

Skin Prick Testing to Aeroallergen Extracts: What Is the Optimal Panel in Children and Adolescents in Turkey?

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Key Words

Aeroallergens · Children · Sensitization · Skin prick test

Abstract

Background/Objective: The skin prick test (SPT) is the standard tool for the diagnosis of IgE-mediated allergic diseases. The number and spectrum of allergen extracts to be applied for the diagnosis of sensitized patients in order to achieve the most cost-effective and informative results are critical from both economic and scientific viewpoints. **Methods:** In order to determine the minimum test battery panel necessary to cover at least 95% of the cases of SPT sensitization in children and adolescents (2–18 years) with suspected respiratory allergies, we retrospectively analyzed the SPT results of the largest referral center of the country. **Results:** Over a 2.5-year period, a total of 2,457 children (male/female ratio 1.51) with a median (range) age of 6.8 years (2.0–18.0) were subjected to SPT. Eight hundred and sixty-two (35.1%) children were found to be sensitized to at least one of the 30 aeroallergen extracts tested. The most common sensitizations were to grasses (*Festuca pratensis*, *Phleum pratense*, *Dactylis glomerata*, and *Lolium perenne*), house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat, weeds (*Chenopodium*, *Plantago*, and *Artemisia*),

and moulds (*Alternaria* and *Cladosporium*). The sensitization rates increased in conjunction with an increase in age. Testing with 12, 8, and 7 allergens was sufficient to identify over 95% of the sensitized preschool children, school children, and adolescents, respectively. **Conclusion:** An SPT panel covering 12 allergen extracts was sufficient to detect most of the sensitized children and adolescents with recurrent respiratory symptoms. As the patients grow older, a smaller test panel is required compared to the panels used at younger ages.

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Introduction

The assessment of immunoglobulin (Ig)E-mediated sensitization may be determined by an allergen-specific IgE in the serum and/or skin tests with the suspected allergens [1, 2]. The skin prick test (SPT) is the standard for the diagnosis of IgE-mediated allergic diseases. An SPT is done either to document the sensitization patterns of populations in epidemiological studies or to identify the allergen responsible for an IgE-mediated allergic disease in clinical practice. Some studies have endeavored to demonstrate the sensitization patterns in different geo-

Table 1. Characteristics of the study population

	Whole group (n = 2,457)	2 to <6 years (n = 918)	6 to <12 years (n = 1,118)	12–18 years (n = 421)
Age, years				
Mean $\pm$ SD	7.7 $\pm$ 0.9	4.3 $\pm$ 0.0	8.5 $\pm$ 0.1	14.3 $\pm$ 0.1
Median	6.8	4.3	8.3	14.2
Interquartile range	4.8–10.2	3.5–5.1	7–10	12.9–16.6
Gender, % (n)				
Male	60.2 (1,478)	60.5 (555)	62.1 (694)	54.4 (229)
Female	39.8 (979)	39.5 (363)	37.9 (424)	45.6 (192)

graphical regions [3–7]. However, most of the studies performed previously concerned the prevalence and distribution of allergens on an epidemiological basis and did not address the issue from the patients' point of view. Recently, the pan-European GA²LEN skin test study answered this question since a large number of patients from 14 countries were studied in detail [8, 9]. However, the study population mainly consisted of adults. As the sensitization to certain allergen sources may be associated with sensitization to others and since the rate of sensitization to some allergen sources is low, usage of a limited number of allergen extracts may be possible for patients. Currently, there is no standard test panel across Europe for children. Furthermore, the optimal number of allergen extracts to be used during the SPT for the diagnosis of sensitized patients that are the least painful and most cost-effective, both of which are important from scientific and economic aspects, remains to be clarified.

The aim of the present study was thus to demonstrate the sensitization patterns among children in different age groups and to define both the number and the type of SPT allergens required to identify a child as sensitized by evaluating the results of the largest referral center of a Mediterranean country.

Patients and Methods

Patients

The study was performed in the outpatient clinic of the Pediatric Allergy and Asthma Unit of Hacettepe University İhsan Doğramacı Children's Hospital. While the clinic serves as a referral center for the entire country, patients may also be admitted upon request; thus, it functions as both a primary and a tertiary health care service. The SPT results of the children and adolescents (2–18 years of age) referred because of recurrent respiratory symptoms were analyzed. Since computerization of the records

was started at the beginning of 2008, the records between January 2008 and June 2010 were taken into consideration.

