



## Research Article

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# Immunoglobulin Levels (IgG, IgM And IgA): Normal Values for Healthy Infants and Children in Sana'a City-Yemen

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## Abstract

**Background:** Ig level assessment is often used in the diagnosis and follow up of immunodeficiency, as well as in studies investigate the prevalence of low serum levels in specific diseases.

**Objectives:** The main objective of this study was to determine the level of immunoglobulin in healthy infants and children in Yemen, to establish a national standard for immunoglobulin level among healthy children based on local data.

**Methods:** Immunoglobulin concentration was estimated in 448 healthy children of both sexes of different age groups in Sana'a city. IgG, IgM and IgA serum immunoglobulins were determined by the commercial immunoturbidimetry method. The mean Levels  $\pm$ SD, 95%CI, minimum, maximum and mode of immunoglobulins (Igs) were calculated and cross tabulation of significant variations were obtained by  $\chi^2$  and p value.

**Results:** Four-point two percentage of children showed a high level of IgG, 78.6 % within normal level, and 17.4 % showed a low level. There was no one of tested children showed a high level of IgM, and 94.2 % of them were within normal level, and only 5.8% with low level. Also, 2.2 % showed high level of IgA, 57.6% within normal level and 40.2 % with a low level. The mean level of IgG for both sexes was  $910 \pm 424$ mg/dl, while for males was  $912 \pm 452$ mg/dl, and for females was  $902 \pm 404$ mg/dl. The total mean level of IgM was  $96.7 \pm 50$ mg/dl, for males was  $96 \pm 56$ mg/dl, and for females was  $97 \pm 41$ mg/dl and the variation between sexes was non-significant. The total mean level of IgA was  $105 \pm 79$ mg/dl, for males was  $98 \pm 76$ mg/dl, and for females was  $112 \pm 82$ mg/dl, but the variation was non-significant. The mean values level of all immunoglobulins tested in this study were well correlated with age, where level increase with increasing age.

**Conclusion:** The study has provided useful information about the normal level of serum immunoglobulins concentration in infants and children, and the results can be taken as a reference values for Yemen. The serum IgG, IgM and IgA levels in most healthy children in our study were within normal range of the international standard, with mean value equal to that reported worldwide.

**Key words:** Immunoglobulin; IgG; IgM; IgA; Normal Values; Infants; Children; Yemen

## Introduction

Activated B cells differentiate into antibody-producing cells called plasma cells that secrete dissolved antibodies or memory cells that remain in the body for years afterwards in order to allow the immune system to remember the antigen and respond faster at future exposure. Immunoglobulin concentrations (IgG, IgM, and IgA) in sera for healthy children and infants in different age groups were measured and reported in several studies. It was believed to be very diverse among different nations due to environmental and

genetic factors [1]. In Yemen, there was no study discussing this issue, and this is the first study of this type while other research studies have been conducted in Yemen to study HLA, immune status against bacterial and viral infections recently [2-6]. There is an important reason to know the concentration of immunoglobulin among children in Yemen as doctors need a precise age-normal range and ethnic-normal range of Igs, so they can diagnose primary immunodeficiency, some autoimmune disorders, HIV Syndromes and various isolated clinical conditions [1,7].

Antibody deficiency is the most common category of primary immunodeficiency for more than 50% of all primary immunodeficiency diseases (PID) [8]. Severe antibody deficiency disease begins in childhood, so early diagnosis and treatment are key to improving better prognosis [9]. Blood immunoglobulin concentrations (IgG, IgA, IgM, IgG subclasses) are used to evaluate the immune status and diagnose PID [10]. A new classification of PID has been identified, [11,12], so age-specific immunoglobulin values are very important [11,12]. The main objective of this study was to determine the level of immunoglobulin in healthy infants and children in Yemen, to establish a national standard for immunoglobulin level among healthy children based on local data.

