference in allergy and asthma prevalence between Africa and the affluent industrialized world. For many of the factors listed, Africa is on the opposite side of the spectrum compared with Europe, the USA or Australia. To the best of our knowledge, there are however no published studies that have focused on the role of diet in the development of allergy and asthma from African countries. Such studies would certainly help us identify and to further characterize protective factors against these diseases that have become such an epidemic in westernized societies.

Infections

Ecological analysis of the data collected during the phase I of ISAAC, has indicated that variables such as Gross National Product (34), diet (35) and pollen (36) among others might influence the worldwide geographical variations in allergic disorders. One of the most controversial factors that has been linked to the development of allergies has been infections. Not only within the ISAAC data (37) but also data from other studies (38–47) have proposed that exposure to some micro-organisms and parasites or products thereof might protect from the development of allergic disorders.

The European studies that have indicated that there are considerable differences in prevalence of allergies in those living in traditional farms in Germany, Austria and Switzerland have lend strong support to the hypothesis that early exposure to environments which would be expected to have high microbial loads, can be protective against the development of allergic disorders (47). Furthermore, the findings that endotoxin levels in farming environment was protective against sensitization and allergic asthma, irrespective of allergen load, indicated that indeed, exposure to microbial products can prevent sensitization and progress to allergic disease (6).

However, it is clear that not all infections are protective (40). There have been consistent reports that respiratory syncycial virus (RSV) infections are associated with increased risk of asthma (48). Moreover, the relationship between infections and allergic disorders may be complex in terms of infection intensity or time of exposure to infection. For example, whereas chronic heavy infections with parasitic helminths have been reported to decrease the risk of being atopic (42–44, 49, 50), light and acute infections might increase the risk of developing an allergic disorder (51–55).

An important aspect of studying the relationship between infections and allergic disorders is to understand the immunological mechanisms that underlie the observed associations. This knowledge can lead to better understanding of how allergic diseases develop and how they can be prevented and/or cured. Therefore, studies are needed that can link changes in the exposures to infections and their effect on the development of the immune system as well as the development of allergic

diseases. Many researchers have become interested in investigating these links in developing countries as well as in migrants from developing countries who start a new life in Europe, Australia/New Zealand or in North America. These studies have the potential to identify risk and protective factors that are associated with allergic disorders worldwide.

Migrant studies

The prevalence of allergic diseases like rhinitis and asthma is influenced by genetic background and by environmental and lifestyle factors. The study of populations from different ethnic origin offers the possibility to address the role of both factors in the expression of the allergic phenotype. Migrant populations are of particular interest for such investigations. Comparison of indigenous and migrant populations living in the same environment can potentially unravel genetic differences that may be responsible for the development of allergies. However, as migrants usually hold on to major elements of their culture and lifestyle in their new environment, it is not always easy to determine whether genetics, lifestyle or a combination of both is the responsible factor. Comparison of migrants with the population in their country of origin can shed light on the role of changes in the environment and lifestyle in development of allergy. These changes can relate to exposure to pollution, allergens, infections, housing conditions, access to health care and diet. Again, however, it cannot be ruled out that differences in genotype only become apparent in a measured phenotype upon change in environment or lifestyle. A recent review on atopy and asthma in migrants gives an excellent overview of epidemiological studies carried out until 2003 (56).

Since then, a few more studies have been published that focus on allergy and migration (57–61). Only a limited number of studies specifically deal with immigrants from Africa (58, 62–64). African emigrants studied in most detail are Ethiopian Jews who moved to Israel (58, 63, 64). The general picture emerging from all migrant studies is that moving from developing countries to affluent industrialized countries results in increased prevalence of allergy and asthma (56). This increase is time-dependent in two ways. It correlates with the duration of the stay in the new country (57, 65–70) and is influenced by the age of the immigrant at time of entry into his/her new country (68, 71). Several surveys have demonstrated that among immigrants the prevalence of allergic diseases like hay fever and asthma is higher than in the indigenous population (59, 60, 62, 64, 68, 72–75). This can point towards genetic predisposition that only becomes apparent upon an altered environment. Another explanation could be that immigrants have been immunologically primed for development of allergy in their country of birth but environment and lifestyle prevented its expression.