Skin Test Procedures

According to the routine procedure of the clinic, all children presenting with recurrent respiratory symptoms suggesting allergy were subjected to SPT with a standard panel consisting of 30 allergen extracts from the upper back of the trunk: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*, cat, horse, dog, *Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium* mixture (*P. digitatum*, *P. expansum*, and *P. notatum*), *Cladosporium herbarum*, *Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, *Avena sativa*, *Cynodon dactylon*, *Parietaria judaica*, *Artemisia vulgaris*, *Plantago*, *Chenopodium* mixture, *Salsola kali*, *Salix caprea*, *Ulmus campestris*, *Quercus robur*, hazel, *Betula alba*, *Populus alba*, *Platanus vulgaris*, and *Olea europaea*, and histamine (10 mg/ml of histamine phosphate) as positive and 0.9% sterile saline as negative controls. Standardized extracts (Stallergenes; Antony, France) were used, and SPTs were evaluated 15–20 min after application and were considered positive if the mean wheal diameter was ≥ 3 mm compared with the negative control. A positive SPT result to at least one of the allergen extracts tested was accepted as the presence of sensitization for that patient. We did not use a common aeroallergen extract, ragweed, of the pan-European GA²LEN skin test study because of the undetectable pollen counts for ambrosia in the atmosphere of Turkey [10, 11].

Statistical Analysis

The prevalence of sensitization to each allergen extract was first determined by using frequencies and percentages. A step by step conditional approach was used to classify allergens from that causing the highest increase in prevalence of sensitization to that causing the lowest increase. Beginning with the most frequent allergen and continuing in decreasing order of frequency, the allergen source causing the highest prevalence of sensitization was investigated in the subgroup of subjects not sensitized to the previous allergen [8]. The procedure was repeated until a coverage of 95% for the presence of SPT sensitization was achieved. In addition, the same procedure was repeated with patients allocated by age group as follows: 2 to <6 years, 6 to <12 years, and 12–18 years of age. SPSS 16.0 software (Chicago, Ill., USA) was used for the statistical analysis.

