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Mucosal immunity and secretory IgA deficiency in recurrent respiratory tract infections: Clinical correlation in Babylon governorate, Iraq

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Abstract
Secretory immunoglobulin is the major antibody of mucosal defense in the respiratory tract. Deficiency of Secretory immunoglobulin has been related to the development of increased susceptibility to recurrent respiratory tract infections, and notwithstanding these facts, regional data of the Middle east and specifically of Iraq are scarce. This study has investigated the association between mucosal Secretory immunoglobulin deficiency and respiratory tract infections in patients from Babylon governorate.

Methods: A case and control study were included among a study population of 400 probable incidents (400 controls matched 200 cases of respiratory tract infections) recruited through private clinics and public hospital in Babylon. Unstimulated saliva specimens were collected and submitted for analysis of Secretory immunoglobulin by the Immunoassay by the Immuno Max-Bride-ELS (Immuno Max-ELSZA; Enzymes Immuno Assay, Conway, MA, USA) and serum IgA concentrations were determined by immunoturbidimetry (Motra suspected SIgAD) using the Technolink ImmunoMax-Well-Serum test (Immuno Max-Well-S-Serum, Enzymed Immuno Assay, Conway, MA, USA). Clinical data such as antibiotic consumption, hospitalization and absenteeism from school/work were recorded.

Results: Median salivary Secretory immunoglobulin was significantly less in the cases (13.2 mg/dL, IQR 8.4-21.1) than that of controls (28.6 mg/dL, IQR 19.5-41.3; $p<0.001$). the results were the prevalence of low sIgA levels was 34.5% in cases and 9% in controls ($p<0.001$). However, Secretory immunoglobulin was more prevalent in cases (3.5%) than in the controls (0.5%; p=0.03). Oh - and low Secretory immunoglobulin was related to higher antibiotic use (91.3 vs 58.8%), hospitalization frequency (29 vs 9.1%) and absenteeism (median 14 vs 7 days; all $p<0.001$). Significant negative correlations were found between Secretory immunoglobulin levels and number of RRTI (r= - 0.62), antibiotic courses (r= - 0.54) and absenteeism (r= - 0.58) (all $p<0.001$). In the combination of serum and mucosal IgA deficiency the risk of serious infections was greatest (62.5%).

Conclusion: Low mucosal Secretory immunoglobulin was highly associated with the risk and severity of respiratory tract infections among pediatric and adult population living in Babylon. These results support the importance of salivary Secretory immunoglobulin as an accessible and useful biomarker to determine persons at high risk for recurrent infections. The use of Secretory immunoglobulin measurement in the primary care setting would offer early identification and selective management of mucosal immune deficiency in Iraq.

Keywords: Secretory IgA, recurrent respiratory infections, mucosal immunity, elimination immunoassay (ELI), selective IgA deficiency, Babylon Iraq

Introduction
Recurrent respiratory tract infections (RRTIs) are a major burden of disease worldwide, and are responsible for tremendous morbidity, antibiotic use, and socioeconomic cost (Troeger *et al*., 2023) [29]. While the majority of infections could be self-limited, a portion of the population demonstrates increased susceptibility to the infection that is thought to be explained by underlying immunological dysfunctions (Sahin *et al*., 2022) [24]. Among the immune defense systems, mucosal immunity is of critical importance for prevention of adherence and invasion of pathogens especially in the respiratory epithelium - an interface that is incessant exposure to environmental microbes (Zhang and Wang, 2022) [33].

Secretory immunoglobulin A (sIgA) is the most abundant antibody at mucosal surfaces that offers protection from respiratory pathogens as a first line of defense through immune exclusion, neutralization of viruses and modulation of microbiota (Agondi *et al*., 2022) [1]. sIgA is abundantly and actively transported across epithelial cells through the polymeric immunoglobulin receptor, forming a secretory complex that is resistant to proteolysis and is

optimized for mucosal defense (Russell *et al*., 2024) [23]. Low mucosal sIgA levels have been strongly associated with resistance to respiratory infections and higher frequency and severity in both Airways, in both pediatrics and adult population (Guan *et al*., 2023) [12].

Selective IgA deficiency (SIgAD) is the most commonly occurring primary antibody deficiency in the world, alongside recurrent sino-right upper respiratory tract infections, allergic diseases and autoimmunity (Agondi *et al*., 2022) [1]. Although levels of serum IgA are useful for studies and to offer useful information, measurements of mucosal sIgA deficiency can be seen even in the case of normal quantities of serum IgA, which highlights the clinical reliability of measures taken at the local mucosal level (Brandtzaeg, 2023) [3]. Modern immunological research thus places emphasis on the value and value of establishing mucosal immunological evaluation within the framework of a broad healthy measure (Russell *et al*., 2024) [23].

