Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Laboratory screening test with inhalant and food allergens in atopic Brazilian children and adolescents: a performance

Ana Carolina Rozalem Reali[a], Felipe Faria Pierotti[a], Carolina Sanchez Aranda[a]*, Renata Rodrigues Cocco[b], Emanuel S Cavalcanti Sarinho[c], Flávio Sano[d], Arnaldo Porto Neto[e], Nelson A Rosário[f], Herberto J Chong Neto[f], Ekaterini Simões Goudouris[g], Lilian Sanches Moraes[h], Neusa Falbo Wandalsen[i], Antônio Carlos Pastorino[j], Jackeline Motta Franco[k], Maria Letícia Chavarria[l], Magnus P Borres[m], Dirceu Solé[a]

[a]*Pediatrics Department, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo, São Paulo, Brazil*
[b]*Pediatrics Department, Albert Einstein Israeli Faculty of Health Sciences, São Paulo, São Paulo, Brazil*
[c]*Pediatrics Department, Federal University of Pernambuco, Recife, Pernambuco, Brazil*
[d]*Pediatrics Department, Nipo-Brazilian Hospital, São Paulo, São Paulo, Brazil*
[e]*Pediatrics Department, Federal University Fronteira Sul, Passo Fundo, Rio Grande do Sul, Brazil*
[f]*Pediatrics Department, Federal University of Paraná, Curitiba, Paraná, Brazil*
[g]*Pediatrics Department, Federal University of Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil*
[h]*Pediatrics Department, Federal University of Mato Grosso, Cuiabá, Mato Grosso, Brazil*
[i]*Pediatrics Department, Faculty of Medicine, ABC's Foundation, Santo André, São Paulo, Brazil*
[j]*Pediatrics Department, University of São Paulo, São Paulo, São Paulo, Brazil*
[k]*Pediatrics Department, Federal University of Sergipe, Aracaju, Sergipe, Brazil*
[l]*Pediatrics Department, Federal University of Goiás, Goiania, Goiás, Brazil*
[m]*Women's and Children's Health, Thermo Fisher Scientific and Uppsala University, Uppsala, Sweden*

Received 12 May 2021; Accepted 17 June 2021
Available online 1 September 2021

KEYWORDS
child;
hypersensitivity;
immunoglobulin E;
allergens;
Phadiatop infant

Abstract
The Phadiatop Infant® (PhInf) is a panel developed to assess allergic sensitization (immunoglobulin E [IgE]) in children aged <5 years and combines inhalant and food allergens. The test has not been evaluated outside Europe. This is a cross-sectional study conducted at 11 pediatric allergy centers to evaluate PhInf as an allergic disease screening method in Brazilian children. Children as controls and patients (aged 6 months-18 years) were grouped according to their primary disease and age group. PhInf and specific serum IgE (sIgE) screening was performed for *Dermatophagoides pteronyssinus* (DP), cat and dog epithelia, a mix of grasses and pollens, eggs, cow's milk, peanuts, and shrimp. Values ≥ 0.35 kU_A/L (or PAU/L) were considered positive. A total of 470 children and adolescents, which included 385 patients and 85 controls, participated in the study (47.7% boys, average age: 6.3 years). In all, 72.6% of the

***Corresponding author**: Carolina Sanchez Aranda, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo, Brazil.
Email address: carolaaranda@yahoo.com.br

https://doi.org/10.15586/aei.v49i5.464

participants had positive PhInf test (n = 341), with a higher proportion of those having food allergy (92.6%), atopic dermatitis (91.9%), and those aged >13 years having allergy (95%). The PhInf and sIgE agreement between patients (Kappa = 0.94, P < 0.001) and controls (Kappa = 0.84, P < 0.001) was high. PhInf and DP agreement in patients aged >13 years was excellent (Kappa = 0.936, P < 0.001). Compared with sIgE dosage, PhInf had high sensitivity (97%) and specificity (93%). Positivity of PhInf test in this population was high and had an excellent correlation with the allergens comprising the panel. It is a useful method for screening children suspected of having allergic diseases in a non-European country.

