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CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF ALLERGIC RHINITIS IN KINSHASA (DEMOCRATIC REPUBLIC OF CONGO)

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Summary

Background

Allergic rhinitis (AR) is a common disorder, which causes a considerable burden both on individual patients and society, particularly in large cities where air pollution is the substantial problem causing respiratory diseases. AR constitutes a worldwide public health problem. However, little is known about allergic diseases in Africa because of a lack of data and resources and by the difficulty, or even absence of diagnostic tools in sub-Saharan Africa.

Objective

The present PhD project aimed to study epidemiology and clinical characteristics of AR and associated diseases in both urban and rural areas of Kinshasa, and to assess the risk factors and allergen sources in order to improve the disease management.

Methods

The present work was done by combining studies in the general population, among patients presenting with nasal symptoms and among individuals exposed to flour dust in comparison to the controls.

The first cross-sectional clustered survey was done from February to May 2010 on inhabitants of 8 health zones randomly selected in Kinshasa. A total of 1412 individuals (aged from 5-83 year-old) were interviewed and 1005 of them skin tested.

The second cross-sectional study enrolled 423 consecutive outpatients presenting (January-May 2009) with nasal symptoms related to rhinitis/rhinosinusitis at the ENT services of Kinshasa. Patients were face-to-face interviewed and skin tested.

The last study was conducted from April to August 2012 among 809 consecutive individuals: 263 workers directly exposed to flour dust, 278 indirectly exposed to wheat flour and 268 controls. Individuals were questioned and skin prick tests (SPT), nasal and pulmonary parameters were assessed.

Results

In the general population, 62% of respondents reported at least one disease in the 12 previous months. The 12-month prevalence of rhinitis, rhinoconjunctivitis, wheezing and skin itch-rash symptoms was of 30.8%, 24.4%, 15.4% and 6.2% respectively. Rhinoconjunctivitis and wheezing were significantly more prevalent in urban individuals, while skin itch-rash was significantly more prevalent in rural individuals. Although not statistically significant, rhinitis seemed more prevalent in urban than in rural areas. Twenty three percent of individuals showed positive SPT results with dermatophagoides pteronyssinus (DPT) and cockroach being the most prevalent allergens. AR and non-allergic rhinitis prevalence was of 13.9% and 27.9% respectively. 59.7% and 48.0% of AR individuals expressed moderate to severe and persistent symptoms respectively. In multivariate analysis having any diseases were associated with active smoking, presence of cockroach in the home, history of atopy among siblings, personal history of atopy, using a straw or herbs mattress and positive SPT responses.

The study of rhinologic patients highlighted that about one third of patients had positive SPT results, with 40.9% of these showing polysensitization. DPT and cockroach were the most common allergens among sensitized patients. Persistent and moderate/severe AR represented 61.4% and 69.3% respectively. Sensitization was indenpendently associated with younger age, rhinoconjunctivitis in the past and reaction to non-specific triggers factors.

The results of individuals exposed to flour dust revealed that, the 12-months prevalence of rhinitis, rhinoconjunctivitis, wheezing and nocturnal cough was of 46.0%, 15.8%, 10.6% and 7.5% respectively among all respondents. Compared to the controls, rhinitis, rhinoconjunctivitis and nocturnal cough were significantly more prevalent in workers directly exposed to flour dust. 37.5% of all respondents showed positive SPT results with DPT and cockroaches being the most prevalent allergens. Sensitization to storage mite was found more prevalent among workers directly exposed than controls, while positive SPT to pollen mix, sunflower pollen and crab were more prevalent in the control group.

In multivariate analysis, belonging to the directly exposed group and the presence of a flour mill in the neighborhood significantly increased the risk of having airway disease. Mice in the house increased the risk of both sensitization and airway diseases.

Conclusion

The present work revealed a high prevalence of allergic diseases in Kinshasa, especially in urban areas compared to rural parts. A substantial portion of the population and patients showed sensitization to at least one allergen. DPT and cockroaches constituted the most prevalent allergen sources. Allergic diseases were associated with many factors. It is important to increase awareness toward allergic disorders and to ensure adequate management and prevention.

Keys words: prevalence, rhinitis, rhinoconjunctivitis, wheezing, itch-rash, sensitization, flour dust, Kinshasa.

Samenvatting

Achtergrond informatie

Allergische rhinitis (AR) is een frequent voorkomende aandoening die een aanzienlijke last met zich meebrengt voor zowel de patiënt als de samenleving, en dit vooral in steden waar luchtvervuiling aan de basis ligt van respiratoire aandoeningen. AR wordt daarom als een wereldwijd gezondheidsprobleem beschouwd. Een groot deel van de getroffen populatie is echter afkomstig van ontwikkelingslanden. In deze regio's, met focus op Sub Saharisch Afrika, zijn er weinig gegevens bekend over allergische aandoeningen gezien het ontbreken van juiste diagnostische methodes.

Objectief

De doelstellingen van het vooropgestelde project zijn zowel inzichten verschaffen in de epidemiologische en klinische karakterisatie van AR en allergische aandoeningen in stedelijke en landelijke regio's van Kinshasa, als een evaluatie van de risicofactoren en allergenen met als doelstelling een verbetering in het ziekte management.

Methoden

Verschillende studies werden uitgevoerd bij patiënten met nasale symptomen en bij individuen die blootgesteld werden aan meelmijt. Deze werden vergeleken met controle individuen. De eerste cross-sectionele cluster analyse werd uitgevoerd van februari tot mei 2010 in 8 willekeurig gekozen zones in Kinshasa. In totaal werden 1412 individuen (leeftijd 5-83 jaar) geïnterviewd en bij 1005 personen werden huid priktesten afgenomen.

De tweede cross-sectionele studie omvatte 423 patiënten met rhinitis/rhinosinusisitis gerelateerde nasale symptomen, gerekruteerd gedurende januari-mei 2009 op de afdeling Neus, Keel, Oorziekten in Kinshasa. Alle patiënten werden persoonlijk geïnterviewd en bij elke patiënt werd een huid priktest afgenomen.

In de laatste studie werden 809 individuen, waarvan 263 werknemers die direct blootgesteld waren aan meelmijt, 278 indirect blootgestelde werknemers en 268 controles gerekruteerd van april tot augustus 2012. Alle individuen werden geïnterviewd alvorens er huidtesten afgenomen werden. Nasale en pulmonaire parameters werden gemeten bij alle patiënten.

Resultaten

De gegevens verkregen van de generale populatie toonde aan dat 62% van de responders ten minste 1 allergisch symptoom in de laatste 12 maanden rapporteerden. De prevalentie van rhinitis, rhinoconjunctivitis, piepende ademhaling, huid uitslag en jeuk was 30.8%, 24.4%,15.4% en 6.2% respectievelijk na 12 maanden. Rhinoconjunctivitis en piepende ademhaling waren significant meer aanwezig in stedelijke gebieden, terwijl huid uitslag en jeuk significant meer aanwezig was in landelijke gebieden. Er was een trend tot hogere prevalentie van rhinitis in landelijke gebieden, hoewel dit niet significant verhoogd was. Positieve huidtesten voor huisstofmijt en kakkerlak werden gediagnosticeerd bij 23% van de gescreende individuen. AR en niet-allergische rhinitis vertoonden een prevalentie van 13.9 en 27.9% respectievelijk. Gemiddeld tot ernstige en persisterende symptomen werden aangetroffen bij 59.7% en 48.0%. Multivariaat analyse toonde aan dat allergische aandoeningen geassocieerd waren met actief roken, aanwezigheid van kakkerlakken in huis, historie van atopische tweelingen, persoonlijke geschiedenis van atopie, gebruik van matrassen van stro en positieve huidtesten.

De studie bij rhinologische patiënten toonde aan dat ongeveer 30% van de patiënten een positieve huidtest vertoonden, waarvan 40.9% van deze patiënten gesensitiseerd waren voor meerdere allergenen. Huisstofmijt en kakkerlak waren de meest voorkomende allergieën bij gesensitiseerde patiënten. Persisterende en gemiddeld tot ernstige AR vertegenwoordigden 61.4% en 69.3% respectievelijk. Sensitisatie was onafhankelijk geassocieerd met een jonge leeftijd, rhinoconjunctivitis en reactie op niet-specifieke triggers.

Individuen blootgesteld aan meelmijt hadden een prevalentie voor rhinitis, rhinoconjunctivitis, piepende ademhaling, nachtelijke hoestbuien van 46.0%, 15.8%, 10.6% en 7.5% respectievelijk na 12 maanden. Ter vergelijking met de controles, was er een significante toename van rhinitis, rhinoconjunctivitis en nachtelijke hoestbuien bij werknemers direct blootgesteld aan de meelmijt. Van alle responders vertoonden 37.5% een positieve huidtest voor huisstofmijt en kakkerlak, wat deze de meest voorkomende allergieën maakte. Huisstofmijt allergie was significant meer aanwezig bij direct blootgestelde werknemers in tegenstelling tot controles waar een mix van pollen, zonnebloem pollen en krab frequenter aanwezig was. Multivariaat analyse bij direct blootgestelde werknemers en de aanwezigheid van meelfabrieken in de omgeving, verhoogde significant het risico op luchtwegaandoeningen. De aanwezigheid van muizen in huis verhoogt het risico op zowel sensitisatie als allergische aandoeningen.

Conclusie

Met dit project is aangetoond dat er een hoge prevalentie van allergische aandoeningen is in Kinshasa, meer specifiek in stedelijke gebieden vergeleken met landelijke regio's. Een merendeel van de populatie en patiënten vertoonden sensitisatie voor ten minste één allergeen. De belangrijkste bron voor allergenen werd gevonden bij huisstofmijt en kakkerlak. Allergische aandoeningen worden geassocieerd met verschillende factoren. Het is daarom van belang om meer aandacht te besteden aan de preventie van allergische aandoeningen om zo adequate behandeling en opvolging van de allergieën te verzekeren.

Sleutelwoorden: prevalentie, rhinitis, rhinoconjunctivitis, piepende ademhaling, jeuk-uitslag, sensitisatie, stofmeel, Kinshasa.

For I know the plans I have for you « declares the Lord » the plans to prosper you and not to harm you, plans to give you hope and future. Jeremiah 29:11 (New International Version).

The purpose of education is to replace an empty mind with an open one.

Malcolm Forbes (1919-1990)

Dedicate

For encouragement, multiples sacrifices and love, I dedicate this work

To my beloved wife Lucie MBuyi Mbiya

To our great children Dieulu, Divin, Dieumi, Daniel, Daniella and Davina Nyembwe

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Abbreviation list

AR: allergic rhinitis

ARIA: allergic rhinitis and its impact on asthma

BMI: body mass index

CI: confidence intervals.

Cm: centimeter

CRS: chronic rhinosinusitis

CysLT: cysteinyl leukotriene

DEwm: directly exposed to wheat, manioc and/or maize flour

DPT : dermatophagoides pteronyssinus

DRC: Democratic Republic Of Congo

ECP : eosinophil cationic protein

ENT: Ear Nose and Throat

FEF: forced expiratory flow at 25, 50 and 75% of FVC exhaled

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

HDM: house dust mites

IEw: indirectly exposed to wheat flour

IgE: immunoglobulin E

IL: interleukin

ISAAC: international study on asthma and allergies in childhood

Kg: kilogram

KU Leuven: University of Leuven

L: liter

M: meter

MAST-CLA : multiple allergosorbent test chemiluminescent assay

N: number

NAR: non-allergic rhinitis

NKT cells: natural killer T cells

NS: not significant.

OR: odds ratio.

P: p-value

PEF: peak expiratory flow

PGD2: prostaglandin D2

PNIF : peak nasal inspiratory flow

RAST: radioallergosorbent test

RC: rhinoconjunctivitis

SD: standard deviation

SPT: skin prick tests

Th: lymphocyte T helper

VAS: visual analogue scale

Chapter 1
GENERAL INTRODUCTION

Allergic rhinitis (AR) is a highly prevalent chronic respiratory disease increasing worldwide. It has a major impact on the quality of life and causes a hard economic burden due to substantial indirect and direct costs [1]. It is a multi-factorial disorder with genomic and environmental factors influencing disease development. This symptomatic disorder is induced by allergen exposure in an immunoglobulin E (IgE)-mediated inflammation of the mucosa lining the nose [2]. Clinically, AR patients express typical nasal symptoms including rhinorrhoea, nasal obstruction, sneezing and/or itching of the nose. Besides the nasal complaints, nasal inhalation of allergens in atopic subjects may be responsible for other symptoms beyond the nose, such as eye, ear and pharyngo-laryngeal symptoms [3]. Ocular symptoms are commonly characterized by tearing, burning, itching and swelling, especially in patients sensitized to outdoor allergens. Furthermore, about two third of AR patients reported that their ocular complaints are as severe as their nasal symptoms. Eye symptoms may be present in 50-70 percent of AR patients and affect around 50 percent of patients with perennial rhinitis [4]. Conjunctivitis is related to both direct allergen contact with conjunctival mucosa and activation of nasal-ocular reflex mechanisms [5;6]. The presence of conjunctivitis in patients with rhinitis is a strong argument in favor of allergic origin of the complaints. The significant loss of smell is relatively infrequent in AR [1], but mild hyposmia is not rare. Individuals with pollen-induced AR (particularly, birch pollen) frequently have an associated oral allergy syndrome [7]. This syndrome includes oral and pharyngeal hypersensitivity (itchiness, tingling, erythema, and angioedema of the tongue, lip and soft palate) after oral contact with various fresh fruits and vegetables. Infections, hormonal imbalance, physical agents, anatomical anomalies and the use of certain drugs can cause symptoms similar to AR [8].

1.1. Epidemiology

Allergic rhinitis, asthma and chronic obstructive pulmonary disease are the most prevalent non-communicable and preventable chronic respiratory diseases constituting a serious public health problem worldwide and in all ages [9]. Despite the fact that the prevalence of AR is increasing [1], there are insufficient epidemiologic data using allergy testing methods. However, the prevalence of an IgE sensitization to aeroallergens in serum (allergen-specific IgE) or in skin (SPT) is over 40–50% in the population of Europe, the United States and Australia-New Zealand [10-13]**.** Most but not all sensitized subjects express clinical symptoms of AR and/or asthma. The prevalence of AR may be overestimated using

questionnaires only [14-16], as slightly over 50% [17] of nasal symptoms are attributable to IgE-mediated allergy.

Approximately, AR affects 500 million people across the world and about 200 million of them also have asthma as comorbidity [1;9;18]. The prevalence of AR is up to 32 % in the United States [19;20]. In the European adult population [21;22], the physician diagnosed AR is a round 25 % as shown in Table 1.1. AR is estimated to affect 20–25% of Canadians [23].

Table 1.1: Prevalence of physician diagnosed allergic rhinitis in adult European population [21].

Country	Prevalence (%)
Belgium	28,5
United kingdom	26,0
France	24,5
Spain	21,5
Germany	20,6
Italy	16,9

The International Study of Asthma and Allergies in Childhood Phase III [24] has shown an increasing prevalence of allergic symptoms across most countries even in Africa [25-27]. Allergic rhino-conjunctivitis over the past year varied from 7.2% to 33.3% among 13-14 year-old African schoolchildren [24]. Table 1.2 shows an overview of prevalence of AR and allergic related diseases across African countries. To have a better idea of the real prevalence of AR and allergic-related diseases and its risk factors in African population where aerobiological sampling is almost lacking, more epidemiological studies are needed.

The prevalence variability across the world depends on study design, methodology and geographic characteristics. Several studies [28-32] have shown that the prevalence of atopy and AR is higher in urban than in rural areas [33]. This resulted in the so-called “hygienic hypothesis”, first introduced by Strachan [34] postulating that growing up in a more hygienic

environment with decreased infections and endotoxin exposure in early age shifts the immune system towards a Th2-profile with predisposition to atopic diseases. Additional factors such as increased exposure to indoor allergens, pollutants, tobacco smoke and westernized lifestyle with increased incidence of obesity may also play a role [34-40]**.**

Table 1.2: Overview of prevalence of allergic rhinitis and allergic related diseases in African Countries

Country, city		Age	AR*	AR**	RC**	Wheeze**	Eczema**
Morocco [41]	Rural Population			37,8			
Morocco Casablanca [24]	Schoolchildren	13-14			28.1	16.0	23.0
Tunisia, Tunis [42]	Schoolchildren	13-14			27,7		
Tunisia, Grand Tunis [24]	Schoolchildren	13-14			14.7	15.4	13.0
Egypt, Cairo [43]	Schoolchildren	11-15			15,3		
Urban Ivory Coast [24]	Schoolchildren	13-14			27,6	19.3	18.2
Togo, Loné [24]	Schoolchildren	13-14			14,6		
Nigeria [44]	Population	18-45		29,6			
Ethiopia, Gondar [45]	Schoolchildren				14,5		
Kenya [46]	Patients		48.6				
Kenya [25]	Schoolchildren	13-14		38,6			
Kenya, Nairobi [24]	Schoolchildren	13-14			19.8	18.0	14.9
Gabon [24]	Schoolchildren	13-14			16,5		
Uganda, Ibanda [24]	Schoolchildren	13-14			16.4	13.0	7.7
Cameroon, Yaounde [24]	Schoolchildren	13-14			8,9	5.7	7.7
Congo, Brazzaville [24]	Schoolchildren	13-14			33,3	19.9	16.2
Democratic Republic of Congo, Kinshasa [24]	Schoolchildren	13-14			11,8	7.5	10.9
Zimbabwe [47]	Children	< 2	15.6				
Zimbabwe [48]	Patients	1-62	33.0				
South Africa, Cape Town [24]	Schoolchildren	13-14			20,7	20.3	13.3
South Africa, Cape Town [49]	Schoolchildren	13-14		33,2			

AR: allergic rhinitis. RC: rhinoconjunctivitis. *: diagnosis clinically confirmed via either skin prick testing or by specific-IgE in serum. **: 12-month prevalence.

1.2. Classification of allergic rhinitis and related diseases

AR was previously subdivided [2] into seasonal, perennial and occupational rhinitis based on the time of exposure to allergens. Perennial AR is most frequently caused by indoor allergens such as dust mites, molds, insects and animal danders. In contrast, seasonal AR is related to a wide variety of outdoor allergens like pollens and molds. Occupational rhinitis arises in response to an airborne agent present in the workplace and may be due to an allergic reaction or non-allergic hyperresponsiveness mechanism [50]. The occupational allergens include several agents e.g. laboratory animals [51], grains/flour [52;53], wood dust, mites, latex [54], enzymes [55], chemicals [56], glues and solvents [57].

However, this classification is not entirely satisfactory for a number of reasons. In certain areas pollens and molds are perennial allergens [21;58]. Symptoms of perennial allergy may not always be present all year round, although the majority of patients are polysensitized to several different allergens and therefore exposed throughout the year [59;60]. In addition, some patients with perennial symptoms experience seasonal exacerbations when exposed.

