Fungal Sensitisation in Children

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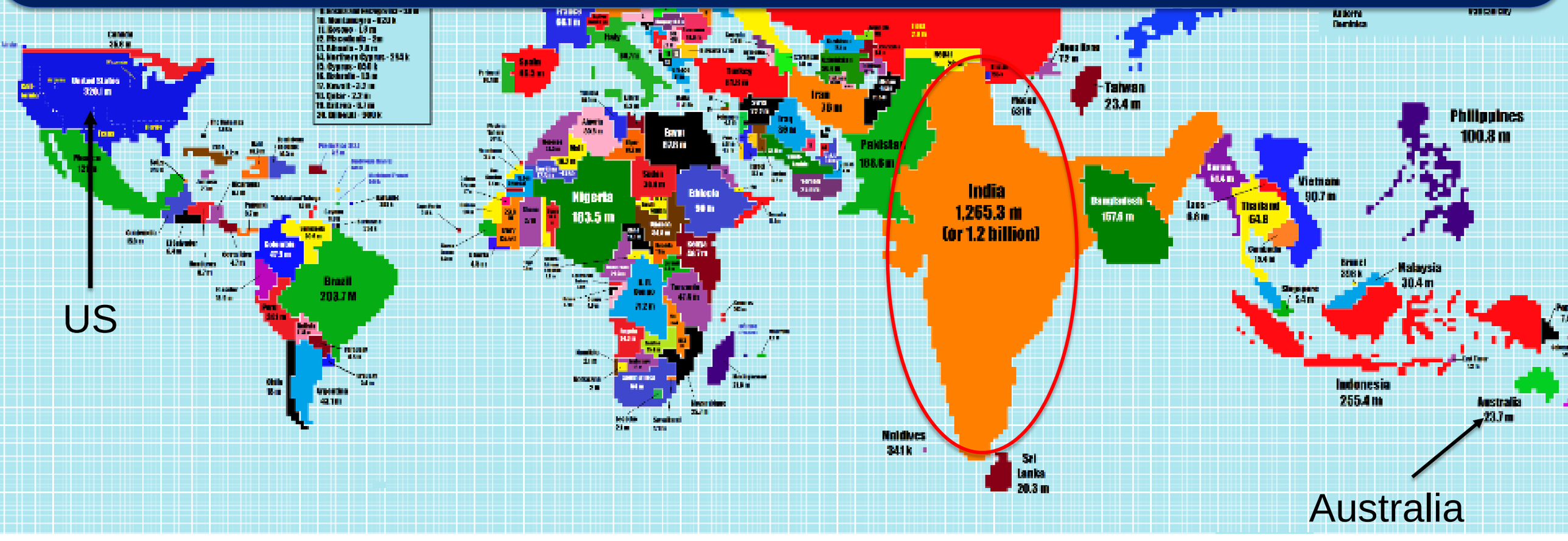
This Is What A World Map Looks Like When Scaled According To Population Size

~20-30% of the Indian population Suffers From at least One of the Allergic Diseases[1]

Allergic burden of ~400 million in India
High burden of disease
High burden on the healthcare providers