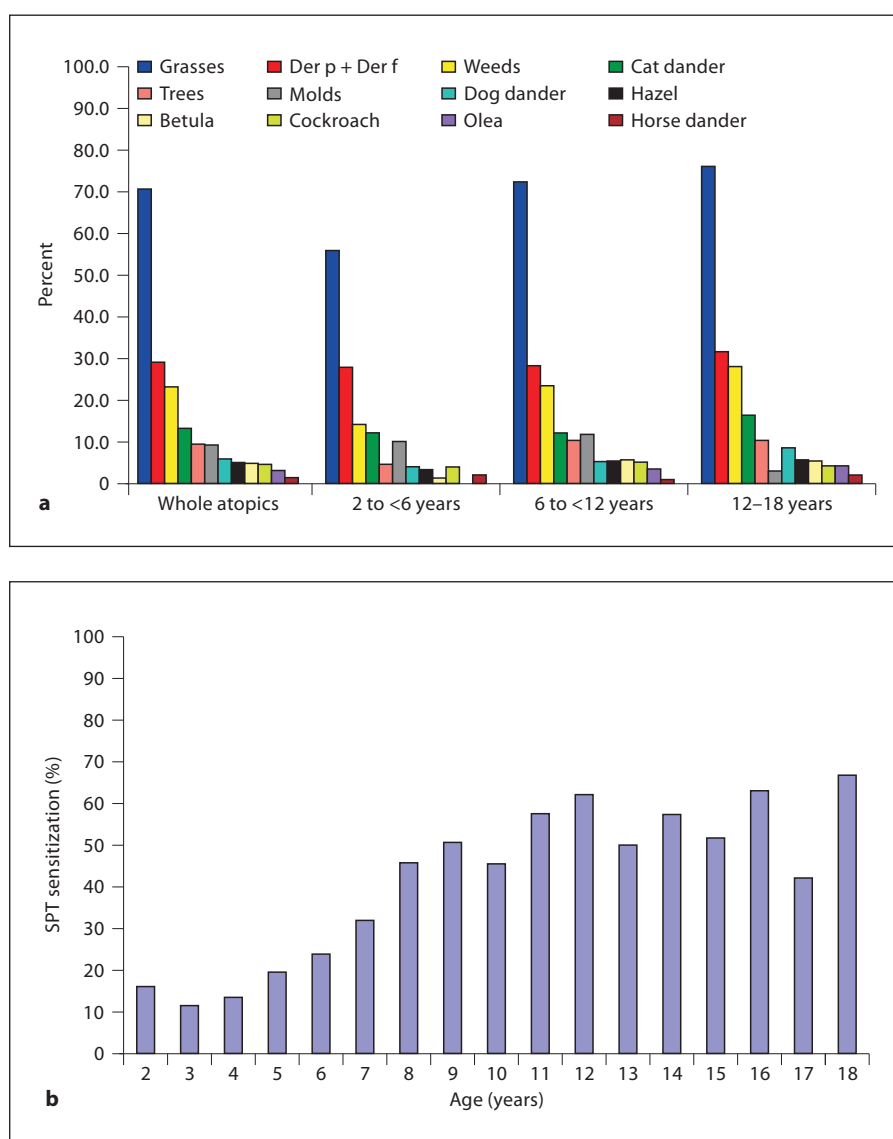


Fig. 1. a Distribution of aeroallergen extracts among the SPT sensitized children for the whole group and according to age groups. ‘Trees’ refers to those other than olive, betula, and hazel. **b** Percentage of SPT sensitization according to age.

Results

A total of 2,526 children and adolescents with SPT results were evaluated. Among them, 69 (2.7%) had to be excluded from the analysis since the SPT results were not available for all of the allergen extracts of the utilized test panel. Finally, 2,457 children (male/female ratio 1.51) with a median age (range) of 6.8 years (2.0–18.0) were included in the study (table 1). Eight hundred and sixty-two (35.1%) children were found to be sensitized to at least one of the 30 aeroallergen extracts tested. The distribution of aeroallergen sources among the sensitized children is shown in figure 1a.

The sensitization rates increased in conjunction with an increase in age, and the sensitizations according to the age groups of 2 to <6 years (preschool children), 6 to <12 years (school children), and 12–18 years (adolescents) were 16.1, 43.1, and 55.1%, respectively (fig. 1b). The most common allergen source was grass, followed by house dust mite, cat, weeds, and *Alternaria* (table 2). Testing with 5 allergen extracts (*F. pratensis*, *D. pteronyssinus*, *P. pratense*, *Alternaria*, and cat) identified approximately 90% of the SPT sensitization. To reach a 95% sensitization rate, 9 allergens (the previous 5 plus *Lolium*, *D. farinae*, *Cynodon*, and cockroach) were shown to be sufficient (table 3). The minimum test battery panel to reach a sensitization rate of 95% for the different age groups can be

Table 2. Distribution of the frequencies of sensitization for each allergen used in SPT by age group and in the whole study population