## Material and Methods

### Study population and sample size

Accordingly, a sample size of 448 subjects was calculated, this was selected by a systematic random method. First, all maternity centers (with children aged 1 month to 5 years), all schools and nurseries with children aged 5 to 15 years in Sana'a city (270 locations) were listed, then by simple random selection, 4 maternity centers, 8 schools and nurseries (4 female and 4 male); were selected. Subsequently, for schools and nurseries using a stratified sampling method, classes were selected by age to cover all relevant age groups (5 to 15 years); finally, each fifth child attending health centers and / or in the selected class list was selected. About 20% of male children and 17% of female children refused to donate blood or their parents were replaced by another cooperative child. All children were asymptomatic with natural immune systems while participating in the study. Successive blood samples were obtained from 448 healthy children. All individuals do not complain of any clinical symptoms and do not have any infection in the sampling period (or in the recent past).

### Laboratory works

5 ml of venous blood were with drawing of each individual and allowed to clot, or with drawing in heparin tubes or EDTA tubes. Serum or plasma was stored at -20° C or tested immediately after collection and separation for total immunoglobulin (IgG, IgM and IgA) by immunoturbidimetry.

### Determination of IgG, IgM, and IgA

Immunoglobulin G, M, and A precipitate in the presence of goat antihuman immunoglobulin G, M, and A antibodies. The light scattering of the antigen – antibody complexes is proportional to the immunoglobulins concentration and can be measured by turbidimetry (the kits were supplied by Biosystems.S.A.Company, Spain). The readings were taken at 540 nm. The results were calculated against the calibration curves and the results were obtained in mg/dl.

### Data analysis

Basic Descriptive statistics, including means, standards deviations, modes, percentage and 95% CI of the mean were used to characterize the study populations. Associations between variables

were measured using chi-square ( $\chi^2$ ) or student's t test. Statistical significance was achieved when  $p < 0.05$ . Statistical analysis was performed by using Epi Info version 6- CDC, Atlanta USA Software.

## Results

The study results illustrated in 8 tables. Four hundred and forty eight apparently healthy infants and children were involved in this study 260 were males (58%) and 188 were females (42%), their ages ranged from 2 months to - 15 years, with mean ages equal to 6.6 years,  $SD \pm 5.1$  years, median=5 years and mode =4 years (Table 1). Table 2 shows the IgG level of immunoglobulin for healthy children tested according to international standards, as 4.2% of children showed a high level of IgG >1660 mg/dl, 78.6% were at the normal level (600 mg/dl / - 1660 mg/dl ), and 17.4% showed a low level of IgG (less than 600 mg/dl). Table 3 shows the level of immunoglobulin M (IgM) for healthy children tested according to international standards. None of the children tested showed a high level of IgM, 94.2% of them were within the international normal level (40mg/dl- 120mg/dl) and only 5.8% showed a low level of IgM (<40 mg/dl). Table 4 shows the level of IgA immunoglobulin for healthy children tested according to international standards, 2.2% showed a high IgA level (>400 mg/dl), 57.6% was within the normal level (70 mg/dl - 400 mg/dl) and 40.2% showed low level% (<70 mg/dl). Table 5 shows the age-related serum IgG level (mg/dl) with 95% CI levels in healthy children, and the crude mean level of IgG was  $910 \pm 424$  mg/dl, with 95% CI equal to 870-950 mg/dl. There was an increase in other values of IgG as age increased. Table 6 shows the age-related blood level of IgM (mg/dl) with 95% CI in healthy children, the mean level of IgM was  $96.7 \pm 50$  mg/dl, and other IgM values increased with increasing age. Table 7 shows the age-related blood level of IgA (mg/dl) with 95% levels in healthy children, the average level of IgA was  $105 \pm 79$  mg/dl, and other means and values of IgA were not statistically different with age. Table 8 shows the mean serum levels of IgG, IgM and IgA and gender comparison, and there was no statistical difference in the different immunoglobulin between male and female.