Introduction

Allergic diseases are examples of chronic noncommunicable diseases common in the modern world. Generally occurring in the early life, these significantly compromise with the quality of life of patients and their families along with the burden of treatment.[1] Diagnosis of allergic diseases begins with a careful anamnesis and an extensive physical examination of patient. However, as the symptoms of allergic diseases are similar to those of other diseases, the medical history alone can cause diagnostic failure in more than 50% of cases.[2] Thus, when the history is compatible with allergies, tests that detect serum immunoglobulin E (sIgE) specific to one or more suspected allergens can be used.[3] This infers that allergic sensitization that is concomitant with allergic symptoms can help in the diagnosis.

Patients who do not have a typical history of allergy can be evaluated with multi-allergen screening tests. These tests were developed to detect sIgE in a panel of allergens in one analysis, with a lower cost, and a smaller amount of serum, presenting the highest negative predictive value available in allergy tests, since it is administered to the population sensitized to their constituent allergen.[3]

Phadiatop Infant® (PhInf) is a qualitative and semi-quantitative panel that uses ImmunoCAP® system to detect sIgE in 11 inhalant and food allergens.[4] Specifically meant for the 0–5-year-old age group, in which food allergens play an important role in allergic sensitization, it combines the most common allergens to which the Brazilian population is sensitized, according to studies conducted by our group.[5,6] This study aims to evaluate PhInf as an allergic disease screening method in Brazilian children.

Materials and Methods:

This study was a part of Allergy Project II (*Projeto Alergia* II or PROAL II), which was aimed to estimate allergic sensitization profile in Brazilian children and adolescents using different methods. The sample was convenient and its calculation was based on the results obtained in our previous study, PROAL I.[6] Hence, the following 11 Brazilian pediatric allergy centers participated in this study between August 2015 and November 2016: Goiás and Mato Grosso (Central-west); Pernambuco and Sergipe (Northeast); Rio de Janeiro, Santo André, and São Paulo (Southeast); and Paraná and Rio Grande do Sul (South). Each center selected 40 patients with allergic diseases divided in the following four groups: asthma and/or rhinitis (A+R), atopic dermatitis (AD), food allergy (FA), and wheezing infant (WI), in addition to 10 nonallergic controls (C), with age ranging from 6 months to 18 years. Those with allergen-specific immunotherapy, immunosuppressive treatment, or with underlying diseases that altered immunoglobulin production were excluded.

The participants' serum PhInf levels were measured from peripheral blood samples. The sIgE was also measured on the following nine allergenic sources or a mixture of PhInf constituent: allergens, *Dermatophagoides pteronyssinus* (DP), cat epithelium, dog epithelium, grasses (combined from *Cynodondactylon*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Sorghum halepense*, and *Paspalum notatum*), pollens (combined from *Ambrosia artemisiifolia* [*Aspidistra elatior*], *Artemisia vulgaris, Plantago lanceolata, Chenopodium album*, and *Salsola kali*), chicken egg, cow's milk (CM), peanuts, and shrimp (ImmunoCAP®, ThermoScientific®, Uppsala, Sweden). All examinations were performed on the Phadia® 250 (ThermoScientific®, Uppsala, Sweden). The sIgE levels were expressed in kU_A/L and PhInf levels in Phadia Arbitrary Units (PAU/L). Values >0.35 indicated the individual as not sensitized.

Depending on the nature of the variables under study, parametric (Student's t-test) or nonparametric tests (Kappa concordance coefficient and Spearman's rank correlation coefficient [rs]) were used, setting the rejection level for the null hypothesis at 5%. Statistical analyses were performed using the IBM® SPSS 20.0 and Stata® 12.0 statistical software.

The study was approved by the Committee for Ethics in Research on Human Beings at the Federal University of São Paulo—UNIFESP-EPM (Technical Opinion No. 795.256) and by all research ethics committees of participating centers.