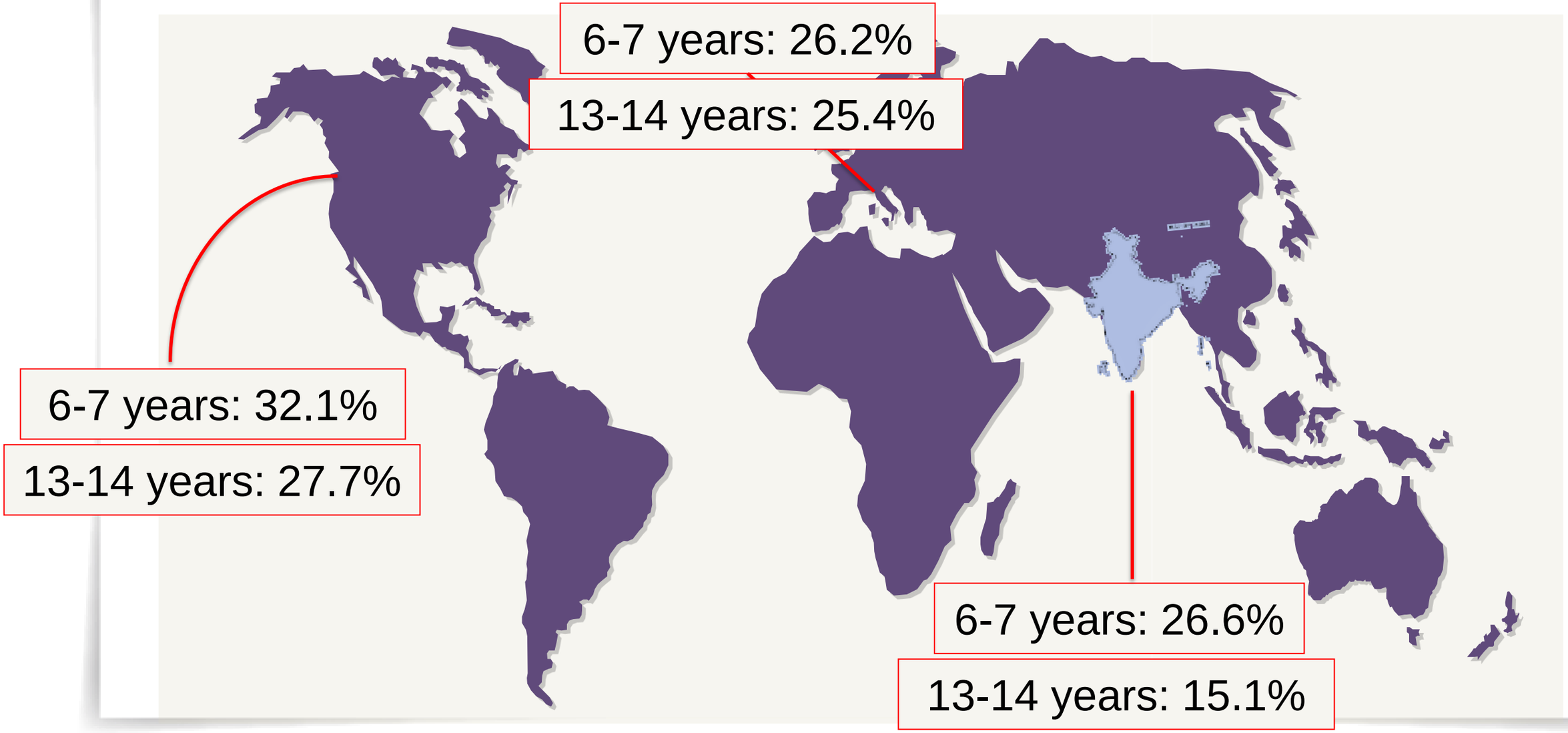


1. Prasad R, Kumar R. Indian J Chest Dis Allied Sci 2013;55:7-8

Burden of Allergy

Children with Rhinoconjunctivitis having concomitant Asthma
ISAAC Phase Three

Similar prevalence was observed globally



Mallol et al. Allergol Immunopathol (Madr). 2013;**41(2)**:73---85

Aero-allergens Are the Most Common Allergens

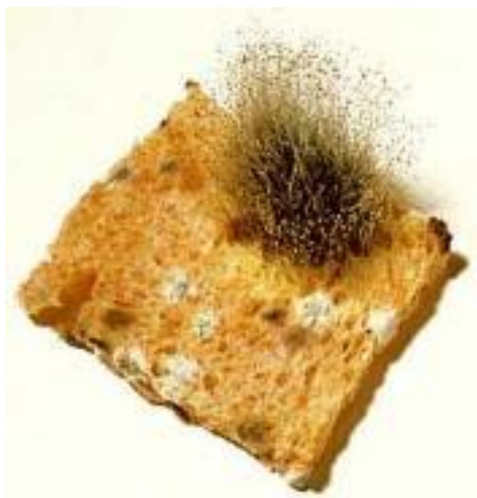
Triggers include:

Dust Mites

Pollen

Cockroach

Animal Dander



Mold

Introduction

- Atopy is a common characteristic of pediatric asthma
- Indoor allergens found to be more predominant
- Fungal sensitisation - Adults versus children
- SAFS - well defined in adults. Not so in children
- Fungal sensitisation and morbidity - association apparent but not confirmed

Fungal sensitisation in children

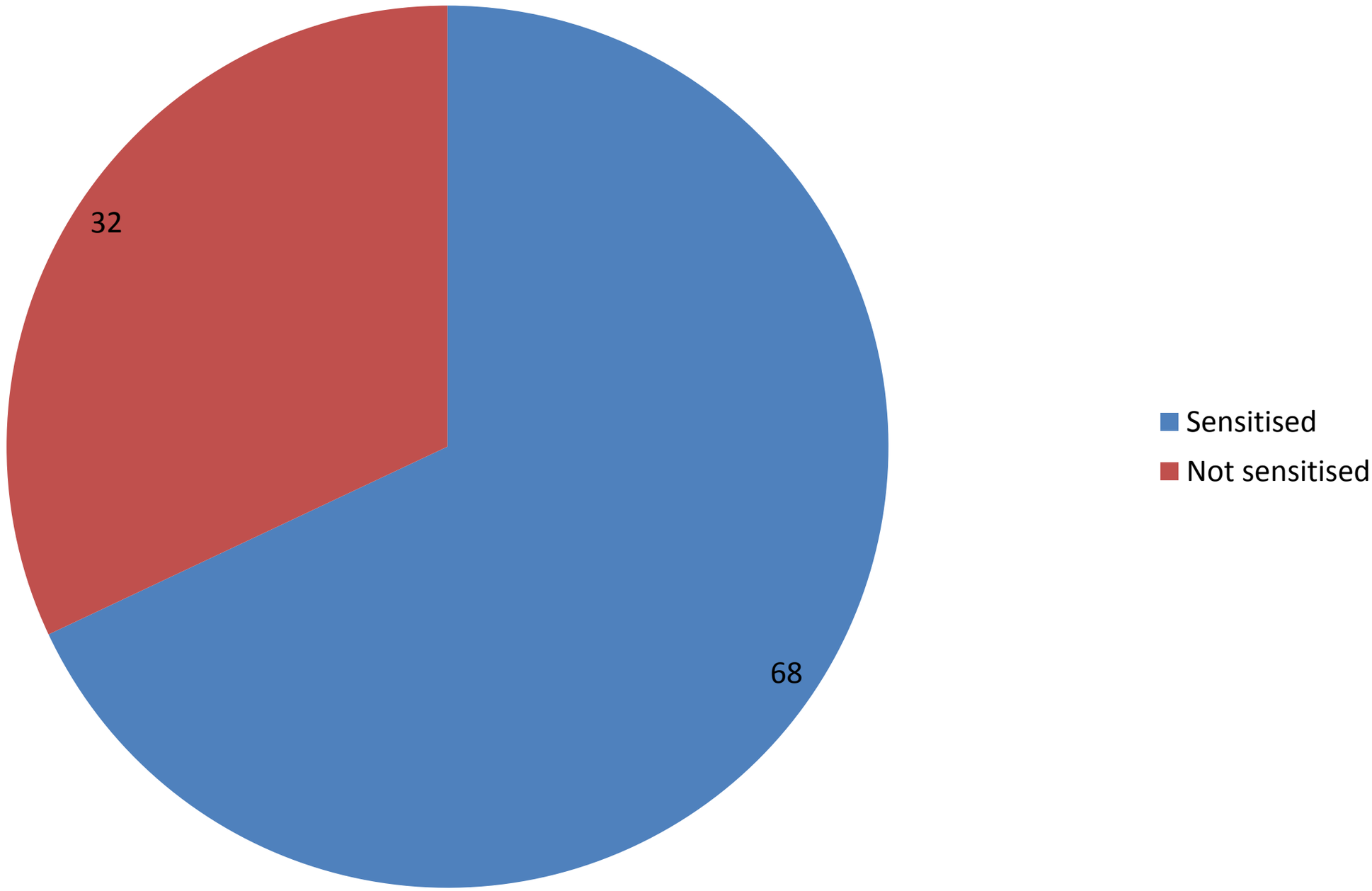
- Increased disease severity
- Increased bronchial reactivity
- Increased airway eosinophilic inflammation
- More exacerbations

Licencio A.G., Santiago M.T., Tsirilakis K., Stone A., Worgall S., Foley E.A. Fungal sensitization in childhood persistent asthma is associated with disease severity. Pediatr Pulmonol. 2014;49:8–14.

