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OPEN ACCESS ORIGINAL ARTICLE

Evaluation of the IgG and IgM Antibodies Specific for Measles Virus among Children Post-Measles Vaccination in Aden-Yemen

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ABSTRACT

Background: Measles is considered a serious problem in underdeveloped nations and can only be eradicated through extensive immunization campaigns. Age at vaccination is the primary known risk factor for primary vaccine failure because it interferes with the effectiveness of the measles immunization due to the persistence of maternal antibodies. In Yemen, measles remains a serious issue even with high vaccination rates.
Objectives: The aim of this study was to determine the level of specific anti-measles virus antibodies (IgM and IgG) in response to measles vaccination among children in Aden governorate, Yemen.
Subjects and Methods: The subjects of the study were children aged 1 up to 10 years, obtained from primary health care centers at Aden-Governorate. The type of study was a cross-sectional study conducted from the 1st of January up to the end of March 2024.This involves quantifying antibody titers at various time points following vaccination to assess the vaccine's ability to induce an immune response.
Results: Out of 125 children participated in the study, the mean age of 4 years & 4 months± 2 years & 6 months of standard deviation (i.e., 4.4±2.6 SD), with the minimum age being 1 year and the maximum age being 10 years. The seroprevalence of infected children with measles virus during this study was 25 out of 125 (20%). Moreover, infected children were higher at ages 1–1.5 and 6–10 years old (46.2%, 20.4%), respectively, without a statistically significant difference (P = 0.7). The male children are more susceptible to measles infection compared to females (21.7% vs. 16.7%), respectively, without a statistically significant difference (P = 0.5). The seroprevalence of measles antibodies among the healthy vaccinated children was 80%; it was lowered than the herd immunity against measles to be achieved (90-95%) after the first & second doses. The seronegative IgG response represented 32.8%, while the seropositivity of IgG was 67.2% after the first & second doses. The seropositive IgG response tends to be high (68.8%) after 1-2 years following the 2nd dose and tends to decrease after ≥7 years old (37.5%). Moreover, the seronegative response of IgG was higher with increasing the time elapse between the 2nd dose and the serodiagnosis (62.5%), but there was no statistically significant association (P = 0.5). The means titers of IgG and IgM post-measles vaccination were different with a highly statistically significant association; $t(124)=19.415$, $P<0.05$.
Conclusion: The Measles vaccine is effective to induce protection against measles outbreaks, but there is a decline of post-vaccination measles-specific antibodies (IgG). Moreover, it has not reached the normal threshold of protection in Aden Governorate.

Keywords: Vaccination, Measles-Specific IgG and IgM, Protection, Measles Threshold

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INTRODUCTION

The measles is a highly contagious viral infection that affects children all over the world. It caused by the Measles virus (MV), which is a member of the Morbillivirus genus and Paramyxoviriviruses family. It shares a close relationship with the viruses that cause canine distemper and rinderpest. It has a diameter of 100–200 nm and a single-stranded RNA core. In pathogenesis, two membrane envelope proteins are crucial. They are the H (hemagglutinin) protein, which is responsible for the process of the virus's adsorption to cells, and the F (fusion) protein, which is in charge of the fusing of virus and host cell membranes, viral penetration, and hemolysis (1).

For up to two hours, the virus may remain in the atmosphere. Respiratory droplets from an infected person's cough, sneeze, or speech can spread the illness. Indirect transmission occurs when infected surfaces are touched and subsequently the mouth, nose, or eyes are touched. Measles symptoms, which include an increased temperature, runny nose, watery eyes, and tiny white spots within the cheeks, typically manifest 7–14 days following viral encounter. 3–4 days after the onset of symptoms, the skin rash develops (2). The immunization against measles is affordable, safe, and efficient. Measles can be eradicated from a population entirely; however, this needs 93% to 95% of the population to receive two doses of the vaccine. Because imported cases disseminate the virus to susceptible individuals who are not immune to it, measles outbreaks happen in nations with high vaccination rates. Endemic transmission might resume if vaccination rates fall below the cutoff point (3).

The measles virus was believed to be the main cause of 2.6 million annual deaths globally, especially in children, before to the development of the measles vaccine in 1963 (2). Surveillance methods and increased vaccination rates are both necessary for the eradication of measles. As demonstrated by the 73% global fall in measles-related deaths and the 66% global drop in measles incidence between 2000 and 2018, the measles vaccination is highly effective at preventing the illness and lowering mortality rates. The measles outbreak in 2018–2019 demonstrated that, despite the effectiveness of vaccination campaigns, widespread vaccination coverage is still necessary to accomplish the disease's global eradication (4). Measles outbreaks in Ghana and India, which can cause significant complications or even death, especially in young children, have been related to low vaccination rates (5).

The measles outbreaks have been linked to inadequate disease surveillance systems, low immunization rates, underdeveloped healthcare infrastructure, and disruptions in healthcare services brought on by the COVID-19 pandemic (6). National Immunization Survey (NIS) data show that 190% of children between the ages of 19 and 35 months and 98% of new pupils had gotten at least one dose of the measles-containing vaccination. There have been noted variations in regions. In 48 United states, students must have two doses of the measles-containing immunization in order to be enrolled in school (7). The measles vaccine coverage in Kenya's Cherangani Sub County was 96.6% for the first dose and 56.2% for the second dose, falling below the WHO recommended ≥95% coverage (8).

Worldwide, the measles-containing-vaccine second-dose (MCV2) immunization coverage by the locally recommended age has improved by increased 57% from 17% in 2000 to 74% in 2023(9). The (MCV2) was not widely used in Ethiopia; there were regional differences in its coverage, and the uptake of MCV2 was influenced by maternal age, birth order, and other basic vaccination history (10). In Gondar city, Northwest Ethiopia, the MCV2 coverage was 75.68% (11). At 31 August 2023—The World Health Organization (WHO) is concerned over increasing cases of measles and rubella among children in Yemen. As of 31 July, this year, the number of suspected cases of measles and rubella in Yemen has reached almost 34,300 cases and 413 deaths, compared to 27,000 cases and 220 associated deaths in 2022(12). There is a lack of clarity in the study settings regarding Yemen's coverage of the MCV2.