Interestingly, several studies have shown that total IgE levels are elevated at the time of immigration compared with the resident population, but that these levels subsequently decrease towards 'local levels' (58, 66–68). In parallel, specific IgE levels to local allergens increase, sometimes to levels higher than those observed in the resident population (74). High total IgE is most likely caused by high incidence of parasitic infections in the country of origin of the migrant. Upon anti-parasitic treatment and removal of the source of infection, IgE titres decline (58). Perhaps early-life infections with for example parasitic helminths have primed the immune system for development of IgE responses, subsequently leading to higher prevalence of allergy in immigrants compared with the local population. With increasing numbers of immigrants in Europe, it would be highly informative to start prospective studies that would allow us to understand how genetic and environmental risk and protective factors play a role in the development of allergic disorders.

Complications of studies in developing countries: the allergic phenotype

Although studies of allergic disorders in migrant populations rely upon standard medical and laboratory diagnostic methods that are well developed and validated in western centers, the characterization of populations residing in developing countries can be problematic.

Clinical diagnosis

One of the most challenging issues facing researchers in developing countries is the diagnosis of allergic disorders. In many epidemiological studies, the diagnosis of allergy (rhinitis, asthma and eczema) is based on the use of questionnaires. The most widely used standardized questionnaire originates from the International Study of Asthma and Allergies in Children (ISAAC) (2). Although this questionnaire has been validated in several different ethnic and cultural settings, and was mostly judged to be adequate for distinguishing cases from controls (2, 76–85), validation was not carried out for many African populations. Even if the questionnaires are translated and back-translated in each country, they are highly sensitive to the cultural and socioeconomic background of the study population tested. This is particularly important in developing countries where there is great variation in socioeconomic status and also enormous variation in ethnic groups and therefore local cultures and languages. In a study establishing the prevalence of eczema in Ethiopian children, the conclusion was that the ISAAC questionnaire did not perform particularly well (84). Studies performed in Korea and China similarly reported poor performance of translated ISAAC questionnaires. (82, 83). For validation of questionnaires and confirmation of questionnaire-derived prevalence data for asthma and

rhinitis, application of other diagnostic tests is therefore essential. *In vivo* techniques to diagnose asthma-like measurement of peak expiratory flow (PEF), forced expiratory volume in 1 s (FEV₁), forced vital capacity (FCV) and exercise-induced bronchospasm (EIB) have been used in several epidemiological studies in Africa (86–95). Many of these studies follow protocols and guidelines established by the European Respiratory Society or the American Thoracic Society. There is however a need to determine whether reference values of healthy populations from affluent industrialized countries are valid for other ethnic groups or socioeconomic backgrounds (96).

Another factor that complicates the diagnosis of allergic disorders in areas where exposure to infectious agents is high, is the accuracy of diagnosis. Wheeze in developing countries can often result from infections, while itchy runny nose or itchy skin rash might be caused by viral, bacterial or fungal infections that are highly prevalent in developing countries. Moreover, while developing countries have many specialists dealing with infectious diseases, there are very few specialists in allergic disorders. It is therefore extremely important to consider data generated by questionnaire-based studies with caution before conclusions are drawn.

SPT

In western countries, the skin-prick test (SPT) has a relatively high predictive value for clinical allergy. The so-called percentage of asthma cases attributable to SPT positivity in children in industrialized countries ranged from 30% to 57% (97), whereas this in Indonesia was up to 15% (S. Wahyuni, M. Yazdanbakhsh, unpublished data). Several issues need to be considered when addressing SPT positivity data in global epidemiological studies. The well-known individual variation amongst performers of the test has always been an important concern and the test although simple, is prone to variation when different individuals are involved in performing the test (98, 99). Therefore it is of utmost importance to standardize and ensure uniformity when studies are set up (<http://www.glofal.org>; accessed 23 January 2006). Another important, yet unexplored factor, is the absence of standard reference values in order to determine a positive reaction. This is not only to an allergen but also to the positive control, histamine and the negative control, the diluent. The question of whether there are racial differences in skin thickness or reactivity to histamine has not been studied in much detail and might influence outcomes of SPTs. Finally, as for other tests, the source of allergen could play a major role in SPT. The issue of local allergens is not always addressed sufficiently and needs attention.

