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Level of Specific Respiratory Syncytial Virus IgA and Interferon Gamma in Serum of Children with RSV

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ABSTRACT
Background: An estimated 33 million children under the age of five worldwide are projected to be infected with the respiratory syncytial virus (RSV), with 10% of those cases necessitating hospital admission and up to 199,000 deaths from the illness.The most prevalent clinical condition seen with RSV infection is an upper respiratory infection known as bronchiolitis, a lower respiratory tract illness with small airway blockage that can rarely lead to pneumonia, respiratory failure, apnea, and death.
Patients and Method: This study involve 58 child infected have been diagnosed infected with RSV, 43 (74.14%) were RSV serotype B and 15 (25.86) were serotype A clinicallywith the help of pediatrician and laboratory by PCR method , The study was conducted at the Ramadi Teaching Hospital for Maternity and Children /Al-Anbar Governorate in period ranging from 1 December 2023 to 15 March 2024. Specific IgA and IFN gamma were detected in serum of infected children their age ranging from 1 months to under 5 years.
Result: In this study, we examine 100 cases of probable RSV.Out of 100 cases 58 child were infected with positive RSV . The major infection was recorded by serotype B 43 (74.1%) while, 15(25.8%) with serotype A, 45 positive for specific RSV IgA test and 28 positive for INF-Y test confirm by ELISA technique. Statistical analysis was performed on data from RSV-infected patients as well as age subgroup populations. Patients were classified into the following age groups: 1–6 monthsN=36(36%), 6 to 12 months N=24(24%), 12 to 18months N=9 (9%) , 18 to 24 months N=17(17%), and more than24 months N=14(14%) .
Conclusion: The variability in specific RSV IgA and IFN-Gamma responses suggests that immune function differs significantly among individuals. This variability may be related to disease progression, susceptibility, or response to treatments such as antivirals or vaccines.

Keywords: Specific IgA RSV, INF-Y , Serotype B RSV, ELISA.

1.INTRODUCTION

Every year, the respiratory syncytial virus (RSV) causes about 100,000 deaths in children under five years old and 33 million instances of lower respiratory tract infections (LRTIs) (1). Even with the high illness burden, supportive care is still the norm, and preventative measures are only authorized for kids who pose a high risk (2).

Serious respiratory tract illnesses are brought on by the respiratory syncytial virus (RSV). Pneumonia and severe bronchiolitis are particularly common in babies under the age of six months. The reason behind some infants' severe illnesses necessitating artificial ventilation and others' minor symptoms is unknown. However, there is evidence that suggests the pathophysiology of severe lower respiratory tract disease (LRTI) is related to a decreased ability to produce adequate type I-like immune responses during first RSV infection(3).

Type I cytokine interferon-gamma (IFN-γ) boosts antigen presentation by inducing MHC molecule expression, has direct antiviral activity, and increases the Natural killer cells and virus-specific T lymphocytes exhibit cytotoxic action(4). Therefore, the clinical course of RSV disease may be largely determined by the strength of the early IFN-γ response. Decreased IFN-γ production may result in extended infection periods and consequently harmful consequences on pulmonary function. Prior research has demonstrated a correlation between reduced mRNA IFN-γ expression in peripheral blood and severe RSV bronchiolitis (5).Furthermore, it has been demonstrated that both peripheral blood and the respiratory tract's IFN-γ secretion are lowered in cases of severe RSV LRTI. Age, the infecting viral pathogen, genetic and developmental variations (e.g., lung/or immunological maturation), and other factors all affect how strong IFN-γ responses are to viral infection. Whether a decreased IFN-γ response is specific to RSV initial infection is still unknown(6)(7).

Greater preinoculation nasal RSV IgA and serum anti-RSV neutralizing antibody titers have been linked to protection against infection and lower virus replication in healthy people undergoing experimental infection(8)(9). Adults' protection against spontaneous RSV reinfection is also connected to RSV-specific nasal IgA, serum IgG, and serum neutralizing titers. Nasal RSV IgA appears to provide stronger protection against experimental infections than serum neutralizing antibodies, and the response may remain longer(10)(11). Similarly, the development of the IgA response seems to be correlated with recovery in infants and children infected naturally . In contrast to typical influenza virus infection, when influenza virus IgA-producing memory B cells are found, during convalescence, circulating RSV IgG-producing memory B cells are present but no IgA-producing memory B cells. Overall, repeated infections could be caused by an IgA memory shortage, especially in childhood, when IgA appears to provide significant immune protection. On the other hand, RSV sickness appears to be prone to in older people due to a decrease in circulating serum neutralizing antibodies(11)(12).

