

Allergic sensitisation in South Africa: Exploring regional variation in sensitisation

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Background. Allergy is a common health problem in South Africa (SA), and a rational approach to allergy testing is essential to ensure cost-effective as well as optimal patient diagnosis and management.

Objectives. To review allergy testing data with respect to current national testing recommendations, and to explore the regional variations in sensitisation.

Methods. Retrospective data review on allergy testing from a private pathology provider in SA over a 2-year period. Data on skin-prick testing (SPT) and allergen-specific IgE testing originating from all the provinces of SA were collected and analysed with regards to allergen positivity rate and regional sensitisation patterns.

Results. Among the patients ($N=45\ 0320$) tested for a suspected inhalant allergy, 46% tested positive. Only 45% of these received additional testing for the nine recommended inhalant allergens included in the current national testing protocol. Among the patients ($N=6\ 775$) who received SPT for a suspected inhalant allergy, 59% yielded one or more positive results. The most frequent sensitising allergens were house dust mite (*Dermatophagoides pteronyssinus*) and grass pollen. The house dust mite, *Blomia tropicalis*, was a significant sensitiser in coastal regions. SPT identified two other important regional allergens which are not included in the current recommendations for inhalant allergen-specific IgE testing.

Conclusions. The current diagnostic recommendations include allergens that demonstrate significant sensitisation in all regions of SA. Two additional allergens that show significant regional sensitisation in the South African population were identified. These findings may aid the recommendations for the most appropriate and cost-effective approach to allergy testing of symptomatic patients in SA.

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Allergies are common health problems throughout the world that contribute significantly to patient populations in both primary care and specialist practices in South Africa (SA). Allergy testing in conjunction with a good patient history remains the cornerstone of allergy diagnosis and appropriate allergy management. The identification of allergic sensitisation patterns in SA, as well as regional variations in these patterns, should guide the ordering of appropriate tests in symptomatic patients and contribute to guidelines for appropriate allergy diagnosis.^[1]

Allergy testing may be expensive if large allergen panels are ordered indiscriminately. Therefore, it is essential to identify the most appropriate allergens to be tested, which will not only benefit the patient financially, but also lead to appropriate diagnosis with the resultant health benefits.

Objectives

To collect and analyse data on national and regional allergen sensitisation patterns in the private healthcare sector of SA. This analysis could indicate whether the current national allergy testing recommendations are relevant, whether additional allergens may need to be considered for future testing protocols and whether there is a distinct regional difference in allergen sensitisation patterns.

Methods

Retrospective data on allergy testing performed from 1 January 2016

to 31 December 2017 at AMPATH, a national private pathology provider in SA, were collected anonymously from patient databases. The site where the SPT was performed or where the patient's blood specimen for allergy testing was collected was used to categorise patients demographically. Patient data originating from the nine provinces of SA were collected. The Northern Cape data were excluded from regional allergen analysis, as the volumes of allergy tests ordered were not sufficient to identify statistically significant regional allergens. Skin-prick testing (SPT) was not available in the Northern Cape or the Free State, therefore no regional SPT data were available for these regions.

Data were collected on SPT (Immunotek, Spain) and allergen-specific IgE testing (ImmunoCAP; Thermo Fisher Scientific Inc., Sweden). Special attention was given to regional allergen sensitisation patterns and differences between SPT and allergen-specific IgE sensitisation results. Data were collected on allergens frequently requested as per the South African Allergic Rhinitis Working Group (SAARWG)/Allergy Society of South Africa (ALLSA) protocol for IgE-mediated allergy, namely Bermuda grass, Rye grass, *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, cat and dog, as well as the more frequently requested regional allergy tests and cross-reactive allergen component tests. Allergen-specific IgE was reported as a value between 0.1 and 100 kUA/L, with allergen sensitisation defined as the presence of allergen-specific IgE

>0.35 kUA/L. A skin test with a mean wheal diameter at least 3 mm greater than the negative saline control was considered to be positive and an indicator of allergen sensitisation.^[2]

For this descriptive study data were presented in tabular form, initially grouping individual allergen positivity nationally, followed by individual allergen positivity per geographic region. A 95% confidence interval was used and data were analysed using STATA version 14 (StataCorp., USA).

Results

A total of 45 032 patients were tested for a suspected inhalant allergy with a Phadiatop screening test (ImmunoCAP) and a total of 6 775 patients were tested for an inhalant allergy by SPT.