**Table 1:** The age and sex distribution of infants and children tested for serum immunoglobulin.

	Male		Female		Total	
	No	%	No	%	No	%
0 -12 months	32	12.3	28	14.9	60	13.4
1-3 years	72	27.7	28	14.9	100	35.7
4-7 years	66	25.5	54	28.7	120	62.5
8-10 years	34	13.1	3	3.2	40	71.4
11-13 years	32	12.3	30	16	62	84.8
>13 year	24	9.2	42	22.3	66	14.7
Total	260	58	188	42	448	100
Mean	6.6 years		6.5 years		6.6 years	
SD	5.1 years		5.3 years		5.1 years	
Median	5 years		5 years		5 years	
Mode	2 years		4 years		4 years	
Min	9 months		2 months		2 months	
Max	15 years		15 years		15 years	

**Table 2:** The level of immunoglobulin IgG of tested healthy children according to the international standard.

IgG	Number	%	T-Test	P
High level- more than 1660 mg/dl	18	4	22	< 0.001
Normal level - 600-1660 mg/dl	352	78.6		
Low level - less than 600 mg/dl	78	17.4		
Total	448	100		

**Table 3:** The Level of Immunoglobulin M (IgM) of tested healthy children according to the international standard.

IgM	Number	%	$\chi^2$	P
High Level more than 120 mg/dl	0	0	19.9	<0.001
Normal Level 40 - 120 mg/dl	422	94.2		
Low level less than 40 mg/dl.	26	5.8		
Total	448	100		

**Table 4:** The Level of Immunoglobulin IgA of tested healthy children according to the international standard.

IgA	Number	%	$\chi^2$	P
High Level >400 mg/d	2.2	10	13.7	<0.0001
Normal Level 70-400 mg/dl	57.6	258		
Low Level - less than 70 mg/dl	40.2	180		
Total	100	448		

**Table 5:** Age- related serum IgG level (mg/dl) with 95% CI levels in healthy children.

Age Groups	Number of Subjects	Geometric Mean $\pm$ SD Mg/dl	Min-Max Mg/dl	95% CI
0 -12 months	60	637 $\pm$ 279	275-1130	566 - 708*
1-3 years	100	799 $\pm$ 287	362-1707	743 - 855*
4-7 years	120	855 $\pm$ 284	335-1380	804 - 906*
8-10 years	40	1004 $\pm$ 275	600-1465	919 - 1090*
11-13 years	62	989 $\pm$ 334	493-1755	906 - 1070*
>13 year	66	1285 $\pm$ 726	707-3360	1110-1460*
Total	448	910 $\pm$ 424	275-3360	870 - 950

\*significant variations  $p < 0.05$ **Table 6:** Age related Serum IgM level (mg/dl) with 95% CI in healthy children.

Ag Groups	Number of Subjects	Geometric Mean $\pm$ SD Mg/dl	Min-Max	95% CI
0 -12 months	60	90 $\pm$ 48	23-196	77.9 - 102
1-3 years	100	103 $\pm$ 54	40-317	92.4 - 114
4-7 years	120	83 $\pm$ 43	9-180	75.3 - 90.7
8-10 years	40	122 $\pm$ 89	42-354	94.4 - 150*
11-13 years	62	96 $\pm$ 30	44-141	88.5 - 103
>13 year	66	101 $\pm$ 35	48-180	92.6 - 109
Total	448	96.7 $\pm$ 50	9-354	92.1 - 101

\*significant variations  $p < 0.05$ **Table 7:** Age related Serum IgA level (mg/dl) with 95% levels in healthy children.

Ag Groups	Number of Subjects	Geometric Mean $\pm$ SD	Min-Max	95% CI
0 -12 months	60	48. $\pm$ 37.6	9-142	38.5 - 57.5*
1-3 years	100	68 $\pm$ 40	17-203	60.2 - 75.8*
4-7 years	120	100 $\pm$ 57	13-240	89.8 - 110*
8-10 years	40	137 $\pm$ 85	50-314	111 - 163*
11-13 years	62	104 $\pm$ 68	10-281	87.1 - 121*
>13 year	66	198 $\pm$ 100	47-412	174 - 222*
Total	448	105 $\pm$ 79	9-412	97.7 - 112

\*significant variations  $p < 0.05$ **Table 8:** Mean Serum Immunoglobulin levels and comparison between the two sexes (mg/dl).

