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DIAGNOSIS OF COUGH: IMMUNOLOGICAL RESPONSE IN IMMUNIZED AND NON-IMMUNIZED CHILDREN

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ABSTRACT: Background: Cough is a frequent symptom in pediatric practice with multifactorial etiologies ranging from viral infections to allergic reactions. Immunization against common respiratory pathogens may modulate the host immune response, thereby altering the clinical and immunological presentation of cough. Objective: This study aimed to compare the immunological responses associated with cough in fully immunized versus non-immunized children and to evaluate their diagnostic implications. Methods: In this prospective, multicenter observational study, 480 children aged 6 months to 12 years presenting with acute cough were enrolled and stratified based on their immunization status into fully immunized (n = 240) and non-immunized (n = 240) groups. Immunological assessments included serum cytokine profiles (interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α], interferon-gamma [IFN-γ]), immunoglobulin levels (IgA, IgM, IgG), and white blood cell (WBC) differentials. Clinical data, including cough duration, severity (using a standardized cough score), and associated symptoms, were recorded at presentation and during follow-up at days 7 and 14.
Results: Fully immunized children exhibited significantly lower mean cough severity scores (4.1 ± 1.3 vs. 5.3 ± 1.6, $p < 0.001$) and shorter duration of cough (median 5 days vs. 8 days, $p < 0.001$) compared to non-immunized children. Immunologically, the fully immunized group showed a balanced cytokine response with lower levels of IL-6 (mean 18.2 ± 5.6 pg/mL vs. 25.4 ± 6.8 pg/mL, $p < 0.001$) and TNF-α, and a higher proportion of regulatory T-cell markers, suggesting an attenuated inflammatory response. In contrast, non-immunized children had elevated pro-inflammatory cytokines and a higher neutrophil-to-lymphocyte ratio. Multivariate logistic regression analysis identified full immunization as an independent predictor for reduced cough severity (adjusted OR 0.47, 95% CI 0.33–0.67, $p < 0.001$). Conclusions: The findings indicate that full immunization is associated with a more favorable immunological response in children with cough, leading to milder clinical manifestations. This study supports the role of immunization in modulating immune responses, thereby aiding in the diagnostic evaluation and management of pediatric cough.

Keywords: Cough, immunization, pediatric, immunological response, cytokines, diagnosis

INTRODUCTION

Background - Cough is one of the most common symptoms in pediatric patients and serves as an important clinical indicator for a range of respiratory conditions. Its etiology can be infectious, allergic, or non-specific, making accurate diagnosis and management a challenge. Immunization programs targeting pathogens such as Bordetella pertussis, influenza viruses, and Streptococcus pneumoniae have substantially reduced the incidence and severity of these infections. Vaccines not only prevent disease but also modify the host's immune response. In fully immunized children, this immunomodulatory effect may result in a less pronounced inflammatory response when cough occurs, compared to non-immunized children who may exhibit heightened immunological activation.
Rationale - While several studies have examined the impact of immunization on the incidence of vaccine-preventable diseases, there is limited data on how immunization influences the immunological profile during acute respiratory events such as cough. Characterizing the

differences in cytokine responses, immunoglobulin levels, and cellular immune markers between immunized and non-immunized children could enhance diagnostic precision and guide targeted treatment strategies. Moreover, understanding these immunological differences might serve as a diagnostic adjunct in evaluating the severity and potential complications associated with cough.

Objective - The primary objective of this study was to compare the immunological responses—measured by cytokine profiles, immunoglobulin levels, and WBC differentials—in fully immunized versus non-immunized children presenting with cough. Secondary objectives included correlating these immunological markers with clinical severity and duration of cough, and assessing their potential utility as diagnostic indicators.

MATERIALS AND METHODS

Study Design and Setting - A prospective, multicenter observational study was conducted from January 2019 to December 2021 at four pediatric centers with affiliated outpatient clinics. The study protocol was approved by the Institutional Review Boards of all participating institutions, and informed consent was obtained from parents or legal guardians.

Participants - A total of 480 children, aged 6 months to 12 years, presenting with an acute cough (duration <14 days) were enrolled. Participants were categorized into two groups: Fully Immunized Group (n = 240): Children who had received all recommended vaccines according to the national immunization schedule (including pertussis, influenza, and pneumococcal vaccines). Non-Immunized Group (n = 240): Children with incomplete or no immunization records. Inclusion Criteria: Acute onset of cough (duration less than 14 days). Availability of accurate immunization records. No underlying chronic respiratory diseases (e.g., asthma, cystic fibrosis). Exclusion Criteria: Immunodeficiency disorders. Recent hospitalization for respiratory illness (within the last 30 days).Concurrent use of immunosuppressive medications.

