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Three-year prevalence of measles antibody seropositivity at a tertiary care hospital in Turkey

Ayfer Bakir[1], Muhammed Furkan Kurkcu[2], Mustafa Guney[2], Fatime Yildiz[1], Mehmet Tevfik Yavuz[2]

[1]*Department of Medical Microbiology, Gulhane Training and Research Hospital, University of Health Sciences, Ankara, Turkey*
[2]*Department of Medical Microbiology, Gülhane Faculty of Medicine, University of Health Sciences, Ankara, Turkey*

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Corresponding author:
Ayfer Bakir.
E-mail: dr.ayfer.bakir@gmail.com;
ORCID: https://orcid.org/0000-0002-9006-5267

Abstract

Objective: Measles virus is an unsegmented, single-stranded and negative-polarized RNA virus belonging to *Morbillivirus* genus in *Paramyxoviridae* family in the order of *Mononegavirales*. This study aimed to evaluate measles antibody seropositivity proportions in different age groups from different geographical regions within three years.

Material and methods: This retrospective study, IgM and IgG antibodies specific to measles were detected in serum samples with enzyme immunoassay method. Measles IgG antibody seroprevalence was calculated by correlating all data with demographic variables.

Results: Median age of patients included in the study was 27 years and while 352 (44.4%) were male. Seropositivity rate of measles IgG antibody was 87.1%. Seropositivity in the age group of 0-18 was 77.7% (p=0.002). IgG seropositivity rates were 82.8%, 88.8% and 90.7% between 2017 and 2019 respectively (p=0.05). Seropositivity rate of IgM antibody in all cases was 11.1% and the highest rate was detected in the age group of 0-18 (13.5%) (p=0.09). IgM antibody seropositivity rate was determined most in the winter months (23.8%) (p<0.001). While measles IgM positivities were 10.6% and 21.1% in Turkish and foreign patients respectively IgG positivities were 86.9% and 92.3% (p=0.32, p=1.00 respectively). Measles IgG seropositivity was the highest in patients living in Aegean region (96.8%).

Conclusion: In conclusion, measles IgG seropositivity was 87.1% in this study. This rate was lower in pediatric age group. Increasing regional seroprevalence studies may help enhancement efforts on vaccination program to reach and sustain high population immunity.

Key words: enzyme immuno assay, measles, measles IgG, seropositivity, Turkey

Introduction

Measles virus is an unsegmented, single-stranded and negative-polarized RNA virus belonging to *Morbillivirus* genus in *Paramyxoviridae* family in the order of *Mononegavirales* [1]. Measles is typically a contagious but vaccine-preventable disease seen in young children [2]. The virus can be transmitted via airborne respiratory droplets or tiny aerosol particles, direct contact with infected secretions and less commonly contact with contaminated fomites [3]. Most of individuals with measles are characterized with fever, fatigue, coryza, conjunctivitis, cough and maculopapular rash [4]. Common complications such as measles virus-induced immunosuppression, diarrhea, keratoconjunctivitis, otitis media and pneumonia, acute disseminated encephalomyelitis and encephalitis can come out as serious and commonly fatal complications. Additionally, it can come out as a rare neurological complication called subacute sclerosing panencephalitis that may have a severe, progressive and fatal course after years [5,6].

Annual measles outbreaks generally occur in mild climates; in late winter and spring. Measles outbreaks in tropical regions have more changeable seasonality and irregular and large measles epidemics can occur in regions with high birth rates [7,8]. In

2012-2020 Global Vaccine Action Plan, the World Health Assembly targeted measles elimination in 2020 or earlier in at least six World Health Organization (WHO) regions including Turkey and European Region [2]. Implementation of measles vaccine resulted in a reduction by 73% in measles deaths worldwide between 2000 and 2018. Although there was a safe and cost-effective vaccine the measles caused more than 140,000 deaths worldwide mostly among the ones under the age of five in 2018 [9]. Although it is possible to regionally or globally eliminate measles with proper vaccination strategies the risk for outbreak is geographically much higher in Turkey since the ongoing war is very close to the borders of Turkey and unvaccinated refugees, especially Syrians migrate to Turkey in masses [10].

Laboratory diagnosis of measles is based on the following laboratory methods. These methods include serological methods, determination of antibodies, molecular researches and virus isolation. Serological method is the most commonly used test to verify measles infection [11-13]. Serological Immunoglobulin M (IgM) testing using either capture or indirect enzyme immunoassays has been a standard laboratory method for diagnosis of acute measles infections. However, because no assay is 100% specific, serologic testing of non-measles cases using any assay will occasionally produce false positive IgM results. Serologic tests can also result in false-negative results when serum specimens are collected too early with respect to rash onset [14].

Although there are seroprevalence studies in different regions of Turkey and different age groups the number of them is limited. This study aimed to evaluate acute measles infection proportions in different age groups from different geographical regions, determine measles IgG positivity rates and research the distribution of measles seronegative population within three years.