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According to a report from the WHO, the number of Yemenis who have received the second dose of the MCV2 at the age at which it is recommended has increased by about 24%, from 21% in 2005 to 45% in 2023 (9) The vaccine used in our country was Measles-Rubella, Live Attenuated (Freeze Dry), given as 0.5ml subcutaneous (S/C) injection.

The standard vaccination against measles results in the production of antibodies known as immunoglobulin M (IgM) and immunoglobulin G (IgG), which provide defense against the virus (13).

Measles is the most common vaccine-preventable disease, cause of childhood mortality worldwide, accounting for about 140,000 fatalities in 2018 even with the availability of vaccines (14). Yemen is among the countries that regularly perform immunization campaigns; however, the number of pediatric measles cases that are documented is rising (15). Nonetheless, it is anticipated that there won't be any measles outbreaks in the country as long as there is continuous vaccination coverage because the attenuated measles vaccine offers both herd immunity and long-lasting immunity to the illness.

The objective of this study was to measure the levels of IgG and IgM specific antibodies against the measles after artificial vaccination and natural vaccine (i.e., acquiring the disease), to look into whether measles antibodies (IgG/IgM) persist or show evidence of declining over time, to find out how long children in the Aden, Yemen, remain immune, and to gather crucial data for public health campaigns to eradicating the measles. There was no published data such as our study in Aden governorate-Yemen. Evaluating IgG and IgM titers post-measles vaccination provides insight into the effectiveness of the vaccination program and identifying vaccine failures. Additionally, assessing the proportion of children who develop protective levels of IgG and IgM antibodies following vaccination or infection.

Case Definition of Measles:

Measles is a highly contagious disease caused by a virus. It spreads by breathes, coughs, sneezes or close personal contact (16). The case definition of measles typically includes a generalized maculopapular rash, fever, and either a cough, coryza, or conjunctivitis. Serological confirmation through tests like hemagglutination inhibition assay, complement fixation assay, or enzyme immunoassays is crucial, especially in settings of low measles incidence, as the positive predictive value of the clinical case definition decreases significantly in such scenarios (17).

SUBJECTS & METHODS

The subjects of the study were children ages one year old up to 10 years old, obtained from primary health care centers, and Al-Wahda Teaching Hospital. The subjects were divided into groups; children who take the 1st dose only, children who take the 2nd dose, and children infected with measles without being vaccinated.

Study Area:

The study design was a cross-sectional study & conducted for three months, from the 1st of January up to the end of March 2024.

Study Design and Period:

The study design was a cross-sectional study & conducted for three months, from the 1st of January up to the end of March 2024.

Sample Size:

According to a study conducted in Addis Ababa-Ethiopia by, (18) the post-vaccination seroprevalence of IgM and IgG was 91.3% and 85.0%, respectively, and 92.9% overall. The sample size for this study has been calculated based on the overall post-vaccination seroprevalence of IgM and IgG which was (92.9%), (18) using the following formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n =expected minimum sample, Z = standard, corresponding to 95% confidence; 1.96, P= the prevalence which equal (92.9%) based on previous

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mentioned study conducted by (18) and d= the maximum likely error taken as 5%

$$\text{By Calculation, } n = \frac{(1.96)^2 X 92.9\%(1-92.9\%)}{(5\%)^2} = 101$$

After the addition of **24%** to the sample size, the sample size had been 101X24%=24.3. So, 101+24=125 for both specific anti-measles antibodies (IgM and IgG) post-vaccination. Hence, we increased the sample size up to 125 to avoid sample error and based on the availability of ELIZA-Kit.

Inclusion Criteria:
Children ages one year old up to 10 years old, either receive one dose, or ≥ 2 doses or children infected with measles.

Exclusion Criteria:
All children aged who was not vaccinated against measles at any age, those having immunological diseases, using immunosuppressed drugs, and who did not consent in the study.

Sample Collection
Two milliliters sample of venous blood from the median cubital veins was aseptically collected from children, and a structural questionnaire was also obtained. The collected samples were put into a sterile gel test tube, capped, coded and placed in a test tube rack while waiting for the blood to clot or centrifuged at 3000G for 5 minutes. The serum has been collected in 1ml Eppendorf & stored at 4oC to be tested at time. The 125 children were obtained from the 25 health centers of the 8 districts in Aden governorate, including Al-Wahda Teaching Hospital, using stratified random sampling.

Sample Analysis Using ELISA
All samples were analyzed for specific anti-measles IgG & IgM antibodies by (Specific Measles ELISA IgG/IgM Kit from VirCell Company).

Ethical Considerations
Ethical approval for the study was given by the Ethics Review Committee at Faculty of Medicine & Health Sciences, University of Science and Technology-Aden, also from Ministry of Health-Aden, Republic of Yemen was informed to facilitate the process of collecting samples from primary health centers. The Medical Ethic Committee (MEC) with a number (MEC/AD012). An informed consent was obtained from child's parents before collection of blood samples. The aims of the study, potential risks (as there no risks) and benefits of the study was explained fully to each of mother/father of the child.

Statistical Analysis
Data collection was included the demographic and clinical data. A structural questionnaire was created. Such data was entered into SPSS program Version-22 and descriptive statistic was used to summaries the data, like tables, figures, and measures of central tendency. Analytic statistics were used to compare between the variables. One sample t Test was conducted. Chi-square (X2) was also used, and the significance was assumed at $p \leq 0.05$.

Description of the Area of Study (Aden Governorate)
Yemen is a developing country located on the Arabian Peninsula. The country has a tropical desert on the coast and lowlands, with mild to moderate rainfall on the western plateau. During the summer months of June to September, the south-west monsoon brings rain to the western highlands but not the rest of the country. The dry season begins in November and ends in February (Travel Ct. Climate—Yemen. 2019). The Governorate of Aden is an important economic and commercial center of the Republic of Yemen. Districts of Aden: It consists of 8 districts; Al Buraiqeh, Dar Sad, Ash Shaikh Outhman, Al Mansura, Khur Maksar, Al Mualla, Craiter, Attawahi. Aden is considered a southern city of Yemen that contains almost 25 health centers that vaccinate children.