The level of circulating RSV IgG in children under one month old, both symptomatic and non-symptomatic, is highest in those who have received it through transplacental maternal antibody transfer (12). IgG levels drop after three months and then rise again after two years. Compared to age-matched controls, symptomatic RSV-infected babies between the ages of one and three months had a substantially lower avidity of IgG. In a similar vein, children with RSV LRTI had lower total IgG affinity than children with milder URTIs when they were younger than 24 months.

Serum RSV IgG and nasal RSV IgA neutralizing activity are significantly higher in children aged 9 to 21 months than in those aged 4 to 8 months (the age group with the highest RSV infection rate). In newborns, there is a negative correlation between preexisting serum IgG and the synthesis of nasal IgA after infection, showing that maternally generated IgG may impede the IgA response(13)(14).These data suggest that having a strong IgG and IgA affinity for RSV protects against both clinical illness and more serious lung involvement. Following spontaneous reinfection in adulthood, serum neutralization titers increase by 8-fold, but this is short-lived, with the majority of patients seeing a 4-fold drop within a year.The serum neutralizing antibody response and nasal IgA and IgG responses to the G glycoprotein are unique to the RSV group. Antibodies to the F glycoprotein cross-react among RSV groups (15)(4)(16)(17).

2.MATERIALS AND METHODS

We tested 100 suspected individuals for RSV infection with the help of a pediatrician . This study was carried out at Ramadi Teaching Hospital for Maternity and Children in Al-Anbar Governorate. The period of study was from 1 December 2023 to 15 March 2024. The study protocol was reviewed and approved by Ethical approval of the College of Medicine, University of Anbar (reference number 79 on 8-5-2024). Every participant have provided an informed consent.

The inclusion criteria were suspects of both sexes with who experienced RSV symptoms including fever, coughing, dyspnes, etc. for two to five days and who were under 5 years old , 57 suspects was male and 43 suspects was females.

2.1 Sample collection

We collect five miles of blood through veins. Punctures with a 5 mL syringe. Blood samples were deposited in a gel tube for 30 minutes at 37 degrees Celsius and centrifuged for 15 minutes at 3000 rpm. The resultant sera were then aspirated with an automated micropipette and placed in a clean fest tube. Each tube was tagged and preserved in deep freeze at -20°C for further immunological tests.

2.2 Quantitative Measurement of Interferon- gamma (INF-y) in serum by ELISA test

The Demeditec INF-γ- human ELISA is a solid phase Enzyme Amplified Sensitivity Immunoassay using microtiterplates. The assay uses monoclonal antibodies (MAbs) that target specific epitopes of IFN-γ (Demeditec, Germany). Calibrators and samples react with a capture monoclonal antibody (MAb 1) coated on a microtiter well and a horseradish peroxidase-labeled monoclonal antibody (MAb 2). After incubating with MAb 1 - human IFN-γ - MAb 2 - HRP, the microtiterplate was washed to remove any unbound enzyme-labeled antibodies. A chromogenic reaction was used to quantify an antibody tagged with an enzyme. The chromogenic solution (TMB) was introduced and incubated. To stop the reaction, halt Solution was added, and the microtiterplate at the appropriate wavelength was read.

The required number of strips for the run was determined. The strips in the holding frame were fastened. 50 µl was added of each Calibrator, Control, and Sample to their respective wells. Then, 50 µl of anti-IFN-γ-HRP conjugate was added to the well. After that, incubate for 2 hours at 18-28 Cº on Dark-a horizontal shaker set (DLabTECh) at 700 rpm. The liquid from each well was aspirated. The plate was washed three times (199 mL D.W+1 mL wash buffer). After washing, 100 µl was added of chromogenic solution TMB to each well within 15 minutes. The microtiterplate was incubated for 15 minutes at (18-28) Cº on a Dark-a horizontal shaker set to 700 rpm. After that, one handed over 100 microliters .After that, 100 microliters of stop solution were applied to

each well. The absorbance was then measured at 450 and 490 nm within 30 minutes, and the results were computed.