Therefore, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [2] proposed a new classification of AR in four subgroups based on the duration and severity of symptoms and their impact on quality of life. According to the symptoms' duration, the term intermittent AR means that the symptoms are present for less than 4 days a week or for less than 4 consecutive weeks. Persistent AR means that the symptoms are present more than 4 days a week and for more than 4 consecutive weeks. Depending on the severity of symptoms and their impact on quality of life, AR is classified as mild or moderate/severe. Moderate/severe AR means that one or more of the following items are present e.g. sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work and troublesome symptoms. While, mild AR means that none of the listed items are present. The ARIA classification closely reflects patients' needs and underlines the close relationship between rhinitis and asthma. This approach is useful in assessment and pharmacotherapy of AR. However, allergen specific treatment needs to be incorporated with seasonal and perennial classification in order to ascertain the correct allergen to be used in desensitization [61].

Although AR is often considered as a trivial disease, its symptoms and complications have been shown to have a major negative impact on quality of life. Unfortunately, chronic rhinitis affects mainly the economically active individuals, leading to reduced work productivity [62;63] impaired school performance [64;65] and disturbed sleep [66]**.** Loss of productivity, missed school and work days, and direct costs associated with treatment of AR create substantial costs for society.

AR is strongly linked to allergic asthma and both share an increasing prevalence, similar immunological pathophysiology mechanisms, same risk factors such as allergens and occupational agents, the therapeutic response in part to the same drugs and constitute the global airway allergy syndrome [1;3]. Most patients with asthma (both allergic and non-allergic) also have rhinitis, whereas 10 to 40 percent of AR patients have asthma comorbidity [67]. It was shown that rhinitis in subjects without asthma is a risk factor for developing asthma both in adults [68] and in children [69]**.** The development of asthma in adult patients with rhinitis is often independent of allergy [68], whereas in childhood, it is frequently associated with allergy [69]**.** Uncontrolled asthma is linked to moderate-to-severe rhinitis which should be identified and treated [70]. Rhinitis and asthma frequently coexist suggesting the concept of one airway one disease [68;71;72]. Besides the continuity of anatomic structures, upper and lower airway inflammation had a reciprocal influence showing a systemic immune activation [73;74] with inflammation at distance of the allergen challenge [5]. The presence of AR commonly exacerbates asthma, increases the risk of asthma attacks, emergency visits and hospitalizations for asthma. Additionally, AR predisposes to development of other upper airway comorbidities such as rhinosinusitis, nasal polyposis, upper respiratory tract infections, adenoid hypertrophy, tubal dysfunction, otitis media with effusion and pharyngo-laryngitis [1;3;75].

About half of the population reporting rhinitis, has neither evidence of allergic sensitization nor infection (infectious rhinitis) of the upper airways [1;76]. The non-allergic non-infectious rhinitis represents a group of heterogenous diseases in which no IgE-mediated mechanism can be demonstrated [77]. The etiology is not well understood, making it difficult to treat. It includes drug-induced rhinitis, occupational rhinitis, food-induced rhinitis, rhinitis induced by environmental factors, hormonal rhinitis, rhinitis related to chemical or physical factors and idiopathic rhinitis [78]**.**

When the inflammation of the nasal mucosa extends to the mucosa of the paranasal sinuses, the term rhinosinusitis is used clinically. Rhinosinusitis [61] including nasal polyps is characterized by the presence of two or more sinonasal symptoms (nasal blockage, anterior discharge or postnasal drip, facial pain and smell impairment) and endoscopic signs (polyps, mucopurulent discharge and oedema) and/or CT-changes typical for the disease. Based upon duration of symptoms, a difference should be made between acute rhinosinusitis (symptoms lasting less than 12 weeks) and chronic rhinosinusitis (CRS) when symptoms lasted for more than 12 weeks. Allergic sensitization constitutes a risk factor for the development of CRS [61]. However, several other conditions such as immunologic, microbiologic, anatomic and genetic factors may contribute to the complex mechanism of CRS with and without nasal polyps [61;79].

1.3. Pathophysiology

Allergy is generally caused by a sustained overproduction of IgE in response to common environmental antigens such as indoor, outdoor, foods and other allergens [1;80]. In genetically predisposed (atopic) individuals, the respiratory exposure to allergen leads to sensitization i.e immune response with production of specific-IgE. This production results from a complex interactions between B-cells and T-cells, mast cells and basophils, involving the presence of cytokines [1]. Inhalant allergens are taken by dendritic cells and presented to CD4+ T-cells in draining lymph nodes. This presentation leads to the differentiation of precursor Th cells in Th2 cells.

Mast cell accumulation in the airway mucosa is an important pathophysiologic event in AR and asthma, as inhaled allergens impact the mucosal surfaces of the nose and/or lungs. IgE is produced in the local lymphoid tissues and locally in both nasal and bronchial mucosa [81;82]. Allergen-specific IgE, synthesized in response to allergens, becomes fixed to high affinity receptor (Fc€RI) on the membranes of mast cells and basophils. Repeated allergen contact in sensitized individuals causes mast cell activation and degranulation within minutes through aggregation of membrane receptor-bound IgE. Besides the known histamine, tryptase, cysteinyl leukotrienes and prostaglandins, mast cells may release a variety of Th2 cytokines (IL-4, IL-5, IL-13), pro-inflammatory cytokines and chemokines [2;83]. Thus, histamine, mediators, cytokines, chemokines, neuropeptides, cysteinyl leukotrienes, adhesive molecules and cells all cooperate in a complex network provoking the specific symptoms and the

nonspecific hyperactivity of AR. The allergic response occurs in two phases, the "early" and "late" response and depends on the structure of the target organ. The early-phase response depends on the structure of the target organ; typically it is characterized by itching, sneezing, rhinorrhoea and blockage in the nose or wheezing, coughing, hyperreactivity with bronchoconstriction in the lungs. The late-phase allergic response occurs 4 to 8 hours after allergen contact and is characterized by nasal congestion/obstruction and bronchoconstriction. Mast cells are the key cell for the early reaction in upper and lower airway allergic inflammation. After the release of mediators by mast cells, several inflammatory cells such as T-cells, additional mast cells, eosinophils are recruited to the airway, via an upregulation of chemokines and adhesives molecules. This characterizes the late phase of allergic inflammation [84;85]**.** However, the allergic inflammation cascade is very complex including many cells types such as structural cells, CD8+ cells, Th17 cells, neutrophils, basophils, macrophages, dendritic cells, mucosal B cells that produce local IgE and NKT cells. Additionally, non-IgE-dependent mechanisms can explain the allergic inflammation as well. Allergens by their enzymatic proteolytic activity may directly activate epithelial cells [57;86] and eventually lead to a Th2-immune response, inducing cytokine and chemokine release, having the potential to induce airway inflammation independent of IgE [87]. It is known that dust mite allergen Der p1 [57] may alter the epithelial junctions, increase the epithelial permeability and elevate the release of inflammatory mediators [88].

Finally, neurogenic mechanisms including a naso-nasal and naso-bronchial reflexes [6] play a role in allergic inflammation. The nose, armed with a complex nervous system including sensory, parasympathetic and sympathetic nerves, provides defensive and homeostatic functions requiring rapid responses to physical and chemical stimuli. Sensory nerves transmit signals from the mucosa generating sensations such as pruritus and motor reflexes such as sneezing and parasympathetic and sympathetic reflexes that affect the glandular and vascular nasal system [89]. Neurotrophins, such as the nerve growth factor [90], are prime candidates as mediators of neural hyperresponsiveness [91]. The nonspecific nasal hyperreactivity characterizes both allergic and non-allergic inflammation of the nose by increased nasal response to a normal stimulus resulting in nasal symptoms and secretion. Although AR is commonly regarded as minor disease, the minimal persistent allergic mucosal inflammation synergises with infective inflammation such as the common cold [92].

1.4. Etiologic factors of allergic diseases and sensitization

Atopy is the abnormal tendency to develop specific IgE in response to various environmental allergens [93]. Atopic diseases include AR with and without conjunctivitis, asthma, dermatitis and food allergies. Allergic rhinitis is a multifactorial disease with genomic as well as environmental factors being involved in the disease development. Atopy has been linked to many genetic loci on chromosomes 2, 5, 6, 7, 11, 13, 16 and 20 [93;94]. Environmental allergens originate from a wide range of plants, animals, insects, fungi, occupational and others sources. They are mostly proteins or glycoproteins and rarely glycans which are able to induce and react with specific IgE antibodies. Allergens are classified in different subgroups such as inhalants, food and occupational allergens [1].

Inhalant allergens are very often implicated in allergic rhinitis and asthma [95] and are usually classified as indoor (principally mites, pets and insects), outdoor (pollen and molds) and occupational agents. According to ARIA guidelines, several studies have shown that more than 50 percent of patients sensitized to pollen suffer from persistent AR [21;60] and a large number of individuals sensitized to house dust mites have mild intermittent AR [21]. The complex modern indoor environment may have a synergistic effect on atopic co-morbidities [96] and contribute to an increasing prevalence of sensitization and allergic diseases.

There are regional differences between allergens, particularly pollens in relation to geographic characteristics and climatic settings. The pollen causing most common allergies is from grasses, trees and weeds. Moreover, most patients are sensitized to many different pollen species [97]. There are an increasing number of animals, especially in urban environments of western countries where approximately one in four residences possesses a cat or dog. The animal danders and secretions carry powerful allergens responsible for allergic reactions, even far in places without animals [13]. The low level of cat allergen that exists in many homes without cats is capable of inducing symptoms in very sensitive patients [98]**.** Other animals such as rodents or horses can induce occupational sensitization in laboratory personnel and in children with exposed parents [99]. Fungus, mold and yeast are plants which do not possess chlorophyll but which liberate large quantities of allergenic spores into indoor and outdoor environments. Other IgE immune responses and allergic diseases are from inhalation of insect allergens such as tropomyosin or haemoglobin [100].

Food allergy is rare in subjects with AR but without other symptoms. However, rhinitis is a common symptom of food allergy in patients with multiple organ involvement [1]. Depending on IgE cross-reactive epitopes shared by pollen and food allergen, pollinosis patients often display adverse reactions upon the ingestion of plant-derived foods [101;102]. Rhinitis and asthma could be caused by occupational agents [50;56] such as isocyanates [103], flour and grain, wood dust [50], glutaraldehyde and anhydrides [50], laboratory animals, insects [104], resins and glues, latex [62], metal salts [56], persulfates [105] and others. The two work-related rhinitis variants (IgE and non-IgE-mediated), could be associated with asthma symptoms [106]. Among bakers, occupational rhinitis and asthma are caused by IgE sensitization to bakery flour [107] or enzymes [108] or contaminants [109].

Beyond the allergens, air pollution, tobacco smoking and occupational exposures are of great concern in respiratory diseases [110]. Allergic and non-allergic rhinitis are characterized by augmented hyperreactivity to non-spectific pollutants. Some studies found that exposure to outdoor air pollutants may increase the risk of AR [111;112], whereas others did not find any relationship [113]**.**

1.5. Diagnosis and management of allergic rhinitis

1.5.1. Diagnosis

The AR diagnosis is based upon a clinical history of allergy and is ascertained by specific IgE reactivity to allergens in skin, in serum or even in end organ challenges [1]. Skin testing provides results within 15 minutes; whereas results of radioallergosorbent test (RAST) blood tests take several days, and are less cost-effective than skin prick tests (SPT). Immediate hypersensitivity skin tests [114] are widely used and represent a major diagnostic tool in the allergy field. There are several methods for skin testing such as SPT, scratch tests and intradermal skin tests. SPT has a high degree of correlation between symptoms and provocative challenges. SPT is considered as a gold standard for determining specific antigens. Carefully performed by trained health professionals and correctly interpreted, SPT with a battery of relevant allergens of the patient's geographic area is a simple, painless and highly efficient method recommended for both IgE-mediated diagnosis and research purposes [1;115]. However, numerous factors may affect the response of skin testing such as the quality of the allergen extract, age of patient, seasonal variations, drugs like oral H1-antihistamines and skin disease [116]. Relevant allergens of patient environment should be

tested. In developing countries where allergy is also booming, local allergens especially pollens are not well identified [117] and therefore cannot be tested. To circumvent the disadvantages of skin test, various in vitro analyses were developed. They include the RAST, the Pharmacia CAP test and the multiple allergosorbent test chemiluminescent assay (MAST-CLA). In vitro tests are useful in patients with dermographism, severe atopic dermatitis, or those unable or unwilling to temporarily stop antihistamine use.

The measurement of allergen-specific IgE in serum is of importance and has a value similar to that of SPT [1;118]. The occurrence of positive responses to skin tests or the presence of specific IgE does not necessarily imply the presence of a clinically relevant allergy [1], as many symptom-free subjects have allergic-specific IgE. In contrast, measurement of total serum IgE has a poor predictive value for allergy screening in rhinitis and should not be used as a diagnostic tool [2;119]. Allergic and parasitic diseases as well as many other conditions increase the levels of total IgE in serum. Some allergic patients may have a local IgE immune response without any systemic release of IgE [120], and show negative SPT and serum-specific IgE.

For inhalant allergens, skin test responses represent one of the first-line diagnostic methods and when they correlate with the clinical history, in vitro tests may not be required [121]**.** Moreover, SPT with fresh foods were used to reduce the poor standardization of food extracts commercially available [122;123]**.** In addition, nasal and ocular challenge tests with allergens are used in research and, to a lesser extent, in clinical practice, and are important in the diagnosis of occupational rhinitis [1]. During the provocation challenge or the allergic reaction, the measurement of mediators such as histamine, PGD2, CysLTs, kinins, tryptase and ECP released into peripheral blood, nasal secretions or urine represent a research tool. Nasal cytology and histology usually represent a research tool. The use of nasal nitric oxide measurements in the diagnosis and treatment of AR still needs to be further evaluated because of the contradictory results [124]**.**

1.5.2. Management of allergic rhinitis

Recent knowledge of the mechanisms underlying allergic inflammation have led to improve therapeutic strategies for the management of allergic rhinitis and allergies [125]**.** The ARIA classification of AR allows the use of appropriate treatment based on the duration and intensity of the patients symptoms and lifestyle disturbance [1]**.** The management of AR

includes patient education, allergen and pollutant (e.g. tobacco) avoidance when possible, pharmacotherapy and allergen-specific immunotherapy. Surgery may be used as an adjunctive intervention in a few highly-selected patients. Moreover, environmental control is more controversial [126]. Some AR patients do not recognize the process as such and do not consult a physician [127]. Others commonly use self-treatment for relief of symptoms using proven or inappropriate therapies. Most AR patients seeking medical care have moderate-to-severe symptoms [128-130]**.**

Many developed countries have specific programs to better understand, manage and prevent allergic diseases. Pharmacological treatment should take into account the efficacy, safety and cost-effectiveness of medications, the patient's preference and the objective of the treatment [127], severity of the disease as well as the presence of co-morbidities. Therefore, a stepwise therapeutic approach has been proposed in ARIA guidelines [1]**.** AR management carries a heavy economic impact with direct costs and more substantial indirect costs [1].

Allergen avoidance and pharmacotherapy are the cornerstones of AR management [131], but it is still difficult to implement the avoidance of allergens. Pharmacotherapy is individualized to the patient based on type of symptoms, their duration and severity, comorbidities, response to prior treatment, and patient preference [1;131]. Pharmacotherapy includes many classes of drugs such as antihistamines, corticosteroids, mast cell stabilizers, decongestants, nasal anticholinergics, leukotriene-receptor antagonists and anti-IgE [1;131;132]. Intranasal corticosteroids are the one most effective class of drug because its anti-inflammatory actions on several different cells types, with some molecules showing no systemic bioavailability with long-term use, even in children. The ARIA guidelines recommend intranasal corticosteroids as treatment for patients with moderate to severe AR and/or persistent symptoms [1].

Allergen specific immunotherapy (vaccination) interferes with the basic mechanisms of the allergy and alters the natural course of allergic diseases, resulting in symptomatic relief and offering the patient a long-lasting and preventive effect. However, specific immunotherapy needs a precise diagnosis of IgE-mediated allergy. Immunotherapy is available via sublingual and subcutaneous routes at present, mainly for individuals with AR uncontrolled by pharmacotherapy and allergen avoidance. Nowadays, immunotherapy remains the only treatment that probably alters the disease course, reduces progression of sensitization and

development of asthma [133]. Additionally, phototherapy and complementary/alternative medicines are extensively used in the treatment of AR and asthma but without objective evidence of efficiency [134].

In developing countries, the management of rhinitis is based on medication affordability and availability [135] and on cultural differences [136]. Specific immunotherapy is rarely used in sub-Saharan countries because of the few number of trained allergists and the lack of appropriate laboratories of immunology and miss-evaluation of relevant local allergens (e.g. pollens) [48]. When treated with adequate medications according to the ARIA guidelines [2], most patients with AR can be controlled. However, up to 20% of patients with moderate to severe symptoms continue to be impaired by their symptoms despite a proper management [77;100;137;138] and constitute the severe chronic upper airways disease. This term is applied to all nasal diseases regardless of the allergic component.

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Chapter 2
OBJECTIVES OF RESEARCH

Allergic rhinitis (AR) is the most frequent IgE-mediated diseases increasing throughout the world. It has a negative impact on (quality of life, work productivity and school performance) and causes substantial social and economic costs [1;2]. Allergic and non-allergic rhinitis have already been recognized as a significant risk factor for asthma occurrence [3-5]**.** However, allergic diseases and AR in particular are under-recognized, under-diagnosed, under-treated and insufficiently prevented especially in developing countries. In many African countries where the government health program is focused on communicable diseases, malnutrition and injuries, data on allergic diseases remain scarce. The quasi absence of data on the pollen season and specific allergens make the adequate therapy and control of allergic diseases difficult [4;6]. This lack of information can be explained by shortness in physicians and other personnel trained in diagnosis and management of allergic disorders. Additionally, immunological laboratories are usually inappropriate or inexistent [7]. Environmental risk factors of allergic diseases such as allergens related to specific fauna and flora are still insufficiently known.

In Democratic Republic of Congo, little is known about allergic diseases because of the lack of an allergy-screening program in medical practice. There are no data on allergen sources as well as environmental risk factors of AR and associated diseases. The management of AR remains inappropriate and immunotherapy is still unavailable. The International Study of Asthma and Allergies in Childhood Phase III [8] has shown that the prevalence of rhino-conjunctivitis symptoms was 11.8%, among 13-14 year-old schoolchildren of Kinshasa (the capital).

The present doctoral thesis focuses on the gaps in the epidemiological profile of AR and associated diseases in our settings. Therefore, several studies were performed in Kinshasa by combining data from the general population (urban versus rural parts of Kinshasa), consecutive patients seeking medical help for nasal symptoms suspected for allergy and individuals exposed to flour dust in comparison to the controls.

General objective

In this PhD project, we aimed to improve the disease management by investigating the epidemiology and clinical characteristics of AR and associated diseases in urban and rural parts of Kinshasa.

The second aim was to assess risk factors and identify specific allergen responsible for AR and related allergic diseases in Kinshasa.

Specific objectives

Following the two main objectives, we have subdivided the current work into several workpackages:

- We first determined the prevalence of AR and associated diseases and their relationship; classified AR according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and evaluated factors associated with allergic symptoms in the general population of Kinshasa.
- Secondly we described the clinical characteristics of rhinitis, determined sensitization rate and specific allergens, classified AR in ARIA subgroups, and evaluated factors associated with sensitization in rhinologic patients of Kinshasa.
- Finally, we assessed the prevalence of airway diseases, the sensitization rate as well as allergen pattern, and evaluated the factors associated with airway diseases or with sensitization among Kinshasa‘s workers exposed to flour dust as compared to a control group.