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RESULTS

Out of 125 children participated in the study the mean age and Stander deviation (SD) was 4.4±2.6SD, the minimum, maximum, and the range were; 1 year, 10 years, and 9 years, respectively. This data represented in Table 1. The total males to females 83(66.4%) vs 42(33.6%), respectively, and shown in (Figure 1) below. The 125 children enrolled in the study was grouped into 4 groups, as shown in Table 2. Those (1-1.5); represent 10.4%, (1.6-2); represent 24.8%, (2.3-5.6); represent 25.6%, (6-7); represent 39.2%.

Table 1: Statistical Description of Ages in Years, and Months

Mean±SD	4.4±2.6SD
Range	9
Minimum	1
Maximum	10

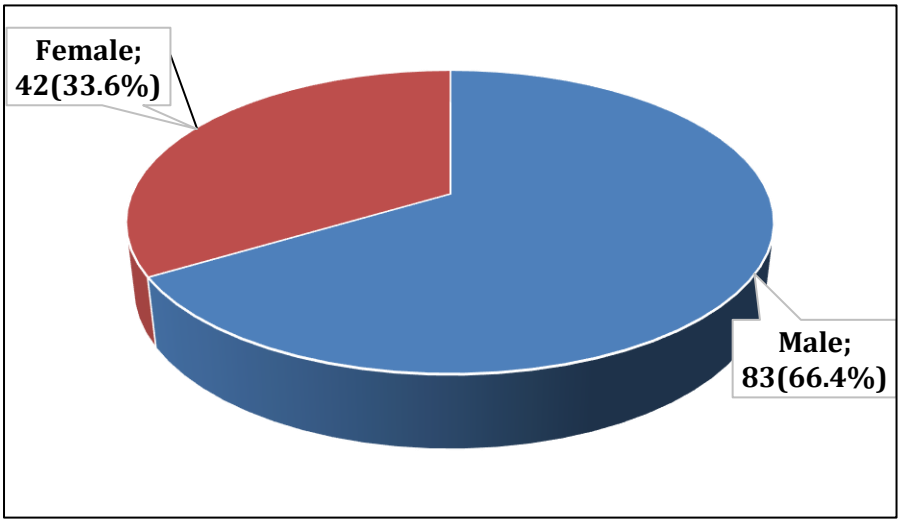

Fig 1. Frequency & % of Sex

Table 2: The Frequency of the Grouped Age

Grouped Age	N	%
1 - 1.5	13	10.4
1.6 - 2	31	24.8
2.1 - 5.6	32	25.6
5.7 - 10	49	39.2
Total	**125**	**100**

The frequencies and percentages of children have been infected with measles to those have been vaccinated was described in Table 3. Those children have been infected with MV in the study was 25 out of 125(20%). The immunization status of children in our study at Aden governorate-Yemen was 100 out of 125(80%). Those get the 1st dose of vaccine was 50(40%), and those get both doses (the 1st & 2nd doses) was also; 50(40%).

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Table 3: The Frequency and Percentage of Vaccinated Child and the Unvaccinated Child

Children having Infected or Not	Frequency (%)
Not Get Measles (Vaccinated)	100(80%)
Yes, Get Measles (Unvaccinated)	25(20%)
Total	**125(100%)**

Perioperative Concerns

Myocardial protection, anticoagulation management, and postoperative pain control are key challenges (19). Multimodal analgesia, regional anesthesia techniques, and fast-track protocols for early extubation are increasingly utilized to enhance recovery (20). Enhanced recovery protocols and non-opioid analgesic strategies are reducing opioid use and promoting faster patient mobilization (21).

Impact of Anesthetic Choice on Outcomes

TIVA appears to reduce postoperative cognitive dysfunction, particularly in elderly patients, while volatile anesthetics offer myocardial protection during surgery (23). Innovations in monitoring and drug selection are associated with improved cardiac and renal outcomes (24,25).

Table 4: The Association between Sex and Grouped Age with the Child Getting Measles

Child Getting Measles	Grouped Age (Years)								Total	
	1 - 1.5		1.6 - 2		2.3 - 5.6		6 - 10			
	N	%	N	%	N	%	N	%	N	%
No	7	53.8	27	87.1	27	84.4	39	79.6	100	80
Yes	6	46.2	4	12.9	5	15.6	10	20.4	25	20
Total	13	100	31	100	32	100	49	100	125	100
Pearson Chi-Square (X^2): The Value=6.921, df=3, & P=0.07										
Child Getting Measles	**Sex**				**Total**					
	Male		**Female**							
	N	%	N	%	N	%				
No	65	78.3	35	83.3	100	80				
Yes	18	21.7	7	16.7	25	20				
Total	83	100	42	100	125	100				
Pearson Chi-Square (X^2): The Value=0.439, df=1, & P=0.5										

The frequency and % of 100 children taken either the 1st dose or 2nd dose, i.e., those taken both doses of measles vaccine were evaluated as seen in (Figure 2) below, the 25 infected cases was excluded. Hence, the prevalence of vaccination was (80%).