Allergen Sensitization in Children with Asthma

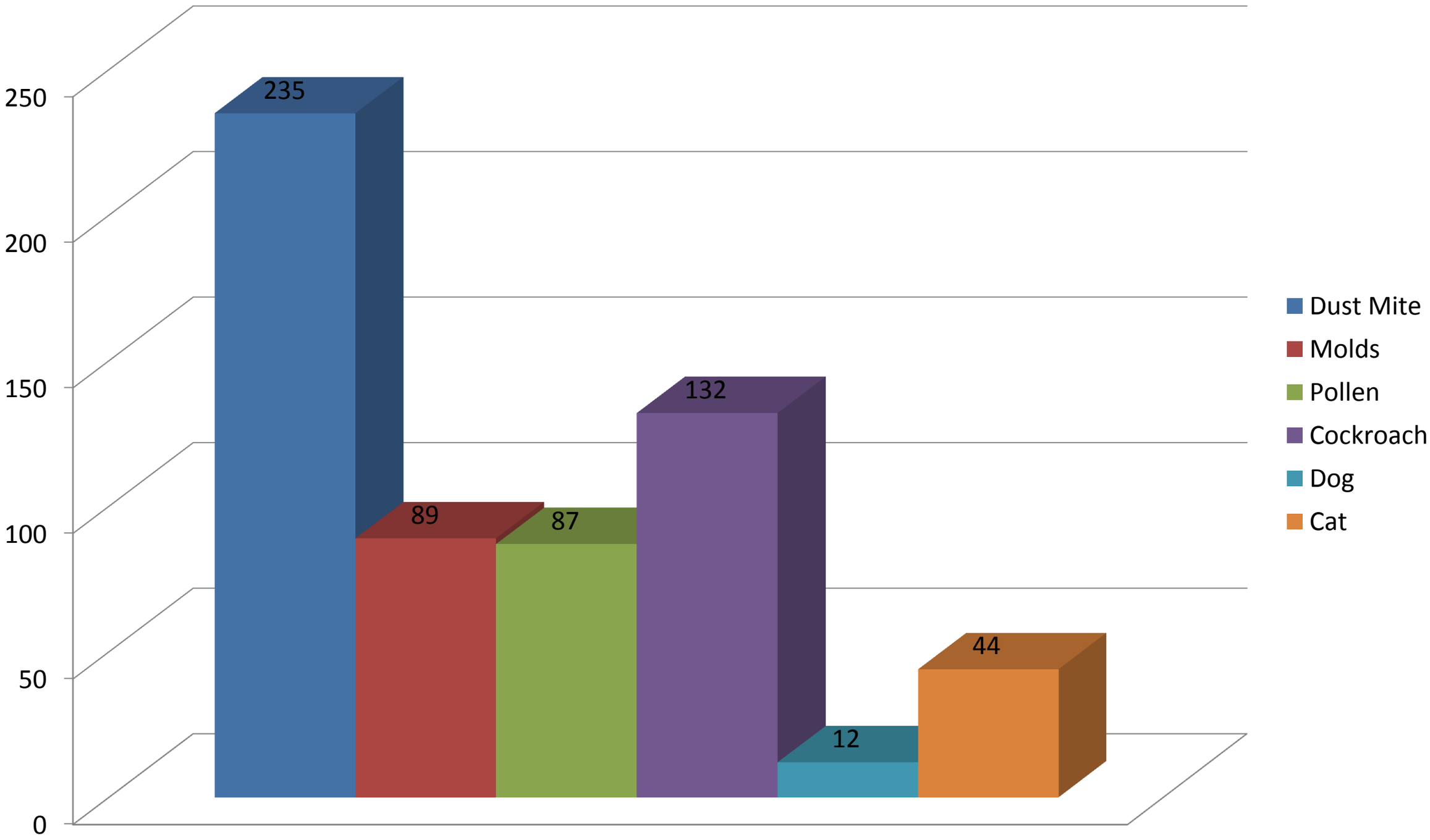
- Study duration: 2 years (2015-2017)
- Total number of children tested – 432
- Age group – 5 years to 18 years
- Gender – Male predominance (60%) – 259
- Rural/Urban – Urban predominance
- Principal Investigator – Dr K R Bharath Kumar Reddy