IgE levels

One of the most important complicating factors in using IgE antibodies as diagnostic markers of allergic diseases in

developing countries is the fact that helminth infections can be prevalent in these areas, leading to strong amplification of the IgE responses. Total IgE levels are extremely high in developing countries, especially in rural areas. Moreover, it is possible that due to cross-reactivity between environmental allergens and parasitic antigens, high levels of allergen-specific IgE are found. One of the concerns for the use of serum IgE testing as a diagnostic tool, is that allergen-specific IgE in parasitized children is often not accompanied by a positive SPT (44). This is in contrast to the findings in western countries where positive IgE to house dust mite could lead to 20 times higher risk of having a positive SPT compared with six times in children in Gabon (J.S. van der Zee, A. van den Biggelaar, M. Yazdanbakhsh, unpublished observations). Assessing biological activity by *in vitro* basophil histamine release instead of SPT offers the possibility to cover a broader dynamic range of allergen concentrations. Preliminary experiments have demonstrated that biological activity of allergen-specific IgE of children with chronic helminth infections is only observed at extremely high allergen concentrations (R. van Ree, A. van den Biggelaar, M. Yazdanbakhsh, unpublished data). This points towards decreased avidity of the interaction between allergen and IgE. It is important to assess normal IgE values linked to clinical allergy, i.e. to determine the right cut-off values from large-scale population studies in rural and urban areas in Africa, in parasitized and in non-parasitized children. Investigations into the role of avidity in the biological activity (and therefore clinical relevance) of allergen- (and parasite-) specific IgE antibodies are needed to explain the lack of concordance between serology and SPT.

The issue of immunological profiles associated with allergic disorders in developing countries

The maturation of the immune system

The immaturity of the immune system at birth and the subsequent development of immune competence during postnatal and early childhood years is a well-recognized phenomenon. The percentage of naïve T cells at birth is high in cord blood, and decreases with increasing age. After birth, the increasing exposure to exogenous antigens, results in this increasing maturation of the immune system. It has been shown that the neonatal antigen-presenting cells are deficient in major histocompatibility complex (MHC) upregulation (100), responses to certain Toll-like receptors (101) as well as IL-12 production (102). A deficiency in interferon (IFN)- γ production by neonatal T cells has also been reported and this defect has been attributed to the hyper-methylation status of the IFN- γ locus (103).

The proper maturation of the immune system has been thought to lead to a well balanced Th1, Th2 and Treg responses that can be promptly upregulated to for example combat infections and downregulated to resolve

and contain inflammation. Exposure to infections might play a crucial role in the development of the immune system as recently demonstrated in a number of elegant studies in germ-free animal models (104–106). Therefore, it is plausible that our immune system should receive sufficient input not only from a plethora of bacteria in the gut but also from micro-organisms and parasites in the environment that reaches other mucosal surfaces of the body. In geographical areas where exposure to micro-organisms and parasites is high not only after birth but even possibly during the *in utero* period of life, the immune system could develop differently compared with when such exposures are few. This differential development of the immune system can have important consequences for the expression of inflammatory responses and subsequent diseases.

Th1 vs Th2 and then again vs Treg

In western countries where the increase in allergic disorders has been observed, the hypothesis was put forward that allergic responses might result from a faulty maturation of the immune system. It was presumed that the decrease in exposure to bacterial and viral infections might follow lead to a slower development of Th1-adaptive responses, allowing pro-allergic Th2 responses to develop unhindered (107–109). The birth cohort studies in Australia supported the notion that a slow-developing Th1 response could indeed be responsible for increased susceptibility to allergic disorders (110).