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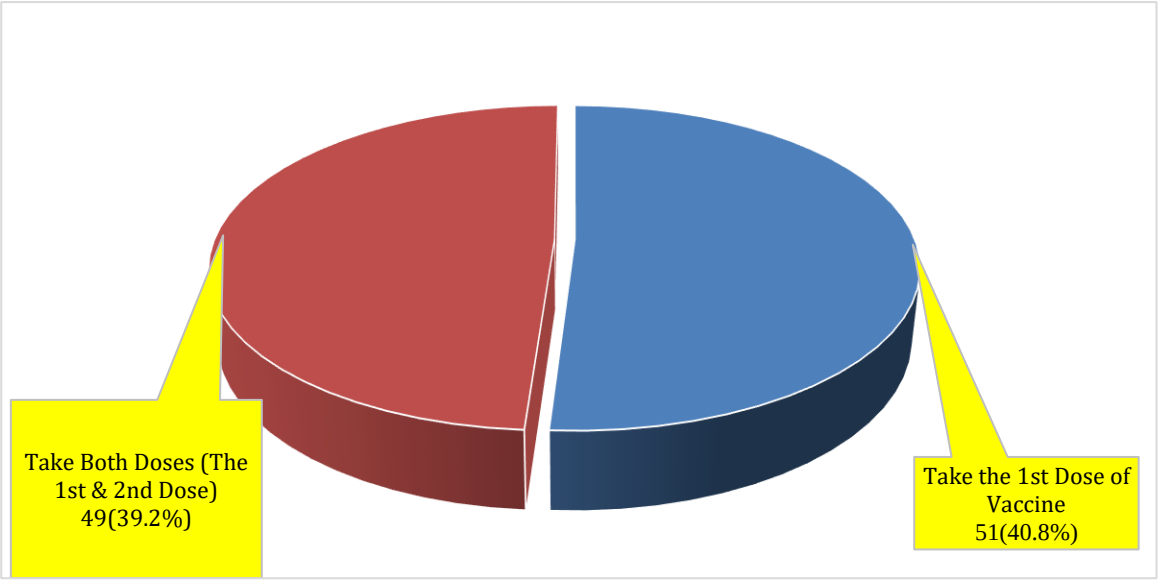

Fig 2. The Frequency and % of Children Taking 1st Dose and those taking Both Doses of Vaccine

The association of between the grouped age with the vaccinated child out of infected cases was evaluated by Pearson Chi-Square (X2) Test. There a statistically significant association (P=0.009), as seen in Table 5. The high percentage of 1st dose of vaccine was taken at age 1-1.5 years old, and lower vaccine was taken at age of 2.3-5.6 years old; 85.7%, and 33.3%, respectively. 17 cases out of 100(43.6%) was delayed in administering the first dose of the measles vaccine at age of 6-10 years old. There only one case 14.3% was reported as taken both doses of vaccine at age of 1-1.5 years old. The high percentage of the two doses was taken at age of 2.3-5.6, and 6-10 years old (66.7%, and 56.4%), respectively. The frequencies and percentages of the seroreactivity i.e., the mean levels of IgG, and IgM; which was; 0.9980 IU/ml, and 0.7529 IU/ml, respectively. Below such value was considered seronegative (lower than the mean value), and above such value was considered as seropositive (higher than the mean value). The mean values of the IgG/IgM were represented in (Figures 3, and 4), respectively.

Table 5: The Association of between the Grouped Age with the Vaccinated Child

Vaccinated Children	**Grouped Age (Years & Months)**								**Total**	
	1 - 1.5		**1.6 - 2**		**2.3 - 5.6**		**6 - 10**			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Take the 1st Dose of Vaccine	6	85.7	19	70.4	9	33.3	17	43.6	51	51
Take Two Doses	1	14.3	8	29.6	18	66.7	22	56.4	49	49
Total	**7**	**100**	**27**	**100**	**27**	**100**	**39**	**100**	**100**	**100**
Pearson Chi-Square (X^2): The Value=11.659, df=3, & P=0.009										

Out of the 25 Infected Cases

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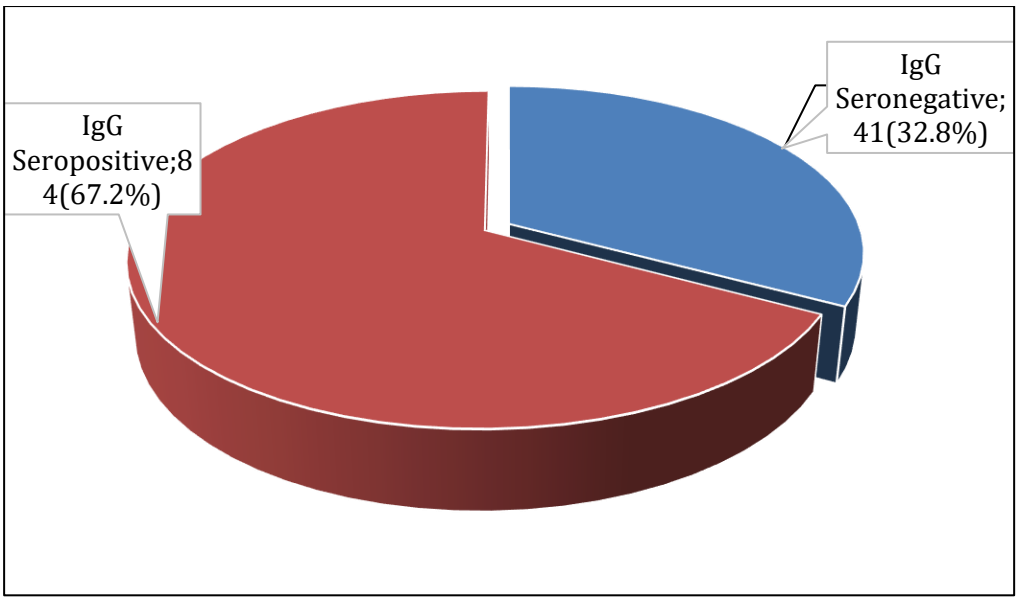