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Chapter 3

PREVALENCE AND DETERMINANTS OF ALLERGIC DISEASES IN KINSHASA

Nyembue TD, Jorissen M, Hellings PW, Muyunga C, Kayembe JM. Prevalence and determinants of allergic diseases in a Congolese population. Int Forum Allergy Rhinol. 2012 2(4):285-293.

Abstract

Background: Allergic rhinitis (AR) is increasing worldwide, but little is known in Africa. We aimed to establish the prevalence of AR and associated diseases, to classify AR according to the ARIA guidelines and to determine factors associated with allergic diseases in Kinshasa. Methods: We conducted a cross-sectional clustered survey of the population of eight randomly chosen health zones of Kinshasa. Information was collected on demographic characteristics, home environment, participant characteristics, atopic story and allergic symptoms. Skin prick testing (SPT) was done.

Results: Of 1508 screened individuals, 1412 (5 to 83 years) were interviewed and 1005 underwent SPT. 65.6% and 34.4% of participants lived in urban and rural areas respectively. Mean (± SD) age was 29 (±16) years and 52% were female. The 12-month prevalence of rhinitis, rhinoconjunctivitis, wheeze and skin itch-rash was 30.8%, 24.4%, 15.4% and 6.2% respectively. Rhinoconjunctivitis and wheeze were more prevalent in urban than rural individuals. Of skin tested respondents 23.2% showed positive results with mainly Dermatophagoides pteronyssinus and cockroach being involved. AR and non-allergic rhinitis prevalence was reported in 13.9% and 27.9% respectively. 59.7% and 48.0% of AR individuals expressed moderate to severe and persistent symptoms. Independent determinants of having any diseases in multivariate analysis were active smoking, presence of cockroaches in the home, history of atopy's siblings, personal history of atopy, using straw or herbs mattress and positive SPT responses.

Conclusion: This study revealed a high prevalence of allergic diseases in Congolese individuals. It is important to increase awareness toward allergic disorders and to ensure adequate management.
Keys words: Prevalence, rhinitis, rhinoconjunctivitis, wheeze, itch-rash, Congo.

3.1. Introduction

Allergic rhinitis (AR) [1] constituted a worldwide health problem, affecting quality of life and carrying economic burden with great costs. Prevalence of the immunoglobulin E (IgE)-mediated diseases is well documented in industrialized settings. In Western Europe [2], AR affects 17 to 29 % of the general population. There is a clear relation between allergen sources/pattern and allergic symptoms, but prevalence of AR is also influenced by many other factors such as local allergens and exposure intensity, environmental factors (air pollution, temperature, and climate), age and genetic characteristics of the population. An allergic inflammation of the nose is characterized by rhinorrhoea, sneezing, nasal blockage and/or itching, which are reversible spontaneously or with treatment. Nose symptoms are often associated with eyes itch-watery. AR is based on interrogation, examination and IgE testing to common allergens in clinical settings. For epidemiological studies [3], questionnaires are used to assess AR despite the fact that non-allergic conditions can provide similar symptoms. AR is strongly linked to lung disease as reported in the new concept of one airway one disease [4;5]. Clinically, both diseases share the increased prevalence, common pathological and physiological features and partially respond to the same medication. AR commonly exacerbates asthma or bronchial hyper-responsiveness and is associated with other upper airway comorbidities [6]. Among 13-14 year-old African schoolchildren, an International Study of Asthma and Allergies in Childhood (ISAAC) phase III [7] reported 7.2% to 33.3% of allergic rhinoconjunctivitis. This allergic symptoms prevalence is higher than in surveys carried out before in some African countries like Morocco [8], Kenya [9] and South Africa [10]. Moreover, there is a lack of diagnostic tools and only a few physicians are trained in diagnosis and management of AR including allergy-related disorders in central Africa [11] where immunological laboratories are inappropriate or inexistent. Local allergen sources are not well-known. Furthermore, priority in developing countries is given toward transmissible diseases, malnutrition, maternal and infant mortality.

In the Democratic Republic of Congo (DRC), the prevalence of specific IgE-mediated diseases and AR in particular is not well known, because of the lack of an allergy-screening program and the quasi absence of allergy testing in daily practice. Neither measurement by serum specific IgE nor skin prick testing (SPT) is currently available. One study [7] carried out among 13-14 year-old schoolchildren of Kinshasa (the capital), reported 11.8%, 10.9% and 7.5% of rhinoconjunctivitis, eczema and wheeze symptoms respectively. Moreover, the

management of allergic diseases remains inappropriate and immunotherapy is not available. This study aimed to determine the prevalence of AR, associated diseases and its relationship, to classify AR according to the ARIA guidelines and to evaluate factors associated with allergic symptoms in the general population of Kinshasa.

3.2. Methods

Study population

This clustered cross-sectional survey in the general population of Kinshasa, the capital of the DRC, was carried out from February to May 2010. Kinshasa has a surface area of 10.000 km2 with about 10 million inhabitants. The largest part of Kinshasa has a rural ecology while the inhabited urban surface is limited to 459 km^2 located along the river Congo (Institut National de Statistiques de la République Démocratique du Congo, rapport 2009, unpublished).The Kinshasa's climate is tropical wet and dry characterized by two seasons: a rainy and dry season. The administrative organization of Kinshasa is subdivided into 35 health zones (zones de santé) and each health zone is splitted in several health areas (aires de santé) (Ministère de la Santé de la République Démocratique du Congo, rapport 2003, unpublished). Because of the lack of a reliable census, household's sampling was taken using a multistage random in four degrees. Eight health zones were randomly selected (first degree); two health areas were randomly selected in every health zone (second degree); three streets were randomly selected in each health area according to the list of all streets (third degree) and the inhabited parcels were randomly selected (fourth degree) according to the list of whole parcels of the chosen streets. In case of several households in a selected parcel, only one household was randomly chosen. From the household members list, we randomly recruited one individual who met the inclusion criteria (aged $\geq$ 5 years and living in Kinshasa for $\geq$ 1 year). The number of participants varied proportionally with the size of the selected health zones. Each selected health area was visited four times. The first visit was to inventory the number of streets, the inhabited parcels and the primary medical center where SPT would be done. During the further visits, participants were interviewed and if they agreed, referred to local primary medical center for SPT.

Procedure

The survey questions were from the ISAAC study [12] translated into French and Lingala (predominant local language) by an independent language center and back translated by health workers. The main question used to assess the prevalence of rhinitis was "Have you had problems with sneezing or a runny or blocked nose when you did not have a cold or the flu in the last 12 months?" If yes, rhinoconjunctivitis was defined by a positive answer to the following question: "In the past 12 months, has this nose problem been accompanied by itchy watery eyes?" Wheeze was assessed by: "Have you had wheezing or whistling in the chest in

the last 12 months?" And skin itch-rash was evaluated by the two questions "Have you ever had an itchy rash which was coming and going for at least 12 months?" If yes, followed by "Has this itchy rash affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes? Additionally, we recorded data on age, sex, education level, profession, number of persons and number of rooms in the house, keeping pets (dog/cat), using fan/air conditioning, having carpet in the living room, presence of tress/flowers around the house and self-assessment of the house's aeration. Furthermore, respondents were questioned about the presence of insects/rodents in house, type of mattress used, materiel/fuel used for cooking, active/passive smoking and alcohol consumption. Experienced interviewers were recruited and underwent one-week training comprising a detailed review of the questionnaire and interview techniques. A pilot study was conducted in 62 subjects from one health area. Afterward, weaknesses were corrected and a standardized explanation was supplemented to the study guidelines.

Skin prick testing

The allergy screening was done with allergen extracts of dermatophagoides pteronyssinus (DPT), cockroach, dog, cat, guinea-pig, rabbit, grass pollen mix (cocksfoot, vanilla, timothy, ray and meadow), artemisia vulgaris, parietaria judaica, cupressus semperviens, alternaria alternate, aspergillus mix (fumigatus, nidulans and niger), crab, soybean and wheat flour (Stallergenes, Waterloo/Belgium). Histamine and saline solution was used as a positive and negative control respectively. Through each allergen's drop placed on the volar side of the forearm, a sterile lancet was perpendicularly pressed for at least 1 second. The cutaneous mean wheal reaction size was measured after fifteen minutes [13]. All SPT were performed by one trained-nurse and interpreted by one ENT specialist.

Operational definitions

Sensitization was defined as the presence of a positive test (mean wheal diameter $\geq$ 3 millimeter) to at least one of the allergens. AR diagnosis was based on the presence of 2 or more symptoms of rhinitis/rhinoconjunctivitis with one or more positive SPT responses, whereas negative SPT results without such symptoms were considered as non-allergic rhinitis (NAR). AR was classified in four subgroups according to ARIA [1] guidelines. Household is defined as a set of people living under the same roof and sharing the same meals.

Ethical issues

The research section of the medical school of Kinshasa University approved the study protocol. From the Provincial Medical Inspection of Kinshasa, we obtained the authorization to visit the selected health areas and to use the primary medical center for SPT. Informed consent was required from all participants or from the person legally responsible for individuals less than 18 year-old.

Statistical analysis

Statistical analyses were performed using STATA software version 11.0 (Stata Corp. College Station, Texas, USA 2009). Qualitative variables were expressed as percents and their 95% confidence intervals (CI). Mean ± standard deviation (SD) or median and 25-75 percentiles were used for continuous variables. Comparison of proportions was tested by chi-squared test or Fisher's exact test if the Chi-square conditions were not fulfilled. A non-parametric Mann-whitney test was applied to assess differences between two continuous variables. Odds ratio (OR) for potentials risks factors were calculated.

All variables associated with having any diseases in the past year ($p \leq 0.10$ in univariate analysis) were included in a backward stepwise multivariable regression model.

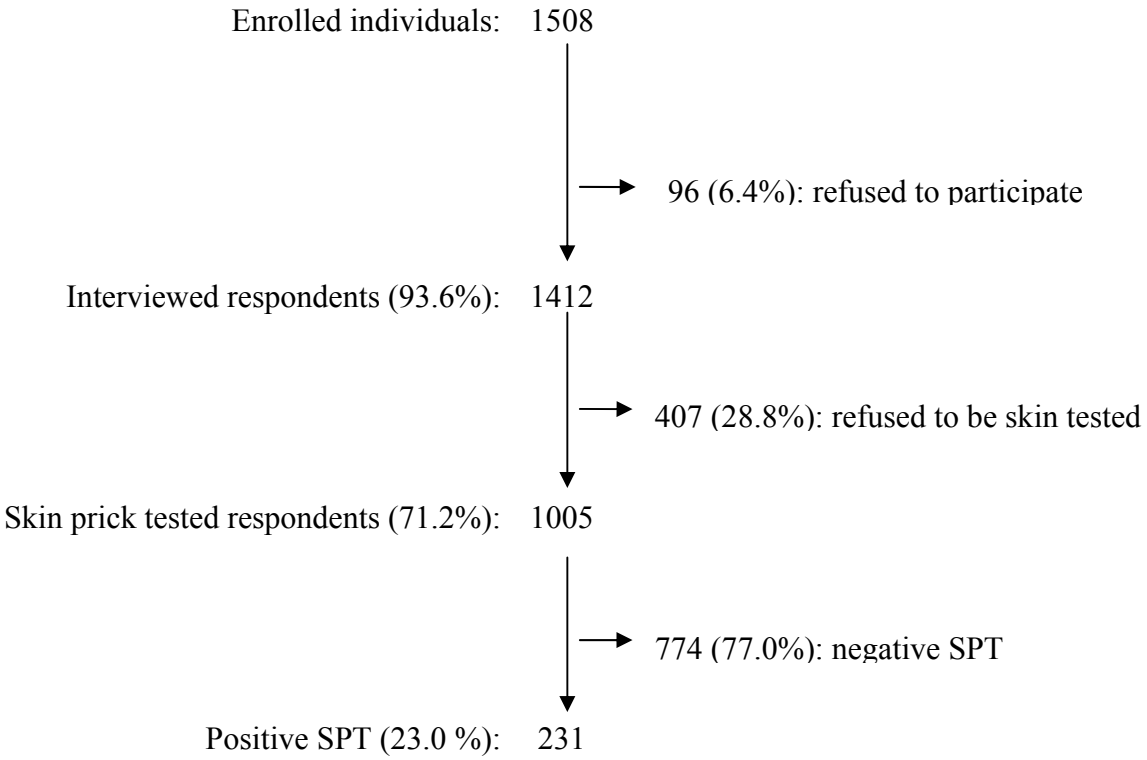
The following binary variables were included: sex, keeping pets, passive and active smoking, cooking with oil, house aeration, presence of cockroach, presence of bedbug, mattress used, atopy history of (mother, siblings and personal) and positive SPT results. Age groups and education level were classified as scaled variables. Cooking with gas was not modeled because of missing values. The model started with all suspected predictors and removed those with p-value ≥ 0.10. The goodness of fit was verified with the Hosmer and Lemeshow method. All tests were done considering a significance level of 0.05 double-sided.

3.3. Results

Characteristics of participants

Of 1508 screened individuals (Figure 3.1), 1412 (737 females and 675 males) were interviewed. Respectively, 65.6% and 34.4% of participants were from urban and rural health areas.

Figure 3.1: Flow chart of the participants



SPT: skin prick testing

The participants' mean age (± SD) was 29 (±16) years ranging from 5 to 83 years. About 64.3% of households included at least 6 persons for a mean of 2 bedrooms. Other respondents' characteristics are shown in Table 3.1.

Table 3.1: Characteristics of 1412 respondents with and without symptoms.

	All Respondents N=1412		Individuals With symptoms		Individuals without symptoms		P-value*
Age group (years)	n	%	n	%	n	%	0.07
≤ 9	122	8.6	76	62.3	46	37.7	
10 -19	318	22.5	198	62.3	120	37.7	
20 – 29	375	26.6	234	62.4	141	37.6	
30 – 39	256	18.1	170	66.4	86	33.6	
40 – 49	160	11.3	107	66.9	53	33.1	
50 – 59	107	7.6	65	60.7	42	39.3	
≥ 60	74	5.2	34	45.9	40	54.1	
Highest level of education reached							0.04
No education	59	4.2	32	54.2	27	45.8	
Primary school	352	24.9	202	57.4	150	42.6	
Secondary school	776	55.0	500	64.4	276	35.6	
University	225	15.9	150	66.7	75	33.3	
Profession							NS
Students	510	36.1	318	62.4	192	37.6	
Independent activities	728	51.6	449	61.7	279	38.3	
Employed	174	12.3	117	67.2	57	32.8	
Mattress used							NS
Sponge/cotton	1308	92.6	828	63.3	480	36.7	
Straw/herbs	104	7.4	56	53.8	48	46.2	
Presence of insects/rodents in house							
Mouse	1200	85.0	756	63.0	444	37.0	NS
Cockroach	1188	84.1	771	64.9	417	35.1	<0.001
Bedbug	415	29.4	279	67.2	136	32.8	0.02
Cooking with:							
Embers	1283	90.9	808	63.0	475	37.0	NS
Electricity	825	58.4	516	62.5	309	37.5	NS
Wood	399	28.3	249	62.4	150	37.6	NS
Oil	103	7.3	77	74.8	26	25.2	0.008
Gas	8	0.6	8	100.0	0	0.0	0.03
Atopic history of:							
Father	74	5.2	49	66.2	25	33.8	NS
Mather	97	6.9	69	71.1	28	28.9	NS
Siblings	214	15.2	164	76.6	50	23.4	<0.001
Personal	157	11.1	121	77.1	36	22.9	<0.001

House aeration							0.007
Insufficient	573	40.6	383	66.8	190	33.2	
Sufficient	839	59.4	501	59.7	338	40.3	
Alcohol	568	40.2	363	63.9	205	36.1	NS
Carpet	332	23.5	216	65.1	116	34.9	NS
Fan	692	49.0	424	61.3	268	38.7	NS
Air conditioning	31	2.2	22	71.0	9	29.0	NS
Pets	381	27.0	258	67.7	123	32.3	0.016
Active smoke	275	19.5	196	71.3	79	28.7	0.001
Passive smoke	325	23.0	215	66.2	110	33.8	NS

Data expressed in number and (percentage by column for all respondents and by row for individuals with and without allergic diseases). *P-value testing difference between individuals with and without complaints. NS: no significant.

Participants with and without any diseases

Among all participants, 62.6% reported at least one disease in the 12 previous months. Complaining individuals more frequently reported: personal and sibling history of atopy, insufficient house aeration, presence of bedbugs and cockroaches at home, active smoking, higher level education, keeping pets, cooking with oil and cooking with gas than non-complaining group. Other characteristics did not statistically differ between the two groups (Table 3.1). Table 3.2 shows the characteristics significantly different between urban and rural participants. All diseases were found to be more prevalent in urban areas, except rhinitis, which was similar in both groups. However, only wheeze was more prevalent among sensitized urban individuals than sensitized rural individuals.

Table 3.2: Difference between urban and rural participants.

	Urban individuals		Rural individuals		P-value (U versus R)	P-value (U1versus R1)
	(U) All (N= 926)	(U1) With positive SPT (N=165)	(R) All (N=486)	(R1) With positive SPT (N=66)		
	n (%)	n (%)	n (%)	n (%)		
Insufficient House Aeration	422 (45,6)	83 (50.3)	151 (31,1)	25 (37.9)	<0.001	0.087
Mattress Used					<0.001	0.006
Straw/Herbs	43 (4,6)	9 (5.4)	61 (12,6)	11(16.7)		
Sponge/Cotton	883 (95,4)	156 (94.6)	425 (87,4)	55 (83.3)		
Cooking With:						
Electricity	666 (71,9)	123 (74.6)	159 (32,7)	18 (27.3)	<0.001	<0.001
Woods	159 (17,2)	25 (15;2)	240 (49,4)	37 (56.1)	<0.001	<0.001
Embers	882 (95,2)	155 (93.9)	401 (82,5)	53 (80.3)	<0.001	0.002
Trees/Flowers Around House	686 (74,1)	118 (71.5)	439 (90,3)	62 (93.9)	<0.001	<0.001
Active Smoke	200 (21,6)	43 (26.2)	75 (15,4)	10 (15.6)	0.005	0.089
Alcohol	394 (42,5)	72 (43.6)	174 (35,8)	26 (39.4)	0.014	0.556
Complaints:						
Rhinitis	273 (29,5)	67 (40.6)	162 (33,3)	30 (45.5)	0.136	0.500
Rhinoconjunctivitis	246 (26,6)	72 (43.6)	98 (20,2)	27 (40.9)	0.008	0.705
Wheeze	165 (17,8)	39 (23.6)	53 (10,9)	6 (9.1)	0.001	0.012
Skin Itchy Rash	48 (5,2)	15 (9.1)	39 (8.0)	3 (4.6)	0.035	0.244

U: all urban individuals, U1: urban individuals with positive skin prick tests results, R: all rural individuals, R1: rural individuals with positive skin prick tests results.

Prevalence of diseases reported in the 12 previous months

The 12-month prevalence of rhinitis, rhinoconjunctivitis, wheeze and skin itch-rash diseases are showed in Table 3.3.