The distorted balance between Th1 and Th2 becomes interesting when considering developing countries and in particular rural areas in these countries where infections leading to Th2-type responses are highly prevalent. The parasitic helminths, are the strongest natural stimuli for the development of Th2 responses characterized by IL-4, IL-5 and IL-13 secretion from T cells and resultant increased IgE antibodies and eosinophils in peripheral blood (111). Importantly, these infections when present during pregnancy can affect the immune response of the foetus. Increased Th2 responses have been measured in neonates born to mothers with parasitic helminths such as schistosomes or filariae (112). However, formal studies are needed to establish the relative development of Th1 and Th2 responses in infancy and early childhood in areas where not only helminth infections, but also other infections, are highly prevalent. These are areas of particular interest because of low prevalence of allergic disorders (54, 113). Studies carried out in areas where helminth infections are highly prevalent have indicated that such Th2-inducing infections might actually reduce the risk of developing atopy or allergic diseases (114). However, not all helminth infections play a protective role and density and/or chronicity of infection might be important in whether allergic diseases are suppressed or exacerbated (53, 54). The question how a Th2-inducing infection might be associated with decreased risk of atopy

has not received a definitive answer. As discussed earlier, the property of the IgE generated during such infections might be different such that no mast cell degranulation occurs when these antibodies present on mast cells see an allergen. Another possibility is that one of the important properties of helminth infections, namely their capacity to induce regulatory responses (115), is responsible for suppression of the effector phase of the allergic response (113). In immuno-epidemiological studies, it has been shown that there might be a link between increased parasite-induced IL-10 production and decreased risk of being atopic to an aeroallergen (44). Although human studies are complicated by confounders that cannot be controlled fully, animal models have recently confirmed the protective role of regulatory immune responses in allergic airway inflammation (116).

Little is known about the emerging concept that regulatory immune cells might be an important component of the so-called ‘maturing immune system’. Thus not only Th1 or Th2 but also regulatory T cells might also need to mature as part of a well-balanced adaptive immune system. Such cells will then ensure that there is no overshoot of Th1 or Th2 responses during childhood. They will ensure that any inflammation resulting from an insult on a pathogen is kept under control, and does not lead to tissue damage or organ failure expected to result from an uncontrolled polarized immune response. The concept that the regulatory immune system will have to mature for a well-balanced response during childhood or even adulthood, is

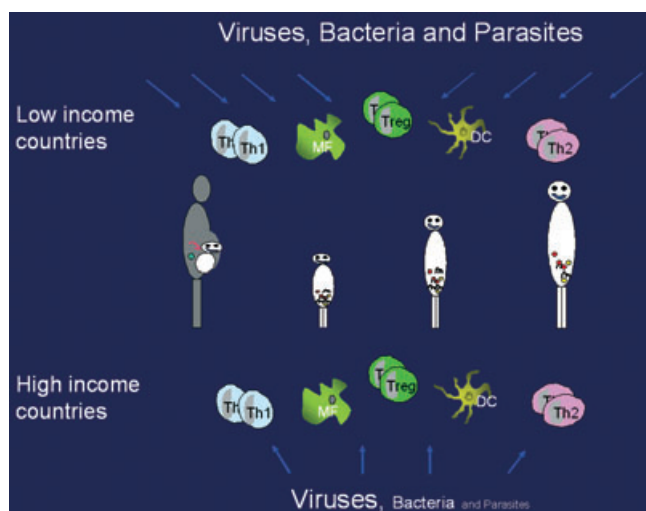


Figure 2. Maturation and development of the immune system under influence of pathogens. Exposure to viruses, bacteria and parasites has great impact on the developing immune system. Exposure to pathogens is different between affluent and developing countries. Bacterial infections and in particular chronic parasite infections are far less common in affluent societies leading to a different maturation of the immune system, i.e. of DCs, Th1 and Th2 cells, regulatory T-cells and macrophages.

a useful unifying paradigm that would help us point towards dysregulation of the immune system as the culprit in the increase of not only Th2-type allergic diseases but also in the increase of Th1-mediated diseases (117).

Concluding remarks

The study of allergy and asthma in African countries (and other developing countries) is of great importance for the

population of this continent. Westernization of lifestyle, in particular in urban Africa, leads to increased burden of allergic diseases, possibly even more dramatic than has been observed in Europe, Australia or the USA, because parasite infections have primed the immune system for IgE responses (Fig. 2). Detailed know-how of the underlying immune-mechanisms of the increase in allergy will help prevent new epidemics. Last but not least, studies in Africa will generate the know-how that will help combat the allergy epidemic in the developed world.

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