Fig 3. The IgG Seroreactivity

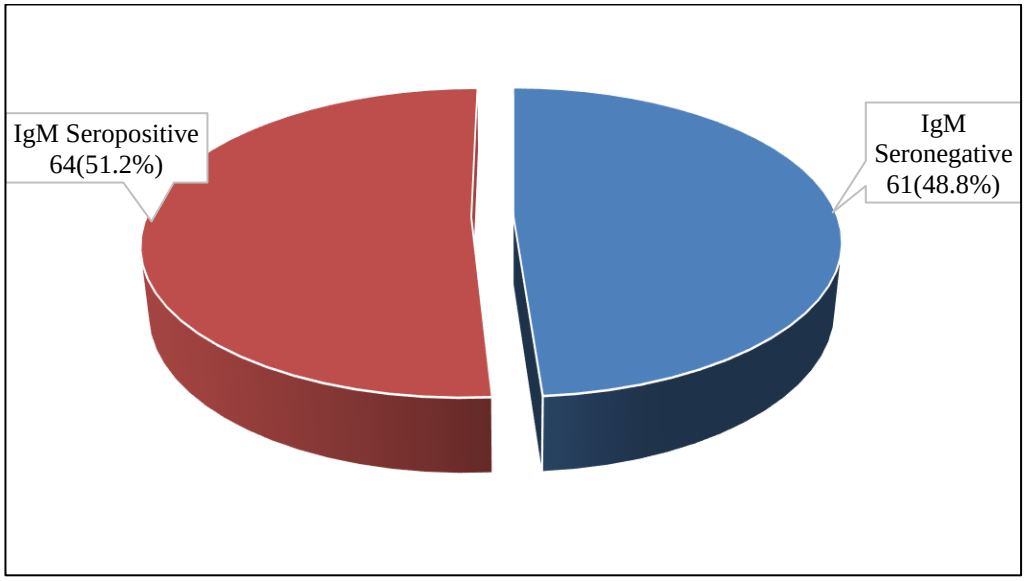

Fig 4. IgM Seroreactivity

The association between the seroreactivity of IgG and IgM with Sex and Grouped Age was evaluated by (X2)-Test, in which there were no a statistically significant association between seroreactivity of IgG and IgM with both sex (P=0.9, and 0.2), respectively. The seropositivity of IgG, and IgM in male was slightly higher than that of female; (67.5% vs 66.7%), and (47% vs 59.5%), respectively it was seen Table (6).

Also, the seroreactivity of IgG and IgM with the Grouped age show no a statistically significant association (P=0.2, and 0.9), respectively. However, the IgG Seropositivity was low at age of 1-1.5 years old (46.2%) and tend to be increased with increasing age. The IgM Seropositive was higher at age of 1-1.5 years old (53.8%).

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Table 6: The Association between the Seroreactivity of IgG & IgM with Sex and Grouped Age

IgG Seroreactivity	Sex				Total	
	Male (n=83)		Female (n=42)			
	No.	%	No.	%	No.	%
IgG Seronegative	27	32.5	14	33.3	41	32.8
IgG Seropositive	56	67.5	28	66.7	84	67.2
Total	83		42		125	
X^2-Test: The Value=0.008, df=1, & P=0.9						
IgM Seronegative	44	53	17	40.5%	61	48.8
IgM Seropositive	39	47.0	25	59.5%	64	51.2
X^2-Test: The Value=1.754, df=1, & P=0.2						

IgG Seroreactivity with Grouped Age:

IgG Seroreactivity	Grouped Age (Years & Months)								Total	
	1 - 1.5		1.6 - 2		2.3 - 5.6		6 - 10			
	N	%	N	%	N	%	N	%	N	%
IgG Seronegative	7	53.8	12	38.7	10	31.3	12	24.5	41	32.8
IgG Seropositive	6	46.2	19	61.3	22	68.8	37	75.5	84	67.2
Total	13		31		32		49		125	100
X^2-Test: The Value=4.674, df=3, & P=0.2										

IgM Seroreactivity with Grouped Age:

IgM Seroreactivity	Grouped Age (Years & Months)								Total	
	1 - 1.5		1.6 - 2		2.3 - 5.6		6 - 10			
	N	%	N	%	N	%	N	%	N	%
IgM Seronegative	6	46.2	14	45.2	15	46.9	26	53.1	61	48.8
IgM Seropositive	7	53.8	17	54.8	17	53.1	23	46.9	64	51.2
Total	13		31		32		49		125	
X^2-Test: The Value=0.604, df=3, & P=0.9										

The vaccinated child taken the 2nd dose was 49(39.2%) as seen in (Figure 3). So, the duration or the time elapsed between the 2nd doses and the serodiagnosis was grouped as shown below Table 7. This was done to evaluate between the time span before serodiagnosis and the IgG response.

Table 7: Time Span Between the 2nd Dose & the Seroreactivity of IgG

Time Before Serodiagnosis	N	%
5 Months Up to 1Year	15	12.0
1.5 – 3 Years	12	9.6
4 – 6 Years	14	11.2
≥ 7Years	8	6.4
Total	**49**	**39.2**

76 out of 125 was Missed as 51 Take 1st Dose, and 25 Infected

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The Association of between the Time Span of the 2nd Dose & IgG response following the 2nd dose of measles vaccine was evaluated by Pearson Chi-Square (X2) Test, as seen in Table 8. There was no a statistically significant association (P=0.5). However, the seropositive IgG response tend to be high (68.8%) after 1-2 years following the 2nd dose, and tend to be decrease after 7, 8, 9 and 11.9 years (37.5%). Moreover, the seronegative response of IgG was higher with increasing the time elapse between the 2nd dose and the serodiagnosis (62.5%).

Table 8: The Association of between the Time Span of the 2nd Dose & IgG Response.

IgG Responses	Time Span Between the 2nd Dose & IgG Response							
	1-2 Years		2.1-4 years		5-6 Years		7-11.9	
	No.	%	No.	%	No.	%	No.	%
Seronegative IgG Response	5	31.3%	6	40%	4	36.4%	5	62.5%
Seropositive IgG Response	11	68.8%	9	60%	7	63.6%	3	37.5%
Total	**16**	**32%**	**15**	**30%**	**11**	**22%**	**8**	**16%**
Pearson Chi-Square (X^2): The Value=2.259, df=3, & P=0.5								

The arithmetic mean titer (AMT) in this study for IgG and IgM was calculated by the summation of all the titers of IgG, and IgM divided by the total sample 125. The result was; 12.36232, and 6.6952, respectively. The ratio of the mean titer of normal IgG post-vaccination (0.9980) with the geometric mean titers (GMTs) of IgG approximately was; 2:20. It was calculated with the equation; 0.9980:9.9536 = 1.996:19.9072≈2:20. This ratio was simplified to be 1:10. The GMT and the AMT as well as the seroreactivity of IgG, and IgM was seen in Table 9. The AMT was higher than GMT of IgG and IgM.