2.3 Quantitative Measurement of specific IgA of RSV in serum by ELISA test

Our human anti-respiratory syncytial virus antibody (RSV-Ab) ELISA kit was designed to detect RSV-Ab levels in human serum. This ELISA kit uses the Sandwich-ELISA method. The ELISA is based on the qualitative enzyme immunoassay technology (Sunlong Biotech, China). The microplate given in this kit has been pre-coated with an antigen specific to anti-RSV, making it solid-phase antigen. Samples were added to the microplate wells and mixed with the specific antigen.Then, a Horseradish Peroxidase (HRP)-conjugated antigen specific for anti-RSV was added to each Microplate well and incubated, resulting in the formation of an antigen-antibody-enzyme labelled antigen complex. After washing to remove any unbound reagent, the TMB substrate solution was applied to each well. Only the wells containing anti-RSV and HRP conjugated RSV antigen showed blue and then turned yellow after adding the stop solution.

In the Microelisa stripplate, two wells were left unfilled as negative controls, two wells as positive controls, and one well as a blank control. The sequential number, corresponding sample of the microporous hole 2 per board should be set negative control and positive control 2 holes, ck 1 hole (ck hole without samples and HRP-Conjugate reagent, continue with the same step operation). A volume of 50µl each was applied to the negative and positive control wells respectively . To each sample well, 10µl was added of sample and 40µl of dilution buffer. Samples were loaded to the bottom without hitting the well wall. Was thoroughly combined with moderate shaking. All samples were incubated at 37℃ for 30 minutes after being sealed with a Closure plate membrane. The concentrated solution was diluted by washing it with distilled water (30 times for 96T). Peeled off the Closure plate membrane, aspirated, and replaced with wash solution. The wash solution was dumped after 30 seconds of sitting. The washing method was performed five times.Each well was added 50 µl of HRP-Conjugate reagent, except for the blank control well, and was incubated. The washing phase has been repeated. 50 µl of Chromogen Solution A and 50 µl of Chromogen Solution B were added to each well, gently shaken, and incubated at 37℃ for 15 minutes. Avoiding light while coloring. To stop the reaction, each well was added 50 µl of a stop solution. The color in the well should go from blue to yellow. The absorbance O.D. was measured at 450nm using a Microtiter Plate reader. The OD value for the blank control well was set to zero. The assay was performed within 15 minutes of introducing the stop solution.

3.RESULTS AND DISCUSSION

The respiratory syncytial virus (RSV) is a single-stranded RNA virus with an envelope that belongs to the Pneumoviridae family of the Mononegavirales order. Infections occur all across the world, with outbreaks typically occurring in temperate climates during the winter. RSV is a major etiological agent of respiratory infections, particularly in children, causing a wide range of illnesses such as upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI), including pneumonia and bronchiolitis, which are associated with higher morbidity and mortality. Natural infection generates poor immunity, allowing for repeated infections in both children and adults, including the elderly(12).

This study involve 58 child have been diagnosed to be infected with RSV, 43 (74.14%) were RSV serotype B and 15 (25.86) were serotype A as show in table 1.

Table 1: The Positivity of RSV serotypes infection among children.

RSV serotype	Frequent (n)	Percent (%)
RSV serotype A	15	25.86
RSV serotype B	43	74.14
Total	58	100

The prevalence of RSV infection occurred in 46% of children in WHO European nations . This percentage is comparable to that of other continents such as Latin America, with an RSV prevalence of 41.5%(18). In this study the percentage of positive RSV has been 58%, Other authors found a global positive rate of RSV infection lower than that of this study, as is the case in Africa, where the prevalence is 14.6%(19) or China with 16% (20). Even studies conducted in European countries like France reveal a lower rate of positive RSV of 12-18% (21).In the US, the percentage of RSV infection in healthy childrens is only 1.8% (22). These data can provide effects of maternal extended half-life monoclonal antibodies of children.

Table 2: Frequency and percent for general characteristic of the study.