Results

A total of 470 individuals participated in the study, 385 allergic and 85 controls, with similar gender distribution (52.3% vs. 47.7%, respectively), with a mean age of 6.3 years (standard deviation [SD] = 4.5 years), and 45.3% were aged between 5 and 13 years.

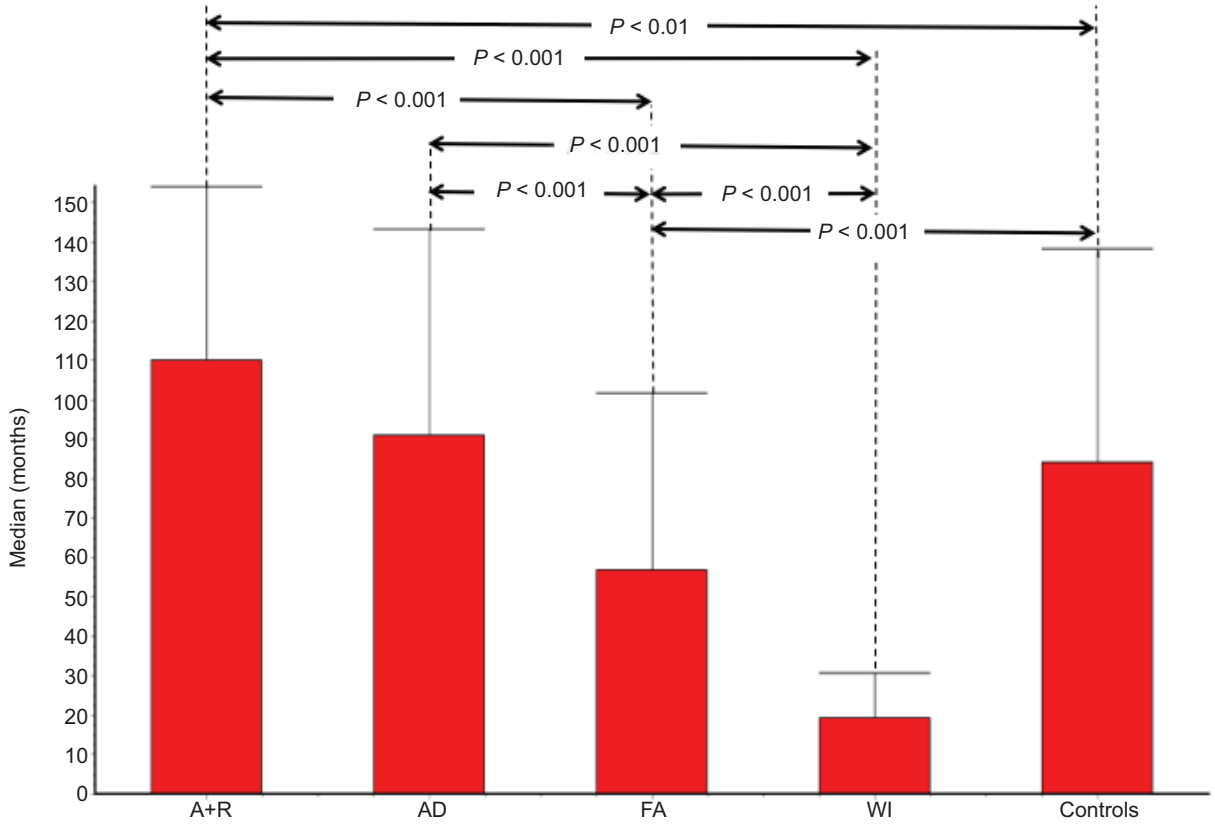
Distribution of patients according to age group and primary disease revealed that WI and those with FA had a mean age significantly lower than those in other groups. There was no statistically significant difference between the age of individuals with A+R, AD, and C (108 vs. 84 vs. 72 months, respectively). The mean age of patients with

A+R and AD was significantly higher than those with FA (36 months), WI (17.5 months), and C (72 months). The mean age of patients of WI was significantly lower than those in other groups (Figure 1); 72.6% of the participants tested had positive PhInf results (79% patients vs. 44% controls), with the highest proportion of positive tests being among patients aged >13 years and in groups FA (92.6%) and AD (91.9%) (Table 1).