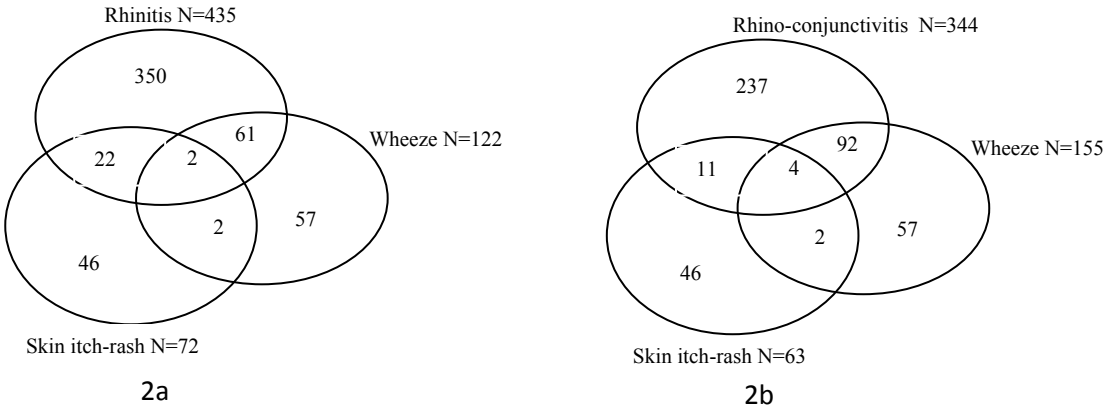
Table 3.3: 12-month prevalence of allergic diseases reported by respondents according to skin prick testing responses.

	All respondents N=1412		Respondents Attending SPT N=1005	Negative SPT N=774	Positive SPT N=231	p-value*
	n (%)	95% CI	n (%)	n (%)	n (%)	
Rhinitis	435(30.8)	28.4-33.2	298 (29.7)	201 (26.0)	97 (42.0)	<0.001
Rhinoconjunctivitis	344 (24.4)	21.1-26.6	292 (29.1)	193 (24.9)	99 (42.9)	<0.001
Wheeze	218 (15.4)	13.6-17.3	178 (17.7)	133 (17.2)	45 (19.5)	0.422
Skin itchy rash	87 (6.2)	4.9-7.6	67 (6.7)	49 (6.3)	18 (7.8)	0.435
No diseases	528 (37.4)	34.9-39.9	338 (33.6)	311 (40.2)	27 (11.7)	<0.001
Any diseases	884 (62.6)	60.1-65.1	667 (66.4)	463 (59.8)	204 (88.3)	<0.001

Percentages within a column do not sum to 100 because of specific diseases are not mutually exclusive. SPT: skin prick testing *P-value based on chi-square testing difference between negative and positive SPT groups.

Females reported significantly more rhinoconjunctivitis than males (27.3% vs. 21.2%; p=0.008). Other diseases were equally distributed between both sexes (all p=NS). The 12-month prevalence of rhinitis (Chi2 for trend, p<0.001) and rhinoconjunctivitis (Chi2 for trend, p=0.03) decreased significantly with increasing age, whereas wheeze increased with age (Chi2 for trend, p=0.03). However, skin itch rash did not change with age (Chi2 for trend, p=0.07). There is an overlap between different diseases reported during the previous twelve months (Figure 3.2 a & b). 78.0%, 21.3% and 0.7% of symptomatic individuals reported one, two and three diseases respectively. The respondents having two or three diseases during the last 12-months more frequently were active smokers (28.3% vs. 20.8%; p = 0.03), reported an atopy history of siblings (25.9% vs. 17.4%; p=0.009) and a personal history of atopy (30.0% vs. 9.5%; p <0.001) than individuals having one disease. Wheezing was more significantly associated with rhinoconjunctivitis than with rhinitis (27.9% vs.14.5%; p<0.001), while skin Itch-rash was as frequently associated with rhinitis and rhinoconjunctivitis (4.4% vs. 5.5%; p=NS).

Figure 3.2 a & b: Association between rhinitis (2a) or rhinoconjunctivitis (2b) with other groups of diseases in 884 participants complaining during the last year.



Allergic diseases according to skin prick testing responses

From respondents who underwent SPT, 23.0% showed positive responses to at least one allergen with DPT and cockroach being the prevalent allergens (Table 3.4). Sensitization was higher among urban individuals than rural (25.1% vs. 19.0%; p=0.028). Among sensitized individuals, 32.0% were poly-sensitized from 2 to 7 allergens. Atopic history of siblings (17.5% vs. 11.2%; p=0.004), personal history of atopy (12.7% vs. 7.6%; p=0.007), cooking with wood (29.9% vs. 24.3%; p=0.04) and cooking with oil (8.4% vs. 4.7%; p=0.02) were statistically more reported by individuals who underwent SPT. In contrast, having carpet (28.0% vs. 21.7%; p=0.01), using fan (55.3% vs. 46.5%; p=0.003) and using air-conditioning (3.4% vs. 1.7%; p=0.04) were predominantly prevalent in the non-attenders. Respondents who underwent SPT more frequently reported rhinoconjunctivitis (29.1% vs. 12.8%; p<0.001) and wheezing (17.7% vs. 9.8%; p<0.001) in the 12 previous months than those who did not. Moreover, rhinitis (29.7%% vs. 33.7%) and skin itchy rash (6.7% vs. 4.9%) were identically reported in both groups (all p=NS).

Table 3.4: Allergens' prevalence among 1005 skin prick tested participants.

	Skin prick tested participants N=1005	
	n (%)	95% CI
Dermatophagoides pteronyssinus	128 (12.7)	10.7 - 14.8
Cockroach	110 (10.9)	9.0 - 12.9
Crab	26 (2.6)	1.7 - 3.8
Grass pollen mix	15 (1.5)	0;4 -2.5
Rabbit	14 (1.4)	0.8 - 2.3
Alternaria alternate	9 (0.9)	0.4 - 1.7
Soybean	8 (0.8)	0.4 - 1.6
Dog	6 (0.6)	0.2 - 1.3
Aspergillus mix	6 (0.6)	0.2 - 1.3
Cat	3 (0.3)	0.1 - 0.9
Guinea pig	3 (0.3)	0.1 - 0.9
Artemisia vulgaris	3 (0.3)	0.1 - 0.9
Cupressus semperviens	2 (0.2)	0.0 - 0.7
Wheat flour	2 (0.2)	0.0 - 0.7
Parietaria judaica	1 (0.1)	0.0 - 0.6
At least one allergen	231 (23.0)	20.4 - 25.6

Prevalence and characteristics of allergic and non-allergic rhinitis

Of 590 individuals who reported rhinitis/rhinoconjunctivitis during the12 previous months, 33.2% and 66.8% had positive and negative SPT respectively. The 12-month prevalence of AR and NAR was 13.9% (95% CI: 12.1-15.7) and 27.9% (95% CI: 25.6-30.2) respectively among all respondents. Keeping pets at home (34.7% vs. 24.6%; p=0.01) was predominantly associated with AR compared to the NAR group. AR was as frequent in males (33.8%) as in females (32.7%) p=NS. Despite the fact that AR did not change according to age groups (Chi2 for trend, p=NS); 57.1% of AR individuals are less than 30 year-old. Other characteristics did not differ between AR and NAR groups (all p=NS, data not shown). Table 3.5 shows that 35.2% of AR individuals reported persistent and moderate to severe symptoms, while 27.5% reported intermittent and mild illness.

Table 3.5: Duration and severity (ARIA classification) of 196 respondents with 12-month allergic rhinitis.

	Moderate/severe	Mild	Total
Persistent	69 (35.2)	25 (12.8)	94 (48.0)
Intermittent	48 (24.5)	54 (27.5)	102 (52.0)
Total	117 (59.7)	79 (40.3)	196 (100.0)

Data expressed in number (percentage); ARIA: Allergic Rhinitis and its Impact on Asthma.

Determinants of having any diseases

The factors associated with having any diseases in multivariate analysis are shown in Table 3.6. Active smoking, presence of cockroach at home, atopy history of siblings, personal history of atopy, using straw or herbs mattress and positive SPT responses independently increased the risk of having any diseases during the 12 previous months.

Table 3.6: Odds ratio of determinants associated with any diseases in Kinshasa (multivariate analysis).

		Adjusted OR	(95%) CI		Z test p-value
Sex					0.06
	Female	1			
	Male	0.7	0.5	1.0	
Age groups (years)					
	≤ 9	1			
	10 -19	0.8	0.4	1.4	0.386
	20 – 29	0.6	0.3	1.2	0.172
	30 – 39	0.6	0.3	1.3	0.189
	40 – 49	0.7	0.3	1.5	0.347
	50 – 59	0.6	0.3	1.2	0.146
	≥ 60	0.3	0.1	0.6	0.001
Education level					
	No education	1			
	Primary school	0.7	0.3	1.6	0.416
	Secondary school	1.4	0.6	3.2	0.387
	University	1.3	0.5	3.2	0.540
Mattress used					0.02
	Sponge/cotton	1			
	Straw/herbs	2.0	1.1	3.4	
Active smoking					0.01
	No	1			
	Yes	1.7	1.1	2.6	
Cockroach in home					0.01
	No	1			
	Yes	1.7	1.1	2.4	
Atopy history of siblings					0.004
	No	1			
	Yes	2.0	1.2	3.1	
Personal history of atopy					0.02
	No	1			
	Yes	1.9	1.1	3.2	
Positive SPT results					<0.001
	No	1			
	Yes	5.5	3.5	8.6	

Goodness of fit by Hosmer and Lemeshow method: p= 0.96. Keeping pets, passive smoking, cooking with oil, self-evaluation house aeration, bedbug, and atopy history of mother were removed from the model.

3.4. Discussion

This first survey in the general population of Kinshasa demonstrated a high prevalence of rhinitis, rhinoconjunctivitis, wheezing and skin itch-rash in 30.8%, 24.4%; 15.4% and 6.2% respectively. These diseases were equally distributed over different age groups. Rhinoconjunctivitis and wheezing were significantly higher among urban individuals. Sensitization was reported in about one quarter of skin prick tested participants with DPT and cockroach being the major allergens. The current rhinitis rate is lower than 37.8% reported in Morocco, where 58.1% of rhinitis individuals simultaneously reported conjunctivitis symptoms [14]. Adults Nigerians [15] aged from 18 to 45 year-old reported 29.6% of AR symptoms. Our 12-month prevalence of rhinoconjunctivitis and wheeze are two times higher than the prevalence reported previously among 13-14 year-old schoolchildren of Kinshasa [7]. The present findings corroborate the fact that allergic symptoms are increasing in Africa as reported in some African countries [8-10] where ISAAC phase I and III were done. However, the current 12-month prevalence of rhinoconjunctivitis is lower than reported in other African cities [7]. Furthermore, our 12-month prevalence of wheeze is in agreement with reports from Grand Tunis and Casablanca (Table 1.2) but differs from the prevalence reported elsewhere [7]. The current skin itch-rash prevalence was lower than the eczema reported in 13-14 year-old schoolchildren in Kinshasa and other African cities (Table 1.2). Govaere E *et al*. [16] reported 23.3% of eczema in Belgian schoolchildren, which is a lot higher than current skin itch-rash rate. This discrepancy is in accordance with the worldwide variability of allergic diseases in relation to different environmental factors. The high prevalence of allergic diseases in urban parts could be attributed to the increased exposure to air-pollution, reduced incidence of infections, sedentary behavior and higher socioeconomic level associated with urbanization diet and lifestyle [17;18]. It has been suggested that the increased hygiene and healthcare in western countries has altered the pattern of exposure to infection in early life, in such a way as to predispose the immune system towards an atopic response.

The urban area of Kinshasa is mainly polluted by roads engineering, uncontrolled expansion of old vehicles, biomass combustion and light industries. Further, a high level of lead was reported in vegetables growing near urban roads and in blood of urban inhabitants of Kinshasa compared to rural areas [19;20]. The reported increasing allergic diseases surveyed in Kinshasa is real and maybe due to the polluted environment factors which can trigger allergic symptoms in predisposed individuals. AR in the present work was found more

frequent in individuals less than 30 year-old. Other studies confirmed this observation that AR is common in childhood, peaks in the early 20s and then decreases [1;15]. Our sensitization rate was not far from the 26.5% and 24.9% reported respectively in Rwanda [21] and Italy [22] where allergy to house dust mites remains prevalent.

Different factors were associated with having any diseases such as active smoking, the presence of cockroaches in the home, using straw or herbs as mattress, positive SPT results, atopy history of siblings and personal history of atopy. Environmental characteristics in poor cities like Kinshasa, where straw or herbs are used in mattresses encourages cockroaches, bedbugs and mites to thrive and could explain the risk of allergic symptoms. The association between the cockroach allergen in rooms and symptoms of asthma or wheezing [23;24] has been shown before. It was demonstrated that the high level of cockroach allergen seem to be associated with lower socioeconomic status [25]. Smoking is known as factor altering mucociliary clearance, causing eye irritation and allergic like-inflammation in the nasal mucosa even in the absence of atopy [26;27]. About one third of AR individuals expressed persistent and moderate/severe symptoms. Allergic complaints could cause significant patient discomfort and impairment in work productivity, school performance, sleep and social interactions similar to other chronic conditions [28]. This high rate of bothersome disease without medical help in our series could be explained by low income and the absence of medical insurance in our country.

The present study has some limitations. Firstly, the interviewers could influence to some extend the respondents during face-to-face questioning. Secondly, exotic allergens like pollens not necessary found in DRC were used. This could underestimate the prevalence of positive SPT results and the AR rate, especially in mono-sensitized individuals. In the years to come we expect to use the specific tropical allergens in a screening tool. Thirdly, the current study was conducted during the rainy season, making the results not extrapolated all year round. This choice was made to avoid the frequent common cold caused by low temperatures and abundant dust air-pollution related to the dry season. Nevertheless, the present work is the first survey to provide with a detailed report on allergic diseases and SPT in randomly selected Congolese individuals living in Kinshasa.

To conclude, this study demonstrates that atopic conditions are common in Kinshasa particularly in urban areas with a negative impact on quality of life. Greater awareness of allergic diseases is needed for effective diagnosis and management in developing countries.

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Chapter 4

SENSITIZATION RATE AND CLINICAL PROFILE OF RHINITIS PATIENTS IN KINSHASA

Nyembue TD, Ntumba W, Omadjela LA, Muyunga C, Hellings PW, Jorissen M. Sensitization rate and clinical profile of Congolese patients with rhinitis. Allergy Rhinol 2012; 3(1):16-24.

Abstract

Background: On the African continent, the sensitization pattern and clinical profile are unknown in patients with rhinitis/rhinosinusitis attending the outpatient ENT clinics. We therefore aimed to analyze the clinical characteristics of rhinitis/rhinosinusitis patients in Kinshasa, classify allergic rhinitis (AR) according to the ARIA criteria and evaluate the sensitization profile and its associated factors.

Methods: From January to May 2009, 423 patients with rhinitis symptoms attending the outpatient ENT clinic of the University hospital and Saint Joseph hospital of Kinshasa were evaluated for allergy symptoms, severity and duration of symptoms and underwent skin prick tests (SPT) for a panel of 15 allergens.

Results: Of 423 patients 35.2% had positive SPT results, with 40.9% showing polysensitization. Dermatophagoides pteronyssinus (DPT) (68.5%) and cockroach (36.2%) were the most common allergens among sensitized patients. Patients with rhinitis/rhinosinusitis mainly presented in decreasing order with sneezing, facial pain/pressure, nasal obstruction, postnasal discharge, nose itching, clear nasal discharge and eye itching. Persistent and moderate/severe AR represented 61.4% and 69.3% respectively. Sensitization was independently associated with younger age, rhinoconjunctivitis and reaction to non-specific trigger factors.

Conclusion: 35.2% of patients attending the ENT Outpatient clinic in Kinshasa for rhinitis problems had a positive SPT to at least one allergen, with mainly DPT and cockroach allergens being involved, and a substantial portion showed persistent and moderate/severe AR. Therefore, allergy should not be neglected as an aetiologic factor in rhinologic disease on the African continent.

Keys words: rhinitis, rhinosinusitis, symptoms, skin prick testing, Kinshasa.

4.1. Introduction

Allergic disorders are increasing and well documented in industrialized countries. The prevalence of allergic rhinitis (AR) is estimated to be as high as 30% in industrialized European countries [1-3]. In addition, nasal allergy is a global health problem, which affects quality of life and adds an economic burden [3]. Environmental factors such as air pollution, local allergens, lifestyle, diet, climate change, temperature and humidity play a role by causing allergic symptoms, particularly in predisposed individuals. In contrast to the abundance of data on Western countries, the immunological, epidemiological and clinic allergological African data are limited [4]. However, an increase of allergic symptoms has been reported in African countries [5;6]. Allergic rhinoconjunctivitis symptom [7] varies from 7.2% to 33.3% among 13-14 year-old African schoolchildren with 11.8% in Kinshasa, Democratic Republic of Congo (DRC). Moreover, 33.0% of AR was reported among Zimbabwean [4] patients with allergic symptoms.

In the DRC, the prevalence of specific IgE-mediated diseases and AR in particular is not known; due to a lack of a screening program for allergic diseases and the quasi absence of specific allergens measurement by serum specific IgE or skin prick tests (SPT) in daily practice. In contrast to rhinosinusitis [8] being reported to be present in 30.9% of patients in primary medical centers of Kinshasa, little is known about the prevalence of AR in DRC. Therefore, we aimed to describe the clinical characteristics of rhinitis/rhinosinusitis, to determine the sensitization rate and the specific allergens profile, to classify AR according to the allergic rhinitis and its impact on asthma (ARIA) guidelines [3] and to evaluate factors associated with sensitization among rhinologic outpatients of Kinshasa.

4.2. Methods

Study population

A cross sectional study was carried out from January to May 2009 in the ENT service of University hospital and Saint Joseph hospital of Kinshasa. Saint Joseph hospital is the referral hospital of more than 20 primary medical centers scattered through Kinshasa [8]. During the study period, consecutive outpatients presenting with nasal symptoms related to rhinitis/rhinosinusitis were included. The exclusion criteria were common cold, use of antihistamines within 5 days before consultation and patients who did not agree with the study protocol. The research section of the medical school of Kinshasa University and the head committee of each hospital approved the study protocol. Furthermore, patients or parents gave an informed consent before enrollment. Two patients were excluded for dermatographism. Of the 423 remaining patients: 74.2% were from University hospital and 25.8% from Saint Joseph hospital.

Questionnaires and clinical examination

A questionnaire was administrated about age, sex, study level, profession, active/passive smoking, number of rooms and persons in the household, keeping cat/dog, having fan/air conditioning, presence of tress/flowers around the house and family/personal history of atopy. We recorded information on medical antecedents such as asthma, rhinoconjunctivitis, eczema and tuberculosis. Finally, the patient's complaints have been registered. The severity [9;10] of symptoms related to allergy, was reported on a visual analogue scale (VAS). In order to categorize AR [3] according to the duration of symptoms, the number of days per weeks and weeks per year with symptoms was reported. The severity was evaluated by questioning the patient's on quality of life: sleep, leisure/sport, daily activities, work and school attendance.