Immuno-globulin	Crude Mean levels $\pm$ SD Mg/dl	Sex difference			
		Males Mean $\pm$ SD mg/dl	Females Mean $\pm$ SD mg/dl	T-Test	P
IgG	910 $\pm$ 424	912 $\pm$ 452	902 $\pm$ 404	0.8	0.3
IgM	96.7 $\pm$ 50	96 $\pm$ 56	97 $\pm$ 41	0.2	0.6
IgA	105 $\pm$ 79	98 $\pm$ 76	112 $\pm$ 82	0.9	0.7

\*significant variations  $p < 0.05$ 

## Discussion

The first objective of this study was to determine the level of immunoglobulin in the circulation of children. IgG is the predominant antibody that is synthesized in a secondary antibody response. IgG is an exclusive antioxidant antibody. Both the intravascular and extra vascular pools contain equal amounts of IgG. In our study, 78.6% of all children tested were at the normal level of IgG according to international standards (Table 2). However, 4% of the children tested showed a high level of IgG in the blood, and 17.4% of our children tested showed a low level of IgG in the blood compared to international standards.

A high level of IgG, especially in the early years of the child, can be provided by passive immunization of the mother and high endogenously production of clonal B cells that respond particularly to high exposure to microorganisms also due to the presence of many natural antibodies directed against disaccharide galactose,  $\alpha$ -galactose ( $\alpha$ -Gal), which is found as a terminal sugar on glycosylated cell surface proteins, and is produced in response to the production of this sugar by bacteria in the human intestine [13]. This IgG elevation may also be due to apparent viral hepatitis, autoimmune hepatitis and cirrhosis as described by Abbas et al. [14]. A higher percentage of current study children show a lower level of IgG in circulation (17.4%). This result can be explained by the high rate of factors that suppress the immune system in Yemen from malnutrition [15].

A secretory form of IgM has been found in body fluids and is transport through the epithelial lining is the same as that for

secretory IgA [16]. In an immune response, IgM is the first antibody produced in both the primary and secondary responses. During fetal development, IgM is the first antibody class to be produced [17].

In the current study, most of the individuals tested (94.2%) showed the normal level of IgM in the circulation according to the international standard level (40-120mg/dl). There is no high level of immunoglobulin among the children in our study and this indicates that the children of the study are healthy, increases occur in IgM usually the following cases: Waldenstrom's macroglobulinemia, trypanosomiasis, malaria, infectious mononucleosis, lupus erythematosus, rheumatoid arthritis, dysgammaglobulinaemia (certain cases) [18]. While 8% of the children tested show a low level of immunoglobulin, this may be due to the prevalence of malnutrition among children in Yemen due to the Saudi-UAE aggression on Yemen.

Humoral responses induced in mucosal follicles result predominantly in the production of IgA antibodies, which have several unique properties that allow them to function efficiently in the mucosal environment [19]. In human the rate of IgA production is approximately twice that for IgG [20]. IgA is more abundant than other types of immunoglobulins, having a rate of excretion exceeding that of all other immunoglobulin combined when calculating its continuous secretion in humans.

In the current study, 57.6% of all children tested were at the normal level of IgA according to international standards (Table 4). However, 2.2% of children tested show a high level of serum IgA, and 40.2% of children currently tested show a low level of IgA in blood compared to international standards. IgA can mediate proinflammatory effects under certain circumstances. Thus, contact with IgA-coated particles can lead to opsonization and phagocyte activation through Fc receptors. Moreover, IgA interacts via its Fc region with lactoferrin and lactoperoxidase and thereby enhances the function of these innate host defense proteins [19]. Circulating IgA increases usually occur in the following conditions: Chronic, nonalcoholic liver diseases, especially primary biliary cirrhosis (PBC), obstructive jaundice, exercise, alcoholism, sub-acute and chronic infection. IgA decreases occur in the following conditions: Ataxia-telangiectasia, chronic sinopulmonary disease, congenital deficit, late pregnancy, prolonged exposure to benzene immunosuppressive therapy, and abstinence from alcohol after a period of 1 year, drugs and dextrin, protein-losing gastroenteropathies [21].