Agreement between PhInf and any other specific allergen showed an almost perfect agreement among patients (Kappa = 0.94, P < 0.001) and controls (Kappa = 0.84, P < 0.001).

In case of separately analyzed specific allergens, we found substantial PhInf and DP agreement for all patients (Kappa = 0.665, P < 0.001) and in groups A+R (Kappa = 0.747, P < 0.001), AD (Kappa = 0.735, P < 0.001), C (Kappa = 0.706, P < 0.001), and in the following younger age groups: 3–4 years (Kappa = 0.764, P < 0.001), 4–5 years (Kappa = 0.677, P < 0.001), and 5–13 years (Kappa = 0.704, P < 0.001). An almost perfect PhInf and DP agreement (Kappa = 0.936, P < 0.001) was observed in patients aged ≥13 years.

The younger groups showed the highest concordance with food allergens: moderate for CM and egg in the age groups of up to 4 years, and only in the WI group in



A+R: Asthma and/or rhinitis; AD: Atopic dermatitis; FA: Food allergy; WI: Wheezing infant.

Figure 1 Age (median) according to main allergic disease.

Table 1 Percentage of changes in Phadiatop Infant® (PhInf) according to main diseases and age groups.

Group	Total N	+ve PhInf	N %	Age (years)	Total N	+ve PhInf	N (%)
A+R	111	95	85.6	< 2	91	44	48.0
AD	99	91	91.9	2-5	113	82	73.0
FA	95	88	92.6	5-13	213	171	80.0
WI	80	30	37.5	>13	53	44	83.0
Total	385	304	79.0				
				Total (PA+C)	470	341	72.6
Controls	85	37	43.5				

+ve PhInf: Positive PhInf; A+R: Asthma and/or rhinitis; AD: Atopic dermatitis; FA: Food allergy; WI: Wheezing infants; PA: Patient; C: Control.

specific disease distributions (Kappa coefficients from 0.429 to 0.554, all P-values < 0.001). The peanut agreement with PhInf was only moderate in children aged 3–4 years (Kappa = 0.497, P < 0.001).

Evaluation of correlation between PhInf quantitative values and those of specific allergens in the entire sample of 470 children revealed a strong and significant correlation for all constituent allergens and a moderate correlation for egg (rs = 0.629) and CM (rs = 0.564) (Table 2).

Regarding the diseases evaluated, PhInf showed a very strong correlation with DP in the A+R group (rs = 0.919) and strong for AD (rs = 0.861), FA (rs = 0.732), WI (rs = 0.721) and C (rs = 0.896) groups (Figure 2).

Cat and dog epithelium also showed strong correlations in group FA (rs = 0.824 and 0.848, respectively), AD (rs = 0.698 and 0.747, respectively), and control (rs = 0.751 and 0.818, respectively) (Table 2).

In relation to the age groups studied, strong and very strong correlations to food allergens tended to be concentrated in patients aged <5 years, while inhalant allergens in 3–4 years old group, with a very strong correlation with the level of dog epithelium in 3–4 years old (rs = 0.913) and DP in 4–5 years old (rs = 0.936) groups (Table 3).

PhInf showed low diagnostic accuracy (sensitivity [Se] = 79%, specificity [Sp] = 56%) with 70% false-negative results. However, it had a high performance in relation to

Table 2 Spearman's rank correlation coefficient (rs) between Phadiatop Infant® and specific allergens, according to the total group and by specific disease.