Table 9: The Mean Value, the GMT, and AMT of IgG, and IgM

Mean of IgG, IgM	N	Mean±SD	GMT±SD	AMT±SD
Mean of IgG Level	125	0.9980±0.32980	9.9536±6.54421	12.3623±6.54421
Mean of IgM Level	125	0.7529±0.24690	5.6617±4.62420	6.6952±4.62420

Case summary of the 125 cases, including the 25 infected cases in each sex was evaluated. The GMT and AMT of IgG and IgM in both 83 males and 42 females were seen in Tables 10 and 11, summarize the 100 vaccinated children in each sex, i.e., 64 and 36 for males and females, respectively. The case summary of the 25 infected cases, in which the cases (Number 19, 20, and 22) indicate recent infection, as the IgM titers was very high; 37.20, 16.30, and 14.30 IU/ml, respectively, it was seen in Table 12.

Table 10: Case Summary of the GMT & AMT of IgG and IgM in 125 Children of each Sex

Sex	Parameters	IgG	IgM	Sex	Parameters	IgG	IgM
Total Males	N	83	83	**Total Female**	N	42	42
	AMT	**12.1529**	**6.3024**		**AMT**	**12.7762**	**7.4714**
	Minimum	1.10	0.90		Minimum	1.50	2.40
	Maximum	32.30	25.70		Maximum	28.60	37.20
	First	4.20	1.70		First	15.90	2.60
	Last	12.30	11.40		Last	14.10	5.80
	SD	6.54633	3.88207		SD	6.59936	5.79660
	GMT	**9.7836**	**5.3729**		**GMT**	**10.2983**	**6.2788**

N; the total Number of males & Females, ±SD; Sta. deviation, AMT; Arithmetic Mean Titer, GMT; Geometric Mean Titer.

Table 11: Case Summary of the GMT & AMT of IgG and IgM in 100 Vaccinated Children of each Sex

Sex	Parameters	IgG	IgM	Sex	Parameters	IgG	IgM
Total Males	N	64	64	**Total Females**	N	36	36
	AMT	**12.8405**	**6.1047**		**AMT**	**13.1806**	**6.7194**
	Minimum	1.10	0.90		Minimum	1.50	2.40
	Maximum	23.30	18.60		Maximum	28.60	16.50
	First	4.20	1.70		First	15.90	2.60
	Last	12.30	11.40		Last	14.10	5.80
	±SD	5.66766	3.33278		±SD	6.58669	3.16975
	GMT	**10.8663**	**5.2576**		**GMT**	**10.5567**	**6.0654**

±SD; Sta. deviation, AMT; Arithmetic Mean Titer, GMT; Geometric Mean Titer

Table 12: Case Summary of the GMT & AMT of IgG and IgM in 25 Infected Cases of each Sex

Sex	Parameters	IgG	IgM	Sex	Parameters	IgG	IgM
Total Males	N	19	19	**Total Females**	N	6	6
	AMT	**9.8368**	**6.9684**		**AMT**	**10.3500**	**11.9833**
	Minimum	1.50	2.80		Minimum	4.70	2.90
	Maximum	32.30	25.70		Maximum	22.50	37.20
	First	14.20	4.00		First	4.70	4.80
	Last	20.20	6.80		Last	8.50	16.30
	±SD	8.68647	5.40103		±SD	6.72243	13.29262
	GMT	**6.8699**	**5.7803**		**GMT**	**8.8754**	**7.7261**

±SD; Sta. deviation, AMT; Arithmetic Mean Titer, GMT; Geometric Mean Titer

One sample T-Test was used to compare the mean value of Anti-measles specific IgG and IgM among children participated in this study i.e., 125 children with the mean of the population. Tables (13, and 14); The AMT of IgG, and IgM was; 12.3623±6.54421SD, and 6.6952±4.62420SD, against the test values 0.9980 & 0.7529 for IgG & IgM, respectively. The mean difference of the children IgG, and IgM was; 11.36432, and 5.94230 with 95%CI (10.2058-12.5229), and with 95%CI (5.1237-6.7609), above the mean population of IgG, and IgM, respectively. This difference was highly statistically significant; t (124) = 19.415, P<0.05. Hence, we reject the null hypothesis and accept the alternative hypothesis.

Table 13: Statistical Description of One Sample *T*-Test

	N	Mean	± Std. Deviation	Std. Error Mean
IgG	125	12.3623	±6.54421	0.58533
IgM	125	6.6952	±4.62420	0.41360

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Table 14: One-Sample *T*-Test

	Test Value = 0.9980 & 0.7529 for IgG & IgM, respectively					
	t	**df**	**Sig. (2-tailed)**	**Mean Difference**	**95% CI**	
					Lower	**Upper**
IgG	19.415	124	0.000	11.36432	10.2058	12.5229
IgM	14.367	124	0.000	5.94230	5.1237	6.7609

CI; Confidence Interval

DISCUSSION

Out of 125 children enrolled in this study, to evaluate the level of IgG, and IgM post-measles vaccine. The coverage of measles vaccine of the 125 children enrolled in the study was 80%. They were vaccinated using the Measles and Rubella vaccine (MR-Vaccine), which was Live Attenuated (Freeze Dry)-India. The study indicate that we could not reach the threshold of protection in Aden governorate-Yemen. Hence, most of children were susceptible to MV infection. The immunization rate in our study was similar to that reported in New Zealand since 1985 (19) Another study in Sana'a-Yemen in which sera obtained from 1368 individuals living in both urban and rural areas of Sana'a, were tested for measles antibodies, the found 11.7% had no antibodies to measles, and of 89 children <5 years of age 49 (55.1%) had no detectable antibodies to measles (20).