Of the patients who were tested by the Phadiatop allergy screening test, 20 696 (46%) returned positive results for an allergic sensitisation. However, only 9 395 (45%) of these patients received additional testing, according to the SAARWG/ALLSA recommendations, to identify the causative inhalant allergen.

Data were assessed to determine the most prevalent sensitisation patterns overall for the individual allergen-specific IgE allergens tested on patients with positive Phadiatop inhalant screens (Table 1). A regional breakdown of the sensitisation patterns for individual IgE allergens tested on patients with positive Phadiatop inhalant screens was performed and reported as a point prevalence (Table 2).

On analysis of SPT data, it was found that 3 980 of the 6 775 SPTs performed (59%) yielded one or more positive results. A regional breakdown was performed of the sensitisation patterns for individual IgE allergens on SPT and reported as a point prevalence (Table 3).

As the house dust mite is one of the most important allergens in SA,^[3] data were further analysed to investigate potential cross-reactivity between *D. pteronyssinus* and *B. tropicalis* on specific IgE testing and SPT. Regional sensitisation to *D. pteronyssinus* IgE (Table 4) or house dust mite (HDM) mix SPT (Table 5) was compared with *B. tropicalis* sensitisation in patients on whom both allergens were tested simultaneously.

As grass pollen is a major allergen in SA and maize pollen, which is only included in SPT profiles from four SA provinces, has demonstrated significant patient sensitisation, further analysis of SPT data for potential cross-reactivity between these two allergens was performed.^[3] Regional sensitisation to Bermuda grass pollen and maize pollen on SPT was compared in patients on whom both allergens were tested simultaneously (Table 6).

Previous SA data have shown an increase in sensitisation rates to foods of plant origin in regions with the highest pollen

Table 1. Positivity rate of patients testing positive on a Phadiatop inhalant screen (N=9 395) for individual inhalant IgE allergens

Allergen	n (%)
<i>D. pteronyssinus</i>	5 269 (56)
Bermuda grass	4 958 (53)
Rye grass	4 653 (50)
<i>A. alternata</i>	3 335 (35)
<i>B. tropicalis</i>	3 101 (33)
Dog	2 719 (29)
Cat	2 217 (24)
<i>A. fumigatus</i>	2 214 (24)
<i>C. herbarum</i>	1 812 (19)

Table 2. Ranking of regional sensitisation for individual IgE allergens

Ranking position	Provincial regions of South Africa								
	Gauteng	Northwest	Mpumalanga	Limpopo	Free State	KwaZulu-Natal	Eastern Cape	Western Cape	
1	Bermuda grass 61%	Bermuda grass 67%	Bermuda grass 60%	<i>D. pteronyssinus</i> 61%	Bermuda grass 72%	<i>D. pteronyssinus</i> 85%	<i>D. pteronyssinus</i> 82%	<i>D. pteronyssinus</i> 74%	
2	Rye grass 55%	Rye grass 63%	<i>D. pteronyssinus</i> 58%	Bermuda grass 50%	Rye grass 71%	<i>B. tropicalis</i> 62%	<i>B. tropicalis</i> 57%	Rye grass 58%	
3	<i>D. pteronyssinus</i> 43%	<i>D. pteronyssinus</i> 38%	Rye grass 49%	Rye grass 48%	<i>A. alternaria</i> 36%	Bermuda grass 25%	Bermuda grass 39%	Bermuda grass 44%	
4	<i>A. alternaria</i> 41%	<i>A. alternaria</i> 38%	<i>A. alternaria</i> 35%	<i>A. alternaria</i> 40%	Dog 35%	Dog 23%	Rye grass 36%	<i>B. tropicalis</i> 43%	
5	Dog 29%	Dog 31%	Dog 33%	<i>B. tropicalis</i> 32%	<i>D. pteronyssinus</i> 30%	Rye grass 21%	Dog 30%	Dog 30%	
6	<i>A. fumigatus</i> 27%	Cat 26%	<i>B. tropicalis</i> 29%	<i>A. fumigatus</i> 27%	<i>A. fumigatus</i> 29%	<i>A. alternaria</i> 16%	<i>A. alternaria</i> 28%	<i>A. alternaria</i> 32%	
7	Cat 26%	<i>A. fumigatus</i> 24%	Cat 27%	Dog 23%	Cat 21%	Cat 15%	Cat 22%	Cat 25%	
8	<i>C. herbarum</i> 22%	<i>B. tropicalis</i> 21%	<i>A. fumigatus</i> 24%	<i>C. herbarum</i> 21%	<i>C. herbarum</i> 21%	<i>A. fumigatus</i> 12%	<i>A. fumigatus</i> 21%	<i>A. fumigatus</i> 19%	
9	<i>B. tropicalis</i> 21%	<i>C. herbarum</i> 20%	<i>C. herbarum</i> 22%	Cat 15%	<i>B. tropicalis</i> 15%	<i>C. herbarum</i> 8%	<i>C. herbarum</i> 18%	<i>C. herbarum</i> 17%	

