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Evaluation of the Efficacy of the Rubella Vaccine in MMR-Vaccinated Children and its Correlation with IL-6 and IFN-γ levels in Thi-Qar Province/ Iraq

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Abstract

Background: This study aimed to evaluate the effectiveness of the Rubella vaccine in children who have received the MMR vaccine.

Material and Methods: The study design is a case - control study. This study was performed in Thi-Qar Province, Iraq, from Sep-2023 to Jan-2024. 176 children were included (117 cases and 59 controls), aged less than thirteen years. The ELISA technique was used to detect anti-Rubella Virus IgG.

Results: The seroprevalence of Rubella Virus IgG in the case group was positive in 110 (94.0%) of 117 children. While within the control group, 29 (49.2%) of 59 children were positive, there was a significant difference in IgG titer between both groups (p-value <0.001), but according to sex, there were no significant differences between males and females in both groups (p- value = 0.957 and p- value = 0.711, respectively). The results found a positive correlation with INF-γ (r = 0.921, p- value < 0.001), but no correlation with IL-6 (r = 0.018, p- value = 0.849).

Conclusions: Our study concludes that the Rubella vaccine is potent for children who have been vaccinated, with effectiveness reaching 94%, which is a very good percentage for controlling disease. We recommend increasing vaccine coverage in Thi-Qar province.

Keywords: Rubella virus IgG, MMR vaccine, IL-6, IFN-γ.

Introduction

Rubella virus (RuV) is an enveloped, positive-sense, non-segmented RNA virus belong to Hepelivirales order, Matonaviridae family, and Rubivirus genus. Prior to 2018, Rubella virus was categorized as a member of the Togaviridae family [1-3]. It is a single-serotype, but Its teratogenicity makes it important for public health [4]. It is normally produces acute febrile infection that affects children and young adults and is characterized by a rash and

lymphadenopathy [5]. RuV infection starts with malaise, low-grade fever, and morbilliform rash of the same day, the face, trunk, and extremities rash usually lasts three days [6]. RuV can cause serious consequences for the developing baby during pregnancy, as well as a variety of birth abnormalities called congenital rubella syndrome (CRS) [7].

Immunization has significantly contributed to enhancing global health by reducing the transmission of infectious diseases [8]. Because humans are the only known hosts for the Rubella virus, it is a natural target for global elimination [9]. One dose of rubella-containing vaccination (RCV) offers lifelong protection [10]. Live-attenuated RuV vaccinations is safe and effective for (95% after a single dose), within measles/mumps/rubella (MMR) vaccine, (RCV) is currently widely used around the world and have successfully reduced global rubella incidence [11]. Additionally, the rubella vaccine has reduced rubella and congenital rubella syndrome (CRS) globally [12], but due to inadequate vaccination rates, many cases still happen globally [13]. Routinely, during childhood, two doses of measles-mumps-rubella (MMR) vaccines are recommended for the prevention of these diseases [14]. According to the CDC, Rubella vaccine is administered to children as part of the MMR vaccine in two doses, usually at the ages of 12 to 15 months and 4 to 6 years [15]. Because this vaccination contains live attenuated virus, the Centers for Disease Control (CDC) recommends avoid giving it to pregnant women [16].

According to the WHO, there are about 100,000 cases of congenital rubella syndrome annually throughout the world [1]. Over the most recent ten years (2013–2022), WHO reported a total of 310,047 cases of Rubella [17]. In Iraq, a study done in Hilla City, found that 58% of pregnant women who are in their first trimester are not immune to rubella (have negative IgG), which makes them more susceptible to CRS, The majority of them reside in rural regions [18]. Additionally, Fayad, A.N., and I.N. Abid conducted a study in Thi-Qar province, Iraq. found that 81% of aborted women were positive for rubella virus (had IgG) when tested for Rubella virus antibodies, but they were all negative for IgM antibodies [19].

Material and methods

A case-control study. Were done in the Thi-Qar province, (Nasiriyah, Suq-Alshouokh, Sid-Dakheel, Qalat Sukkar, and Shatra cities), which is located in the south of Iraq, from 10/9/2023 to 5/1/2024. One hundred seventy-six children's samples were involved. The history of child immunisation for the Rubella virus was considered. The case group had 117 children (males 68 and females 49) and the control group consists 59 (males 36 and females 23) with an age range of one month to 12 years old. In addition to primary health clinics records, also parents provided the following details: age, sex, and immunization history. Enzyme-linked immunosorbent assay (ELISA) was the method utilised in this study to find Rubella Virus IgG in clinical samples.