	Main allergic disease					Total
	A+R	AD	FA	WI	Controls	
Egg	0.481	0.485	0.482	0.632	0.656	0.629
Cow's milk	0.347	0.453	0.565	0.574	0.686	0.564
Peanut	0.624	0.699	0.560	0.426	0.708	0.726
Shrimp	0.596	0.658	0.677	0.508	0.741	0.745
D. pteronyssinus	0.919	0.861	0.732	0.721	0.896	0.890
Dog	0.688	0.698	0.824	0.475	0.751	0.815
Cat	0.690	0.747	0.848	0.676	0.818	0.863
Mixed grasses	−0.035	−0.265*	−0.058	0.299*	0.230*	−0.037
Mixed pollens	0.659	0.683	0.632	0.546	0.666	0.748

All rs: P < 0.001 except those with *P < 0.05.
A+R: Asthma and/or rhinitis, AD: Atopic dermatitis, FA: Food allergy, WI: Wheezing infants.

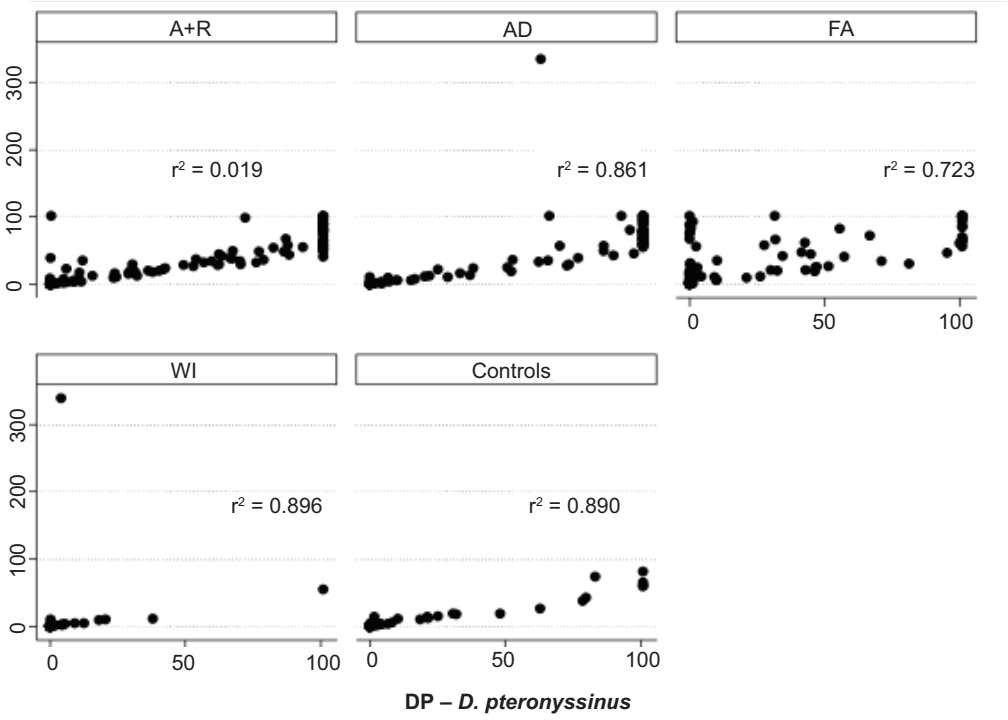


Figure 2 Scatter plot of Phadiatop Infant® levels in relation to *D. pteronyssinus* in each atopic disease.
A+R: Asthma and/or rhinitis; AD: Atopic dermatitis; FA: Food allergy; WI: Wheezing infants.

Table 3 Spearman's rank correlation coefficient (rs) between Phadiatop Infant® and specific allergens according to age group.