Environmental and regional factors - pollution, exposure to pathogens, nutrition, and vaccination habits may impact on mucosal immunity (Hamed and Al-Jubouri, 2024) [13]. However, data are still scarce from Iraq, especially the Babylon Governorate, which is the most common place in Iraq where recurrent respiratory infections occur in primary healthcare. Research of mucosal sIgA concentrations in this population has the potential to fill an important research gap and contribute to regional diagnostics and preventive measures.

Thus, the purpose of this study is to evaluate the relationship between mucosal sIgA level and RRTI susceptibility among patients from private clinics and hospitals in Babylon. By establishing local reference values and evaluating clinical correlations, the role of this research could be played in the early recognition and clinical management of mucosal immune impairment in Iraq could be improved.

Materials and Methods

Study design and setting

The present case control study was carried out from January to September 2025 in Babylon Governorate, Iraq in private otolaryngology and pediatric clinic, and in outpatient's department of Al-Hilla Teaching Hospital and Imam Al-Sadiq Hospital. A case-control design was chosen as it was effective for exploring biomarker disease associations among established clinical outcomes, especially for immunology and respiratory studies, and has been suggested for use in such studies (Olsen *et al*., 2023) [18]. performance of the study in more than one clinical center allows us to raise the external validity and is a typical method of the clinical immunology study (von Elm *et al*. 2024) [30].

Study population: Case definition

Items were given out to participants aged >=5 years. Cases were defined as individuals with a physician-diagnosed respiratory tract infection (RTI) at least 3 times within the past 12 months including pharyngitis, sinusitis, otitis media, bronchitis, or pneumonia. Controls were age- and sex-matched patients attending the same facilities for non-infectious indications without recurrent infections of the respiratory tract. The clinician based diagnostic history as the case definition reflects the international infectious disease surveillance criteria (Global Initiative for Respiratory Health, 2023) [11]. In case-control matching, the rating of distinctions is few with respect to those related to demographics of exposures, socioeconomic factors (Pereira *et al*., 2023) [20].

Eligibility criteria and exclusion criteria

Inclusion and exclusion criteria - Resident in Babylon for >= 12 months and with written informed consent, parental consent for children. Exclusion criteria were known primary or secondary immunodeficiencies, autoimmune diseases, chronic inflammatory disorders, recent immunosuppressive therapy or active laboratory-confirmed Covid-19 infection other than selective IgA deficiency. Placebo-controlled studies particularly in mucosal immunology (Snoeck *et al*., 2023) [27] emphasize the need to restrict the study participants with immunomodulatory disease in order to improve the specificity of mucosal immunoglobulin assessment.

Questionnaire and medical data

Demographic information, smoking exposure, vaccination status, history of allergic rhinitis/asthma symptoms, frequent respiratory infections, antibiotics usage, hospitalizations and absenteeism from school/work were collected by using a structured questionnaire. Structured data collection schemes decrease the disproportionate biases in information and serve in achieving the uniformity of classification with regard to respiratory outcomes (Global Initiative for Respiratory Health, 2023) [11]. To confirm the self-reported history, which is best practice in clinical epidemiology (Olsen *et al*., 2023) [18] medical records were examined.

Collection and preparation of saliva

Unstimulated saliva samples were collected at 08:00 - 10:00 hour following at least 60 min of fasting and refraining from brushing or oral rinsing. Morning sampling is to ensure that we control diurnal variation in the secretion of mucous membrane IgA. Saliva pooling and spitting into sterile polypropylene tubes was done by the subjects. Samples were stored on ice and kept at minus 20 degrees within 30 minutes. the pre-treatment of the saliva was extremely important in order to maintain the integrity of the immunoglobulins (Salimetrics, 2024) [25].

Equipment and/or supplies to be gathered for serum IgA measurement

Venous blood (5mL) was serum found under Andersen aseptic techniques for the quantification of serum IgA, by immunoturbidimetric. Immunodeficiency, selective IgA deficiency was selected as a low (reduced) level of serum IgA (<7 mg/dL) based on currently recognized diagnostic criteria (World Allergy Organization, 2024) [31]. Serum IgA measurement was used to supplement yearly value from mucosal finding and are used together with sIgA analysis for assessing of immunodeficiency status as routine in clinical study (Melo and Aranda, 2023) [17].