Allergy testing

SPT were performed with 15 allergens (Stallergenes, Belgium). The allergen extracts included dermatophagoides pteronyssinus (DPT), grass pollen mix, artemisia vulgaris, parietaria judaica, cupressus semperviens, dog, cat, guinea-pig, rabbit, cockroach, crab, soybean, wheat flour, alternaria alternata and aspergillus mix. Histamine dihydrochloride 10mg and saline were used as positive and negative control respectively. The drop of each allergen was placed on the volar side of the forearm. And a sterile lancet was pressed for at least 1 second through the allergen's drop by one trained nurse. Fifteen minutes after, one ENT specialist evaluated the mean size of the cutaneous reaction [11]. A positive reaction was defined as a mean weal diameter of ≥ 3 mm.

Operational definitions

Sensitization was defined as the presence of a positive test to one or more allergens. AR diagnosis[3] was based on nasal symptoms including clear nasal discharge, nasal obstruction, sneezing and/or itching with positive SPT results. While, patients with similar symptoms and negative SPT were considered to be non-allergic rhinitis (NAR). Intermittent AR was defined as symptoms lasted for up to 4 days a week or symptoms lasting less than 4 consecutive weeks per year. Whereas, persistent AR when symptoms lasted for more than 4 days a week and for more than 4 weeks per year. Depending on the quality of life, patients were classified as moderate/severe AR if one or more of the following items (sleep, leisure/sport, daily activities, work and school attendance) was disturbed. When symptoms did not impair the quality of life, then AR was taken as mild. Rhinosinusitis [12] including nasal polyps leaned upon two or more following symptoms: nasal blockage/congestion, anterior discharge or postnasal drip, facial pain, smell impairment and endoscopic signs such as polyps, mucopurulent discharge and oedema/mucosal obstruction. We assessed for acute rhinosinusitis when symptoms lasted less than 12 weeks and for chronic rhinosinusitis (CRS) when they lasted for more than 12 weeks.

Statistical analysis

Analyses were conducted using STATA software version 11.0 (Statacorp., Texas, USA, 2009). Qualitative variables were expressed as percents, while mean ± standard deviation (SD) or median were used for quantitative variables. Comparison of proportions was tested by chi-squared test and Fisher's exact test was used if the chi-square conditions were not fulfilled. For continuous variables, Student t-test was used to assess differences between two means. However, a Mann-Whitney U test was applied in case of not normally distributed data or unequal variances. Odds ratio (OR) and its 95% confidence intervals (CI) for potentials risks factors for sensitization were assessed by univariate analysis and independent association confirmed by multivariable analysis. Variables significantly ($p \leq 0.05$) associated with sensitization outcome in univariate analysis were included in the multivariable logistic regression model. The exposure variables included sex, age group, study level, parent history of atopy, sibling's history of atopy, personal allergy to food, personal reaction to non-specific triggers factors, presence of flowers/trees around the home, active smoking, medical antecedents of asthma and rhinoconjunctivitis. The backward stepwise selection process started with all suspected variables and removed those with p-value ≥ 0.10. The significance level was set with a p-value ≤ 0.05.

4.3. Results

Four hundred twenty three patients were included. They ranged from 4 to 89 years with a mean age ± SD of 36 ± 15 years; 62.6% patients were females. Of all patients (Table 4.1), 64.5% lived with more than 5 members per household, 54.8% shared the same bedroom with at least three persons, 66.7% grew trees/flowers around the house and 51.1% had a university education. Others characteristics according to SPT results are shown in Table 4.1.

Table 4.1: Patients' characteristics in accordance to skin prick test responses

	All patients N=423		Patients with positive SPT N=149		Patients with negative SPT N=274		P-value
	n	%	n	%	n	%	
Sex							NS
Male	158	37.4	54	36.2	104	38.0	
Female	265	62.6	95	63.8	170	62.0	
Age group (years)							<0.001
4 - 19	55	13.0	30	20.1	25	9.1	
20 - 39	199	47.0	77	51.7	122	44.5	
40 - 59	142	33.6	35	23.5	107	39.1	
60 - 89	27	6.4	7	4.7	20	7.3	
Number of persons by household							NS
1 - 5	150	35.5	55	36.9	95	34.7	
> 6	273	64.5	94	63.1	179	65.3	
Number of persons by bedroom							NS
1 - 2	191	45.2	65	43.6	126	46.0	
> 3	232	54.8	84	56.4	148	54.0	
Study level							0.043
University	216	51.1	86	57.7	130	47.4	
Under university	207	48.9	63	42.3	144	52.6	
Profession of patients							NS
Students	167	39.5	54	36.2	113	41.2	
Paid work	100	23.6	40	26.8	60	21.9	
Unpaid work	156	36.9	55	36.9	101	36.9	
Home environmental							
Grow flowers/trees a round house	282	66.7	89	59.7	193	70.4	<0.05
Self-declared dampness in house	67	15.8	30	20.1	37	13.5	NS

SPT: skin prick tests. N: number. NS: no significant.

Sensitization rate

Table 4.2 showed that CRS, NAR and AR were the most prevalent diseases in 39.5%, 28.8% and 23.9% respectively. Sensitization to one or more allergens was reported in 149 patients (35.2%). About one quarter and half of patients with rhinosinusitis and rhinitis respectively, had positive SPT results. Sensitized patients were significantly younger than non-sensitized (mean age ± SD: 32 ± 14 vs. 38 ± 15 years; t-test: $p<0.001$). The sensitization rate was similar in males and females (34.2% vs. 35.6%, $p=0.728$). No sex and age groups difference were observed for diagnoses, except AR which decreased significantly with increasing age (Chi2 for trend, $p<0.001$). Among sensitized patients, 59.1% were mono-sensitized and 40.9% poly-sensitized from 2 to 6 allergens. Mono and polysensitization were not statistically different between sexes and between age groups ($p>0.05$ for all comparaisons).

Table 4.2: Sensitization pattern among rhinitis/rhinosinusitis patients

	Positive SPT	Negative SPT	All patients
	n (%)	n (%)	n (%)
Rhinitis	101 (45.3)	122 (54.7)	223 (52.7)
Non-allergic	-	122 (100,0)	122 (28,8)
Allergic	101 (100,0)	-	101 (23,9)
Rhinosinusitis	48 (24.0)	152 (76.0)	200 (47.3)
Chronic	39 (23,4)	128 (76,6)	167 (39,5)
Acute	8 (31,8)	18 (69,2)	26 (6,1)
Nasal Polyps	1 (14,3)	6 (85,7)	7 (1,7)
Total	149 (35,2)	274 (64,8)	423 (100,0)

SPT: skin prick tests, n: number.

Sensitization pattern

Table 4.3 shows the allergen profile. The most prevalent allergens were DPT and cockroach, followed to a lesser extent by grass pollen mix. Moreover, sensitization did not differ significantly between sexes and between age groups ($p>0.05$ for all comparaisons). Allergens profile was similar between AR and sensitized rhinosinusitis patients ($p>0.05$ for all comparaisons).

Table 4.3: Prevalence of allergens sensitization

	Positive SPT responses	Among sensitized patients N=149	Among all Patients N=423
	n	%	%
Indoor allergens	138	92.6	32.6
Dermatophagoides pteronyssinus	102	68.5	24.1
Cockroach	54	36.2	12.8
Cat dander	12	8.1	2.8
Dog dander	5	3.4	1.2
Guinea pig dander	2	1.3	0.5
Rabbit dander	2	1.3	0.5
Outdoor allergens	24	16.1	5.7
Grass pollen mix*	15	10.1	3.5
Parietaria judaica	5	3.4	1.2
Artemisia vulgaris	4	2.7	0.9
Aspergillus mix**	4	2.7	0.9
Alternaria alternata	3	2 .0	0.7
Cupressus semperviens	3	2.0	0.7
Food allergens	19	12.8	4.5
Crab	13	8.7	3.1
Wheat flour	5	3.4	1.2
Soybean	2	1.3	0.5

SPT: skin prick tests; *: Grass pollen mix (cocksfoot, vanilla, timothy, ray and meadow); **: Aspergillus mix (fumigatus, nidulans and niger). N: number.

Clinical profile

The most prevalent complaints (Table 4.4) were in decreasing order: sneezing, facial pain/pressure, nasal obstruction/blockage, postnasal drip, itching nose, clear nasal discharge and itching eyes.

Table 4.4: Clinical complaints of rhinitis/rhinosinusitis patients

	Among all patients	Sensitized patients	Non sensitized patients	P-value
n (%)	423(100.0)	149 (100.0)	273 (100.0)	
Sneezing	326 (77.1)	132 (88.6)	194 (70.8)	<0.001
Facial pain/pressure	310 (73.3)	104 (69.8)	206 (75.2)	NS
Nasal obstruction/blockage	304 (71.9)	109 (73.2)	195 (71.2)	NS
Post-nasal discharge	293 (69.3)	99 (66.4)	194 (70.8)	NS
Itching nose	217 (51.3)	100 (67.1)	117 (42.7)	<0.001
Clear nasal discharge	178 (42.1)	78 (52.3)	100 (36.5)	<0.01
Itching eyes	172 (40.7)	80 (53.7)	92 (33.6)	<0.001
Itching ears	163 (38.5)	68 (45.6)	95 (34.7)	<0.05
Smell loss/decreased	156 (36.9)	66 (44.3)	90 (32.8)	<0.05
Shortness of breath	93 (22.0)	36 (24.2)	57 (20.8)	NS
Dental pain	86 (20.3)	29 (19.5)	57 (20.8)	NS
Nocturnal cough	83 (19.6)	40 (26.8)	43 (15.7)	<0.01
Fever	77 (18.2)	27 (18.1)	50 (18.2)	NS
Purulent/discolored nasal discharge	71 (16.8)	27 (18.1)	44 (16.1)	NS
Ear pain/fullness	65 (15.4)	23 (15.4)	42 (15.3)	NS
Halitosis	64 (15.1)	24 (16.1)	40 (14.6)	NS
Wheezing	45 (10.6)	24 (16.1)	21 (7.7)	<0.01

Percentages within column do not sum 100 because of symptoms are not mutually exclusive. NS: no significant.

Females complained more than males about facial pain/pressure (78.9% vs. 63.9% p<0.001); postnasal drip (73.6% vs. 62.0%, p=0.013); itching nose (57.0% vs. 41.8% p=0.002); itching eyes (46.0% vs. 31.6% p=0.004); nocturnal cough (23.4% vs. 13.3% p=0.011) and ear pain/fullness (19.2% vs. 8.9% p=0.004). Clear nasal discharge, sneezing and wheezing decreased significantly (Chi2 for trend, p<0.05 for all) with increasing age. Postnasal drip and facial pain/pressure increased significantly with age (Chi2 for trend, p<0.05 for all).

The average level of VAS for sneezing, itching nose, itching eyes and clear nasal discharge was statistically higher in sensitized than in non-sensitized patients (Table 4.5).

Table 4.5: The average score level of patients' auto-evaluation complaints according to visual analogue scale.

Complaints	Sensitized patients	Non-sensitized patients	Tests	p-value
Sneezing*	6 (4-7)	4 (3-6)	Mann-Whitney	<0.001
Nasal obstruction/blockage**	5.9 ± 1.9	5.5 ± 2.0	t-test	0.073
Itching nose**	5.8 ± 2.1	5.1 ± 2.0	t-test	0.027
Clear nasal discharge**	6.5 ± 1.8	5.1 ± 1.9	t-test	<0.001
Itching eyes**	5.5 ± 2.1	4.9 ± 2.1	t-test	0.049
Itching ears**	6.1 ± 2.3	6.1 ± 2.6	t-test	0.999
Shortness of breath**	4.8 ± 1.8	4.4 ± 1.9	t-test	0.303
Purulent/discolored nasal discharge**	5.5 ± 1.9	5.3 ± 2.1	t-test	0.79
Wheezing*	5 (3-7)	3 (3-5)	Mann-Whitney	0.113

Data presented as *: median (percentile 25-75) and **: mean ± standard deviation

Between sexes, only itching eye had a significantly higher level of VAS in females than in males (mean ± SD: 5.4 ± 2.1 vs. 4.6 ± 2.3; t-test p=0.038). According to the ARIA criteria, about two thirds of AR patients had persistent and moderate/severe illness (Table 4.6). Endoscopically, nasal mucosa was more congestive or pale in allergic than in non-allergic patients (77.2% vs. 63.5%; p=0.004).

Table 4.6: Duration and severity according to ARIA subdivision in 101 allergic rhinitis patients.

	Moderate/severe	Mild	Total
	n (%)	n (%)	n (%)
Persistent	48 (47.5)	14 (13.9)	62 (61.4)
Intermittent	22 (21.7)	17 (16.8)	39 (38.6)
Total	70 (69.3)	31 (30.7)	101 (100.0)

ARIA: Allergic rhinitis and its impact on asthma, n: number.

Patient characteristics according to sensitization

In univariate analysis (Table 4.7), personal reaction to non-specific triggers factors, parent history of atopy, personal history of food allergy, siblings history of atopy, university education and medical antecedents such as asthma and rhinoconjunctivitis increased significantly the risk of sensitization. The opposite however was observed with active smoking. Passive smoking, keeping pets, tuberculosis in the past and the presence of more than 6 persons per household were also negatively but not significantly linked to positive SPT.

Using a multivariate model (Table 4.7), rhinoconjunctivitis in the past and personal reaction to non-specific triggers factors remained statistically associated with sensitization. Compared to the first age group, sensitization was statistically lower when the patient age increased in both univariate and multivariate analysis. In addition, reduced odds were observed with the presence of trees/flowers around the house in both analyses.

Table 4.7: Odds ratio (95% CI) of co-variables associated with sensitization (univariate and multivariate analysis) (**N**=423, 149 sensitized patients).

Variable		Number	OR (Univariate analysis)	95% CI	P-value	OR*(Multivariate analysis)	95% CI	p-value
sex					0,727			
	Male	54/158	1					
	Female	95/265	1.07	0.70 – 1.67				
Age group in years					0.0006			
	≤ 19	30/55	1			1		
	20 - 39	77/199	0.52	0.28 - 0.96		0.38	0.19 - 0.75	
	40 - 59	35/142	0.27	0.14 - 0.52		0.23	0.11 - 0.48	
	≥ 60	7/27	0.29	0.10 - 0.80		0.27	0.09 - 0.84	
Personal reaction to non-specific triggers factors					<0.001			<0.001
	No	26/172	1			1		
	Yes	123/251	5.39	3.25 - 9.12		5.08	2.99 - 8.64	
Parent history of atopy					<0.001			0.063
	No	109/352	1			1		
	Yes	40/71	2.87	1.65 - 5.01		1.73	0.97 - 3.08	
Personal history of food allergy					<0.001			0.065
	No	131/395	1			1		
	Yes	18/28	3.62	1.53 - 9.03		2.26	0.95 - 5.37	
Flowers/trees around house					0.026			0.01
	No	60/141	1			1		
	Yes	89/282	0.62	0.4 0- 0.96		0.54	0.33 - 0.86	
Rhinoconjunctivitis in the past					0.014			0.027
	No	130/388	1			1		
	Yes	19/35	2.35	1.10 -5.06		2.44	1.11 - 5.39	
Siblings history of atopy					<0.001			
	No	101/333	1					
	Yes	48/90	2.62	1.58 - 4.34				
Eczema in the past					0.200			
	No	134/390	1					
	Yes	15/33	1.59	0.72 - 3.45				
Asthma in the past					0.002			
	No	134/400	1					
	Yes	15/23	3.72	1.43- 10.36				
Tuberculosis					0.608			
	No	144/406	1					
	Yes	5/17	0.75	0.20 – 2.37				
Study level					0.043			
	Under university	63/207	1					
	University	130/216	1.51	0.99 - 2.30				
Passive smoke					0.741			
	No	129/363	1					
	Yes	20/60	0.90	0.66 - 1.66				
Active smoke					0.027			
	No	139/375	1					
	Yes	10/48	0.44	0.19 - 0.95				
Keeping pets					0.649			
	No	85/235	1					
	Yes	64/188	0.91	0.59 - 1.39				
Dampness in house								
	No	119/356	1					
	Yes	30/67	1.61	0.91 – 2.83	0.074			
Number of person by household								
	1 - 5	55/150	1					
	> 6	94/273	0.91	0.59 – 1.41	0.645			

*: Adjusted OR (odd ratio) for others variables in the model. CI: confidence intervals. Goodness of fit by Hosmer and Lemeshow method (p=0.671). Sibling history of atopy, asthma in the past, active smoking, study level and sex were removed from the multivariate model.

4.4. Discussion

The present study reported 35.2% of positive SPT responses mainly to DPT and cockroach among rhinitis/rhinosinusitis outpatients of Kinshasa. This sensitization rate is near to 30.7% reported among Ugandan women [13] with asthma and/or eczema; and to 31.6% in Belgian patients [14] with rhinologic symptoms. The prevalence of sensitization depends on study design, population and SPT method used. The allergens profile reported in the current study is in accordance with several African studies [4;13;15-17] predominated by house dust mites (HDM) and to a lesser extent by pets or cockroach or pollens. Further, HDM [18] are mainly associated to skin sensitization throughout the world, particularly in hot and humid conditions. The tropical climate which is favorable to HDM, could explain its high prevalence. Additionally, Brazilian patients [19] with AR were predominantly sensitive to HDM and cockroach. In the US [20] population, HDM was reported as the main allergen followed by pollens. By contrast, Norwegian schoolchildren [21] were mostly sensitive to pollens, pet and lowly to mite and mould. Similarly, rhinologic patients in Belgium [14] predominately reacted to pollens (69,9%) and DPT (62,1%) followed by animals allergy (26,3%). These results confirm that sensitization patterns vary between regions of the world. In order to better understand allergy, each region needs allergens related to environmental exposures and climate. The same goes for cockroaches [22], abundant in low-income housing and in warm and humid areas. Also, cockroaches may be present in Western countries [20;23;24]. The high exposure and sensitization to cockroach in our study could be explained by underprivileged settings. The deterioration of dwellings, hygiene and work condition is associated with civil war during the two last decades in DRC.

In addition, our study reported large family size and at least half of the patients shared the same bedroom with more than three persons. Pollens allergy is reported as low in African studies [4;15;25] as in our series. The explanation for this relative low pollen allergy is that pollens extracts used are often from a Mediterranean climate and not necessary found in Africa. Although pollens [26] are universally distributed, their nature differs worldwide depending on vegetation, geography, temperature and climate. The observed reactivity to non-native pollens may indicate that there is possible cross-reactivity with local pollens families or maybe individuals were first sensitized outside the country's borders. Furthermore, this low sensitization to exotic pollens could underestimate atopy particularly among patients solely reactive to pollens. Food and molds allergy in the present work was low as reported elsewhere

in African studies [4;13;27;28]. The prevalence of AR (23.9%) in our series was less than 33.0% and 48.6% reported among Zimbabwean [4] and Kenyan [27] patients respectively. AR was three times more self-declared than NAR in Europeans studies [1;29]. The high prevalence of NAR in the current study could be due to the negative SPT to exotic pollens used, not always compatible with tropical flora. Furthermore, some patients with nasal symptoms should probably have only a local nasal IgE inflammation [30], independent of systemic allergy detectable on skin or in serum and thus classify as NAR. Nevertheless, the reported 45.3% of sensitization among all rhinitis patients; corroborates the fact that 53% of rhinitis symptoms in many population-based studies [31] are attributed to atopy.

