Original article

Arch Argent Pediatr. 2026;e202510978

Impaired immune response to polysaccharide antigens and warning signs in children with recurrent respiratory infections

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ABSTRACT

Introduction. Inborn errors of immunity constitute a group of genetic disorders that may present with warning signs. Among their most common presentations are recurrent respiratory infections, which may reflect abnormalities in humoral immunity. In this context, specific antibody deficiency (SAD) is characterized by an inadequate response to polysaccharide antigens, with normal serum immunoglobulin levels and antibody responses to protein antigens.

Objective. To identify SAD by testing for antibodies against *Streptococcus pneumoniae* in pediatric patients with recurrent respiratory infections and to describe the presence of the Jeffrey Modell Foundation warning signs.

Population and methods. Observational, analytical, and retrospective study. Pediatric patients with recurrent respiratory infections were included. Baseline levels of anti-*S. pneumoniae* were measured; when values were ≤113 mg/L, the 23-valent pneumococcal polysaccharide vaccine was administered, and the post-vaccination response was evaluated. SAD was defined as the absence of an adequate serological response (post-vaccination titer ≤113 mg/L). Warning signs were analyzed descriptively in patients with SAD.

Results. A total of 146 patients were included; 50.68% had anti-pneumococcal IgG levels ≤113 mg/L; of these, 18% remained low after vaccination, and SAD was diagnosed (prevalence: 8.9%). Among patients with SAD, a proportion exhibited three or more warning signs.

Conclusion. SAD was a common finding in children with recurrent respiratory infections. The presence of warning signs could help identify patients who require immunological evaluation.

Keywords: *child; primary immunodeficiency disorders; respiratory tract infections; recurrent infection.*

doi: http://dx.doi.org/10.5546/aap.2025-10978.eng

To cite: Pury S, Marini V, Lozano NA, Sasia LV, Córdoba EA, Saranz RJ, et al. Impaired immune response to polysaccharide antigens and warning signs in children with recurrent respiratory infections. *Arch Argent Pediatr.* 2026;e202510978. Online ahead of print 6-AUG-2026.

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Funding*: None.*

Conflict of interest*: None.*

Received*: 11-30-2025*
Accepted*: 5-24-2026*

INTRODUCTION

Inborn errors of immunity (IEIs) encompass a group of diseases linked to 508 genetic defects.[1] They are characterized by immune dysregulation associated with increased susceptibility to infections, autoimmunity, allergies, and cancer.[1-3]

Recurrent respiratory infections are a common reason for seeking medical care and a relevant clinical indicator for identifying possible immune deficiencies.[4,5] From a clinical perspective, IEI can present with warning signs that allow for early suspicion of the condition.[6] In this context, the criteria proposed by the Jeffrey Modell Foundation serve as a useful tool for guiding the diagnostic workup and identifying patients who require a more detailed immunological evaluation.[6]

In the latest update to the International Union of Immunological Societies (IUIS) classification of inborn errors of immunity, these are divided into ten categories. Specific antibody deficiency (SAD), is included among the predominant antibody deficiencies.[1] It is characterized by inadequate production of antibodies against polysaccharide antigens, while maintaining normal levels of response to protein antigens such as tetanus and diphtheria toxoids, as well as immunoglobulins—including IgG subclasses—and a normal number of B lymphocytes.[1,7]

This diagnosis should be suspected when low levels of antibodies against *Streptococcus pneumoniae* are detected following administration of the 23-valent pneumococcal polysaccharide vaccine (PPSV23), as assessed four to six weeks after vaccination.[8]

The adaptive response to *S. pneumoniae* involves the activation of T and B cells, as well as a T-cell-independent response mediated by B cells from the splenic marginal zone and B1 cells. This response matures during early childhood, reaching peak competence between the ages of 2 and 4.[8-10]

The underlying genetic and molecular defects are not yet fully understood.[1,11] Reduced numbers of class-switched memory B cells have been reported, a population that may play an important role in defense against encapsulated microorganisms.[12-14]

Given this background, we propose the hypothesis that a proportion of children with recurrent respiratory infections have SAD and that the presence of warning signs could help identify these patients. The primary objective of this study was to identify the presence of SAD by evaluating the antibody response to *S. pneumoniae* in this population. Secondary objectives included determining baseline levels of anti-pneumococcal IgG, evaluating the serological response following vaccination, and describing the presence of warning signs proposed by the Jeffrey Modell Foundation.