Statistical Analysis: The IBM SPSS 26 version (Statistical Package for the Social Sciences) was used. For categorical data, frequency and percentage were employed, while mean and standard deviation (SD) were utilised for continuous data. Chi-square, t-test, and ANOVA were used to investigate the relationship between variables. with a P-value of less than 0.05.

Ethical approval: The research was carried out in conformity with the ethical principles outlined in the Helsinki Declaration. The Thi-Qar Health Directorate's research committee (No. 2023/163 on 7/8/2023) reviewed and approved the study. The individuals' agreement was obtained verbally at hospitals and clinics when collecting samples.

Results

1. Demographic Statistic

1.1. The Case and Control Groups According to results.

The results of the Rubella virus IgG titre revealed a statistically significant difference between the case and control groups (p-value < 0.001). In the vaccinated group (case group), there were 110 (94.0%) who tested positive and 7 (6.0%) who were negative of the 117 children. In the unvaccinated group (control group), there were 29 (49.2%) who tested positive and 30 (50.8%) who were negative of the 59 children, by using Chi-square at a p-value < 0.05, as shown in Table1.

Table (1): distribution of child based on RuV IgG positive in both groups.

IgG	Child Status	Positive		Negative		Total		Chi-Square
		No.	%	No.	%	No.	%	
Rubella Virus IgG	Case	110	94.0	7	6.0	117	100	Calx2= 47.549 P. Value < 0.001
	Control	29	49.2	30	50.8	59	100	
	Total	139	79.0	37	21.0	176	100	

1.2. The Case and Control Groups According to Sex and Results.

In the comparison between sex and result according to child status (within the same group), the study found no significant difference in the Rubella Virus IgG (in both groups). The case group had a p-value of 0.957, and the control group had a p-value of 0.711. at p-value < 0.05 by using Chi-square, as shown in Table 2.

Table (2): shows the number and percentage of RuV IgG results according to sex.

IgG	Child Status	Sex	Positive		Negative		Total		Chi-Square
			No.	%	No.	%	No.	%	
Rubella Virus IgG	Case	Male	64	94.1	4	5.9	68	58.12	Calx2= 0.003 P-Value 0.957
		Female	46	93.9	3	6.1	49	41.88	
		Total	110	94	7	6.0	117	100	
	Control	Male	17	47.2	19	52.8	36	61.02	Calx2= 0.138 P-Value 0.711
		Female	12	52.2	11	47.8	23	38.98	
		Total	29	49.15	30	50.85	59	100	

2. Estimation of Immune Parameters.

2.1. The Case and Control groups.

The current study found that levels of Rubella Virus IgGs were significantly higher in the case group (vaccinated children) compared to the control group (unvaccinated children). at a p-value < 0.05 by using the t-test, as shown in Table 3.

Table (3): levels of Immune Parameters in Case and Control groups.

Parameters	Case No. 117	Control No. 59	P-Value
	Mean ± S. D		
Rubella Virus Igg	↑ 4.64 ± 1.63 U/ml	1.64 ± 0.77 U/ml	< 0.001*

*= Significant differences

2.2. The Case group according to Sex.

The current study revealed that the titre of Rubella Virus IgG did not change significantly according to sex at a p-value < 0.05. shown in Table 4.

Table (4): levels of Rubella virus IgG in the case group according to sex

Parameters	Female No. 49	Male No. 68	P-Value
	Mean ± S.D		
Rubella Virus IgG	4.54 ± 1.55 U/ml	4.70 ± 1.70 U/ml	0.605

2.3. The Case Group According to the Dosage of the MMR Vaccine

In this study, levels of Rubella virus IgG titre were not statistically different when compared between children who got one dose and those who got two doses at a p- value < 0.05, as shown in Table 5.

Table (5): Rubella virus IgG in Case group based on MMR vaccine dosage.

Parameters	One Dose Of MMR Case No. 16	Two Dose Of MMR Case No. 101	P. Value
	Mean ± S. D		
Rubella Virus IgG	3.92 ± 1.58 U/ml	4.75 ± 1.62 U/ml	0.059

2.4. The Case Group according to the age group.

The case group's age was split up into five groups. There were no statistically significant differences among these age groups by the levels of Rubella Virus IgG. at p- value < 0.05. shown in Table 6.

Table (6): levels of immunoglobulin G in the case group according to age.