The herd immunity against measles to be achieved it should be equitable to 95% coverage with 2 timely childhood doses of MCV (21). One study was conducted in the Republic of Belarus, they found that the level of seroprevalence against measles was 84.6%, that is lower than the threshold level (90–95%) sufficient to prevent wide transmission of the measles virus (22). Different studies having various seroprevalence of measles antibodies among the healthy children. In a study conducted in India, reported the overall prevalence of anti-measles antibodies was 93.5%, which greater than our study (23). Another two studies which was less than our study conducted in Brazil, (24) and the other study conducted in Kosovo, (25) with a total seropositivity of 75.8%, and 74.5%, respectively.

Table 3; The prevalence of infected children during our study was 20%, with greater in males than female (76% vs 24%), respectively. However, there no a statistically significant association (P=0.1). The measles which was reported in our study area was determined based on the case definition and by the history obtained from the child's parents. The lower prevalence of measles during our study may related to time of blood sampling which not occurred during the measles outbreak, since our study was conducted from the 1st of January up to the end of March 2024. Measles outbreaks in Yemen are most common from late winter to early summer, typically peaking between February and May. In addition to the seasonal variation of measles outbreak, the ongoing conflict and humanitarian crisis in Yemen was exacerbated the situation. Another possible reason is the real excess in male incidence rates may be overestimated by the excess of males in the study.

Geographical location, age group, and gender all have different risks of getting the measles. Nonetheless, many studies reported an excess in prevalence of measles among males than females (26-28) others report a higher prevalence among females (29,30) The Attack Rate (AR) of measles was; 2.9/100000, this calculated as the total population of Aden governorate was 865,000. The Population Data Source was obtained from: 'Yemeni Central Statistics Office's Population Projections for 2015'.

The measles AR in Yemen varied by governorate and age group. The total attack-rate for a measles outbreak in Shabwah governorate was 82 per 100,000 individuals. Measles infection was strongly correlated with traits such as contact with cases,

undernourishment in children 6 to 60 months of age, and immunization status (15). The AR of measles, as identified through a systematic review and meta-analysis, was found to be 34.51 per 10,000 population during outbreaks in Ethiopia, with a case fatality rate of 2.21% (31). These results were greater than our finding as it conducted during the measles outbreak.

The association between the grouped age with the vaccinated child out of infected cases was evaluated by Pearson Chi-Square (X2) Test. There a statistically significant association (P=0.009), as seen in Table 6. The high percentage of 1st dose of vaccine was taken at age 1-1.5 years old, and lower vaccine was taken at age of 2.3-5.6 years old; 85.7%, and 33.3%, respectively. 17 cases out of 100(43.6%) was delayed in administering the first dose of the measles vaccine at age of 6-10 years old. There only one case 14.3% was reported as taken both doses of vaccine at age of 1-1.5 years old. The high percentage of the two doses was taken at age of 2.3-5.6, and 6-10 years old (66.7%, and 56.4%), respectively. This means that infants who were immunized before the age of nine months also showed lower antibody titres after consecutive doses than those who were immunized later. Thorough studies found that later ages at first immunization are linked to better immunogenicity and protection against measles. A study conducted in Pakistan was agreed with our study, revealed that the age of children between 6-10 years have a much greater incidence of measles (30). One study conducted by (26), they were found that three cases (1.08%) received the 1st dose of the measles, mumps, rubella vaccine (MMR) at the age of 4 years (26). A study emphasized the importance of administering the 1st measles-containing vaccine dose (MCV1) to infants younger than 9 months in high-risk areas to reduce measles-related mortality and morbidity (32) Moreover, the early measles vaccinated child at age 9-17 months was prone to measles infection. A Study has shown that early measles vaccination can provide immediate protection, but it may lead to a long-term decrease in neutralizing antibody responses compared to vaccination at a later age, potentially leaving some children susceptible to measles. Furthermore, early vaccination-generated antibody functions may be degraded more quickly than those received later, which could lead to inadequate long-term protection (33). The frequencies and percentages of the mean levels or the seroreactivity of IgG, and IgM was; 0.9980 IU/ml, and 0.7529 IU/ml, respectively, as shown in Figures 3, and 4, respectively. Any values below the mean of IgG and IgM responses were considered seronegative, and values above such mean levels were seropositive. The total seropositive IgG and IgM was 67.2% and 51.2%, respectively. Additionally, the total seronegative IgG and IgM was 32.8% and 48.8%, respectively. One study showed a seropositivity of IgG (78.02%), this was slightly higher than our study (34).

The age, immunization status, length of time after infection or vaccination, and other factors all affect the overall seropositivity of IgG and IgM anti-measles response. The IgG titer was different in natural and artificial vaccination (35). It is important to monitoring antibody levels post-measles vaccination, as low percentage of vaccine recipients may still have inadequate protection against measles (36). The association between the seroreactivity of IgG and IgM with Sex and Grouped Age was evaluated by (X2)-Test, in which there were no a statistically significant association between seroreactivity of IgG and IgM with both sex (P=0.9, and 0.2), respectively, as seen in Table 6. However, the seronegativity of IgG and IgM was lowered in males than females (32.5% and 33.3%) vs (44.6% and 40.5%), respectively. Hence, greater susceptibility of male children to measles infection, demonstrating the significance of focused immunization programs and public health initiatives to reduce the risk of measles in this demographic group. Many studies agree with our study, as they found that the reporting rate for measles was higher among male children compared with female children (26-28). Additionally, the association between the seroreactivity of IgG and IgM with the grouped age

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was evaluated, and show no a statistically significant association between them (P=0.2, and 0.9), respectively. The seronegativity of IgG was reduced with increasing age of the vaccinated child, 53.8% at age of 1-1.5 years old, while it was 24.5% at age of 6-10 years old. The seropositivity of specific anti-measles IgG was increased with increasing age of child, it was 68.8%, and 75.5% at age of; (2.3-5.6, and 6-10 years), respectively. Such result point to the possibility of the exposure to natural infection beside the two doses of anti-measles vaccine in older children. A study conducted in Kosovo was revealed similar result; the seropositivity in those had gotten two doses of the measles vaccination and at age between 8-17 years were exhibited a higher seropositivity than younger age groups (37). Another study conducted in Iran; reported that children aged 18 months showed the highest positive level of specific anti-measles IgG, while those aged 6 and 12 months had the lowest levels, i.e., an age-dependent increase in seropositivity (38). Two studies more conducted in Nigeria, and Zaria, were agreed with our study,(39,40) respectively. All of these results were indicated to the significance of age in determining immunity levels, since older children anti-measles IgG antibodies being wane.