	Children sensitized by the given allergen, % (n)			
	study population	2 to <6 years	6 to <12 years	12–18 years
Grass				
<i>F. pratensis</i>	20.5 (504)	5.9 (54)	25.9 (290)	38.0 (160)
<i>P. pratense</i>	19.8 (487)	6.2 (57)	24.9 (278)	36.1 (152)
<i>D. glomerata</i>	18.9 (465)	5.3 (49)	23.3 (261)	36.8 (155)
<i>L. perenne</i>	18.9 (465)	5.3 (49)	23.5 (263)	36.3 (153)
<i>P. pratensis</i>	18.9 (465)	5.2 (48)	24.1 (269)	35.2 (148)
<i>A. sativa</i>	15.8 (387)	3.5 (32)	20 (224)	31.1 (131)
<i>C. dactylon</i>	15.6 (383)	3.6 (33)	19.8 (221)	30.6 (129)
House dust mite				
<i>D. pteronyssinus</i>	8.9 (218)	3.6 (33)	10.6 (119)	15.7 (66)
<i>D. farinae</i>	7.6 (187)	3.5 (32)	9.3 (104)	12.1 (51)
Weed				
<i>Chenopodium</i> mixture	3.6 (88)	1.0 (9)	4.7 (52)	6.4 (27)
<i>Plantago</i>	3.5 (87)	0.5 (5)	4.7 (53)	6.9 (29)
<i>A. vulgaris</i>	2.8 (68)	0.3 (3)	3.2 (36)	6.9 (29)
<i>S. kali</i>	1.6 (39)	0.4 (4)	1.6 (18)	4.0 (17)
<i>P. judaica</i>	0.6 (15)	0.3 (3)	0.7 (8)	1.0 (4)
Tree				
Hazelnut	1.8 (44)	0.5 (5)	2.3 (26)	3.1 (13)
<i>B. alba</i>	1.7 (41)	0.2 (2)	2.4 (27)	2.9 (12)
<i>P. alba</i>	1.6 (39)	0.1 (1)	2.1 (24)	3.3 (14)
<i>S. caprea</i>	1.1 (28)	0.0 (0)	1.9 (21)	1.7 (7)
<i>O. europaea</i>	1.1 (27)	0.0 (0)	1.5 (17)	2.4 (10)
<i>U. campestris</i>	0.9 (22)	0.2 (2)	1.3 (15)	1.2 (5)
<i>P. vulgaris</i>	0.7 (18)	0.1 (1)	0.7 (8)	2.1 (9)
Mold				
<i>A. alternata</i>	2.5 (62)	1.3 (12)	4.1 (46)	1.0 (4)
<i>C. herbarum</i>	0.8 (19)	0.4 (4)	1.3 (14)	0.2 (1)
<i>A. fumigatus</i>	0.4 (9)	0.1 (1)	0.6 (7)	0.2 (1)
<i>Penicillium</i> mixture	0.2 (5)	0.0 (0)	0.3 (3)	0.5 (2)
Animal dander				
Cat	4.7 (115)	2.0 (18)	5.3 (59)	9.0 (38)
Dog	2.1 (51)	0.7 (6)	2.2 (25)	4.8 (20)
Horse	0.5 (13)	0.3 (3)	0.4 (5)	1.2 (5)
Cockroach	1.6 (40)	0.7 (6)	2.1 (24)	2.4 (10)
Total number of children tested	2,547	918	1,118	421

seen in table 4. Accordingly, utilization of SPT panels with 12 allergen extracts for preschool children (*P. pratensis*, *D. pteronyssinus*, cat, *Lolium*, *Alternaria*, *D. farinae*, *Cynadon*, *Festuca*, *S. kali*, *Artemisia*, *Cladosporium*, and cockroach), 8 allergens for school children (*Festuca*, *D. pteronyssinus*, *Alternaria*, *P. pratense*, *Poa* mix, *D. farinae*, cat, and *Chenopodium* mix), and 7 allergen extracts for adolescents (*Festuca*, *D. pteronyssinus*, cat, *Lolium*, *Alternaria*, *Artemisia*, and cockroach) were required to identify 95% of the SPT sensitized patients (table 4).

Discussion

In the present study, we identified the sensitization patterns of children presenting with recurrent respiratory symptoms to aeroallergen sources in different age groups and we defined both the number and spectrum of SPT allergen extracts required to identify a child as sensitized. As Turkey is located in the Mediterranean region adjacent to the Middle East, a diverse exposure to aeroallergens exists in the study population. The most

Table 3. The offered test panel for all ages and the percent of sensitization by given aeroallergen sources

Allergen	Cumulative percentage of children sensitized by the given allergen(s), n (%)	Increase in identification of sensitized patients by addition of an allergen (in the following row) in the SPT	
		n	%
F. pratensis	504 (58.5)		
D. pteronyssinus	661 (76.7)	157	18.2
P. pratense	704 (81.7)	43	5.0
A. alternata	740 (85.8)	36	4.1
Cat	768 (89.1)	28	3.3
L. perenne	787 (91.3)	19	2.2
D. farinae	804 (93.3)	17	2.0
C. dactylon	815 (94.5)	11	1.2
Cockroach	823 (95.5)	8	1.0
<i>P. pratensis</i>	831 (96.4)	8	0.9
<i>Chenopodium</i> mixture	837 (97.1)	6	0.7
<i>A. vulgaris</i>	841 (97.6)	4	0.5
Dog	844 (97.9)	3	0.3
<i>D. glomerata</i>	846 (98.1)	2	0.2
<i>C. herbarum</i>	848 (98.3)	2	0.2
<i>Penicillium</i> mixture	850 (98.5)	2	0.2
Others	862 (100.0)	12	1.5

The names of the allergen extracts used in the panel are ordered from the most frequent allergen to the allergen extract with the least increase in identifying additional sensitized subjects. Out of the panel of 30 aeroallergen extracts chosen to identify the sensitized children in the study population, 9 allergen extracts (presented in bold) diagnosed 95% of all sensitized children in the study population.

common aeroallergen sources were found to be grass pollens, as documented previously in the same region, followed by house dust mite, *Alternaria*, cat, and cockroach [12, 13]. It seems that a limited number of allergen extracts (7–12) is sufficient to detect most of the sensitized children and adolescents. Interestingly, the required allergen extract number increases with a decrease in age (table 4).