Age In Months	Cases No.	Rubella Virus Igg
		Mean ± S. D
< 25	14	5.18 ± 1.64
25 - 48	39	4.52 ± 1.76
49 - 72	30	4.44 ± 1.58
73 – 96	9	5.26 ± 1.51
> 96	25	4.51 ± 1.55
P. Value		0.471

3. A Pearson correlation between Immune Parameters.

The parameters in this study have linked to each other. It was discovered that there were significant differences between Rubella Virus IgG and some cytokines, as illustrated below in table 9. Rubella virus IgG, had very significant positive correlation with INF-γ, in contrast, for IL-6 cytokine, there were no significant correlations. as shown in Table 7.

Table (7): A Pearson correlation between immune-parameters.

Parameter			IL-6	INF-γ
Rubella Virus IgG	Vaccinated group	r	0.018	0.921*
		P. Value	0.849	< 0.001
	Control group	r	0.010	-0.242
		P. Value	0.942	0.065

*Correlation is significant at the 0.05 level (2-tailed).

Discussion

Serological and epidemiological findings imply that pathogen-caused natural immunity may last longer than vaccine-induced immunity. So, Outbreaks may increase when vaccination rates rise and natural exposures decrease [20]. In vaccinated children, vaccine-specific antibody responses vary widely [3]. Also, over time, antibodies produced by vaccination decline and may become undetectable [4]. Antibodies to measles, mumps, and rubella drop at a rate of 3% each year on average, with a considerable degree of individual variation; these individual differences as well as variations between antigens are poorly understood [21]. It is unknown how long after the measles, mumps, and rubella (MMR) vaccination, antigen-specific memory B-cells (MBCs) remain in children and young adults [22]. Hansashree, P., et al. found that the measles vaccine requires several doses to reach long-term protection, in contrast to the rubella vaccine [23].

The purpose of this article is to evaluate the seroprevalence of anti-rubella IgG in children who have the MMR vaccine under the age of 13 in the Thi-Qar province, Iraq. Out of the 117 children in this study who had been vaccinated against the rubella vaccine, their seropositive were 110 (94.0%) of them. while seronegative were only 7 (6.0%).

The current vaccination is considered to be highly effective in the majority of people (around 95% efficacy) and provides adequate immunity to prevent illness [7]. Our study revealed that the rubella vaccine used in Thi-Qar province was highly effective, positive Virus IgG carrying percentage reaching 94.0%. regarding vaccine effectiveness. this is compatible with Crooke, S.N., et al. [24]. and Mora-García, G.J., et al., (93%) [25], and somewhat with Gupta, M., et al., (86.2%) [26], and with Gupta, R., N. et. al, (96%) [27]. But disagreement with other studies such as Seagle, E.E., et al., (79% for rubella) [21]. And with Wanlapakorn, N., et al. (78.7%) [28], and with Kukule, L.(89.2%) [29], and Madi, N., et al. (74.9%) [30]. This difference may be due to May due to sample size or methodology, proportion of vaccine coverage.

The US health authority was eliminated rubella virus (RuV) in 2004, so yet a small percentage of the population does not obtain long-term RuV protection following two MMR vaccines [31], and this compatible with this study. Our findings revealed there were 6.0% of vaccinated children do not develop immunity against rubella. The cause of this is may be due to the true that antibody titers may drop with time, reducing disease protection [24]. As shown in a study conducted in Hangzhou, China, in 2023 which assess the seroprevalence of rubella antibodies following vaccination, discovered a decrease in rubella antibody positivity in children aged five to fourteen years [32]. This may have attributed to type of vaccine that used there not corresponding to wild-strain spread, feeding habits or genetic bases (SNPs).

Although the rubella vaccine is effective for the vast majority of people, data from the literature show that some vaccinated individuals (ranging from 2 to 17%) have inadequate long-term immunity, and antibody levels are below the level for protection [7]. In the same context, a study performed by Voigt, E.A., et al., found that while rubella vaccination is effective for most subjects in producing immunity against the rubella virus, up to 5% of people fail to develop or maintain a long-term protective immunity [5]. This is compatible with our study. Our findings are in line with this. We believed that the causes for this phenomenon is genetics, and unfortunately, More than half of people who are antibody negative following a first dose of rubella remain negative or fail to develop long-term protective immunity after two doses vaccinating [33].

The source of IgG in unvaccinated children is not only reflect the infection by the Rubella virus but also come from the mother (across the placenta or breast feeding) [34]; especially in newborns . Only several months after birth can infants receive protection from maternal antibodies transmitted transplacentally; following that, everyone is susceptible to the infection [35, 36].