POPULATION AND METHODS

An observational, analytical, and retrospective study was conducted based on a review of medical records. The study included pediatric patients aged 2 to 16 years of both sexes who were treated at the Clínica Universitaria Reina Fabiola in the city of Córdoba, Argentina, with recurrent respiratory infection; these patients were evaluated between January 2021 and March 2023.

The criteria for defining a child with recurrent respiratory infections were established as follows: six or more respiratory infections per year between the first and third years of life, five or more episodes between three and six years of age, and three or more episodes per year between six and twelve years of age. In all age groups, the presence of at least one episode of pneumonia—including severe pneumonia—or two episodes of mild pneumonia confirmed by clinical and/or radiographic criteria within one year was also considered.[5]

All patients underwent an immunological evaluation including a complete blood count, serum immunoglobulin measurements, serum protein electrophoresis, tetanus toxoid IgG, and anti-*S. pneumoniae* IgG measured by total ELISA. Baseline anti-pneumococcal IgG concentrations >113 mg/L were considered protective. In patients with baseline values below this cutoff point, who had preserved antibody responses to protein antigens and adequate immunoglobulin concentrations, the 23-valent pneumococcal polysaccharide vaccine (Pneumovax23™ or PNEUMO23™) was administered. Anti-*S. pneumoniae* IgG concentrations were reassessed 4 weeks after vaccination. An adequate response was defined as post-vaccination levels >113 mg/L, and SAD as the persistence of values below that threshold.

All patients had a complete vaccination schedule for their age, according to Argentina's National Immunization Schedule, including the 13-valent pneumococcal conjugate vaccine (2+1 schedule). None had previously received the 23-serotype pneumococcal polysaccharide vaccine. Consequently, the administration of

PPSV23 in the context of the study constituted the first exposure to non-conjugated polysaccharide antigens and was used for diagnostic purposes.

Warning signs of inborn errors of immunity were identified according to the criteria of the Jeffrey Modell Foundation (*Table 1*).[6]

Patients with a previous diagnosis of IEI, a diagnosis of secondary immunodeficiency (HIV, immunosuppressive therapy, etc.), and those with autoimmune disorders were excluded. Additionally, patients who did not meet vaccination criteria after testing positive for low levels of pneumococcal antibodies, or who did not undergo serological follow-up after vaccination, were excluded.

Statistical analysis

The statistical analysis included summary statistics for the descriptive variables. The warning signs were characterized descriptively in patients diagnosed with polysaccharide-responsive failure (PRF). A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using the R-medic™ software.[15]

Ethical considerations

This study was classified as "no risk" according to PAHO/WHO guidelines; it was approved by the Institutional Committee on Health Research Ethics (CIEIS, by its Spanish acronym) of the Clínica Universitaria Reina Fabiola (registration no. AEI20240605bTF) on June 7, 2024. It was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice, and in accordance with Law 9694/09 of the province of Córdoba (Argentina) on Research Involving Human Subjects. Confidentiality was ensured in accordance with Law 25326 on the Protection of Personal Data.

RESULTS

During the sample selection process, 210 patients with recurrent respiratory infections were evaluated during the study period. Of these, 64 were excluded from the final analysis because they did not complete the initial evaluation, did not accept the vaccine challenge, or did not undergo the post-vaccination serological follow-up. Ultimately, 146 patients met the inclusion criteria and had complete data for the analysis (*Figure 1*).

Of the 146 patients included, 75 were anti-*S. pneumoniae* IgG concentration was 94.23 mg/L, with a range of 0 to 266 mg/L. The median was 95 mg/L (IQR: 53-128.75), with no statistically significant differences observed by sex ($p = 0.07$). A total of 74 patients (50.68%) had anti-pneumococcal IgG levels ≤113 mg/L, with a mean of 51.97 mg/L, a median of 53 mg/L (IQR: 32-74), and a range of 0-95 mg/L.

Following PPSV23 immunization, 61 of the 74 patients achieved protective antibody concentrations, while 13 had persistently low antibody concentrations and were diagnosed with SAD, yielding an overall prevalence of 8.9%.