Collect organs on the shelf laboratory sIgA assay

Salivary sIgA was quantified by means of a research grade enzyme-linked immunosorbent assay (ELIZA), according to the manufacturers' instructions. All the specimens were assayed in duplicates, featuring internal and external permanent quality controls. ELIZA is the best method for the quantitative measurement of mucosal immunoglobulins; it was a well-sensitive and specific measurement in

respiratory immunology (Tokarz-Deptuła *et al*., 2022) [28]. Standardized assay procedures are used to ensure the reproducibility of the assay and analytical accuracy (Yamamoto *et al*., 2025) [32].

Outcome measures

The main finding was that the link between low mucosal sIgA and recurrent respiratory tract infections. Secondary outcomes were the establishment of local sIgA reference values and correlations with antibiotic prescribing, hospitalization and absenteeism. Both clinical and laboratory endpoints should be measured for improved interpretation/translational value of mucosal immunity research (Cannon and Pabst, 2025) [5].

Statistical analysis

Data was analyzed using SPSS version 26. Continuous data was presented in mean + SD or median (IQR), whereas categorical data were presented as frequencies and percentages. Independent t-test or Mann - Whitney U test was used according to the distribution of data and chi-square/Fisher's exact test for categorical variables. Multivariable logistic regression was used to assess the relationship between sIgA levels and RRTIs by adjusting confounders, including age, sex, smoking, allergy and vaccination. Mucosal studies were important because of numerous behavioral and environmental modifiers (Low *et al*., 2024) [14], so having adjusted model(s) was necessary for mucosal immunity studies. $p<0.05$ was considered statistically significant.

Ethical considerations

Ethical approval was taken from the Institutional Review Board of the College of Medicine, University of Babylon (Approval no.: 2025-SIgA-IMM-01). Written informed consent was signed by all the participants or legal guardians. Ethical behavior was conducted according to the international standards of biomedical research, including the subject's privacy and information confidentiality (World Allergy Organization, 2024) [31].

Results

A total of 400 participants were enrolled in the study; in particular, 200 cases of recurrent respiratory tract infections (RRTIs) and 200 matched controls were enrolled in the study. The average age was similar among the groups (case 12.8 pm 6.1 years vs control 12.5 plus 6.4 years) and the sex distribution was also similar. Exposure to passive smoking, allergic rhinitis and antibiotic use were significantly increased in the RRTI group.

Table 1: Demographic and clinical characteristics of study participants

Variable	Cases (n=200)	Controls (n=200)	p-value
Age, Mean ± SD (years)	12.8±6.1	12.5±6.4	0.62
Male, n (%)	104 (52%)	102 (51%)	0.87
Passive smoking exposure, n (%)	88 (44%)	41 (20.5%)	<0.001
Allergic rhinitis, n (%)	63 (31.5%)	28 (14%)	<0.001
Antibiotics use ≥3 courses/year	145 (72.5%)	49 (24.5%)	<0.001
Hospitalization past year	32 (16%)	9 (4.5%)	<0.001
School/work absence days/year (median, IQR)	10 (6-15)	2 (1-4)	<0.001

Median salivary sIgA concentration was significantly less in cases than controls. Nearly 1 out of 3 RRTI subjects had low sIgA levels as determined by age-adjusted cut-off values.

Table 2: Salivary sIgA concentrations in study groups

Parameter	Cases (n=200)	Controls (n=200)	p-value
sIgA (mg/dL), median (IQR)	13.2 (8.4-21.1)	28.6 (19.5-41.3)	<0.001
Low sIgA (<10th percentile), n (%)	69 (34.5%)	18 (9%)	<0.001

Selective IgA deficiency (SIgAD) was detected in 7 patients (3.5%) of the RRTI group, as opposed to 1 of the controls.

Table 3: Level of serum immunoglobulin (IgA) and frequency of SIgAD (Immunoglobulin Acute Diarrheal)

Variable	Cases (n=200)	Controls (n=200)	p-value
Serum IgA (mg/dL), Mean ± SD	71.4±32.8	98.2±41.6	<0.001
SIgAD (<7 mg/dL), n (%)	7 (3.5%)	1 (0.5%)	0.03

Lower sIgA levels correlated with increased antibiotic use, hospitalization, and school/work absenteeism.

Table 4: Relationship between sIgA status and clinical outcomes in RRTI patients

Outcome	Normal sIgA (n=131)	Low sIgA (n=69)	p-value
Antibiotics ≥3 courses/year, n (%)	77 (58.8%)	63 (91.3%)	<0.001
Hospitalization, n (%)	12 (9.1%)	20 (29%)	<0.001
Absence days/year, median (IQR)	7 (4-10)	14 (10-20)	<0.001

Low salivary sIgA was strongly associated with RRTIs still after adjustment for age, sex, passive smoking, allergic rhinitis and vaccination status.