When IgG was calculated with age, it was found to increase in quantity with age at which the lowest concentration of IgG (637mg/dl) occurred in the age group of 0-12 months and the highest amount in the age group >13 years (1285mg/dl) (Table 5). The results of the present study are like those reported elsewhere where IgG serum concentration increases with age [22,23]. This result can be explained by the fact that IgG is provided at an early age by passive immunization of the mother and is produced by endogenous IgG produced by clonal B cells that respond specifically

to antigens such as previous infection, vaccination, external exposure to other antigens, and increased quantity over time due to increased frequency of antigens exposure, due to any previous infection, vaccination or exposure of another foreign antigen [24]. Also, part of the amount of IgG is due to the production of natural antibodies by the immune system (mostly IgG) which are defined as antibodies produced without any previous infection, vaccination, exposure to other foreign antigens, or passive vaccination. These antibodies can activate the classical complement pathway leading to lysis of enveloped virus particles long before the adaptive immune response is activated. Many natural antibodies are directed against the disaccharide galactose  $\alpha$  [25,26] galactose ( $\alpha$ -Gal), which is found as a terminal sugar on glycosylated cell surface proteins and generated in response to production of this sugar by bacteria contained in the human gut [26].

Also, a large amount of IgG at a young age has a low affinity because of that at a young age, after activation with the antigen, B cells begin to multiply rapidly. In these rapidly dividing cells, genes that symbolize the variable domains in heavy and light chains pass at a high rate of point mutation, through a process called somatic hypermutation (SHM). SHM produces approximately one nucleotide in each variable gene, for each cell division [27]. As a result, any daughter cells will acquire slight differences in amino acids in the variable domains of their antibody chains. This increases the diversity of antibody assembly and affects the affinity of antibody binding to the antigen [28]. Some point mutations will produce antibodies with a weaker reaction (low affinity) with their antigen than the original antibody, and some mutations will generate stronger antibodies (high affinity) [29].

The crude mean of IgG levels in the children of the current study (Table 5) is close to the average in Oman [30] and Helsinki-Finland [31], but higher than that observed in Spain [18], Kashmir (India) [22], California [32], and less than Nigeria [33].

When IgM serum concentration considering with age, we found no significant difference related with age. (Table 6). Our result is like that reported elsewhere in which IgM serum concentration is not age related except in 0-30 days infant in which geometric mean  $\pm$  SD mg/dl of IgM is very low ( $18.5 \pm 3.5$ mg/dl) [34]. This result can be explained by that IgM in an immune response, IgM is the first antibody produced in both the primary and secondary responses and disappear rapidly after cure of infection [18]. When IgA serum concentration considering with age, a statistical analysis revealed a significant relationship between age and IgA concentrations up to ages 8 to 10 years (Table 7). Our result is like that reported elsewhere in which IgA serum concentration is age related and rise to the peak concentration in 7 and 8 years old [23]. Also, no correlation was present between age and immunoglobulin concentrations beyond that time, suggesting that the adult concentrations of IgA are normally reached and maintained after ages 7 and 8 years [23]. When concentration of immunoglobulins tested among our subjects, no truly significant differences were found in immunoglobulin concentrations (IgG, IgM, and IgA)

which could be attributed to sex (Table 8). Our result is like that reported in Turkey and USA among children in whom they found no truly significant differences of immunoglobulin concentrations attributed to sex [35-37].

## Conclusion

The study provided useful information on the normal level of serum immunoglobulins concentration in infants and children. The results can be considered as reference values for Yemen. Serum levels of IgG, IgM and IgA in most healthy children in our study were within the normal range of international standards, with an average value equal to that reported worldwide. Also, future studies should be conducted aimed at determining the values of IgG subcategories.

## Acknowledgment

None.

## Conflict of Interest

No conflict of interest.

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