Furthermore, our study revealed that the seropositivity of IgG was less than that of IgM at age of 1-1.5 years old (46.2%, vs 53.8%), respectively, this means that the younger children were protected only by the 1st dose of vaccination, since infection was rarely at this age as they were protected by immunized mother. Regarding the seropositivity of IgM was higher in younger children than the old age children. Immunoglobulin M seropositivity at age of 1-1.5 years old which was 53.8% than those at age of 6-10 years old (46.9%). Younger children actually had higher seropositivity of anti-measles specific IgM than older age groups, according to numerous studies. In an Iranian study, the measles IgM seropositivity was 63.6% in children <1 year old and 3.0% in those over 1 year old (41) Furthermore, a study in India revealed that higher seropositivity of IgG in younger children (42).

The association of the duration or the time elapsed between the 2nd doses and the serodiagnosis was evaluated by (X2)-Test, as seen in Table 8, in which there were no a statistically significant association between (P=0.5). However, the seropositive IgG response tend to be high (68.8%) after 1-2 years, and very low after 7-11.9 years (37.5%). Hence the IgG response or its seropositivity was lowered with increasing the time elapsed during the 2nd dose of measles vaccine. The dosage schedule and number of doses to measles has significant importance on IgG response. Furthermore, the use of 2 doses of vaccine, significantly increase the IgG responses, but increasing the gap between getting vaccine and time of sero-evaluation will lowering the immune response. A study was indicates that children who received their first measles vaccine dose at 11-22 months of age showed an increase in protective antibody levels (43). The Geometric Mean titers of IgG and IgM was considered to be better as it represents the typical immune response in a population. The ratio of the mean titer of normal IgG post-measles vaccination (0.9980) to the GMTs of IgG approximately was; 2:20. It was calculated with the following equation; 0.9980:9.9536 = 1.996: 9.9072 = 2:20, which was simplified as 1:10, indicates that the mean titer of normal IgG was one-tenth of the GMT of IgG. A potentially better or more constant immune response among the population was suggested by the GMT, which was much greater than the mean titer of the standard post-measles vaccine IgG and IgM, as seen in Table 9. Table 10; represent a case summary of the 125 cases, including the infected cases (n=25). The arithmetic mean titer and the GMT in females was greater than that of males. Various data provides insights into the levels of IgG and IgM antibodies in both sexes. When the AMT is greater than the GMT, it signifies a deviation from the typical relationship between these two means, as described in the arithmetic mean-geometric mean (AM-GM)

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inequality (44). A mix of hormonal and genetic factors can account for the fact that females usually have higher IgG titers than males following vaccination or infection. First, because estrogen, the primary female sex hormone, activate B cells, which are responsible for producing antibodies like IgG (45). While Testosterone, the primary hormone in men, has immunosuppressive effects that reduce the synthesis of antibodies and B cell activity, this results in lower IgG titers in males. Second, males only possess one X chromosome, whereas females have two. The X chromosome carries numerous immune-related genes, including those which produce antibodies. Because of this genetic advantage, females are able to produce more antibody such as IgG (46). Studies show that adult females produce greater IgG responses to vaccines, such as influenza, compared to males, attributed to increased antibody diversity and germinal center B cell activity (47). One more study which disagrees with our study found that there was no significant difference in the average IgG antibody titer between male and female healthcare workers, indicating similar immune responses between sexes (48). According to the study conducted by (49), there was a real difference between the maximal IgG and IgM titers reported after a natural measles infection and those following a measles vaccination. Also, Studies comparing the immune response after natural infection and vaccination showed that individuals with natural immunity had higher neutralizing antibody titers and IgG avidity levels than those who received the measles, mumps, and rubella (MMR) vaccine, indicating a more robust immune response from natural infection (49). Tables 13, and 14; Compare the means of IgG and IgM by One Sample t-Test. The means of IgG, and IgM was; 12.3623±6.54421SD, and 6.6952±4.62420SD), against the test values 0.9980 & 0.7529 for IgG & IgM, respectively. The mean difference of the children's IgG, and IgM was; 11.36432, and 5.94230 with 95% CI (10.2058-12.5229), and (5.1237-6.7609), above the mean population of IgG, and IgM, respectively. This difference was highly statistically significant; t (124) = 19.415, P<0.05. Hence, we reject the null hypothesis and accept the alternative hypothesis.

CONCLUSION

It would be concluded that the seroprevalence of measles infection was 20%, infection was higher at age of 1-1.5 years old, and 6-10 years (56.2%%, and 20.4%), respectively. The seroprevalence of specific anti-measles antibodies among the children were 80%, it was lower than the threshold of herd immunity against measles to be achieved which should be (90-95%) after the first & second doses. The seronegative of IgG response represent 32.8%, while the seropositivity of IgG was 67.2%, after the first & second doses. The seronegativity of IgG was reduced with increasing age of the vaccinated child, 53.8% at age of 1-1.5 years old, while it was 24.5% at age of 6-10 years old. These results were indicated to the significance of age in determining immunity levels, since older children anti-measles IgG antibodies being wane. The AMT and GMT of IgG and IgM in those have been vaccinated was greater in females than males, hence, males were at a higher risk of measles infection compared to females.

Recommendations

Despite the MR-vaccine is effective to induce protection against measles outbreak, Complete or partial decline of post-vaccination measles-specific antibodies (IgG) titers suggest; the necessity to apply precaution in order to protect the immunized population from disease, it should be important to monitoring the old children 10-15 years, it could be important to implement an alternative vaccine with very high efficacy, since our measles immunization program was 80% not achieving the protection threshold.

Conflict of Interest

The authors declare that no conflict of interest.

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