Sensitisation of single or more allergens

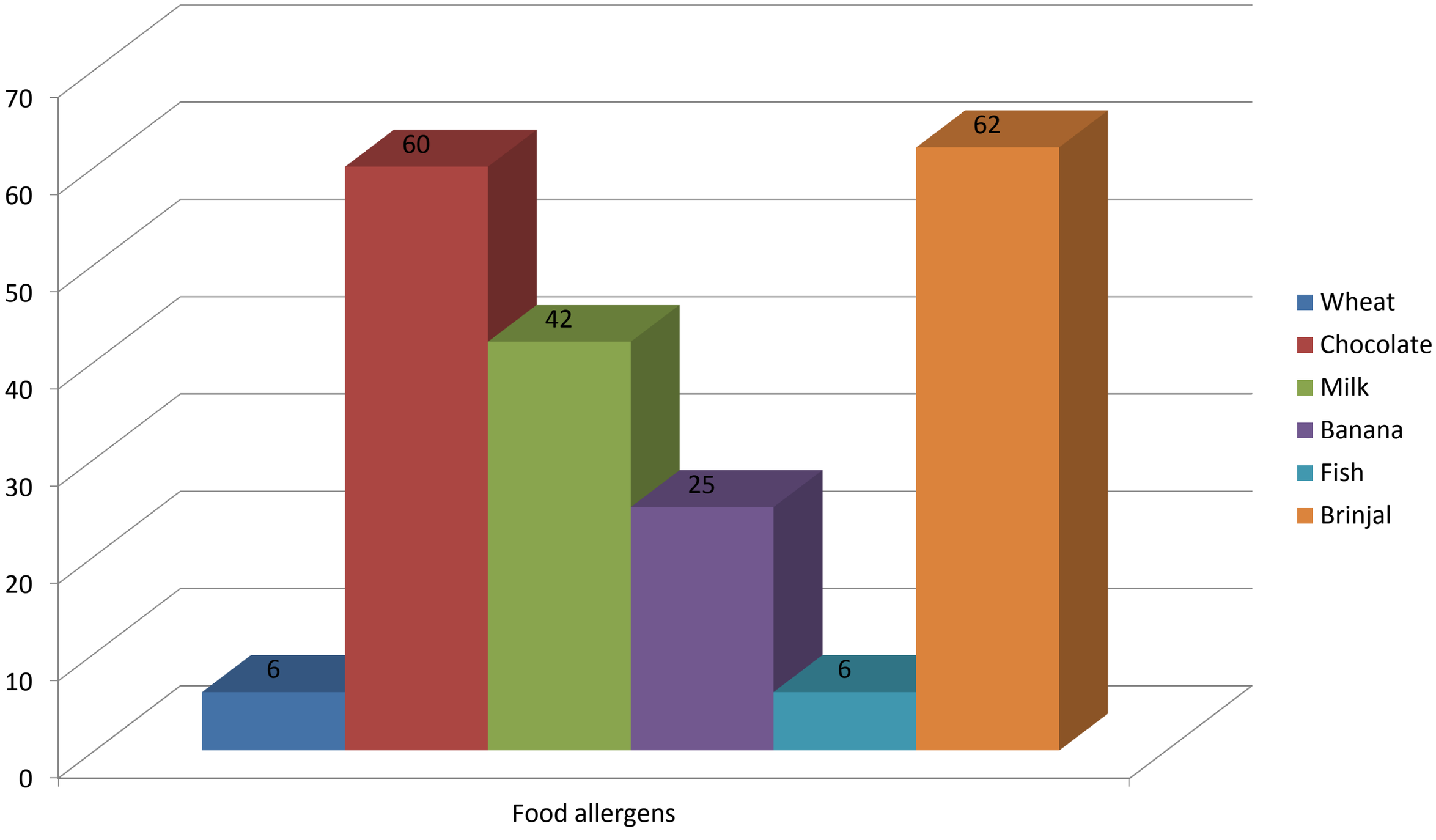


Total number – 294/432

Aeroallergen sensitization out of total 294 sensitized children



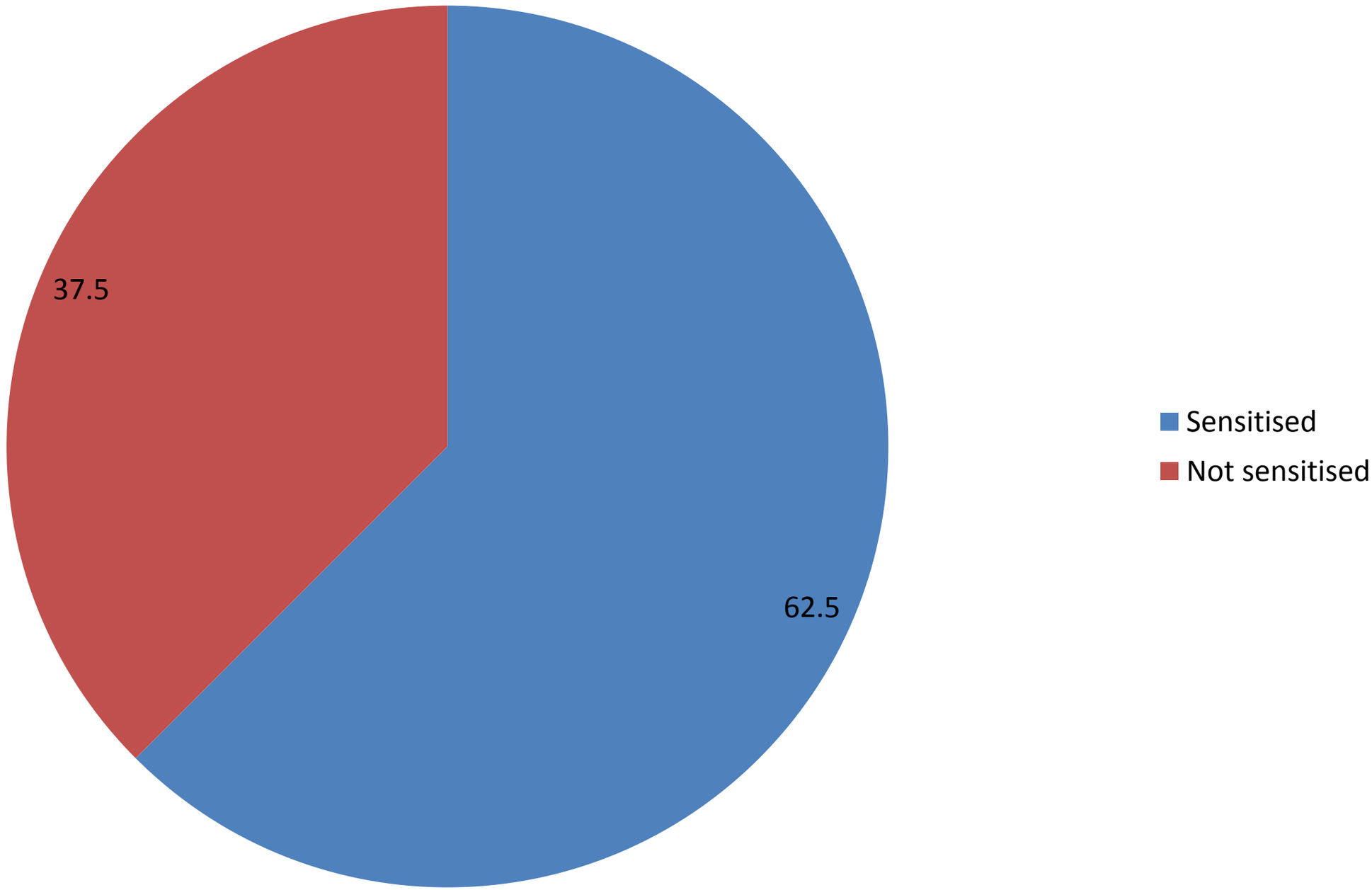
Food allergen sensitization out of 294 children