Studies concerning the formation of a standard SPT panel across Europe started with the population-based European Community Respiratory Health Survey [3, 4]. They found that a standardized battery of 7 allergen extracts would be sufficient for the epidemiological studies in Europe. These allergen extracts were *D. pteronyssinus*, cat, grass, birch, olive, *Alternaria*, and *Cladosporium*. In the study designed by the GA²LEN study group, the sensitization pattern of the patients who applied to allergy clinics was evaluated, and a similar test panel was found. That 8-allergen extract panel (differing from country to country ranging from 2 allergen extracts in Switzerland to 9 allergen extracts in France) identified over 95% of the

sensitized patients. In a cohort of preschool children 4 years of age, 94% of the SPT sensitized children were detected with 4 allergen extracts (house dust mite, grass pollen, cat, and *Alternaria*) [14]. In the present study, we found that a test battery including 12 allergen extracts would be sufficient to identify over 95% of the SPT sensitized children; as the children aged, the sensitization of the panel increased to almost 100% for school children and adolescents. Our results were comparable with those of some countries but divergent from others [8]. The minimum test battery panel needed to confirm a 95% coverage was found to be higher than in most of the European countries. This can probably be attributed to the wide geographical diversity of the country since it contains Mediterranean, Black Sea, and Turanian climate regions. The impact of some allergen sources was lower than expected in our study, especially when we consider the rates of tree pollens like olive, hazel, and birch which mainly grow in the coastal regions of the country. This may be due to the location of our center (in central Anatolia), since patients from close districts might have presented

Table 4. The offered test panel for different age groups and the percent of sensitization by given aeroallergen extracts

	N	%	Cumulative %
2 to <6 years			
P. pratense	57	38.5	38.5
D. pteronyssinus	28	18.9	57.4
Cat	13	8.9	66.3
L. perenne	12	8.2	74.5
A. alternata	9	6.1	80.6
D. farinae	6	4.1	84.7
C. dactylon	5	3.3	88.0
F. pratensis	3	2.0	90.0
S. kali	3	2.0	92.0
A. vulgaris	2	1.3	93.3
C. herbarum	2	1.3	94.6
Cockroach	2	1.3	95.9
Others	6	4.1	100.0
6 to <12 years			
F. pratensis	290	60.1	60.1
D. pteronyssinus	89	18.4	78.5
A. alternata	27	5.6	84.1
P. pratense	23	4.7	88.8
P. pratensis	10	2.1	90.9
D. farinae	9	1.8	92.7
Cat	8	1.6	94.3
Chenopodium mixture	6	1.2	95.5
L. perenne	5	1.0	96.5
Cockroach	4	0.8	97.3
C. dactylon	4	0.8	98.1
Others	9	1.9	100.0
12–18 years			
F. pratensis	160	68.9	68.9
D. pteronyssinus	41	17.7	86.6
Cat	6	2.5	89.1
L. perenne	6	2.5	91.6
A. alternata	3	1.3	92.9
A. vulgaris	3	1.3	94.2
Cockroach	3	1.3	95.5
B. alba	2	0.8	96.3
D. glomerata	2	0.8	97.1
D. farinae	2	0.8	97.9
Dog	2	0.8	98.7
Others	3	1.3	100.0

The names of the allergen extracts used in the panel are ordered from the most frequent allergen to the allergen extract with the least increase in identifying additional sensitized subjects. Out of the panel of 30 aeroallergen extracts chosen to identify the sensitized children, a total of 12, 8, and 7 allergen extracts (presented in bold) diagnosed 95% of all sensitized children in each age group, respectively.

dominantly, though it is a referral center for the entire country.

The minimum test battery panel required to cover over 95% of all of the sensitizations differed slightly among the three age groups. For preschool, school, and adolescent age groups, the minimum necessary test numbers were 12, 8, and 7, respectively. SPT sensitization is related to environmental exposure, which is unavoidable for certain allergens as the child gets older. As a result, the spectrum of sensitized allergen sources is more uniform in older children compared to younger ones. This is documented in our study by the increasing percentage of grass sensitization with the age. This predominance decreases the diversity of the allergen extract test panel that is necessary to reach a total sensitization rate of 95% (table 4).