The most prevalent symptoms in our work were sneezing, facial pain/pressure, nasal obstruction/blockage and postnasal drip, each of them present in more than 2/3 of the patients. Sensitized patients expressed a higher VAS score than non-sensitized for sneezing, itching nose, clear nasal discharge and itching eyes. Molgaard *et al*. [29] reported sneezing and eyes itching more prevalent in AR subjects; while nasal congestion, rhinorrhea and reduced sense of smell were similar in both allergic and non-allergic subjects. In a Belgian survey [1] AR patients reported significantly more symptoms than NAR. AR was found to be persistent and moderate/severe in 36.1% and 89.3% respectively during the pollen season [32]. Also, Bachert *et al*. [1] reported that AR patients suffered more from moderate/severe and persistent symptoms than NAR. In our series, about two third of AR patients, had persistent and moderate/severe symptoms. These results suggest that patients seek medical help when they have worse symptoms affecting thier activities. The high cost of treatment in developping countries, where few people are insured, and the alternative medicine could explain that patients with mild or intermittent complaints are not usually seen at ENT service. Used univariate analysis, the family history of atopy and the personal previous allergic diseases are risk factors for sensitization. This reinforces the fact that atopy is known to be mediated by heredity and environmental factors in consonance with several studies.

Active smoking was negatively correlated to sensitization, and passive smoking showed a statistically non-significant tendency to reduce the risk of atopy. In this study, smoking is not detailed and it does not specify the duration and intensity of exposure to smoke.

Others studies reported an association between exposure to smoke and sensitization in infancy with statistically significant heterogeneity [33;34]. After adjustement, senstization is strongly

associated with younger age, history of rhinoconjunctivitis and reaction to non-specific triggers factors. Arbes SJ *et al*. [20] reported that younger age was independently associated with allergy in the American population. Non-specific triggers factors such as air-pollutants and climate change are known to increase the nasal response to a normal stimulus resulting in nasal hypereactivity in both atopic and non-atopic patients. During the last two decades Kinshasa is mainly polluted by second hands vehicles and biomass fuels used as energy source. There is evidence that pollutants [3;35] promote the effects of aeroallergens and increase the prevalence and severity of allergic respiratory diseases in both non-allergic and allergic individuals. Interestingly, the presence of trees/flowers around the house had an inverse association with sensitization. Pollens monitoring however is to be higher nearest the trees and flowers. While, pollen monitoring is not available in several African countries including our. This finding agrees with a large ecological European study[35], which reported inverse association between pollens counts and prevalence of allergic rhinitis. It seems that high pollen exposure plays a protective role against atopy. Mostly, allergic diseases [36] were found lower in rural than in uban areas and lowest in farming parts suggesting that contact with animals is also protective against sensitization.

There are some weaknesses and constraints associated with the present study. A selection bias may be present as we did not use a representative sample of Kinshasa. However, this bias was minimized by including patients from several primary health care centers scattered throughout Kinshasa and referred to Saint Joseph hospital. A second limitation is related to cross-sectional study which can establish the relationship between a risk factor and outcome, but only a single association. Thirdly, we used exotic pollens extracts, as most specific tropical allergens extracts were not commercially available. Nevertheless, this is the first time to provide new insights on allergy of the upper respiratory airway in Congolese patients particularly allergen profiles. The current calls for further epidemiological study to better understand allergic diseases in order to improve its management in our settings.

In conclusion, sensitization is highly prevalent in rhinologic outpatients of Kinshasa with mainly DPT and cockroach. CRS, NAR and AR represented the most prevalent diagnoses. A substantial portion of AR patients showed persistent and moderate/severe symptoms. Allergic patients expressed higher VAS scores for sneezing, itching nose, clear nasal discharge and itching eyes. Atopic sensitization was significantly associated with younger age, a history of rhinoconjunctivitis in the past and personal reaction to non-specific trigger factors.

Conflicts of interest statement

None declared.

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Chapter 5

ALLERGIC SENSITIZATION, AIRWAY DISEASES, NASAL AND PULMONARY FUNCTION PARAMETERS AMONG INDIVIDUALS EXPOSED TO FLOUR DUST AND CONTROLS IN KINSHASA

Nyembue TD, Kembia E, Lusamba L, Nkoy MJ, Kamanga B, Kayembe JM, Vanoirbeek J, Scheers H, Buntinx F, Hellings PW, Jorissen M. Allergic profile of Congolese individuals exposed to flour dust as compared with a non-exposed work group. Abstract accepted to the 9th Symposium on Experimental Rhinology and Immunology of the Nose (SERIN/EAACI) March 21-23, 2013. Leuven/Belgium.

Nyembue TD *et al*. Article in preparation.

Abstract

Background: Airway symptoms are common among workers exposed to flour dust. However, no such evaluation had been done in Kinshasa.

Methods**:** From April to August 2012, we performed a cross-sectional study among 263 workers directly exposed to flour (wheat, manioc and/or maize), 278 indirectly exposed to wheat flour and 268 controls. Skin prick tests (SPT), peak nasal inspiratory flow and pulmonary function were recorded.

Objective: To determine the prevalence of airway diseases, sensitization rate and allergens profile, to evaluate the risk factors associated with airway diseases and with sensitization among individuals exposed to flour in comparison to those not exposed.

Results: The 12-month prevalence of rhinitis, rhinoconjunctivitis, wheezing and nocturnal cough was 46.0%, 15.8%, 10.6% and 7.5% respectively among all respondents. Compared to controls, rhinitis, rhinoconjunctivitis and nocturnal cough were significantly more prevalent in workers directly exposed. 37.5% of all respondents had positive SPT to at least one allergen, with DPT and cockroaches being the most prevalent allergens. SPT positive to one or more allergens was lower in the directly exposed group compared to controls. Sensitization to storage mite was found to be more prevalent among workers directly exposed than among controls, while positive SPT to pollen mix, sunflower pollen and crab were more prevalent in the control group. Within the directly exposed group, sensitization to manioc flour was higher among individuals exposed to manioc and/or maize flour than among those exposed to wheat flour. 37.0% of individuals reporting rhinitis in the 12 previous months, had positive SPT results. Current smokers had a lower lung function (Tiffeneau index <70%) than never smokers but without statistical significance.

In multivariate analysis, belonging to the directly exposed group, having a flour mill in the neighborhood and having mice in the house significantly increased the risk of having airway disease. Mice in the house increased the risk of sensitization among respondents. However, cooking with electricity was negatively associated with both airway symptoms and sensitization.

Conclusion: Although sensitization was lower in the directly exposed group, flour dust in Kinshasa, like elsewhere implies an increased risk for having airway symptoms compared to controls. Awareness should be raised in matters of hygiene and improved flour dust control measures at workplace.

Key words: Airway symptoms, sensitization, bakery, wheat, manioc, maize, flour.

5.1. Introduction

Occupational rhinitis is an inflammation of the nasal mucosal caused by airborne agents attributable to a particular work environment and not to stimuli encountered outside the workplace [1;2]. It manifests by the occurrence of nasal symptoms such as sneezing, nasal obstruction, nasal discharge and/or itching. Work-related rhinitis is frequently under-diagnosed due to under-reporting of cases, a lack of doctor awareness and an insufficient work medicine especially in developing countries. Although chronic rhinitis is often considered as a trivial disease, symptoms of both occupational rhinitis and asthma are bothersome and affect well-being and productivity. Occupational asthma is the most common occupational lung disease in developed countries ranged from 9 to 15% of the cases of adult asthma [3]. Occupational rhinitis occurs two to four times more frequently than occupational asthma, starts earlier than asthma and is a risk factor for developing occupational asthma [4;5]. Many occupational agents may generate and increase both upper and lower airway symptoms particularly in predisposed individuals. The causes of airway work-related complaints are various. They include animal dander, flours, wood and textile dust, food, spices, storage mites, enzymes, natural rubber latex and chemical agents [1;6-11]. Exposure to flour increases the risk of respiratory diseases, such as occupational rhinitis and occupational asthma. Wheat flour acts as a complete antigen, inducing the production of IgE antibodies and the release of different inflammatory cytokines [12]. These mediators induce damage to the upper and lower airway tract in workers with continuous exposure. The prevalence of occupational rhinitis [13] among people exposed to high molecular weight compounds ranged from 18 to 29% for flour, 28 to 64% for grain dust and 6 to 33% for laboratory animals. There is evidence that the level of exposure is a major determinant of IgE-mediated sensitization to occupational agents and occupational rhinitis [5;13].

Environmental control and surveillance of occupational respiratory diseases are less available in many African countries and little is known about the prevalence and morbidity of occupational respiratory diseases. However, respiratory symptoms were reported to be more prevalent among individuals exposed to grain and flour dust [14-16], detergents [17], cement [18] and welding [19]. Rhinitis and conjunctivitis were reported at 29.5% and 26.0% respectively among Moroccan bakers.

In the Democratic Republic of Congo, Panda L *et al*. [20] and Elenge MM *et al*. [21] reported a high prevalence of occupational symptoms among textile workers and mine workers respectively in comparison to non-exposed individuals. Nevertheless, there is no accurate information about respiratory symptoms and sensitization profile among individuals exposed to flour dust.

This paper aimed to determine the prevalence of airway diseases, the sensitization rate and sensitization patterns, to evaluate the risk factors associated with airway diseases or with sensitization among workers exposed to flour dust as compared to controls.

5.2. Methods

Study population

From April to August 2012 we conducted a cross sectional study in Kinshasa, among individuals exposed to flour for at least one year and controls. We included (a) individuals directly exposed (DEwm) to wheat flour (bakers and pastry cooks of 6 bakeries) and to manioc and/or maize flour (millers and flour sellers of 2 public markets); (b) individuals indirectly exposed (IEw) to wheat flour such as bread sellers, dealers, assistants, messengers, housekeepers of the same bakeries and (c) controls (employees of public ministries and market sellers of other articles without flour exposure).

Individuals with recent and chronic respiratory infections, recent surgery (eye, thoracic or abdominal), thoraco-abdominal wall deformities, and pregnant or lactating women were excluded from the study.

Questionnaire

An adapted International Study of Asthma and Allergies in Childhood questionnaire [22] was interviewer-administered to collect data on respiratory symptoms during the 12-previous months. Rhinitis was evaluated by the item “Have you had problems with sneezing or runny or blocked nose when you did not have a cold or flu in the last 12 months?” If yes, rhinoconjunctivitis was defined by a positive answer to the question: “In the past 12-months, has this nose problem been accompanied by itchy watery eyes?” Wheeze was assessed by: “Have you had wheezing or whistling in the chest in the last 12-months?” If yes, “does this chest problem happen during or after physical activity? Nocturnal cough was assessed by “In the 12-months, have you had a dry cough at night, apart from a cough associated with cold or chest infection? Symptoms of rhinitis and rhinoconjunctivitis were categorized as upper airway symptoms, while wheeze and nocturnal cough as lower airway symptoms.

Additionally, we gathered information on socio-demographic characteristics, lifestyle, home baking of bread, home environment, smoking, alcohol status, and atopy. Smoking status was subdivided in three categories: non-smokers (had never smoked regularly), ex-smokers (had stopped completely at least 1 month prior the study) and current smokers. Passive smokers were defined as subjects who are regularly exposed to environmental tobacco smoke at least during the last 6 months. Bakery workers were examined in a quiet room at the work place

between 7 and 11 a.m. whereas, millers, flour sellers and controls were seen at the medical center closest to their workplace.

Weight and height measurements

A weighing scale (Seca 761, Germany) with a precision of 100 g and a Stadiometer (Seca 213, Germany) with a precision of 0.1 cm were used with the subject standing without shoes. Weight and height were assessed in kilogram (kg) and centimeter (cm) respectively. A body mass index (BMI) in kg/m2 was calculated by the weight (kg) divided by the square of the height expressed in meter [23]. Subjects were classified as underweight (BMI < 18.5), normal (BMI: 18.5-25.0) and overweight (BMI > 25.0)

Skin prick testing

Skin prick tests (SPT) were performed using 19 allergens (Stallergenes, Belgium) and 3 unstandardized local freshly prepared allergen solutions. They included Dermatophagoides pteronyssinus (DPT), storage mite, cockroach, dog dander, cat dander, grass pollen mix (cocksfoot, vanilla, timothy, ray and meadow), sunflower, bakery beer yeast, aspergillus mix, alternaria alternata, maize seed, bean, tomato, banana, peanut, egg, soybean, wheat flour and crab. The local freshly prepared allergens were cassava raw, manioc flour and maize flour. Cassava raw was crushed with a clamp press to obtain juice. Manioc flour (400 mg) and maize flour (400 mg) were separately mixed with 1 milliliter of sterile water to obtain a homogenous solution. Histamine dihydrochloride 10 mg/ml and saline were used as positive and negative control solutions respectively. A drop of each allergen extract was placed on the anterior side of the forearm. And a sterile lancet was held perpendicular to the skin and pressed for at least 1 second through each allergen extracts drop by a single nurse. Fifteen minutes later, an ENT specialist measured the mean wheal diameter reaction on the grid. A test [24] was interpreted as positive if the mean wheal diameter was at least 3 mm greater than the negative control. Sensitization was defined as the presence of a positive SPT results to at least one allergen.

Peak nasal inspiratory flow

Nasal patency was assessed using the peak nasal inspiratory flow (PNIF) device (Clement-Clark, England). An anaesthesia mask was placed over the mouth and nose, and after expiration the individual was asked to close the mouth and forcedly inspire air through the nose. The highest of three measurements was used for analysis.

Micro-spirometry

Pulmonary function was assessed with a portable spirometer (Spirobank, Clement Clarke International, England) according to the manufacturer's instructions. The forced expiratory maneuvers were performed after a brief demonstration and training. After a deep breath and with a clip on the nose, the individual was asked to (a) place the mouthpiece in the mouth, (b) close lips tightly around the mouthpiece and (c) blow through the mouthpiece into the spirometer as completely as possible. The highest of three measurements of forced vital capacity in liters (FVC), forced expiratory volume in 1 second in liters (FEV1), peak expiratory flow (PEF) and forced expiratory flow (FEF) at 25, 50 and 75% in liters of FVC exhaled were used. The ratio FEV1/FVC (Tiffeneau index) was calculated. For smokers, lung function was carried out at least two hours after the last cigarette had been smoked. Lung testing was not performed if the participant had used an inhaler in the last four hours or had oral medication (or long acting beta-2-agonist) in the last eight hours.

Statistical analysis

Statistical analysis was performed using STATA version 11.0 (StataCorp, College Station, TX, USA). Differences between frequencies of categorical variables were tested using chi-square tests. For continuous variables, Student t-test and Anova were used for normal data, and the Mann-Whitney U test and Kruskal-wallis test for nonparametric variables. Odds ratios (ORs) and their 95% Confidence intervals (CI) were generated in uni- and multivariate analysis, to evaluate risk factors of having airway diseases and sensitization.

The association with having airway diseases in the past year ($p \leq 0.10$ in univariate analysis) was used in a backward stepwise multivariable logistic regression model 1. The model included the binary variables: flour mill in the neighborhood, sawmill in the neighborhood, mice in the house, study level, air-conditioning at home, cooking at home with electricity and alcohol intake. Active smoking, age groups and respondents groups were included as scaled variables as well. For multivariate model 2 we included variables univariately associated with sensitization such as mice in the house, trees/flowers around the house, fan in the house, cooking at home with electricity and respondents groups. In addition gender and age groups were added.

However, baking bread using electricity or a wood or diesel generator in bakeries were not modeled because of missing values. The goodness of fit was verified with the Hosmer and Lemeshow method. A two-sided p-value less than 0.05 was considered as significant.

Ethical conditions

The study protocol was approved by the medical inspection of Kinshasa and the research section of medical school, University of Kinshasa. An informed consent was given by consecutive participants after being given the details about the study and before enrollment.

5.3. Results

Participant's characteristics

Of 1102 consecutive individuals invited to be screened, 263 out of 383 DEwm individuals, 278 out of 350 IEw individuals and 268 out of 369 controls agreed to participate and constituted the study population. DEwm individuals comprised 146 exposed to wheat flour and 117 to manioc and/or maize flour. One quarter of all participants was females, and 17% had university education. The participants' median age (P25-75) years was 35 (27-45), ranged from 16 to 72 years with the elderly individuals (≥ 60 years) more prevalent in the control group (Table 5.1). Female gender, university education, having carpet and air conditioning in the house were significantly less prevalent in DEwm group. However, having a flour mill in the neighborhood, presence of dog and mice in the house significantly predominated in the control group. Alcohol intake was found less in the control group (Table 5.1). Other participants' characteristics (Table 5.1) did not differ between respondents groups. Bakeries used electricity, diesel generator and wood in 86.3%, 60.0% and 40.1% respectively.

Table 5.1. Socio-demographic characteristics of respondents

	Not exposed		Indirectly exposed*		Directly exposed**		P-value***
	n	%	n	%	n	%	
Gender							0.002
Females (n= 204)	79	38.7	79	38.7	46	22.5	
Males (n=605)	189	31.2	199	32.9	217	35.9	
Age (year) median (P25-75) (n=809)£	34 (25-50)		36 (28-45)		35 (28-42)		NS
Age group (years):							<0.0001
16-39 (n=506)	153	30.2	173	34.2	180	35.6	
40-59 (n=247)	82	33.2	91	36.8	74	30.0	
≥ 60 (n=56)	33	58.9	14	25.0	9	16.1	
Study level							<0.0001
Under-university (n=672)	206	30.7	215	32.0	251	37.3	
University (n=137)	62	45.3	63	45.9	12	8.8	
Baking bread/cake at home (n=73)	24	32.9	22	30.1	27	37.0	NS
Home bread frequencies:							
< 3 times a week (n=18)	5	27.8	5	27.8	8	44.4	NS
≥ 3 times a week (n=55)	19	34.5	17	30.9	19	34.5	
Carpet in house (n=254)	79	31.1	104	40.9	71	28.0	0.034
Fan in house (n=415)	123	29.6	161	38.8	131	31.6	NS
Air conditioning in house (n=47)	11	23.4	29	61.7	7	14.9	0.001

Having in the neighborhood (≤ 250 meters):							
	Flour mill (n=197)	93	47.2	51	25.9	53	26.9	<0.0001
	Metal workshop (n=54)	19	35.2	20	37.0	15	27.8	NS
	Sawmill (n=110)	42	38.2	41	37.3	27	24.5	NS
Cooking at home with :							
	Electricity (n=545)	177	32.5	198	36.3	170	31.2	NS
	Embers/wood (n=595)	181	30.4	209	35.1	205	34.5	NS
	Oil/gas (n=65)	17	26.2	31	47.7	17	26.2	NS
Cat (n=157)		50	31.8	66	42.1	41	26.1	NS
Dog (n=99)		49	49.5	25	25.3	25	25.3	0.002
Cockroaches in house (n=588)		191	32.5	198	33.7	199	33.8	NS
Mice in house (n=696)		249	35.8	228	32.8	219	31.5	0.001
Trees/flowers around house (n=488)		158	32.4	168	34.4	162	33.2	NS
Childhood's vaccination (n=695)		237	34.1	233	33.5	225	32.4	NS
Alcohol (n=517)		155	30.0	183	35.4	179	34.6	0.006
	Alcohol frequencies:							NS
	Every day (n=99)	38	38.4	31	31.3	30	30.3	
	Occasionally (n=417)	117	28.1	152	36.5	148	35.5	
Persons number by bedroom (mean (SD) (n=806)#		3 (2)		3 (2)		3 (2)		NS
Passive smoke (n=202)		77	38.1	60	29.7	65	32.2	NS
Active smoke								NS
	Never smoke (n=537)	183	34.1	193	35.9	161	30.0	
	Current smoker (n=202)	68	33.7	56	27.7	78	38.6	
	Ex-smoker (n=36)	9	25.0	15	41.7	12	33.3	
Atopic history of :								
	Father (n=46)	12	26.1	23	50.0	11	23.9	NS
	Mother (n=46)	11	23.9	20	43.5	15	32.6	NS
	Siblings (n=31)	31	37.3	26	31.3	26	31.3	NS

*Indirectly exposed to wheat flour; ** directly exposed to wheat, manioc and/or maize flour; *** P-value based on chi-square testing differences between the three groups of respondents. NS: not significant; n: number; £: data expressed as median (Percentile 25-75) and compared with Kruskal-Wallis test; #: data expressed as mean (Standard Deviation) and compared with Anova.