Allergen Sensitization in Pre school children

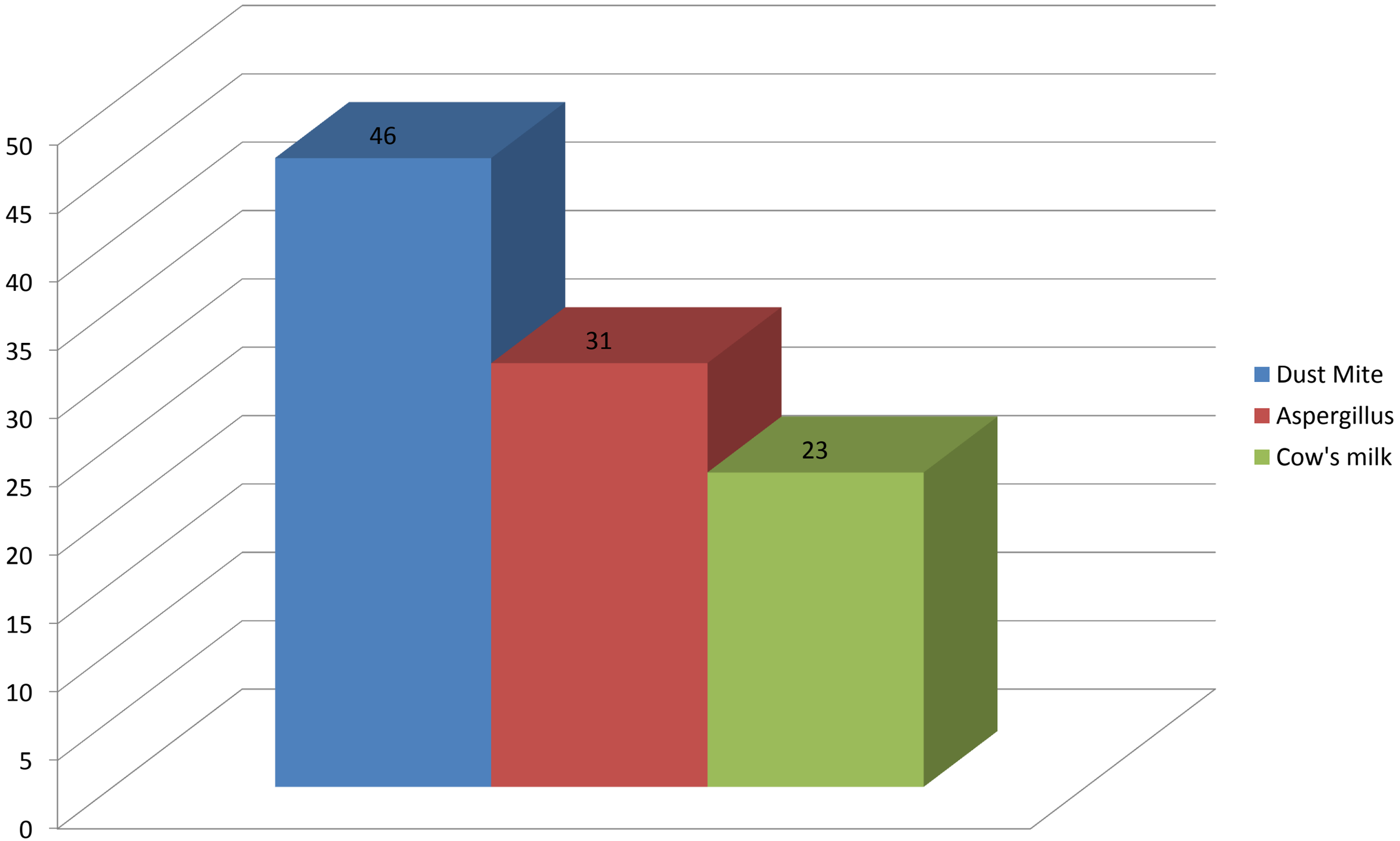
- Study duration: 1 years (2016-2017), Indira Gandhi Institute of Child Health, Bangalore
- PG dissertation – Dr Jay Kumar
- Total number of children tested –160
- Age group – 6 months to 5 years
- Gender – Male predominance (54%) – 81
- Rural/Urban – Urban predominance
- Principal Investigator – Dr K R Bharath Kumar Reddy

Sensitisation of single or more allergens



Total number – 100/160

Allergen Sensitization in children with Pre school wheeze



Clinical Characteristics of Fungal Sensitisation in children (Turkey)

- 3,120 children evaluated
- 1750 SPTs carried out and studied
- 112 had symptoms during mould season and sensitisation of 6.4%
- Alternaria alterna sensitisation 5%

Table 1. Characteristics of children with mould allergy

Characteristics (n=112)	Values
Age (month) Mean ± SD	107.46±47.21
Age of the symptoms (month) Mean ± SD	61.08±41.64
Diagnosis age (month) Mean ± SD	89.76±46.8
Gender (%) Male	63 (56.2%)
Parental atopy history (%)	28 (25%)
Diagnosis (%) Asthma only Allergic rhinitis only Asthma and allergic rhinitis Allergic conjunctivitis	 19 (16.9%) 33 (29.4%) 48 (42.9%) 12 (10.8%)
Asthma (%) Mild Moderate Severe	 27 (40.2%) 27 (40.2%) 13 (19.4%)
Allergic rhinitis (%) Intermittant Persistant	 28 (34.5%) 53 (65.5%)

Sensitization type	
Monosensitization	43 (38.3%)
Polysensitization	69 (61.7%)
Total IgE	
Mean ± SD	527.6±160.1
Fungal allergen sensitization by SPT (%)	
Fungal aeroallergens	
Alternaria alterna	51 (45.5%)
Cladosporium herbarum	36 (32.1%)
Penicillium spp.	18 (16 %)
Aspergillus fumigatus	7 (6.2%)
Non-fungal aeroallergens	
Grass	42 (82.3%)
Olive	32 (62.7%)
Dust mite	23 (45%)
Animal dander	19 (37.2%)
Spirometric analysis	
FEV_1%	89.3±21.51
FEV_1/FVC	91.53±23.11
PEF%	83.97±20.31
MF25-75%	94.77±18.95

Clinical Characteristics of Fungal Sensitisation in children (Turkey)

- The patients with mild asthma were mostly monosensitized (p=0.003), but with SA were polysensitized (p=0.007).
- *Alternaria alterna* sensitization was significantly higher in persistent allergic rhinitis compared to intermittent allergic rhinitis (p>0.05).
- *Aspergillus spp.* sensitization was higher in children with allergic rhinitis and conjunctivitis (p=0.038).
- *Alternaria alterna* was the most common fungal allergen in both mono and polysensitized groups (p=0.002, p=0.004, respectively).