Table 3. Ranking of regional sensitisation for individual allergens based on SPT

Ranking position	Provincial regions of South Africa					
	Gauteng	North West	Mpumalanga	KwaZulu-Natal	Eastern Cape	Western Cape
1	Maize pollen 35%	Bermuda grass 29%	HDM mix [†] 30%	HDM mix [†] 41%	HDM mix [†] 48%	HDM mix [†] 44%
2	Bermuda grass 31%	House dust mite [†] 27%	Bermuda grass 24%	<i>B. tropicalis</i> 32%	<i>B. tropicalis</i> 29%	Grass mix 34%
3	HDM mix [†] 30%	Maize pollen 25%	<i>B. tropicalis</i> 24%	Cockroach 17%	Grass mix* 24%	Bermuda grass 30%
4	Grass mix* 26%	Grass mix* 20%	<i>A. alternaria</i> 23%	Bermuda grass 15%	Bermuda grass 24%	<i>B. tropicalis</i> 30%
5	Cat 21%	<i>B. tropicalis</i> 14%	Maize pollen 19%	Mould mix [‡] 13%	Cockroach 19%	Cat 25%

*Grass mix consists of *Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Festuca pratensis*.

[†]HDM mix consisted of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

[‡]Mould mix consisted of *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus* and *Penicillium notatum*.

Table 4. Regional breakdown of patients on whom *D. pteronyssinus* and *B. tropicalis* were requested for simultaneous IgE testing and where dual sensitisation was detected

Provincial region	Test requests, n	Dual sensitisation, n (%)
KwaZulu-Natal	1 789	1 067 (60)
Western Cape	1 029	433 (42)
Eastern Cape	611	229 (37)
Limpopo	247	73 (30)
Mpumalanga	226	62 (27)
North West	636	124 (19)
Gauteng	6 075	1 044 (17)
Free State	94	11 (12)

Table 5. Regional breakdown of patients on whom House dust mite mix and *B. tropicalis* were tested simultaneously by SPT and where dual sensitisation was detected

Provincial region	Test requests, n	Dual sensitisation, n (%)
Eastern Cape	460	124 (27)
Western Cape	329	87 (26)
Kwazulu-Natal	244	48 (20)
Mpumalanga	70	12 (17)
Gauteng	2 788	401 (14)
Limpopo	33	4 (12)
North West	98	9 (9)

Table 6. Regional breakdown of patients on whom Bermuda grass pollen and maize pollen were tested simultaneously by SPT and where dual sensitisation was detected

Provincial region	Test requests, n	Dual sensitisation, n (%)
Gauteng	1 948	557 (29)
North West	92	19 (21)
Mpumalanga	62	11 (18)
Limpopo	33	4 (12)

sensitisation rates.^[4] A potential explanation may be cross-reactivity caused by sensitisation to food-pollen cross-reactive components,

e.g. lipid transfer proteins (LTP), Profilin, PR-10 and cross-reactive carbohydrate determinants (CCD).

Food allergen-specific IgE data were analysed; 16 202 of positive IgE food allergen screens (F_x5 multitest and ImmunoCAP) were broken down into individual food allergen components. A total of 4 072 (25%) of the positive screens on which individual allergen-specific IgE tests (ImmunoCAP) were performed, demonstrated combined sensitisation to wheat, soy and peanut. Only 22 (0.5%) patients with triple sensitisation underwent additional allergen-specific IgE component testing to the four most common food-pollen cross-reactive components, namely LTP, Profilin, PR-10 and CCD, and 90% of these patients were sensitised to one of the four common cross-reactive components, with the most frequent sensitisation being to CCD and then to LTP.