Table 5: Logistic regression model for risk of recurrent RTIs

Variable	Adjusted OR	95% CI	p-value
Low sIgA	4.62	2.61-8.17	<0.001
Passive smoking	2.41	1.51-3.87	<0.001
Allergic rhinitis	1.89	1.12-3.16	0.01
Serum IgA deficiency	3.78	0.91-15.6	0.06

Children and adolescents who had RRTIs in Babylon had significantly lower salivary sIgA levels than healthy children. Low sIgA was associated with greater antibiotic exposure, rates of hospitalization and school/work absenteeism. Selective IgA Deficiency was More Common in RRTI Cases. Low sIgA by adjustment maintained its independent status as a predictor of recurrent infections.

To examine the age-related variability, the participants were grouped as pediatric (5-17 years) and adult (>=18 years groups). Children with RRTIs displayed significantly lower sIgA than age-matched controls while this effect remained but was less profound in adults.

Table 6: Salivary sIgA levels in stratified by age

Age Group	Cases sIgA Median (IQR mg/dL)	Controls sIgA Median (IQR mg/dL)	p-value
5-17 years (n=268)	12.4 (7.8-20.2)	27.9 (18.8-39.4)	<0.001
≥18 years (n=132)	15.6 (10.3-23.5)	30.8 (21.4-44.9)	<0.001

assive smoking was found to be significantly associated with lower sIgA in both groups; however, the effect of the interaction was strongest in the group of RRTI patients.

Table 7: Effect of passive smoking on salivary sIgA

Group	Passive Smoking	Median sIgA (IQR mg/dL)	p-value
Cases	Yes (n=88)	10.1 (6.9-16.2)	<0.001
Cases	No (n=112)	15.3 (10.5-23.7)	—
Controls	Yes (n=41)	22.4 (14.8-32.1)	0.03
Controls	No (n=159)	30.9 (20.8-42.5)	—

Children with allergic rhinitis had significantly lower sIgA which indicates mucosal immune dysregulation.

Table 8: SIgA level of allergic vs. non-allergic participants

Status	sIgA Median (IQR mg/dL)	p-value
Allergic (n=91)	13.1 (8.1-21.3)	0.01
Non-Allergic (n=309)	22.9 (15.4-35.6)	—

Lower sIgA levels were associated with frequency of infections, antibiotic treatment and school/work absence.

Table 9: Correlation of sIgA level with clinical outcome

Variable	Spearman r	p-value
Number of RTI episodes/year	−0.62	<0.001
Antibiotic courses/year	−0.54	<0.001
Days absent/year	−0.58	<0.001
Hospitalizations/year	−0.33	<0.001

There are also strong negative correlations that are consistent with a protective effect of mucosal IgA.

Table 10: Diagnostic accuracy of salivary sIgA

Parameter	Value
AUC	0.83
Optimal cutoff	17.5 mg/dL
Sensitivity	81.2%
Specificity	74.6%

Patients that had both low salivary sIgA and low serum IgA had the highest risk for severe RRTIs.

Table 11: Risk stratification last name by IgA status

Group	n	Severe RRTIs (%)	p-value
Normal serum + normal sIgA	296	7.4%	—
Normal serum + low sIgA	78	28.2%	<0.001
Serum IgA deficiency + low sIgA	8	62.5%	<0.001

Low sIgA was a good predictor of RRTIs even after adjusting for confounding factors. Passive smoker children and passive-smoke exposed people were more immunologically compromised. ROC analysis showed high diagnostic accuracy for sIgA for risk of RRTI. Combined mucosal and systemic abnormalities for IgA impaired the most severe clinical phenotype.

Discussion

The current study can provide strong indications that mucosally applied sIgA insufficiency was closely associated with predisposition to recurrent respiratory tract infections (RRTIs) in children and adults in Babylon Governorate. These findings strengthen the important immunological function of secretory IgA at the airway surface where it prevents pathogen adherence and was important in the immune exclusion and functions in epithelial homeostasis. Mucosal IgA was a frontline immunoglobulin that is immediately neutralizing viruses and toxins, before engaging the systemic immunity (Reboldi and Cyster, 2023) [22]. A decrease in sIgA breaks this defense barrier and pathogens colonize the mucosal surface and enter the respiratory epithelium.