Clinical Characteristics of Fungal Sensitisation in children (Turkey)

- Serum total IgE was high in 88 (78.5%) participants. No statistically significant difference was determined in serum total IgE levels among different types of fungal sensitization ($p>0.05$).
- sIgE levels were correlated with SPT diameter in patients with allergic rhinitis sensitized to fungal allergens ($r=0.466$, $p<0.001$)
- In spirometric analysis, FEV_1 and FEV_1/FVC values were lower in polysensitized children with asthma and children with asthma and coexisting allergic rhinitis compared to children with allergic rhinitis only ($p=0.004$, $p=0.001$, respectively)

Incidence of Fungal Sensitisation

- GALEN study (Europe) - 5% (Adults & children)
- Iranian children with asthma - 10.9%
- Argentinian children with wheezing - 8%
- Middle East - 6.3% in Allergic Rhinitis

Mereidouni M, Hossini RF, Azad FJ, Assarehzadegan MA, Varasteh A. Skin prick test reac vity to common aeroallergens among allergic rhini s pa ents in Iran. Allergol Immunopathol (Madr) 2009; 37: 73-9.

Severe Therapy Resistant Asthma (STRA) and Fungal Sensitisation

- SAFS children were mainly boys (p<0.001)
- Earlier asthma onset (0.5 years [0-12.5] vs 1.5 [0-12.5], p=0.006)
- Higher total IgE (637 IU/mL [12-6737] vs 177 [1-10881], p=0.002)
- More likely prescribed maintenance oral steroids (18/76 (24%) vs 8/88 (9%), p=0.02).
- Children with STRA and SAFS had earlier asthma onset, more atopy and bronchodilator reversibility, and were more often given prednisolone.
- We need a randomised controlled trial of antifungal therapy in paediatric SAFS.

Paediatric Aspergillosis

- Aspergillus fumigatus - 90% of infection
- Aspergillus flavus - 10%
- Sinusitis - A.flavus
- Otomycosis - A.niger
- ABPA occurs in 1-2% of patients with asthma and in 11% of patients with CF.

Immunocompromised children

- Profound neutropenia (<100) and prolonged (>12days) - increased risk of invasive aspergillosis
- Allogenic HSCT patients, develop neutropenia in the first month - more prone
- Children with Neutrophil functional defects - Chronic granulomatous disease (CGD) highly prone
- Only cell mediated defects - rarely develop invasive disease.
- Only advanced HIV - develop invasive aspergillosis in children

ABPA Diagnosis

A diagnosis of ABPA often requires fulfilment of the following criteria:

- Asthma
- Elevated total serum immunoglobulin E (IgE) level
- Peripheral blood eosinophilia
- Precipitating serum antibodies against A fumigatus
- Proximal bronchiectasis
- Immediate cutaneous reactivity to A fumigatus antigens or specific serum IgE to A fumigatus, based on radioallergosorbent test (RAST) results

Aspergillus in children

- **Hypersensitivity Syndromes**
- Asthma
- Extrinsic Alveolar Alveolitis
- Allergic Bronchopulmonary Aspergillosis (ABPA)
- **Saprophytic Non-invasive Syndromes**
- Otomycosis
- Primary cutaneous aspergillosis
- Sinusitis
- Aspergilloma

ABPA in Children

- Not as frequent as reported in adults in the 3rd -4th decade of life
- 7-10% children with corticosteroid dependent asthma
- 7% of children with cystic fibrosis
- Progress - 3 stages: Steroid responsive asthma, steroid dependent asthma, end-stage pulmonary fibrosis with honey-combed lung

Treatment of ABPA in children

- Oral steroids mainstay of treatment
- 0.5- 1 mg/kg/day for one week followed by alternate days till Serum IgE levels reduce
- Oral itraconazole - Not studied adequately in children

ABPA in Cystic Fibrosis

- Prevalence 0.6-11%
- Fulminant to insidious
- Early pick-up & Screening is vital
- Diagnosis may be difficult as similar symptoms & signs may be present even in the absence of ABPA

ABPA in Cystic Fibrosis

The **four minimal diagnostic criteria** in order to make a diagnosis of ABPA are:

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise induced asthma, decline in pulmonary function, increased sputum) NOT attributable to another aetiology.
- Immediate cutaneous reactivity to aspergillus **OR** *in vitro* presence of *A fumigatus* specific Ig E antibodies (strongly positive Aspergillus RAST)
- Ig E > 500IU/ml
- Positive aspergillus precipitans **OR** new abnormalities on CXR or CT scan not
  responding to standard therapy.

Treatment

- Oral Prednisolone - 2mg/kg/day for 2 weeks, 1 mg/kg/day for 2 weeks, then alternate day therapy
- Oral Itraconazole - 5mg/kg/day for 3-6 months
- Voriconazole - 200mg twice daily
- Nebulised Amphotericin - 5-10mg twice daily after physiotherapy