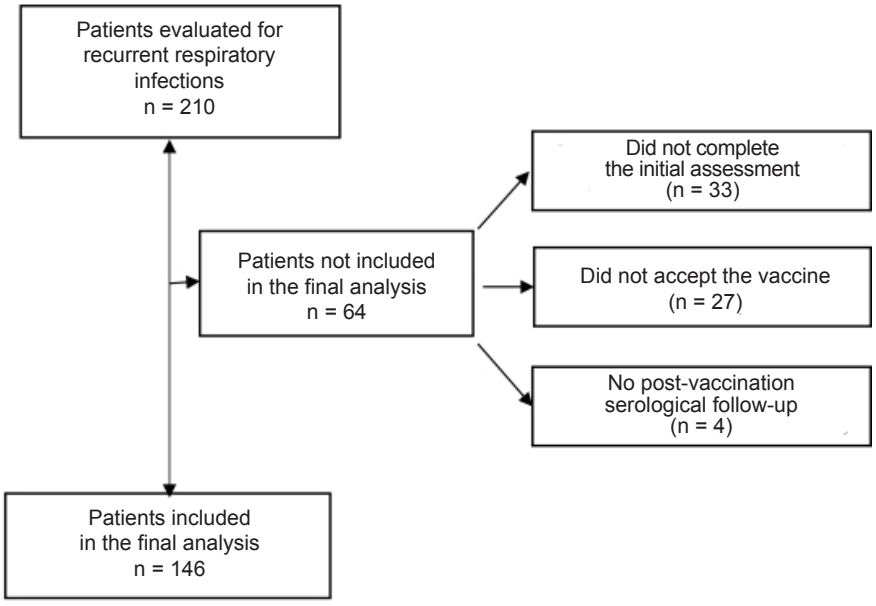
Regarding clinical manifestations in patients with SAD (n = 13), all presented with upper airway involvement. Nine (69%) had recurrent lower respiratory tract infections; two (15%) had skin and soft tissue infections; two (15%) developed

Table 1. Warning signs for inborn errors of immunity according to the Jeffrey Modell Foundation's criteria

10 warning signs for IEIs
1. Four or more new episodes of otitis in one year.
2. Two or more severe sinus infections in one year.
3. Two months or more of antibiotic treatment with little effect.
4. Two episodes of pneumonia in one year.
5. Difficulty gaining weight and growing normally.
6. Recurrent organ abscesses or deep skin abscesses.
7. Persistent mouth sores or fungal skin infections.
8. Need for intravenous antibiotics to treat infections.
9. Two or more deep-seated infections, including sepsis.
10. Family history of primary immunodeficiencies.

IEI: inborn errors of immunity.

Figure 1. Patient selection flowchart



severe infections requiring hospitalization. These categories are not mutually exclusive.

With regard to treatment, 7 patients received prophylactic antibiotics (trimethoprim-sulfamethoxazole), 1 patient required gamma globulin replacement, and 5 were managed with a watch-and-wait approach.

Seven of the 13 patients with SAD presented with three or more Jeffrey Modell Foundation warning signs.

DISCUSSION

According to the Jeffrey Modell Foundation, specific antibody deficiency (SAD) is the fifth most common inborn error of immunity worldwide.[16] A study conducted at a pediatric center in New

Table 2. Descriptive analysis of the patients included

Variable	Value
Age, months	
Median (range)	48.50 (24-192)
Sex, n	
Male	71
Female	75
Baseline anti-pneumococcal IgG	
Mean (95% CI)	94.23 mg/L (85.14-103.32)
Median (IQR)	95 (53-128.75)
Range	0-266
>113 mg/dl	72 (49.32%; 95%CI 40.89-57.11)
≤113 mg/dl	74 (50.68%; 95%CI 42.89-59.11)
Patients who received a post-primary pneumococcal IgG vaccine booster	
>133 mg/dl	61 (82.43 %; 95%CI 73.25-90.75)
≤133 mg/dl	13 (17.57 %; 95%CI 9.25-26.75)

95%CI: 95% confidence interval, IQR: interquartile range.
For the age variable, the values in parentheses indicate the range.
In 12 patients, the values exceeded the method's upper limit of quantification.