Discussion

ImmunoCAP IgE sensitisation data revealed that house dust mite sensitisation (*D. pteronyssinus* IgE on ImmunoCAP) was the most common sensitiser overall, followed by grass pollen (Bermuda and rye grass) and then by the mould *A. alternata*. However, overall *A. alternata* sensitisation patterns may be biased by the inclusion of the highest percentage of patients from Gauteng, where this fungus is a common allergen. The lowest overall sensitisation for one of the nine recommended ImmunoCAP IgE allergens to be tested in the ALLSA/SAARWG panel was for the fungus *C. herbarum*, with a positivity rate of only 8% in KwaZulu-Natal. Generally, an allergen is seen to contribute significantly to allergy in a community if sensitisation levels rise above 2%.^[5]

A regional breakdown of allergen-specific IgE sensitisation to the individual allergens in the ALLSA/SAARWG panel demonstrated that two of the top three allergens in all provinces were *D. pteronyssinus* and Bermuda grass. Gauteng and North West provinces demonstrated similar sensitisation patterns, and KwaZulu-Natal and Eastern Cape provinces demonstrated similar sensitisation patterns. The most notable regional differences were lower sensitisation levels to *B. tropicalis* in Gauteng, the Free State and North West provinces and very high levels of sensitisation in KwaZulu-Natal and the Eastern Cape, with the Western Cape lagging slightly behind.

A regional breakdown of SPT data also confirmed house dust mite (*D. pteronyssinus* and/or *D. farinae*) and Bermuda grass to be very prominent allergens. It is interesting to observe that maize pollen was amongst the top five sensitising allergens in Gauteng, Mpumalanga and North West provinces. Also of note is that cockroach was among

the top five sensitising allergens in KwaZulu-Natal and Eastern Cape provinces. This is a concerning finding, as maize pollen and cockroach are not included in the current ALLSA/SAARWG profile for allergen-specific IgE inhalant allergen testing.

There are few data available on the sensitisation and potential cross-reactivity between *B. tropicalis* and *D. pteronyssinus* in the SA setting. A previous study with limited numbers of private patients in KwaZulu-Natal and Johannesburg, Gauteng, showed a 52% sensitisation rate to *B. tropicalis* in KwaZulu-Natal on SPT (Stellargenes, France) and a sensitisation rate of 3% in Johannesburg.^[6]

As a secondary aim potential cross-reactivity between *D. pteronyssinus* and *B. tropicalis* was investigated. It is important to identify patients sensitised to *B. tropicalis*, as these patients only respond to *B. tropicalis*-specific immunotherapy vaccines.^[7] Regional data of patients co-sensitised to *D. pteronyssinus* and *B. tropicalis* were analysed on both ImmunoCAP IgE (Thermo Fisher Scientific, Sweden) and SPT. The co-sensitisation rates were higher in coastal areas (KwaZulu-Natal, Eastern Cape and Western Cape), suggesting true sensitisation in these regions. These areas have suitable climates for the mite, *B. tropicalis*, to thrive in.^[6,7] However, there was not enough information available to determine true levels of cross-reactivity between *B. tropicalis* and *D. pteronyssinus*, as *B. tropicalis*-specific IgE allergen components are currently not available on ImmunoCAP. The sensitisation levels to *B. tropicalis* detected in Gauteng were higher than reported previously and may be attributed to the different tests and test manufacturers, which may influence test sensitivity and specificity, as well as differences in study patient populations.

There are currently no data available on the true sensitisation levels to maize pollen in SA. Cross-reactivity between maize pollen and Bermuda grass pollen has been suggested, as these two plant species are more closely related than maize pollen and rye grass.^[8,9] Maize pollen testing is not included in the top nine allergens recommended in the SAARWG/ALLSA diagnostic protocol for inhalant allergen testing. However, it is included in local SPT protocols in four SA provinces. These SPT data revealed that 29% of patients in Gauteng who were sensitised to Bermuda grass, were also co-sensitised to maize pollen. As the overall sensitisation rate in Gauteng on SPT was 31% to Bermuda grass and 35% to maize pollen, these results indicate that some patients are primarily sensitised to maize pollen and that it may be a significant allergen in the Gauteng region. There is a great need for a maize-specific IgE allergen component to identify patients primarily sensitised to maize pollen.