A study performed by Hefele, L., et al., in Central Lao PDR, found a large proportion of unvaccinated children (38.4%) were positive for or borderline for rubella [37]. Anti-rubella IgG levels were high in some newborns at birth, then declined after 7 months and subsequently increased after immunization [28]. In the Moroccan region of Rabat, 408 (85.9%) of the pregnant women evaluated had anti-rubella IgG antibodies [38]. This explains why a high percentage of the

unvaccinated group had rubella IgG, especially in the first months of birth. In our study, the control group consisted of 29 (49.2%) who tested positive and 30 (50.8%) who tested negative of the 59 children.

Our study revealed there was a significant difference between case and control groups results (CalX2 = 47.549; p value < 0.001). This is compatible with a study performed in Uganda, found a statistically significant difference in the pre- and post-vaccination campaign (p-value = 0.001). As well as regarding sex, the same study showed no significant difference in sex according to results in pre- and post-vaccination ($\chi 2 = 0.12$, $p = 0.719$ and $\chi 2 = 1.10$, $p = 0.295$, respectively). This agreed with our study, both with the case group (CalX2 = 0.003, p-value 0.957) and with the control group (CalX2 = 0.138, p-value 0.711), respectively [39]. But, our findings revealed there was no significant difference in RuV IgG according to sex (male and female) (p-value = 0.605) by using t test analysis. This agrees with Muthiah, N., et al.'s (p-value = 0.271 and p-value = 0.156) [40], but disagrees with Pedranti, M., et al.'s results that anti-rubella IgG antibodies were substantially greater in females than in males (p-value = 0.036) [41]. And a Thai study analysing males and females found that males were considerably lower than females (p = 0.023) this may be due to methodology, sample size (1781) or statistical analysis [42].

According to a study by Madi, N., et al., females between the ages of 5 and 10 were the most protected individuals from rubella infection [30]. Klein, S.L., et al. found that sex is often, but not always, a strong predictor of vaccine reactions; females have larger humoral immune responses to immunizations than males in most viral vaccines, but in the case of the MMR vaccine (human/antibody response and cell-mediated immunity; of female were equivalent to male) [43].

Our study showed there were no significant differences regarding Rubella virus IgG according to age in vaccinated children (p-value 0.471); this agreed with Pedranti, M., et al. (p = 0.144) [41], but this is incompatible with a study performed in Colombia (p-value < 0.001) [25]. The difference is may be due to vaccine schedule in this country, vaccine doses and the number of booster dose and may be to causes regarding in study, such as sample size (1528), and study design (a cross-sectional study).

A study indicated children getting the second dosage at 2-3 years old had stronger immunity levels compared to those receiving the second dose at 4–5 years old [44] In our findings, there was no statistically significant differences in the concentration of rubella IgG levels between children who have received one dosage and those who have received two doses of the MMR vaccine (p values = 0.059). In addition a study found after the second dose, antibody titres for rubella dramatically increased (P-value < 0.001) compared to the first dose, according to Verma, S.K., et al. [45]. This disagrees with our study.

For case group our study revealed a strong positive correlation for Rubella virus IgG with INF-γ ($r = 0.921$ and p-value = < 0.001). This is compatible with Lambert, N.D., et al.'s ($r = 0.21$, p-value = 0.0004) [46], and with ($r = 0.439$, $p = 0.003$) Crooke, S.N., et al. [31]. But our results disagreed with Kennedy, R.B., et al., whose results showed that a median IFN-γ response indicates a weak Th1 response; this may be due to differences in methodology (cohort study), sample size

(1145 participants), and range of age (11–22 years). For the control group our study found there was no correlation or significant difference (r = -0.242, p- value = 0.065) regarding INF-γ.

In contrast to the IFN-γ there were no correlation or significant between rubella virus IgG and IL-6 case group (r = 0.018 and p-value = 0.849). This agrees with Lambert, N.D., et al., (r = 0.1045, p = 0.08) [46], but disagrees with Crooke, S.N., et al., who found that negative correlations were observed between the secreted levels of IL-6 (r = -0.431, p = 0.004) and (r = -0.277, p = 0.05) in both high and low responders, respectively, at Day 28 and neutralizing antibody titers at the same time point [31]. This difference may due to methodology.

For control group our findings revealed there were no correlation or significant difference in both INF-γ and IL-6 (r = -0.242, p- value = 0.065) and (r = 0.010, p-value = 0.942), respectively.

Conclusion

Our study concluded that the Rubella vaccine is potent for children who have been vaccinated, with effectiveness reaching 94%, which is a very good percentage for controlling disease. We recommend increasing vaccine coverage in Thi-Qar province, and we also advise giving a single dose to females in their bearing years to limit the incidence of congenital rubella syndrome (CRS).

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