Variables		Frequent (n)	Percent (%)
Age period	1-6 months	36	36
	6-12 months	24	24
	12-18 months	9	9

	18-24 months	17	17
	more than **24** months	14	14

Detailed demographic and clinical data were available on 100 patients suspectedRSV infection ; The age period of patients from 1 months to under 5 years and 57% were male while 43 were female .
Statistical analysis was performed on data from RSV-infected patients as well as age subgroup populations. Patients were classified into the following age groups: 1 to 6 months, 6 to 12 months, and 12 to 18 months , 18 to 24 months, and more than24 months .Incidence among patients 1–6 month ages was approximately 36% , than incidence among patients more than 24 months of age approximately14%. This study is consistent with a study in Germany(23).In this study, the incidence was higher in urban areas than in rural areas. This is consistent with a study in the USA(24).
We identified risk factors that enhance viral exposure and highlight the potential for nonpharmacologic therapies to avoid infection(25).The earliest birth month was the biggest risk factor; we hypothesized that parental activities based on infant age influence exposure intensity. The risk factors of neighborhood poverty and public insurance highlight the importance of addressing socioeconomic determinants of RSV prevention.

Table 3: Level of specific RSV IgA and IFN-gamma

Variables	Status	N	Mean	Std. Error	Minimum	Maximum	F	p-value
IgA-specific RSV	negative	13	0.0592	0.0084	0.012	0.099	10.123	0.002
	positive	45	5.3733	0.892	1.033	35.337		
	Total	58	4.1822	0.750	0.012	35.337		
IFN-gamma	negative	30	0.0113	0.001	0.001	0.029	133.36	0.0001
	positive	28	1.3347	0.118	0.512	2.407		
	Total	58	.65020	.1040	.0010	2.407		

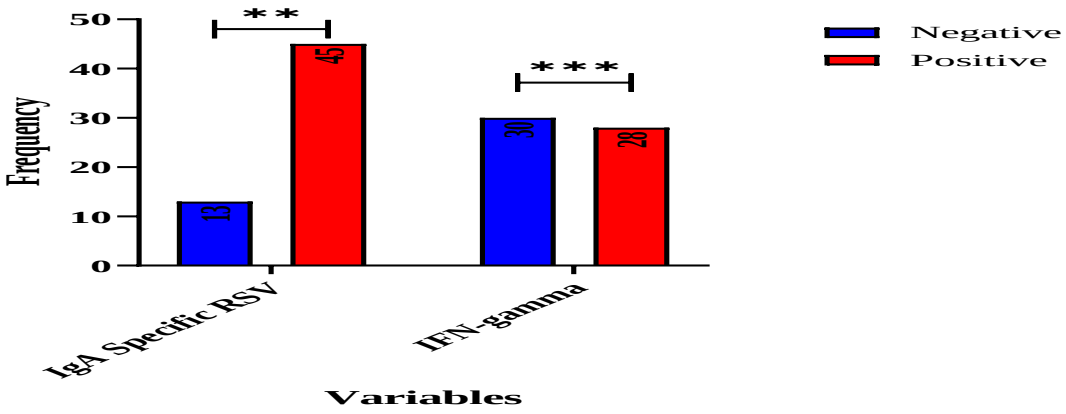

Fig 1. Level of specific RSV IgA and IFN-gamma

The IgA test mean was 4.182 in children who were diagnosed with RSV (Positive specific RSV IgA > 0.1)RSV infection causes the production of IgM, IgA, and IgG antibodies in the blood and mucosa. These antibodies, produced by the adaptive immune response to RSV, protect the host from reinfection. The original immune response against RSV is ineffective, but when a reinfection occurs, such as in children, IgG and IgA antibody levels greatly increase (26).In infants, in the first months of life, the establishment of a mucosal IgA response appears to be associated to convalescence, while IgG production is delayed.(4). Serum-neutralizing antibodies and mucosal IgA and IgG against the G glycoprotein are RSV group-specific, but antibodies against the F glycoprotein display cross-reactivity across multiple RSV groups(27). The IgA response appears to correlate with recovery in both experimental and spontaneous infections(10).
In this study the IFN-γ test mean was 0.650 (Positive specific RSV IFN-γ > 0.03) Plasmacytoid dendritic cells release IL-12, which promotes differentiation of naive T cells into Th1 cells and causes modest IFN-γ production by T cells. Low IFN-γ production causes a Th2 overreacting response(28).The significance of IFN-g in the development of RSV-mediated airway illness is not fully understood. Several studies have shown an imbalance in Th1/Th2 cytokine production, with a predominant Th2 response following RSV infection(29).For the most part, this imbalance was linked to insufficient IFN-g production associated with RSV lower respiratory

tract infection at a young age(30).The findings show that IFN-g is essential during the initial RSV infection to express protective responses against the development of AHR and lung histopathology with subsequent reinfection. Some of the findings of these research were previously published in the form of an abstract(31).This IFN-γ levels were elevated in moderate cases, relative to severe (32,33)

Table 4: Descriptive results for Age, IgA specific RSV and IFN gamma for study samples.