Allergen data were examined to determine potential food-pollen cross-reactive component sensitisation. Previous SA data have shown an increase in sensitisation rates to foods of plant origin in regions with the highest pollen sensitisation rates.^[4] From the authors' experience, patients with triple sensitisation to wheat, peanut and soy are often sensitised to pollen cross-reactive components. Only a minority of these patients have clinical symptoms when ingesting these plant foods.^[10-12] If symptomatic, the most frequent symptoms are those of oral allergy syndrome, but urticaria and even anaphylaxis have been described in patients sensitised to LTP.^[13] It is important to diagnose the relevant cross-reactive component, as it will have clinical implications regarding dietary and allergen avoidance advice to patients. Identification of patients with only CCD sensitisation will also avoid unnecessary dietary exclusion of wheat, peanut, soy and other plant-based foods from the patient's diet.

It was notable that 25% of all patients with a positive food allergen-specific IgE screen demonstrated positive sensitisation to wheat,

soy and peanut in combination. These sensitisation levels are much higher than the expected prevalence of food allergy.^[14] As these plant foods are not phylogenetically closely related, the likelihood that these patients could be sensitised to unique allergens in each of these diverse plant allergens is extremely low.

Only 22 patients (0.5%) had additional ImmunoCAP allergen-specific IgE component testing for the four most common food-pollen cross-reactive components, namely LTP, Profilin, PR-10 and CCD IgE. Some patients had ImmunoCAP ISAC component microarray tests performed. However, the data are not included in this analysis. Although these numbers were small, it was notable that 90% of triple sensitised patients were positive to one of these four food-pollen cross-reactive components on ImmunoCAP IgE, most frequently CCD followed by LTP. The distinction between these two sensitisation patterns is relevant, as CCD sensitisation does not cause symptoms after allergen exposure, while LTP sensitisation may cause a severe systemic allergy upon allergen exposure.^[13]

Study limitations

One of the main disadvantages when analysing anonymous retrospective data is the lack of access to patient history and clinical records. Therefore, the authors could only report on allergen sensitisation and not clinically relevant allergy. Gauteng was the most represented province, therefore the national sensitisation data may be biased. Another limitation is that data were only available for patients with access to private healthcare, therefore the data may not be representative of patients in the public sector. SPT data couldn't be compared for all allergens between all regions, as some SPT profiles vary regionally and SPT is also restricted to larger towns and cities in SA.

Conclusions

Inhalant allergy testing positivity rates were 46% for the Phadiatop atopy screen and 59% for inhalant SPT panels, indicating appropriate use for the diagnosis of inhalant allergies. This is comparable with international data.^[5,15] However, only 45% of patients with a positive Phadiatop atopy screen received additional testing for specific inhalant allergens, according to SAARWG/ALLSA recommendations, to identify the causative inhalant allergen. This is sub-optimal, as no therapeutic recommendations can be made regarding allergen avoidance or immunotherapy if additional testing is not performed.

Of the nine recommended inhalant allergens tested on allergen-specific IgE tests, the lowest sensitisation level was 8% to *C. herbarum* in KwaZulu-Natal, which is significantly higher than recommended sensitisation levels for relevant allergens in a community.^[5] The current allergen selection appears to be appropriate if applying this criterion. However, there is some regional variation in sensitisation patterns, particularly to *B. tropicalis*, cockroach and maize pollen, which is not reflected in these recommendations. International studies have indicated that the minimum battery of inhalant allergy tests needed to identify all sensitised patients may vary. Up to 13 allergens are required to identify sensitised patients in some European countries.^[5] It is of concern that there may be additional allergens, as were identified in this study, that may contribute significantly to patients' allergy symptoms and which are not included in the current testing protocols.

There was a high percentage (25%) of patients who were co-sensitised to wheat, soy and peanut, suggesting food-pollen cross-reactivity rather than primary food allergen sensitisation. However, the uptake of component testing to resolve potential cross-reactivity is very low, despite result comments and recommendations suggesting

their use. Consideration should be given to the implementation of testing algorithms and protocols for patients with suspected food-pollen cross-reactivity, as the unnecessary dietary exclusion of these allergens has a significant social, nutritional and financial impact on patients and their families.

The results of the present study confirm the relevance of the current inhalant allergens tested in SA testing protocols, identify new potential allergens and regional sensitisation patterns. Awareness is also raised about a significant level (25%) of potential food-pollen cross-reactivity which may impact patient management. These findings may aid the recommendations for the most appropriate and cost-effective approach to allergy testing in symptomatic patients in SA.

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