Role of Cytokine IL-33 in children with asthma

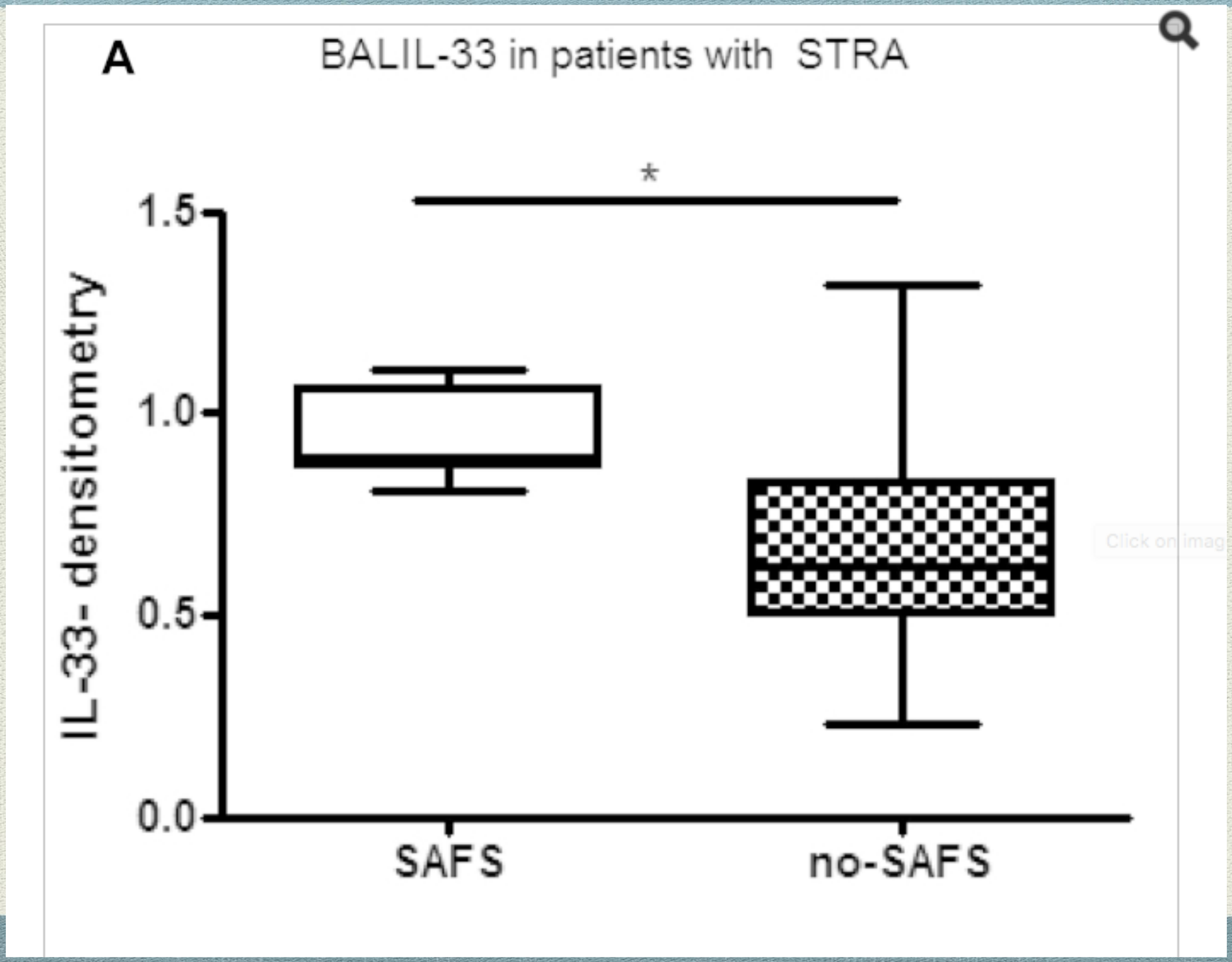
Patients' demographics

Characteristics	STRA with SAFS (n = 38)	Non–fungus-sensitized STRA (n = 44)	*P* value
Sex (male/female)	30/8 (male = 78.9%)	22/22 (male = 50%)	.007
Age at symptom onset (y), median (range)	0.42 (0-12.5), n = 36)	1 (0-12.5), n = 43	.015
Atopy, no./total no. with data available (%)	37/38 (97.4)	33/44 (75)	.004
Total IgE (IU/mL), median (range)	634 (24-6737), n = 37	298 (7-4610), n = 43	.015
Sum of nonfungal inhalant SPT wheal diameter (mm), median (range)	16 (3-38), n = 27	9 (0-29), n = 41	.008
Sum of nonfungal inhalant sIgE (IU/mL), median (range)	68.4 (0-287), n = 33	30.8 (0-220.5)	.02
Body mass index (kg/m^2), median (range)	19.7 (7.1-29.7), n = 18	18.3 (14.9-36.6), n = 28	NS
Successful trial of omalizumab, no./total no. with data available (%)	8/10 (80)	11/18 (61)	NS
Prescribed maintenance OCS, no./total no. with data available (%)	16/38 (42.1)	6/42 (14.3)	.02
ICS dose (budesonide equivalent μg/d), median (range)	1500 (800-3000), n = 38	1600 (800-4800), n = 44	NS
ACT score, median (range)	13 (6-23), n = 34	13 (6-25), n = 40	NS
FEV_1 (% predicted, median (range)	71 (29-121), n = 38	71.5 (34-99), n = 42	NS
FVC (% predicted), median (range)	94.5 (36-133), n = 38	91.3 (57-123), n = 42	NS

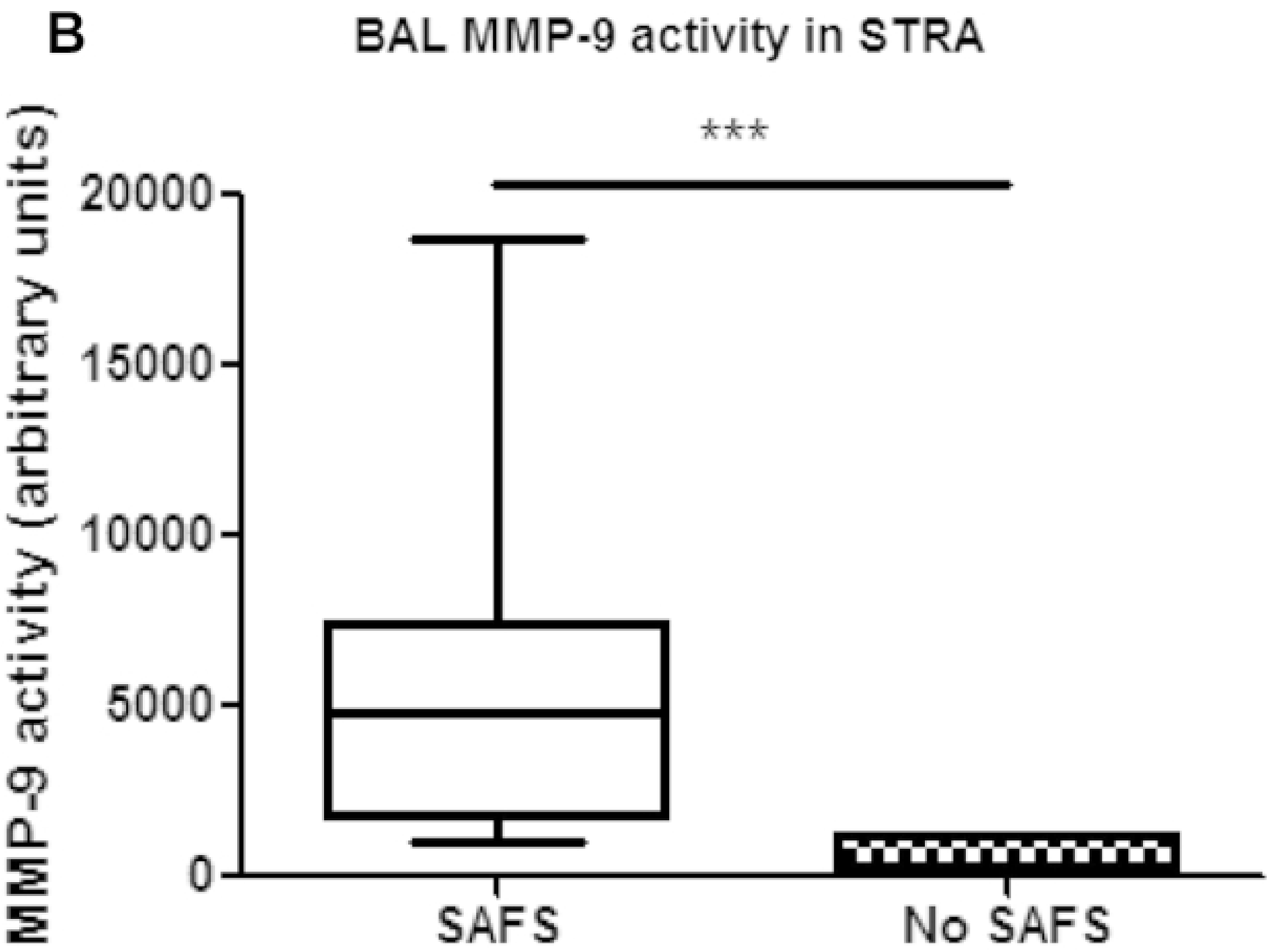
ACT, Asthma Control Test; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroids; *NS*, not significant; *OCS*, oral corticosteroids.