Airway symptoms

Among all respondents (Table 5.2), the 12-months prevalence of rhinitis, rhinoconjunctivitis, wheezing and nocturnal cough was of 46.0%, 15.8%, 10.6% and 7.5% respectively. Except for wheezing, airway diseases were significantly more prevalent in DEwm group than the two others respondents groups.

Table 5.2. Twelve-month prevalence of airway symptoms, anthropometric, nasal and pulmonary measurements of participants.

	Whole sample (N=809)		Controls (N=268)		Indirectly exposed* (N= 278)		Directly exposed** (N= 263)		P-value
Symptoms during the 12-previous months:	n	%	n	%	n	%	n	%	
Rhinitis	372	46.0	100	37.3	121	43.5	151	57.4	<0.0001
Rhinoconjunctivitis	128	15.8	31	11.6	41	14.7	56	21.3	0.007
Wheezing	86	10.6	26	9.7	24	8.6	36	13.7	NS
Wheezing exacerbated by physical activity	43	5.3	13	4.9	16	5.8	14	5.3	NS
Nocturnal cough	61	7.5	17	6.3	15	5.4	29	11.0	0.031
Any symptoms	417	51.6	121	45.1	128	46.0	168	64.0	<0.0001
No symptoms	392	48.4	147	54.9	150	54.9	95	36.1	<0.0001
Measurements:	Whole sample		Controls		Indirectly exposed*		Directly exposed**		
Height (cm)#	168 (9)		168 (9)		168 (9)		167 (9)		NS
Weight (kg)£	62 (55-71)		62 (54-69)		65 (56-73)		60 (52-65)		<0.0001
BMI (kg/m^2)£	21.93 (19.84-24.78)		22.6 (19.5-24.4)		22.6 (20.7-26.4)		21.2 (19.6-22.7)		<0.0001
BMI (kg/m^2) classes :									<0.0001
Underweight n (%)	88 (11.0)		43 (16.4)		18 (6.5)		27 (10.5)		
Normal n (%)	519 (64.6)		166 (61.9)		168 (60.6)		185 (71.7)		
Overweight n (%)	196 (24.4)		59 (22.0)		91 (32.9)		46 (17.8)		
PNIF (L/min)#	131.36 (44.51)		124.09 (38.87)		134.67 (48.23)		135.18 (44.68)		0.014
FVC (L)£	3.08 (2.52-3.61)		3.01 (2.18-3.71)		3.16 (2.72-3.69)		3.00 (2.47-3.45)		0.034
FEV1 (L)£	2.85 (2.30-3.34)		2.81 (2.02-3.34)		2.99 (2.53-3.37)		2.80 (2.33-3.23)		0.018
Tiffeneau index (ratio %)£	95.74 (89.63-99.42)		95.64 (88.87-99.68)		95.64 (89.62-99.34)		95.87 (90.62-99.31)		NS
Tiffeneau classes:									0.020
< 70% n (%)	16 (2.7)		10 (5.2)		5 (2.3)		1 (0.6)		
≥ 70% n (%)	580 (97.3)		184 (94.9)		214 (97.7)		182 (99;5)		
PEF (L)#	5.67 (2.06)		5.53 (2.11)		5.84 (2.17)		5.59 (1.86)		NS
FEF25 (L)#	5.30 (2.00)		5.15 (1.98)		5.41 (2.10)		5.33 (1.89)		NS
FEF50 (L)#	4.35 (1.54)		4.21 (1.54)		4.44 (1.56)		4.37 (1.52)		NS
FEF75 (L)#	2.66 (1.05)		2.55 (1.01)		2.77 (1.15)		2.64 (0.95)		NS

*Indirectly exposed to wheat flour; **directly exposed to wheat, manioc and/or maize flour; *** P-value based on chi-square testing differences between the three groups of respondents. N: number; %: percentage; #: data expressed as mean (Standard Deviation) and compared with Anova; £: data expressed as median (Percentile 25-75) and compared with Kruskal-Wallis test; Cm: centimeter; Kg: kilogram; m: meter; BMI: body mass index; L: liter; PNIF: Peak nasal inspiratory flow; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; PEF: Peak expiratory flow; FEF: Forced expiratory flow at 25%, 50% and 75% of FVC (FEF25, FEF50 and FEF75). NS: not significant.

Baking breads using wood, a sawmill in the neighborhood, alcohol intake, current smoking and belonging to DEwm group significantly increased the risk of having airway diseases (Table 5.3). On the other hand, baking bread using a diesel generator, cooking at home with

electricity, university education, air-conditioning at home and age ≥ 60 years decreased the risk of having airway diseases (Table 5.3). Other characteristics were not related to the presence of symptoms (data not shown). Of 417 individuals with airway diseases, 73.6% had solely upper airway symptoms, 10.3% had lower airway symptoms and 16.1% had both upper and lower airway disease.

Sawmill in the neighborhood OR (95% CI): 3.21 (1.72-6.02), mother atopy OR (95% CI): 3.28 (1.43-7.51), cooking bread at home OR (95% CI): (2.47 (1.18-5.21) and belonging to the DEwm group OR (95% CI): 3.31 (1.67-6.6) compared to controls increased the risk of having both upper and lower airway disease symptoms.

Table 5.3. Univariate analysis of variables associated with airway diseases and with sensitization.

Variables		Associated with having airway diseases (N =809; 417 with diseases)		Associated with sensitization (N=755; 283 with positive SPT to any allergen)	
		Number	OR (95% CI)	Number	OR (95% CI)
Gender	Females	103/204	1	74/180	1
	Males	314/605	1.06 (0.77-1.45)	209/575	0.82 (0.58-1.15)
Age group (years)	16-39	275/506	1	190/484	1
	40-59	126/247	0.87 (0.64-1.17)	76/228	0.77 (0.55-1.07)
	60-72	16/56	0.34 (0.18-0.62)***	17/43	1.01 (0.53-1.91)
Respondents groups	Not exposed	121/268	1	106/240	1
	Indirectly exposed*	128/278	1.04 (0.74-1.45)	85/265	0.59 (0.41-0.86) ***
	Directly exposed**	168/263	2.15 (1.52-3.04)***	92/250	0.74 (0.51-1.06)
Electricity used for baking bread	No	28/51	1	28/48	1
	Yes	166/322	0.87 (0.46-1.57)	87/307	0.28 (0.15-0.52) ***
Baking bread using woods	No	117/247	1	60/233	1
	Yes	97/165	1.58 (1.07-2.36)***	67/161	2.05 (1.34-3.15) ***
Baking bread using diesel generator	No	96/163	1	67/159	1
	Yes	114/244	0.61 (0.41-0.91)***	57/230	0.45 (0.29-0.69) ***
Having a fan in house	No	176/324	1	125/302	1
	Yes	203/415	0.81 (0.60-1.08)	133/393	0.72 (0.53-0.98) ***
Cooking at home with electricity	No	110/181	1	80/175	1
	Yes	269/545	0.63 (0.45-0.86)***	170/503	0.61 (0.43-0.86) ***
Study level	Under-university	357/672	1		
	University	60/137	0.69 (0.48-0.99)***		
Air-conditioning in house	No	333/625	1		
	Yes	17/47	0.50 (0.27-0.91)***		
Sawmill in the neighborhood (≤ 250 meters)	No	339/683	1		
	Yes	69/110	1.71 (1.13-2.58)***		
Alcohol intake	No	112/250	1		
	Yes	286/517	1.53 (1.13-2.07)***		
Active smoker	Never smoker	257/537	1		
	Current smoker	125/202	1.77 (1.27-2.46)***		
	Ex-smoker	17/36	0.97 (0.46-1.92)		
Flour mill in the neighborhood (≤ 250 m)	No	299/600	1		
	Yes	113/197	1.35 (0.98-1.87)		
Mice in house	No	47/106	1		
	Yes	369/696	1.42 (0.94-2.13)		

*Indirectly exposed to wheat flour.

**Directly exposed to wheat, manioc and/or maize flour.

*** $P < 0.05$.

OR: odds ratio.

CI: confidence intervals.

Nasal and lung parameters

The pulmonary parameters in general were not different between respondents groups (Table 5.2). The IEw group had significantly highest values of FEV1 and FVC compared to other respondents groups. Sixteen respondents showed an obstructive lung impairment (Tiffeneau index <70%) with high prevalence in the control group. However, the mean (SD) value of PNIF was statistically lower among controls (Table 5.2). Lung impairment (Tiffeneau index <70%) was more prevalent among current smokers (40.9% vs. 24.6%, p=0.084) than among never smokers, but without statistical significance.

Skin prick testing response

Sensitization was found in 37.5% of all participants with DPT and cockroaches being the most prevalent allergens in 18.0% and 13.9% respectively. They were followed by grass pollen mix, sunflower pollen and storage mite (Table 5.4). Positive reaction to storage mite was significantly more prevalent in DEwm group, while grass pollen mix, sunflower and crab sensitization statistically predominated in the control group (Table 5.4). Among the sensitized patients, 61.8% were poly-sensitized from 2 to 11 allergens. Polysensitization was not different between respondents groups. About 7.0% of all skin tested participants reacted to unstandardized food allergens, without statistical difference between groups.

Within the DEwm group, sensitivity to maize seed was more prevalent among individuals exposed to wheat flour than among those exposed to manioc and/or maize flour (9.2% vs. 2.8%; p=0.038). Sensitivity to manioc flour was higher among individuals exposed to manioc and/or maize flour than among subject exposed to wheat flour (8.3% vs. 1.4%; p=0.009). However, other occupational allergens (maize flour, wheat flour, soybean, storage mite and bakery beer yeast) did not differ between the two subgroups (data not shown).

In contrast to baking bread using wood, baking bread using electricity or a diesel generator, having a fan at home and cooking at home with electricity decreased significantly the risk of sensitization in univariate analysis (Table 5.3). Symptoms, nasal and lung parameters were not statistically different between individuals with positive and negative SPT response (data not shown).

Table 5.4. Skin prick tests results of 755 individuals by respondents group

	Whole sample (n = 755)		Controls (n= 240)		Indirectly exposed* (n = 265)		Directly exposed** (n = 250)		P-value***
	n	%	n	%	n	%	n	%	
Inhalants allergens	259	34.3	94	39.2	81	30.6	84	33.6	NS
DPT	136	18.0	53	22.1	45	17.0	38	15.2	NS
Cockroaches	105	13.9	38	15.8	29	10.9	38	15.2	NS
Grass pollen mix	74	9.8	33	13.8	17	6.4	24	9.6	0.021
Sunflower pollen	71	9.4	39	16.3	13	4.9	19	7.6	<0.0001
Storage mite Ṫ	60	7.9	13	5.4	18	6.8	29	11.6	0.028
Dog	29	3.8	12	5.0	6	2.3	11	4.4	NS
Cat	23	3.0	11	4.6	4	1.5	8	3.2	NS
Alternaria alternate	16	2.1	7	2.9	2	0.8	7	2.8	NS
Bakery beer yeast Ṫ	7	0.9	3	1.3	3	1.1	1	0.4	NS
Aspergillus mix	6	0.8	4	1.7	0	0.0	2	0.8	NS
Food allergens	111	14.7	57	23.8	17	6.4	37	14.8	<0.0001
Crab	49	6.5	34	14.2	5	1.9	10	4.8	<0.0001
Maize seed Ṫ	44	5.8	17	7.1	11	4.2	16	6.4	NS
Bean	34	4.5	15	6.3	6	2.3	13	5.2	NS
Tomato	15	2.0	5	2.1	2	0.8	8	3.2	NS
Peanut	12	1.6	5	2.1	2	0.8	5	2.0	NS
Soybean Ṫ	8	1.1	4	1.7	2	0.8	2	0.8	NS
Egg	7	0.9	4	1.7	1	0.4	2	0.8	NS
Banana	7	0.9	1	0.4	1	0.4	5	2.0	NS
Wheat flour Ṫ	5	0.7	4	1.7	1	0.4	0	0.0	NS
Unstandardized food allergens	57	7.5	17	7.1	15	5.7	25	10.0	NS
Cassava raw	36	4.8	11	4.6	10	3.8	15	6.0	NS
Manioc flour Ṫ	24	3.2	7	2.9	6	2.3	11	4.4	NS
Maize flour Ṫ	15	2.0	7	2.9	3	1.1	5	2.0	NS
At least one allergen	283	37.5	106	44.2	85	32.1	92	36.8	0.019

*Indirectly exposed to wheat flour. **Directly exposed to wheat, manioc and/or maize flour; *** P-value based on chi-square testing differences between the three groups of respondents. NS: not significant, n: number and $^{\dot{T}}$ occupational allergens.

Allergic and non-allergic rhinitis

Among 357 respondents reporting 12-previous month rhinitis and who had skin tested, 63.0% had negative SPT results (non-allergic rhinitis) and 37.0% had positive SPT results (allergic rhinitis). Non-allergic and allergic rhinitis were equally distributed among different respondents groups.

Baking bread using electricity OR (95% CI): 0.4 (0.16-0.97), baking bread using a diesel generator OR (95% CI): 0.51 (0.28-0.96) and cooking at home with electricity OR (95% CI): 0.50 (0.31-0.81) decreased the risk of having allergic rhinitis. Other characteristics were similarly distributed between non-allergic and allergic rhinitis groups (data not shown).

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification, 36.6% and 43.5% of allergic rhinitis subjects expressed persistent and moderate to severe symptoms respectively (Table 5.5).

Table 5.5. ARIA Classification of 131 respondents having allergic rhinitis during the 12 previous months.

ARIA subgroups	Mild n (%)	Moderate/severe n (%)	Total n (%)
Intermittent	58 (44.3)	25 (19,1)	83 (63.4)
Persistent	16 (12.2)	32 (24.4)	48 (36.6)
Total	74 (56.5)	57 (43.5)	131 (100.0)

ARIA: allergic rhinitis and its impact on asthma, N: number

Risk factors of airway symptoms and sensitization

After adjustment (multivariate analysis model 1), flour mill in the neighborhood and mice in the house significantly increased the risk of having airway disease. However, cooking at home with electricity decreased this risk (Table 5.6).

The second model (Table 5.6) showed that cooking at home with electricity was negatively associated with sensitization. In contrast, the presence of mice in the house was positively associated with sensitization. Compared to the control group, belonging to the DEwm group significantly increased the risk of having airway diseases (model 1) and belonging to the IEw group (model 2) was associated with reduced risk of sensitization.

Table 5.6. Adjusted OR (95% CI) of co-variables associated with airway diseases (model 1) and sensitization (model 2) using a multivariate logistic regression.

Co-variables		Co-variables associated with having airway diseases (model 1) N=519		Co-variables associated with sensitization (model 2) N=623	
		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age group (years)	16-39	1	0.595	1	0.339
	40-59	1.04 (0.70-1.56)		0.77 (0.53-1.11)	
	60-72	0.66 (0.28-1.55)		0.76 (0.36-1.61)	
Respondents groups	Not exposed	1	0.0001	1	0.047
	Indirectly exposed*	1.35 (0.87-2.09)		0.59 (0.39-0.86)	
	Directly exposed**	2.77 (1.72-4.46)		0.77 (0.51-1.16)	
Mice in house	No	1	0.048	1	0.015
	Yes	1.80 (1.01-3.21)		1.91 (1.13-3.21)	
Cooking at home with electricity	No	1	0.004	1	0.014
	Yes	0.54 (0.35-0.83)		0.63 (0.44-0.91)	
Trees/flowers around house	No			1	0.064
	Yes			1.38 (098-1.95)	
Alcohol intake	No	1	0.078		
	Yes	1.42 (0.96-2.10)			
Flour mill in the neighborhood (≤ 250 meters)	No	1	0.016		
	Yes	1.7 (1.10-2.59)			

*Indirectly exposed to wheat flour, **directly exposed to wheat, manioc and/or maize flour, OR: odds ratio, CI: confidence intervals.

Model 1. Goodness of fit by Hosmer and Lemeshow method p=0.6607. Sawmill in the neighborhood, study level, active smoke and air-conditioning in house were removed from this model. Model 2. Goodness of fit by Hosmer and Lemeshow method p=0.3410. Gender and fan in the house were removed from this model. Age group (years) was forced into the models.

5.4. Discussion

Our study indicated that belonging to the DEwm group was associated with the risk of having airway symptoms compared to controls. This finding is in consistence with several studies [14-16] reporting a higher prevalence of respiratory symptoms among individuals exposed to flour compared to those without flour exposure. Flour dust is known as an organic fine particle with an array of allergenic and antigenic proteins. Exposure to flour dust in the workplace can affect people by immunologic mechanism as well as by irritation especially for the upper airway [2;13]. In univariate analysis, our study showed that baking bread using wood, currently smoking, alcohol intake and the presence of a sawmill in the neighborhood (Table 5.3) were positively associated with airway symptoms. This could explain the high prevalence of upper airway symptoms in our series, and is suggestive for mucosal irritation by these pollutants. Pollutants are known to affect the airway mucosa, increase nasal and/or bronchial hyperreactivity and increase the susceptibility to infections and allergens with high incidence of airway symptoms [25-27]. Van Miert *et al*. [26] reported that the use of wood fuel particulate was mainly associated with increased risk of respiratory symptoms among adolescents. In our study, using a diesel generator, cooking with electricity and having air-conditioning at home were negatively associated with airway symptoms. This could be due to the low level of exposure to pollutants related to these conditions.

Although the sensitization to mice allergen has not been evaluated, the presence of mice at home was a risk factor of both airway symptoms and sensitization in the current work. This finding is in consistence with many studies [28-30] reporting the contact of mice as a risk factor for the development of IgE-mediated mouse sensitization. In addition mouse allergen exposure was found associated with asthma morbidity [31;32]. We did not perform dust measurements in order to estimate the real impact of exposure level to flour and different allergens or pollutants on respiratory diseases. However based on our observation, five out of six bakeries were traditional ones with underprivileged conditions without any hygiene protection measures against airborne flour, suggesting a high exposure to flour dust and pollutants. Bulat P *et al*. [33] when comparing traditional and industrial bakeries according to the degree of automation, reported that exposure to flour dust and amylase allergens is higher in traditional bakeries.