Data Collection - Clinical and immunological data were collected at the time of presentation (baseline) and during follow-up visits at 7 and 14 days post-enrollment. Data collection included: Clinical Assessment: Demographic data, cough duration, severity scoring (on a scale of 0–10), associated symptoms (fever, wheezing), and physical examination findings. Immunological Assessments: Blood samples were obtained for: Cytokine Profiling: Quantitative measurement of serum IL-6, TNF-α, IFN-γ, and interleukin-10 (IL-10) using enzyme-linked immunosorbent assay (ELISA). Immunoglobulin Levels: Serum IgA, IgM, and IgG levels measured via nephelometry. Complete Blood Count (CBC) with Differential: Including calculation of the neutrophil-to-lymphocyte ratio (NLR). Flow Cytometry: For assessing regulatory T-cell markers (CD4+CD25+FOXP3+).

Outcome Measures - The primary outcomes were differences in the immunological markers between the fully immunized and non-immunized groups and their correlation with cough severity and duration. Secondary outcomes included the rate of complications (e.g., secondary bacterial infections) and the need for additional interventions (e.g., antibiotic therapy, hospitalization).

Statistical Analysis - Data were analyzed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and compared using Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were expressed as frequencies and percentages, with comparisons performed using the chi-square test or Fisher's exact test. Multivariate logistic regression analyses were conducted to adjust for potential confounders (age, nutritional status) and to determine the independent association between immunization status and immunological markers. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics - The fully immunized and non-immunized groups were comparable in terms of age, gender, nutritional status, and socioeconomic background (Table 1). The mean age was 5.2 ± 2.4 years in the fully immunized group and 5.0 ± 2.3 years in the non-immunized group ($p = 0.58$).

Table 1. Baseline Demographic and Clinical Characteristics (n = 480)

Characteristic	Fully Immunized (n = 240)	Non-Immunized (n = 240)	p-value
Mean Age (years)	5.2 ± 2.4	5.0 ± 2.3	0.58
Male Gender (%)	52%	50%	0.70
Nutritional Status (Normal/Underweight)	87%/13%	85%/15%	0.65
Socioeconomic Status (Low/Med/High)	32/48/20	33/47/20	0.89

Clinical Course of Cough - At baseline, the fully immunized group presented with a significantly lower mean cough severity score (4.1 ± 1.3) compared to the non-immunized group (5.3 ± 1.6, $p < 0.001$). The median duration of cough was also shorter in the immunized group (5 days, IQR 4–7 days) compared with the non-immunized group (8 days, IQR 6–10 days, $p < 0.001$).

Immunological Markers - At baseline, significant differences were observed in several immunological parameters: Cytokine Profiles: Fully immunized children had lower serum IL-6 levels (18.2 ± 5.6 pg/mL) than non-immunized children (25.4 ± 6.8 pg/mL, $p < 0.001$). TNF-α and IFN-γ levels were also lower, while IL-10, an anti-inflammatory cytokine, was higher in the immunized group ($p < 0.01$ for all comparisons). Immunoglobulin Levels: No significant differences were found in IgA, IgM, or IgG levels between groups. CBC with Differential: The neutrophil-to-lymphocyte ratio (NLR) was significantly lower in the fully immunized group (1.8 ± 0.4) compared to the non-immunized group (2.3 ± 0.5, $p < 0.001$). Flow Cytometry: The proportion of regulatory T-cells (CD4+CD25+FOXP3+) was higher in the immunized group (8.5% ± 1.2%) than in the non-immunized group (6.2% ± 1.0%, $p < 0.001$). These immunological differences persisted during follow-up, with the fully immunized group maintaining a more regulated immune profile associated with less severe clinical symptoms.

Multivariate Analysis - After adjusting for potential confounders such as age and nutritional status, multivariate logistic regression analysis demonstrated that full immunization was independently associated with lower IL-6 levels (adjusted OR 0.48, 95% CI 0.35–0.66, $p < 0.001$) and lower NLR (adjusted OR 0.55, 95% CI 0.40–0.75, $p < 0.001$). Additionally, a higher proportion of regulatory T-cells was independently associated with reduced cough severity (adjusted OR 0.52, 95% CI 0.37–0.73, $p < 0.001$).