	Age group (years)						Total
	<2	2-3	3-4	4-5	5-13	≥13	
Egg	0.806	0.792	0.852	0.722	0.581	0.757	0.629
Cow's milk	0.738	0.626	0.754	0.590*	0.556	0.626	0.564
Peanut	0.614	0.663	0.800	0.725	0.634	0.784	0.726
Shrimp	0.557	0.473	0.747	0.652	0.662	0.719	0.745
D. pteronyssinus	0.671	0.767	0.898	0.936	0.878	0.885	0.890
Cat	0.620	0.728	0.769	0.842	0.738	0.769	0.815
Dog	0.827	0.773	0.913	0.855	0.764	0.816	0.863
Mixed grasses	0.136	−0.060	−0.134	−0.156	−0.042	−0.083	−0.037
Mixed pollens	0.615	0.657	0.812	0.702	0.669	0.673	0.748

All rs: P < 0.001.

the dosage of nine isolated specific allergens: Se = 97%, Sp = 94%, positive predictive value (PPV) = 98%, and negative predictive value (NPV) = 93%.

Discussion

Global statistics point to an increase in the prevalence of allergic diseases. Although genetic predisposition is increasingly established, environmental influences seem to play a major role in the etiology and prognosis of these diseases (epigenetics).[7]

Along with the real increase in prevalence, there is also tremendous suspicion and "overdiagnosis," with an increase in spending on unnecessary investigations, and expensive and ineffective treatments, in addition to hampering the quality of life. At the same time, it is common knowledge that the symptoms of allergic diseases are common to numerous other diseases, especially infectious diseases and that differentiating them only by history and physical examination becomes a very difficult task, especially among younger people.[8]

Previous PhInf studies have demonstrated that it was a flaw to define patients as allergic or nonallergic on the basis of clinical history and physical examination. Fiocchi et al. documented that in 51.2% of children they had assessed, atopy was not determined with clinical data only.[9] The figure reduced to 0.5% when they linked with sIgE detection tests.[9] Duran-Tauleria et al. published a study in which primary care physicians were able to correctly diagnose allergic diseases in less than 60% of patients without using sIgE tests.[10] However, this number increased to 93.2% when doctors were trained on when and how to order three types of allergen panels, including PhInf.[10]

In a previous study comprising the same individuals, our group evaluated the results of PhInf and Phadiatop Europe as a tool for identification of sensitized individuals, regardless of age. PhInf showed a better performance.[11] Thus, the present study evaluated the diagnostic power of PhInf, developed specifically for infants and preschool children, in detecting sensitization to foods and inhalants relevant to IgE-mediated diseases in this age group.

However, unlike other published studies that used the same test on the general population[12] with risk factors,[4] or at the most referred for a suspected allergic disease,[7,9,10,13,14] the present was performed on a population of children and adolescents highly sensitive to the allergens it included, with follow-up programs in reference allergy services throughout the Brazilian territory.

Multi-sensitized patients were tested, and the potency was calculated, comparing it separately with the sIgE dosage of constituent allergens, thus evaluating their ability to detect any sensitization and its intensity. In addition, the decision was made to test children and adolescents in all age groups and not just infants and preschool children, since it was important to assess agreement with inhalant allergens to which patients become more sensitive later.[15]

Thus, using PhInf as a screening test, we observed 79% positivity in allergy patients, 66% if we only consider the target group of the test aged up to 5 years (Table 1). Halvorsen et al. evaluated the PhInf test in children aged <5 years, who were referred to their allergy service in Olso, Norway and had a more severe phenotype, and found a similar result with 72% PhInf positivity.[7]

Nilsson et al. found PhInf positivity to be 30% on evaluating the children (up to 5 years old) of allergic parents in a prospective birth cohort.[4] Given that the children were not chosen because they were allergic, the results are comparable to the PhInf positivity of 44% in our control group (Table 1).

PhInf performance was separately compared with sIgE dosages. Among the 385 patients evaluated, 304 were evaluated as atopic, and 305/385 could be atopic if we considered the presence of sIgE ≥ 0.35 for any of the tested allergens (Table 2). A similar result was observed with the controls (n = 85): 37/85 were identified as sensitized by PhInf and 38/85 by sIgE dosage. In both groups, the agreement level was very high (Kappa > 0.8) between the two tests (Table 2). As such, we verified in the studied population that PhInf proved to be a screening test that combines good characteristics: Se, Sp, PPV, and NPV, when the sIgE is compared to at least one of the allergens separately. Nilsson et al. also found similar values, except for a slight decrease in sIgE-Se: 84% versus 97% in our sample.[4]

The data observed herein indicated that the allergen panel was simpler to order, less expensive, and required a smaller volume of serum to function (an important detail in the pediatric age group). The panel had an excellent correlation between sIgE and the nine constituent allergens, and was quantified by ImmunoCAP®.