J Allergy Clin Immunol. 2015 Aug;136(2):312-22.e7. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33.
Castanhinha S1, Sherburn R2, Walker S2, Gupta A3, Bossley CJ3, Buckley J2, Ullmann N1, Grychtol R2, Campbell G2, Maglione M1, Koo S1, Fleming L4, Gregory L2, Snelgrove RJ2, Bush A4, Lloyd CM2, Saglani S5.

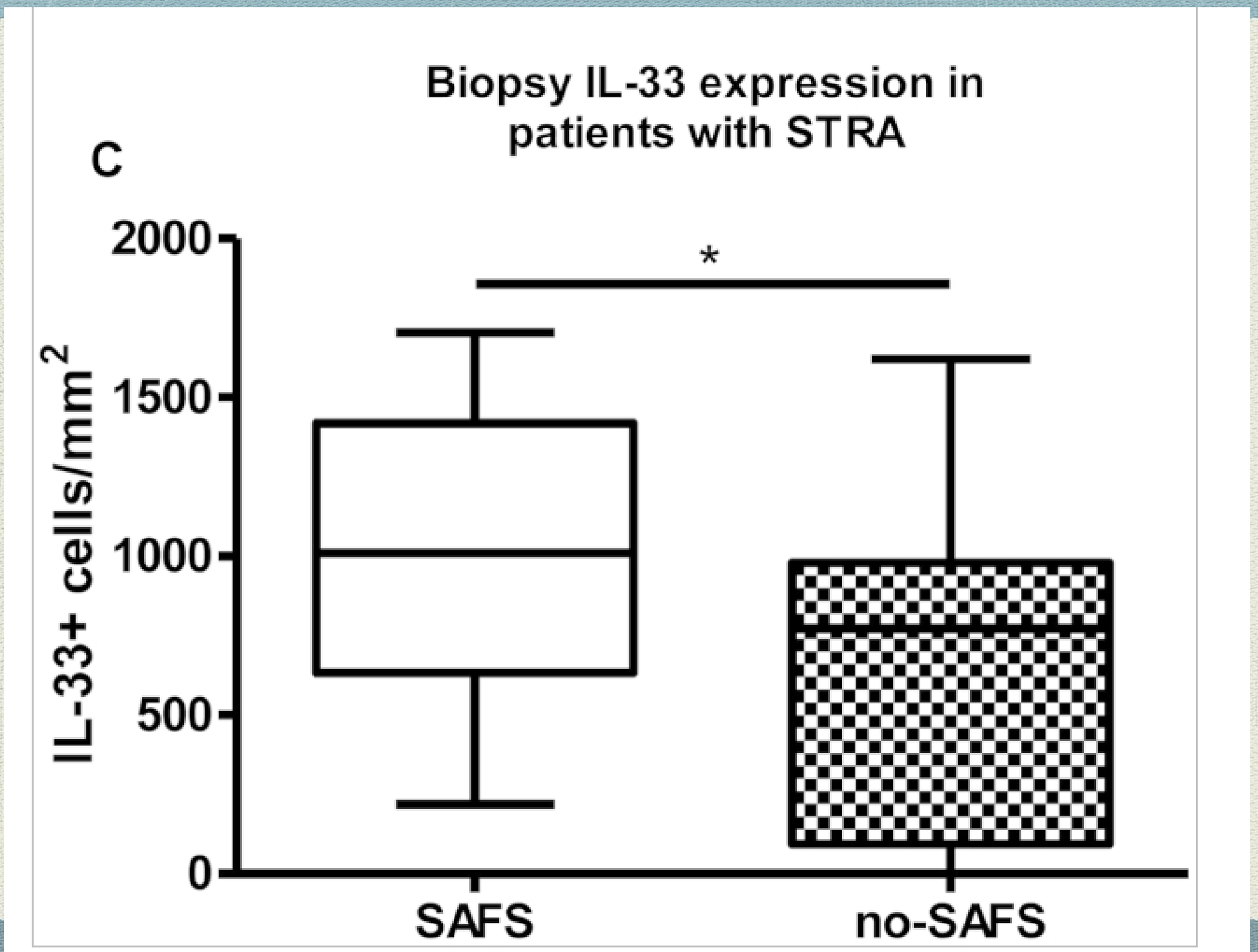
Role of Cytokine IL-33



Role of Cytokine IL-33



Role of Cytokine IL-33



Novel therapy

- Pediatric SAFS was associated with more oral steroid therapy and higher IL-33 levels.
- *A alternata* exposure resulted in increased IL-33–mediated ILC2 numbers, TH2 cell numbers and steroid-resistant AHR.
- IL-33 might be a novel therapeutic target for SAFS.

Thank You!


Wheeze, Sneeze
Cough and Crease
By
Dr. K.R. Bharath Kumar Reddy
The guide to understand
your child's allergies!