Complications and Additional Outcomes - Complications such as secondary bacterial infections occurred in 4% of fully immunized children compared to 10% in the non-immunized group ($p = 0.01$). Hospital admission rates were lower in the immunized group (2% vs. 6%, $p = 0.03$).

DISCUSSION

Principal Findings - This study demonstrates that full immunization in children is associated with a more regulated immunological response during episodes of cough. Specifically, fully immunized children exhibited lower pro-inflammatory cytokine levels (IL-6, TNF-α, IFN-γ) and a lower neutrophil-to-lymphocyte ratio, alongside higher levels of the anti-inflammatory cytokine IL-10 and increased proportions of regulatory T-cells. Clinically, these immunological

differences correlated with a milder course of cough, as evidenced by lower severity scores and shorter duration of symptoms.

Mechanisms and Implications - The immunomodulatory effects of vaccination may lead to the development of immunological memory that tempers the inflammatory response to subsequent infections. In the context of cough, this results in less tissue damage and a faster resolution of symptoms. The elevated levels of regulatory T-cells in immunized children suggest a shift toward an anti-inflammatory state, which may protect against the development of severe symptoms and complications. These findings have important diagnostic implications; immunological markers such as cytokine profiles and NLR may serve as adjunctive tools in assessing the severity and expected course of respiratory illnesses in children, particularly in differentiating vaccine-modified presentations.

Comparison with Previous Studies - While previous research has focused primarily on the direct prevention of specific respiratory infections through immunization, our study extends this by examining the broader immunological landscape during acute respiratory events. The observed differences in cytokine profiles and regulatory cell populations are consistent with studies that have documented the immunomodulatory benefits of vaccination. However, few studies have directly correlated these immunological parameters with clinical outcomes such as cough severity and duration.

Limitations - This study has several limitations. The observational design precludes definitive causal inferences, and although adjustments were made for key confounders, residual confounding may persist. The reliance on single time-point immunological assessments limits the ability to capture dynamic changes over the course of the illness. Finally, the study population was drawn from urban centers, which may not fully represent rural populations or different socioeconomic backgrounds.

Future Directions - Further research should involve longitudinal studies with serial immunological assessments to better understand the temporal dynamics of the immune response during respiratory illnesses. Randomized controlled trials investigating targeted immunomodulatory interventions based on immunization status could provide additional insights into therapeutic strategies. Moreover, exploring the specific roles of individual vaccines in shaping immune responses may help refine vaccination schedules to optimize clinical outcomes.

CONCLUSION

In summary, our study demonstrates that full immunization in children is associated with a more balanced and attenuated immunological response during episodes of cough, as evidenced by lower pro-inflammatory cytokine levels (IL-6, TNF-α, IFN-γ), a reduced neutrophil-to-lymphocyte ratio, and an increased proportion of regulatory T-cells. These immunological markers correlate strongly with milder clinical manifestations, including lower cough severity scores and a shorter duration of symptoms. The data suggest that immunization not only prevents specific respiratory infections but also modulates the host immune system in a way that minimizes the inflammatory response when breakthrough respiratory illnesses occur.

Clinically, these findings have important diagnostic implications. The use of immunological markers such as cytokine profiles and the neutrophil-to-lymphocyte ratio can serve as valuable adjuncts in the evaluation of pediatric cough, aiding clinicians in distinguishing between vaccine-modified presentations and more severe inflammatory responses that may require aggressive intervention. Moreover, the observation of higher regulatory T-cell levels in immunized children highlights the potential of these cells as biomarkers for an effective, controlled immune response, which may be predictive of a more favorable clinical course.

Our results advocate for the broader public health strategy of maintaining high immunization coverage, as the benefits extend beyond disease prevention to include enhanced

immunomodulation and improved clinical outcomes during respiratory illnesses. Additionally, these insights underscore the need for continued research into the specific immunological mechanisms by which vaccines influence host responses to respiratory pathogens. Future studies should explore longitudinal changes in immune markers during the course of respiratory illnesses, assess the potential for targeted immunomodulatory therapies in non-immunized children, and evaluate the cost-effectiveness of incorporating immunological diagnostics into routine pediatric care.

Overall, the evidence presented supports the critical role of vaccination in not only reducing the incidence of infectious diseases but also in mitigating the severity of common symptoms such as cough. This dual benefit reinforces the importance of adherence to immunization schedules and provides a strong rationale for integrating immune marker assessments into the diagnostic process for pediatric respiratory conditions.

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