Variables	N	Minimum	Maximum	Mean ± SEM	Kurtosis
Age (months)	100	1.00	60.00	14.54 ± 1.48	1.344
IgA Specific RSV	100	0.004	35.337	2.45 ± 0.47	24.873
IFN.Gamma	100	0.001	2.407	0.38 ± 0.068	1.970

The age range (1–60 months) indicates that the study is focusing on a pediatric population, which is crucial since respiratory syncytial virus (RSV) primarily affects young children. The mean age of 14.54 months suggests that most participants are infants and toddlers, an age group that is particularly vulnerable to RSV infections and related immune responses.

IgA is an important immunoglobulin found in mucosal areas, such as the respiratory tract, where RSV infection occurs. The mean IgA specific for RSV (2.45 ± 0.47) indicates the typical immune response of the study population against RSV. The high kurtosis value (24.873) shows significant variability, suggesting that some children may have a heightened or diminished IgA response. This could reflect individual differences in immune defense against RSV or variations in disease severity.

Clinically, higher IgA levels may indicate a more robust mucosal immune response, which is critical in clearing viral infections like RSV. Understanding this variation can help tailor treatments or preventive measures (such as vaccines) for RSV.IFN-Gamma is a cytokine that plays a critical role in the immune response to viral infections by activating macrophages and promoting antiviral states in cells. The mean level of 0.38 ± 0.068 suggests a relatively low but measurable immune activation in the participants.

The kurtosis value of 1.970 implies some variability in the immune response. Children with higher IFN-Gamma levels might have stronger immune responses to viral infections, while lower levels could indicate a weaker antiviral defense. Understanding these differences is important for assessing the overall immune competence of the study group.

The levels of IFN-Gamma could be particularly relevant in identifying children who may be more prone to severe RSV infection or complications, thereby influencing clinical decisions around RSV management and care (34)(35).

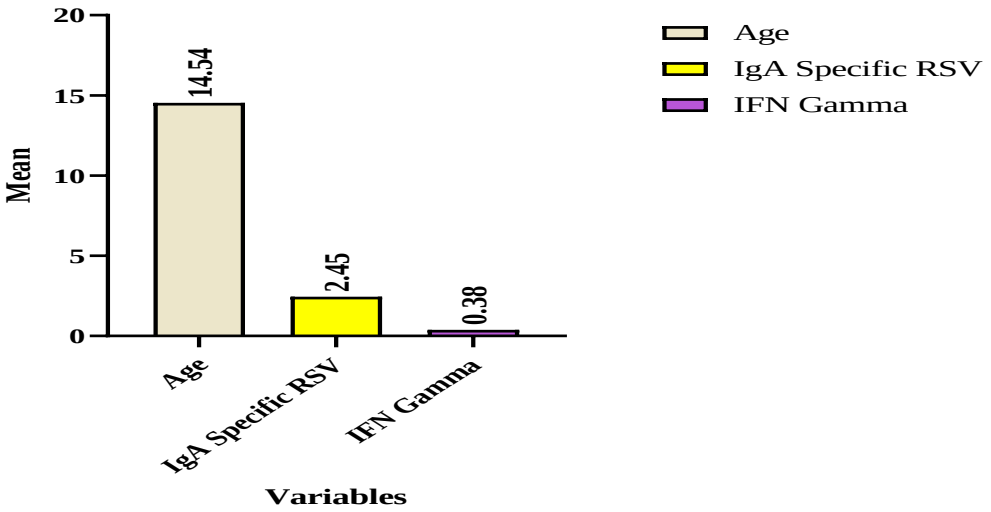

Fig 2. Results for Age, IgA specific RSV and IFN gamma for study samples.

4. CONCLUSION

The variability in IgA specific RSV and IFN-Gamma responses suggests that immune function differs significantly among individuals. This variability may be related to disease progression, susceptibility, or response to treatments such as antivirals or vaccines.

5. Ethical approval

The Medical Ethics Committee of the University of Al-Anbar Governorate in Ramadi, Iraq, accepted this study in accordance with the Helsinki declaration. All research participants, including parents of the patients, gave an informed permission.(reference number 79 on 8-5-2024).

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