Consistent with our results, clinical studies have been conducted in Iran, Turkey, and Europe which have shown higher rates of respiratory morbidity in individuals with deficient levels of mucosal IgA, notably in the pediatric population (Ghaderi *et al*., 2023; Orfali *et al*., 2022) [10, 19]. Children have an immunologic vulnerability due to mucosal immune immaturity and higher exposure of the respiratory tract to respiratory pathogens in school settings. This vulnerability was demonstrated in our age-stratified results in which particularly low sIgA levels were observed in young RRTI patients. These findings are in favour of the hypothesis that mucosal immune surveillance develops gradually during childhood and is receptive to stimuli, environmental and microbial (Zheng *et al*., 2024) [34].

Importantly, in this study, the effects of passive smoking were found to be important modifiers of sIgA response. Tobacco smoke exposure was likely to cause interference with mucosal immunity through oxidative stress and epithelial damage and alteration in polymeric immunoglobulin receptor (pIgR) transport pathways (Sharma *et al*., 2023) [26]. Similarly, allergic rhinitis became a significant factor linked to low sIgA, which was consistent with findings on a conclusive relationship between chronic allergic inflammation and changes in epithelial barrier function and mucosal cytokine homeostasis as well as the recruitment of IgA-producing plasma cells (Calderon-Garcidueñas *et al*., 2024) [4]. In an area where tobacco use was on the rise, combined with high exposure to environmental allergens, such synergistic combined exposures may exacerbate mucous protection abnormalities.

The manifestation of the selective IgA deficiency (SIgAD) in a subset of RRTI patient cases was further suggestive of the contribution of systemic and mucosal IgA in predisposition to the disease. Although in many people SIgAD was asymptomatic, it predisposes others to recurrent respiratory tract infections in a subclinical state, via the affected better clearance of microorganisms as well as through altered interaction of mucosa and microbiome (Davis *et al*., 2023) [7]. This combined immunological defect was mirrored in our study by a substantially higher severity of infection in patients at once with dual mucosal and systemic IgA deficiency.

From a translational point of view, the found resource discriminative capacity of salivary sIgA in RRTI risk delineation was an important step forward in exploiting the potential of salivary sIgA as a convenient, non-invasive biomarker, which could be used for routine clinical screening. Saliva-based immunology testing matches the latest global curiosity in point of care biomarkers and individualized immunoprofiling and was probably of specific value in locations lacking advanced immunological diagnostics (Marquina-Ruiz *et al*., 2023) [16]. Inclusion of such screening into the preventive medicine and pediatric care programs in Iraq may facilitate an earlier identification of those children who are immunologically susceptible and avoid overuse of antibiotics as well as prevent long-term

pulmonary complications.

Environmental and public health background also needs to be looked at. Like other regions of the Middle East, Babylon has high seasonal viral load, intra-seasonal pollution, dust storms, and population density - all of which might put additional demands on mucosal immune defense (Al-Haddad *et al*., 2023) [2]. Mucosal immune parameters may also be affected, meaning nutritional factors such as vitamin A/D deficiency and a reduction in dietary probiotic exposure may also be of importance, importance possible immunonutrition strategies to be used in conjunction with clinical management (Freitas *et al*., 2024) [9].

While the study was useful, longitudinal follow-up would allow for measurement of sIgA dynamics over time and determination to assess if restoration of mucosal immunity (either through improved environmental hygiene, improved nutrition or specific immunomodulatory therapies) leads to decreased RRTI frequency. Furthermore, the combination of microbiome characterization with host-derived immune markers could be used to improve our knowledge of host-microbial interactions leading to mucosal immune resistance or susceptibility. the current research develops local insight in the region on mucosal immunity, demonstrates the need for screening for mucosal immunology in wary groups of clinical patients and provides evidence in support of customized public-health approaches in addressing the burden of infection in the respiratory tract in Iraq.

Conclusion

This study has revealed some convincing evidence that the low salivary secretory IgA (sIgA) level has a high correlation with an increased susceptibility and severity of recurrent respiratory tract infections (RRTIs) in both children and adults in Babylon Governorate, Iraq. Reduced mucosal IgA was associated with increased infections, more antibiotic consumption, more hospitalization and higher absenteeism. These results demonstrate the important role of mucosal immunity in respiratory defense and the importance of salivary sIgA as a useful biomarker of clinical risk. Routine assessment of mucosal IgA concentrations in primary care environments may be useful in their potential role in the early identification of susceptible persons and in directing preventive interventions and ultimately decreasing the healthcare burden of recurrent respiratory infections.

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Conflict of Interest

The author receives no conflict of interest for this piece of work.

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