The prevalence of symptoms reported in the present study was based on interviewed items and may be misestimated according to the influence of the interviewer. However, self-administered questionnaires have been mainly used in epidemiological settings [34;35]. In our series upper airway symptoms (rhinitis/rhinoconjunctivitis) were more prevalent than lower airway symptoms (wheezing and nocturnal cough). This is in accordance with many studies which reported that among bakers the risk of nasal symptoms was about double even four times higher compared to the risk of lung symptoms [4;5;36;37]. Brisman J *et al*. [36] reported that all kind of bakers ran an increased risk for rhinitis, while dough makers and bread formers ran increased risk for having asthma because of high peak exposure of short duration and exposure to fungal amylase enzyme. Nasal symptoms may be triggered at a lower concentration of flour exposure than lung symptoms. It is also known that nasal mucosa is more exposed to higher amounts of inhaled pollutants and only small amounts reach the lung mucosa [2;4]. Unlike other studies that showed an impairment of lung function related to exposure to wheat flour [38;39], our study did not find such an impact. The fact that we excluded participants using inhaler or beta-2 agonist from lung test could explain the low rate of lung dysfunction. In this regard inhalant flour dust may play a role together with the cumulative duration of the exposure [39].

Our study showed that around one third of all respondents and of DEwm individuals (Table 5.4) had positive SPT response to at least one allergen tested. Dermatophagoides and Cockroaches remained the most prevalent allergens as reported in previous studies in Kinshasa [40;41]. The current study reported the high prevalence of sensitization and in particular sensitization to grass pollen mix, sunflower and crab among the control group. This finding could partially be due to the methodology of sampling. As we did not make a random selection, control individuals who had an allergic background might be more likely to attend the survey and SPT investigation than did individuals without such history. The opposite tendency might be found among workers directly exposed to flour dust who did not approve the medical examination at the workplace for fear of being misjudged and losing their job. Additionally, it has been established that sensitization to occupational allergens depends on level and duration of exposure at workplace. We did not evaluate the sensitization rate according to the time of employment at the workplace. Nevertheless, the present work found a relation between exposition to manioc and/or maize flour and the sensitization to manioc flour within the directly exposed individuals. Of all workplace allergens, the sensitization rate to

storage mite was higher among workers directly exposed to flour (Table 5.4) compared to controls. Storaas T *et al*. [42] reported storage mite as the most frequent source of sensitization among Norwegian bakers with occupational rhinitis. It has been demonstrated that storage mites mainly affect stored products producing flour.

Although cassava is the main source of carbohydrates especially in subtropical African countries [43-45], our series reported a low prevalence of positive SPT to cassava raw and flour. An IgE-mediated allergic reaction to cassava was recently reported in patients after the ingestion of fresh or cooked cassava [44;45]. In these cases cassava allergy was usually secondary to latex allergy due to the cross-reactivity in the latex-fruit syndrome. However Antolin-Amerigo D *et al.* [43], described a unique case of anaphylaxis after ingestion of boiled cassava without associated latex-fruit syndrome.

There are several limitations in the present study. First the data collection was restricted to six bakeries because of lack of a bakeries census in Kinshasa, refusal by many managers of bakeries to cooperate and limited means. Second, the reported symptoms could be influenced by the interviewers or underestimated by bakery workers when screened at the workplace without strict confidence. Third, all participants were consecutively invited and could more easily agree to participate if they had an atopic background. This bias could partly explain the high prevalence of sensitization and lung dysfunction among control individuals. Nevertheless, the present work is the first to assess respiratory symptoms, sensitization and lung parameters among bakery workers of Kinshasa. Further studies with random selection of individuals exposed to flour dust and with exposure measurements to check differences of exposure among bakery workers performing different tasks, in comparison to individuals without such exposure are needed.

To conclude, belonging to the directly flour dust exposed group was a risk factor for airway symptoms. DPT, cockroaches and occupational allergens should be incorporated when assessing individuals with such exposure. Measures to reduce flour exposure and environmental hygiene surveillance at the workplace may be the most effective means to reduce the prevalence of work related airway diseases.

Conflicts of interest statement

The authors state that there is no conflict of interest.

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Chapter 6

GENERAL DISCUSSION AND PERSPECTIVES

6.1. General discussion

The present study was carried out in order to provide new insights into allergic diseases in Kinshasa. Before our studies, only very limited work was done about allergic diseases in the Democratic Republic in Congo (DRC). The International Study on Asthma and Allergies in Childhood (ISAAC) [1] reported that the prevalence of rhinoconjunctivitis, eczema and wheezing was 11.8%, 10.9% and 7.5% respectively among 13-14 year-old schoolchildren of Kinshasa, the capital of DRC. However, the comprehension of both prevalence and determinants of allergic rhinitis (AR) and associated diseases among the general or specific fringe of population of Kinshasa were not known. Furthermore, locally prevalent allergen sources causing allergic diseases are not evaluated in our settings.

In chapter 3 of this thesis [2], we conducted a cross-sectional clustered survey on the general population of Kinshasa using an adapted ISAAC questionnaire [3] and skin prick testing (SPT) procedure. We randomly selected 1412 individuals (1/3 from rural and 2/3 from urban areas of Kinshasa) aged from 5 to 83 years and 1005 were skin tested. Chapter 4 [4] was devoted to the clinical characteristics of rhinitis/rhinosinusitis and the allergic sensitization profile of outpatients presenting with nasal symptoms at the Otorhinolaryngology services of Kinshasa. A total of 423 patients aged from 4 to 89 years were included. Finally, in chapter 5 of the present work we investigated the airway diseases, sensitization, nasal and pulmonary function among individuals exposed to flour compared to the individuals without such environmental exposure. In this cross-sectional survey were included: 263 workers directly exposed to flour dust (wheat, manioc and/or maize), 278 individuals indirectly exposed to wheat flour and 268 unexposed individuals as control group.

Prevalence of allergic diseases

The prevalence of allergic diseases in the general population of Kinshasa is shown in table 3.3. Rhinitis, rhinoconjunctivitis, wheeze and skin itch rash were reported in 30.8%, 24.4%, 15.4% and 6.2% respectively. Rhinitis remains one the most frequent chronic diseases with many data available especially in childhood [5]. The overall prevalence of current rhinoconjunctivitis across the world [6] was 14.6% for the 13-14 year-old children, with higher rates observed in middle and low income countries such as in Africa and Latin America. Unfortunately it seems not easy to compare the prevalence observed in the current studies to that in other countries due to a different methodology used and to the heterogeneity

of the populations targeted. Moreover, African data available (Table 1.2) on allergic diseases are restricted to the ISAAC survey in 13-14 year-old schoolchildren [1].

Based only on a questionnaire, the prevalence of allergic diseases could be misestimated depending on the recalling of symptoms without any objective testing. In addition, the possible real explanation of difference in reported prevalence of allergic diseases between countries was due to different environmental exposure (allergens and pollutants) and the different methods used for treatment. Our study carried out in general population [2], showed a high prevalence of allergic diseases in urban areas compared to rural areas with lower pollution. This could partly be due to the pollution mainly encountered in urban parts of Kinshasa [7-9]. Several studies [10-14] reported atopy and AR to be more prevalent in urban areas related to increasing levels of allergens, pollutants and to the westernized lifestyle. This is consistent with the "hygiene hypothesis" which stipulated that growing up in urban areas with more hygiene, decreased infections and reduced endotoxin exposure predispose to development of allergic diseases [15-17].

According to the SPT results, the 12-month prevalence of AR (nasal symptoms and positive SPT) was 13.9% in the general population [2]. This prevalence was not far from the 16.9% of clinical diagnosis of AR among Italians (aged over 18 years) in a population-based study; and was lower than that in other Western European [18] countries (Table 1.1).

The current work reported 23.9% of AR among patients at Congolese ENT services [4]. This rate was lower than 33.3% reported among Zimbabwean patients [19] and 48.6% among Kenyan patients [20]. In addition, chapter 5 of the current work reported that 37.0% of workers directly exposed to flour dust and having rhinitis/rhinoconjunctivitis symptoms showed positive SPT ascertained AR diagnosis. Therefore, according to our findings, AR and associated diseases are common in Kinshasa and are frequently undiagnosed. More attention is needed from the health care program to diagnose and manage allergic diseases in DRC.

Determinants of allergic diseases

The variable prevalence of allergic disease is mainly due to different environmental exposure. Our study [2] showed that active smoking, siblings and personal atopy, the presence of cockroaches in the house, using straw or herbs as a mattress and positive SPT increased the risk of having any diseases in the general population of Kinshasa. This confirms the role of pollutants as non specific triggers of allergy. The importance of atopy and sensitization as a

risk factor for allergic diseases has been reported elsewhere [21;22]. Among patients (Table 4.7) we found that reaction to non specific triggers and rhinoconjunctivitis in the past increased the risk of sensitization. However, growing trees/flowers around the house was negatively associated with sensitization to at least one allergen. Epidemiological studies have confirmed a strong association between air-pollution and both development and exacerbation of both AR and other allergic diseases.

Air pollutants [23] may intensify allergic reactions by modifying the epithelium, influencing immunity and increasing the allergenicity of particular antigens. Several studies demonstrated diesel exhaust particulate [24;25] as a potential carrier of allergens and are characterized by both adjuvant activity for sensitization against common allergens and by enhancing effects on allergic symptoms in sensitized patients.

Our findings showed that environmental exposure to flour dust (Table 5.6) at work or in the neighborhood significantly increased the risk of having airway disease. However, the presence of mice in the house was positively associated with both airway disease and sensitization. This is in agreement with many studies [26-28] reporting that upper and lower respiratory symptoms are more prevalent among individuals exposed to flour dust. Both immunologic reactions and the irritative role of flour exposure were involved.

Allergic Rhinitis and its Impact on Asthma classification

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [29] categorized AR in four subgroups depending on duration and severity of symptoms. Our studies reported that half of AR individuals in the general population [2] and about two thirds of AR patients presenting at ENT services of Kinshasa [4] expressed moderate to severe and persistent symptoms. Despite the fact that AR is considered a trivial disease, a substantial portion of people had bothersome symptoms and co-morbidities affecting their quality of live and productivity. Among Western European population, one third of subjects with AR reported persistent symptoms [18]. Demoly P *et al*. [30] in medical practice in France reported that nearly half the subjects with seasonal AR had persistent symptoms. It has been shown that many patients seek a appropriate medical help when symptoms are severe and bring about high societal costs [5].

Allergic sensitization profile

Cross-sectional studies regarding children and adults strongly suggest that there is a close association between allergen exposure and sensitization to specific allergens [31;32]. In our

series we found that one quarter of individuals [2] had positive SPT responses to at least one allergen in the general population of Kinshasa. Furthermore, about one third were sensitive among ENT patients [4] and among individuals exposed to flour dust (Table 5.4) in Kinshasa. Dermatophagoides pteronyssinus (DPT) and cockroaches remain the most prevalent allergens in our series. Several studies reported DPT as the predominant allergens in many countries [19;33;34]. Bakken HN *et al* [35] reported cat as a predominated allergen followed by dog, pollen and by low rate of mites among Norwegians school children.

The difference in allergens could be due to climate differences [36] which determine the flora and fauna within particular geographic regions and thus determine the sources of airborne and food allergens. Grasses are the most common cause of hay fever in Europe, with more than 40% of allergic patients sensitized against grasses [37]. Airborne perennial allergens (mites, cockroach and animal dander) and seasonal allergens (pollens, molds) may both elicit or exacerbate allergic diseases. The development of hypersensitivity to cockroaches is associated with the presence of their droppings and secretions in house dust [38]. Cockroach allergen levels have been associated with allergen sensitivity and development of asthma [39;40] and wheezing in young children [41]. In our studies, the unprivileged conditions could explain the presence of cockroaches and mice mainly reported in houses. Furthermore, prenatal exposure to cockroach and mouse allergens may prime the immune system of fetuses and contribute to the development of allergies [42]. The present work reported the low rate of pollen sensitization similar to that in other central African countries. This finding might underestimate the real prevalence, as the pollen extracts used for SPT were exotic because of the unavailability of commercial local pollen reagents. Indeed, the positive reaction to exotic pollen allergens probably does not correspond to real clinical allergy, but could be due to cross-allergenicity or pan-allergens [37].

Allergy to unstandardized food allergens such as cassava (raw/flour) and maize flour was low in our series (Table 5.4) as reported elsewhere [43-45]. These studies described cases of allergy to ingested cassava linked to latex-fruit syndrome.

We found that at least one out of three individuals with positive SPT responses were polysensitized in the general population survey [2] and in the hospital-based study [4]. However, about two thirds of sensitive individuals exposed to flour dust reacted to two or more allergens tested. As other African studies [46;47], the present work showed a low rate of multiple sensitizations. This could be due to the low positive skin prick reactions to exotic pollen used in these studies, as specific African pollen extracts are not commercialized.

By contrast, the European studies showed a low rate of monosensitized patients of 17.8% to 25% in Italy [48;49], 36 % in French [50] and 46 % in Belgium [51]. Polysensitization may widely range from 20 to 90% in different evaluated populations through the world [48-54]. The increasing number of sensitizations in the same patient seems to characterize the natural history of allergic disease and may represent a typical evolution of allergy [55;56].

It was been documented that allergic diseases in infants [55] start always with single sensitization. However, there are patients that remain monosensitized during their life. Polysensitization is an immunological phenomenon clinically more significant and relevant. Many studies reported that polysensitization is associated with different clinical features in respect to monosensitized patients, and especially with a more impaired quality of life and economic burden [54;57]. Peternel R *et al*. [58] reported that polysensitized patients had more severe symptoms than monosensitized ones. In addition, Ciprandi G *et al*. [54] has observed that polysensitized patients with rhinitis present higher asthma comorbidity than monosensitized patients. Indeed, it has been hypothesized that a functional defect of T regulatory cells may explain the tendency to develop polysensitization [59] and this could explain two different phenotypes for mono- and polysensitized subjects. Children with persistent monosensitization produced higher quantity of IL-10 and IFN-γ than children developing polysensitization [59]. Compared to the monosensitized ones, polysensitized patients may react less favorably to allergen specific immunotherapy [60;61].

Strengths and Limitations

The present study is the first population-based one conducted in urban and rural areas of Kinshasa**.** It is an opportunity to get an overview of AR and associated diseases according to the ARIA guidelines. This thesis demonstrated the prevalent allergen sources which should constitute the tool for clinical diagnosis of allergic diseases in Kinshasa in order to plan an appropriate management. Therefore, the current studies opened a new area in AR and associated diseases in the Democratic Republic of Congo.

However, there are limitations related to the present work. Due to restricted resources we could not yet analyze environmental exposure both in houses and at the workplace in order to establish the relationship between the sensitization profile and allergic diseases. One of the weaknesses is that patients presenting at ENT services and workers exposed to flour dust and their controls were consecutively selected. This could reduce the representativity of the population. We assessed prevalence using the face-to-face questionnaire. In that case

interviewers could partly influence the outcomes. Finally, exotic pollen allergens were used for SPT as local pollen resources are not well known and therefore not available commercially. The use of exotic allergens may underestimate the sensitization rate especially among mono-sensitized individuals who reacted to pollens. Nevertheless, the current work provides with allergen sensitization profile in Kinshasa.

6.2. General Conclusions

This doctoral project conducted in Kinshasa, the capital of the Democratic Republic of Congo provides a better understanding of clinical and epidemiological aspects of allergic rhinitis and associated diseases. The studies analysed determinants and sensitization profiles of allergic diseases in our settings. The present work showed that allergic diseases and sensitization are common in Kinshasa, with higher prevalence in urban than in rural parts. Dermatophagoides pteronyssinus and cockroaches remain the most prevalent allergens and should be included in the panel of allergen extract to be used for skin prick test in our country. Therefore, greater awareness of allergic diseases is needed to improve its diagnosis, control measurements and management.

6.3. Perspectives

This research project opens a freeway in the field of allergic diseases in the Democratic Republic of Congo. We are planning to implement ARIA classification in order to optimize the management of allergic diseases. Studies are needed to improve the inhabitants' settings, to reduce the indoor perennial airborne allergens and pollutants such as cockroaches, mice and others. In addition environmental exposure measurements should be involved for understanding the real importance of air-pollution in our country.

With allergic diseases, knowing the relationship to specific or potential allergens is important to determine the best therapeutic intervention such as immunotherapy and the subsequent prevention measurements. In that event, the role of local specific pollen allergens related to the Congolese flora will be subject of future studies.

Despite the guideline-directed treatment algorithms, some patients still experience bothersome symptoms and constitute the patient group with uncontrolled chronic upper airway disease. That being the case, our future projects will focus on reduction of underdiagnosed and undertreated AR in Kinshasa in order to improve insight into the allergic diseases in the African continent.

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Curriculum vitae

The author of this thesis, Dieudonné Nyembue Tshipukane was born on 25 December 1966 in Mbujimayi, D R of Congo. In 1985 he graduated from the secondary school at Institut Luse (Mbujimayi). In 1993 he received the degree of medical doctor at the University of Kinshasa. In 1996, under the supervision of Professor Dr Christophe Muyunga, he started his specialist training at the Otorhinolaryngology Department of the University Hospital of Kinshasa. He became certified in Otorhinolaryngology in 2001 at the University of Kinshasa. After a short training funded by KU Leuven Alumni at the ENT Department of the University of Leuven in 1996, he received a Belgian Development Agency (BTC) scholarship for PhD training program. From 2007 to 2008 he followed a pre-doctoral program at the Ear Nose Throat Head and Neck Surgery Department of the University of Leuven under the supervision of Professors Drs Mark Jorissen and Peter Hellings. He then obtained the pre-doctoral degree. Afterwards, he started a sandwich PhD program supervised by the same Professors of the University of Leuven. The Congolese research part is under the guidance of Professors Drs Christophe Muyunga and Jean-Marie Kayembe. In 2009, he completed the "Epidémiologie et statistiques appliquées à la santé" summer course at the Université Libre de Bruxelles.

Presently, he is a "chef de travaux" at the Otorhinolaryngology Unit of the Faculty of Medicine at the University of Kinshasa. Furthermore, he is a member of the Belgian Society of Otorhinolaryngology Head and Neck Surgery, the Congolese WHO collaborating centre of Allergic Rhinitis and Its Impact on Asthma, the "Societé d'Otorhinolaryngologie et de chirurgie cervico-faciale d'Afrique Francophone" and the "Societé Congolaise d'Otorhinolaryngologie".

After his PhD program, he will continue a career at the Medical School of the University of Kinshasa and from time to time will be involved in a clinical training at KU Leuven.

He is married to Lucie Mbuyi Mbiya. Their sons are Dieulu, Divin and Daniel and their daughters are Dieumi, Davina and Daniella Nyembwe.

List of publications

Articles in International peer reviewed journals

- Prevalence and determinants of allergic diseases in a Congolese population.
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- Allergic sensitization, airway diseases, nasal and pulmonary function parameters among individuals exposed to flour dust and controls in Kinshasa.
Nyembue TD, Kembia E, Lusamba TL, Nkoy LM, Kamanga MB, Kayembe JM, Vanoirbeek JA, Scheers H, Buntinx F, Hellings PW, Jorissen M. Manuscript in preparation.

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