However, 20% (n = 76) of the patients showed no signs of sensitization to the allergens in either test. Among the 81 patients with negative PhInf results, 50 were from the WI group, a group known to have a lower proportion of sensitization, with only 38% positive PhInf results, a value similar to 33% found in the WI sample of Fiocchi et al.[9]

In 2004, the performance of Phadiatop® was assessed (a screening test created by the manufacturer of PhInf), which at that time comprised only *D. pteronyssinus* and *D. Farinaemites*.[16] In all, 457 allergic children (1–12 years old) were tested and the percentage of positive tests (since the total number of children in each age group was different) was much more favorable to the greater positivity of PhInf—with the addition of four food allergens and six types of inhalant allergens—in the target age range of the test (up to 5 years old).

According to the "atopic march," proved by numerous studies for more than two decades, sensitization to food allergens and the presence of AD were the risk factors for developing a persistent allergic disease during childhood, most notably asthma.[15,17] In our sample, 93% of children with FA and 92% of those with AD had positive PhInf results, and in all age groups aged <5 years, there was moderate agreement between PhInf and sIgE for CM and egg. If we consider that AD and FA are the two most common allergic morbidities with a high prevalence of sensitization in the target age of the test, it is one more reason to corroborate their importance and practical usefulness.

The Brazilian population is most sensitive to domestic mites, a common allergen, with DP being the most prevalent of these.[6] Hence, as expected, 60% of the individuals tested were sensitized to DP, with rates lower than this in only WI and control groups and, consequently, with moderate PhInf agreement for the total sample, A+R and AD, the age group aged >13 years, and the agreement was perfect (Table 3).

Therefore, we observed an excellent correlation between PhInf levels and sIgE concentrations to separately quantified allergens. However, it is important to note that PhInf is a screening test and should not *per se* serve as an end to the investigation of allergic diseases. Once positivity is established, a specialist should be referred and requested to target likely allergens to complete the investigation.

Conclusion

We conclude that frequency of positive PhInf tests in allergic Brazilian children and adolescents is high and has a significant correlation with their separately dosed constituent allergens. This is the first evaluation of the performance of PhInf outside Europe. Thus, it is observed that this is a method with good performance in screening non-European children with a low probability of sensitization or when little is known about involved allergens, when compared with the most widely used serological method, ImmunoCAP®. Correct diagnosis is required for individualized treatment with fewer symptoms and reduced medication.