We did not perform the test with grass mixture; thus, with grass mixture usage, the number of allergen extracts needed would decrease to 10, 6, and 6 allergen extracts for preschool, school, and adolescent age groups, respectively. Taken together, these results suggest that among children of all ages with complaints of respiratory symptoms a limited number of allergens would be sufficient to evaluate the clinical condition throughout Europe [8].

Grasses were identified as the most common aeroallergen sources in the study. This was true for most of the European countries, including Denmark, the UK, Greece, Poland, and The Netherlands, and the sensitization rates varied between 19.5 and 69.9%; however, in some countries, house dust mite was the leading allergen (Portugal, Italy, France, and Belgium) [9]. In previous reports from Turkey, grass pollen sensitizations varied between 43 and 74%, and in our study we found a cumulative rate of 70.3% grass pollen sensitization among the sensitized subjects [12, 13, 15].

Sensitization to dust mites was common. House dust mite sensitization (*D. pteronyssinus* or *D. farinae*) was found to be 29% (25.3% to *D. pteronyssinus*) in the present study. This result was similar to the results of previous studies from the same region of the country [12, 13, 15]. In the GA²LEN skin test study, positive sensitizations against house dust mites were the lowest in Central/Western Europe and significantly higher in Nordic countries and the Mediterranean. In Mediterranean countries, the sensitization rates ranged between 32.7% in Greece and 68.8% in Portugal for *D. pteronyssinus* [9].

Cat ownership is low in our country [16] and sensitization to cat was found to be 13.3% in the present study, which was similar to a previous population-based study

from the same region [13]. We believe that as pet ownership is more common in Europe the sensitization rates were much higher than our results (ranging between 18.4% in Belgium and 42.1% in Switzerland) [9].

The weed sensitization reached 23.1% in our study, which ranged between 7 and 23% in previous reports from Turkey [12, 13, 15]. When we compared *Artemisia* sensitization (tested both in the GA²LEN study and in our study), a rate of 7.9% was found in the present study; however, sensitization to *Artemisia* reached 44.3% in Hungary, while in Mediterranean countries it ranged between 6.7% in Greece and 16.9% in Italy [9]. In Europe, most of the countries belong to the Cfb (warm temperate, fully humid, and warm summer) and Dfb (snow, fully humid, and warm summer) climate regions according to the Köppen-Geiger climate map [17]. As a result, the weed and grass sensitizations in these countries are higher than in Turkey.

Among the molds, *Alternaria* and *Cladosporium* led with sensitization rates of 7.2 and 2.2%, respectively. The sensitization rates in Europe were high in Hungary (18.6% for *Alternaria* and 12.8% for *Cladosporium*), whereas in the other countries low levels were observed, as in our study [9].

We believe that the low levels of *Oleaceae* sensitization (3.1%) can be best explained by the location of our center in Central Anatolia, where olea plantations are far less common compared to the shores of the country. This is supported by the finding that in a previous study from the Aegean region of the country a rate of 30% sensitization to olive pollen was reported [18].

Cockroach was found to be positive in 4.6% of the sensitized children, and addition of its antigen caused a 1% increase in identifying sensitized patients with SPT. Cockroach allergy is most likely to be relevant in some countries with a hot and humid climate and particularly in deprived populations [19].

There are some limitations to the study. First, this is a study designed to focus on children with complaints of respiratory symptoms, so this is a patient-based survey and results may differ from those of the epidemiological studies. However, the number of children tested is high and well distributed among all age groups, which may decrease the selection bias. The present study searched only for the sensitization and did not explore the clinical relevance of the sensitization. Since this is a single-center study, the impact of some local allergen sources may be reinforced while some other may be omitted. Nevertheless, the center is the largest in the region, presenting a patient profile of over two thirds of the country.

In conclusion, demonstration of the sensitization patterns of children in different age groups may be useful for selecting the allergen extracts to be added to SPT panels. A limited number of allergens may be used to identify most of the sensitized children in a patient-based study. A standardized 12-allergen extract panel (in the case of a grass mixture usage of a 10-allergen panel) would be sufficient to define 95% of the sensitized children and adolescents.

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