Orleans reveals that this deficiency is the most prevalent in this age group.[17] In studies evaluating children with recurrent infections, the prevalence was estimated to be between 11% and 15%.[18-20] In our study, the prevalence was 8.9%.

With regard to serological antibody testing, the currently accepted gold standard for measuring the specific anti-pneumococcal IgG response is the third-generation ELISA or Luminex™ multiplex technology, which allows for the quantification of serotype-specific IgG.[21] The global ELISA assay, which simultaneously measures antibodies directed against all serotypes included in the 23-valent polysaccharide vaccine, is an accessible and clinically useful alternative in resource-limited settings because of its lower cost and technical simplicity.[22] However, it has significant limitations.[11] Since it does not distinguish the response to individual serotypes nor allow for the assessment of the proportion of serotypes that achieve protective titers, its diagnostic capacity for detecting a failure of the polysaccharide response is lower, and the results must be interpreted with caution. Nevertheless, it remains an option used in many centers where advanced methodologies are not routinely available. In our country, serotype-specific methods are not available, which constitutes a limitation.

Another aspect of great diagnostic importance is the availability of the unconjugated vaccine. The assessment of a deficient response to polysaccharides depends on the immune system's ability to generate antibodies via the T-cell-independent pathway, which can only be measured using unconjugated polysaccharide antigens such as PPSV23. When these vaccines are unavailable and replaced by conjugated formulations, the response becomes T-cell-dependent, making it impossible to evaluate the traditional T-cell-independent response to polysaccharide antigens.[8]

Alternative diagnostic tools for evaluating the response to polysaccharide antigens include measuring antibody levels following stimulation with the *Salmonella typhi* vaccine (Typhim Vi™).[8] However, its implementation has limitations, given that the vaccine is not included in the national immunization schedule and, in our setting, anti-*S. typhi* IgG testing is not readily available.

The diagnostic interpretation of the SAD in young children requires special caution, as the response to polysaccharide antigens matures progressively during early childhood. In children under four years of age, a suboptimal response may reflect transient immunological immaturity rather than a persistent defect. In this regard, although the inclusion of patients as young as two years old is based on the minimum age for the 23-valent pneumococcal polysaccharide vaccine, some cases may require longitudinal reevaluation.

The clinical manifestations of SAD include recurrent respiratory infections, otitis, and sinusitis, which can progress to severe infections or bronchiectasis.[13,14] The "10 warning signs" developed by the Jeffrey Modell Foundation are intended to facilitate the early recognition of inborn errors of immunity and remain relevant in clinical practice.[23,24] In our cohort, a significant proportion of patients with SAD presented with three or more warning signs, reinforcing their value as a clinical tool for suspecting inborn errors of immunity.

Treatment for SAD includes early identification of infections, antibiotic therapy, antibiotic prophylaxis, or, in selected cases, immunoglobulin therapy.[25] Several authors, including Pandya *et al.* and the group led by Smits *et al.*, have demonstrated that antibiotic prophylaxis can be as effective as immunoglobulin therapy for treating this disorder.[26,27] Vaccination with PPSV23 may also improve both serological and clinical outcomes in patients who have failed to respond adequately to previous conjugate pneumococcal vaccines.[11,28]

One limitation of the study is the lack of systematic microbiological identification of the etiological agents responsible for each infectious episode, due to its retrospective design and the outpatient management of most pediatric respiratory conditions. Although this limits the ability to directly attribute cases to *S. pneumoniae*, this microorganism remains a significant pathogen in pediatric bacterial respiratory infections.[29] Future prospective studies with standardized surveillance will help strengthen the correlation between the immune response and clinical presentation. Second, since this is a cohort referred to a referral center, there is a possibility of selection bias, with a potential overrepresentation of patients with more persistent or complex presentations.

Despite its limitations, this study has significant strengths. It includes a pediatric cohort representative of routine clinical practice, applies a systematic diagnostic approach, and provides local evidence. Furthermore, it links immunological findings to simple clinical variables that may be useful for early detection.

CONCLUSION

In children with recurrent respiratory infections, SAD was identified in 8.9% of patients. The presence of clinical warning signs could help guide the initial immunological evaluation. ■

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