References

1. Antó JM, Bousquet J, Mubeccel A, Auffray C, Keil T, Momas I, et al. Mechanisms of the development of allergy (MeDALL): Introducing novel concepts in allergy phenotypes. J Allergy Clin Immunol. 2017 Feb;139(2):388–99. https://doi.org/10.1016/j.jaci.2016.12.940
2. Williams PB, Ahlstedt S, Barnes JH, Soderstrom L, Portnoy J. Are our impressions of allergy test performances correct? Ann Allergy Asthma Immunol. 2003 Jul;91(1):26–33. https://doi.org/10.1016/S1081-1206(10)62054-6
3. Hamilton RG, Williams PB. Specific IgE testing task force of the American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology. Human IgE antibody serology: A primer for the practicing North American allergist/immunologist. J Allergy Clin Immunol. 2010 Jul;126(1):33–8. https://doi.org/10.1016/j.jaci.2010.03.014
4. Nilsson C, Lilja L, Nordlund M, Berthold M, Borres MP. Phadiatop Infant detects IgE-mediated diseases among preschool children: A prospective study. Pediatr Allergy Immunol. 2012 Mar;23(2):159–65. https://doi.org/10.1111/j.1399-3038.2011.01203.x
5. Naspitz CK, Solé D, Jacob CA, Sarinho E, Soares FJ, Dantas V, et al. Sensitization to inhalant and food allergens in Brazilian atopic children by in vitro total and specific IgE assay. Allergy Project—PROAL. J Pediatr (Rio J). 2004 Jun;80(3):203–10. https://doi.org/10.2223/1184
6. Aranda CS, Cocco RR, Pierotti FF, Mallozi MC, Franco JM, Porto A, et al. Increased sensitization to several allergens over a 12-year period in Brazilian children. Pediatr Allergy Immunol. 2018 May;29(3):321–4. https://doi.org/10.1111/pai.12860
7. Halvorsen R, Jenner A, Hagelin EM, Borres MP. Phadiatop infant in the diagnosis of atopy in children with allergy-like symptoms. Int J Pediatr. 2009 Aug; Article ID 460737, 4 pages. https://doi.org/10.1155/2009/460737
8. Williams P, Siegel C, Portnoy J. Efficacy of a single diagnostic test for sensitization to common inhalant allergens. Ann Allergy Asthma Immunol. 2001 Feb;86(2):196–202. https://doi.org/10.1016/S1081-1206(10)62691-9
9. Fiocchi A, Besana R, Ryden A-C, Terracciano L, Andreotti M, Arrigoni S, et al. Differential diagnosis of IgE-mediated allergy in young children with wheezing or eczema symptoms using a single blood test. Ann Allergy Asthma Immunol. 2004 Oct;93(4):328–33. https://doi.org/10.1016/S1081-1206(10)61390-7
10. Duran-Tauleria D, Vignati G, Guedan MJA, Petersoon CJ. The utility of specific immunoglobulin E measurements in primary care. Allergy. 2004 Aug;59(78):35–41. https://doi.org/10.1111/j.1398-9995.2004.00566.x
11. Pierotti FF, Aranda CS, Cocco RR, Sarinho E, Sano F, Porto A, et al. Phadiatop Infant and total IgE evaluated in allergic Brazilian children and adolescents. Allergol Immunopathol (Madr). 2020 Jun;48(3):259–64. https://doi.org/10.1016/j.aller.2019.06.013
12. Ballardini N, Nilsson C, Nilsson M, Lilja G. Immuno CAP™ Phadiatop® Infant—A new blood test for detecting IgE sensitisation in children at 2 years of age. Allergy. 2006 Mar;61(3):337–43. https://doi.org/10.1111/j.1398-9995.2005.00936.x
13. Lau S, Nilsson M, Sulser C, Schulz G, Borres MP, Wahn U. Use of Phadiatop Infant in diagnosis of specific sensitization in young children with wheeze or eczema. Pediatr Allergy Immunol. 2008 Jun;19(4):337–41. https://doi.org/10.1111/j.1399-3038.2007.00649.x

14. Fiocchi A, Pecora V, Petersson CJ, Dahdah L, Borres PB, Amengual MJ, et al. Sensitization pattern to inhalant and food allergens in symptomatic children at first evaluation. Ital J Pediatr. 2015 Dec;41:96. https://doi.org/10.1186/s13052-015-0204-9
15. Alduraywish SA, Standl M, Lodge CJ, Abramson MJ, Allen KJ, Erbas B, et al. Is there a march from early food sensitization to later childhood allergic airway disease? Results from two prospective birth cohort studies. Pediatr Allergy Immunol. 2017 Feb;28(1):30–7. https://doi.org/10.1111/pai.12651
16. Naspitz CK, Solé D, Aguiar MC, Chavarria ML, Rosário Filho N, Zuliani A, et al. Phadiatop in the diagnosis of respiratory allergy in children: Allergy project—PROAL. J Pediatr (Rio J). 2004 Jun;80(3):217-22. https://doi.org/10.2223/1186
17. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol. 1999 Jun;103(6):1173–9. https://doi.org/10.1016/S0091-6749(99)70195-8