Material and methods

Study design

Patient samples of which measles IgM and IgG antibodies were sent to Microbiology Serology Laboratory of Ankara Gulhane Training and Research Hospital, University of Health Sciences between January 2017 and December 2019 and analyzed were included in this retrospective study. Required demographic information was obtained from information system of the hospital in order to evaluate all patients in terms of age, gender, nationality and cities they lived in. Patients' ages were grouped as 0-18, 19-40, 41-60 and 60 and above and the cities they lived in were divided according to current seven regions of Turkey.

Inclusion and exclusion criteria for study

Patients from all age groups who were Turkish citizens, who were not Turkish citizens but lived in Turkey and whose test results were sent to our laboratory with suspected measles between 2017 and 2019 were included in our study. Female, male or pediatric patients whose antibody results did not cover the planned years were excluded from the study. Duplicate or erroneous reports were also excluded.

Serological analysis

Measles IgM and IgG antibodies in serum samples were analyzed with VirClia EIA/CLIA device (Vircell S.L, Granada, Spain) by using MEASLES VIRCLIA® IgM and IgG MONOTEST (Vircell S.L, Granada, Spain) commercial kit in accordance with the recommendations of manufacturer. The test kit detects Measles IgM and IgG antibodies in serum samples with indirect chemiluminescent enzyme immunoassay (CLIA) principle. The kit qualitatively detects measles antibody level in serum or plasma.

The results of VIRCLIA® IgM and IgG MONOTEST were assessed through antibody index (sample RLU/calibrator RLU) and antibody index < 0.9 was accepted as negative, 0.9-1.1 as intermediate value and >1.1 as positive.

Statistical analysis

SPSS 25 (SPSS Inc., Chicago, IL, USA) software package program was used in statistical analysis of the data obtained from this study. Continuous variables were expressed as median and categorical variables were expressed as numbers and percentiles. Whether the variables were normally distributed was assessed with visual methods and Kolmogorov-Smirnov test. Quantitative variables were compared with Mann-Whitney U test. Pearson Chi-Square or Fisher's exact tests were used in comparison of qualitative variables. Measles seropositivity was presented with a 95% confidence interval (CI). Statistical significance level was accepted as $p<0.05$.

Ethical principles

This study was performed with the approval of the Non-Interventional Clinical Research Ethical Committee of the University of Health Sciences Ankara Gulhane Training and Research Hospital (reference number: 2020/03/90).

Results

Median age of 793 patients included in the study was 27 years (interquartile range [IQR]:21-36) and while 352 (44.4%) were male. Median age of male patients was 26 years (IQR: 20-34) and that of female patients was 28 years (IQR: 22-37).

Measles IgM antibodies were positive in 52 (11.1%) out of 470 patients (95% Cl:8.4-14.3) and measles IgG antibodies were positive in 661 (87.1%) out of 759 patients (95% Cl:84.5-89.4). Measles IgM seropositivity rates were 9.9% (20/202) and 11.9% (32/268) in male and female gender respectively ($p=0.50$). Measles IgG seropositivity rates were 86.9% (286/329) and 87.2% (375/430) in male and female gender respectively ($p = 0.87$). While median ages of measles IgM negative and positive patients were 28 and 24 those of measles IgG negative and positive patients were 24 and 28 and their p values were 0.02 and 0.14 respectively.

Measles IgG seropositivity rate was 77.7% in the age group of 0-18 ($p=0.002$). The highest measles IgG positivity rate was 95.8% (46/48) in the age group of 41-60 among male patients and 89.6% (267/298) in the age group of 19-40 among female patients ($p=0.005$, $p=0.04$ respectively).

Measles IgM positivity rate was the highest in the age groups of 0-18 (13.5%) and 19-40 (12.8%) ($p=0.10$).

IgM antibody seropositivity rates were 9.7%, 11.5% and 12.9% between 2017 and 2019 respectively while IgG antibody seropositivity rates were 82.8%, 88.8% and 90.7% ($p=0.04$, $p=0.05$ respectively).

Measles IgM seropositivity rate was the highest in December (35.7%), January (18.9%) and November (17.6%). IgM antibody seropositivity rate was determined most in the winter months (23.8%) ($p<0.001$) (Figure 1).

Of the patients included in the study, 767 (96.7%) were

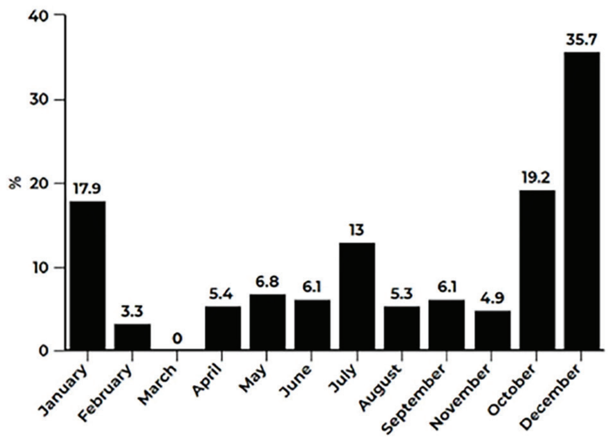

Figure 1 - Seasonal distribution of Measles IgM seropositivity

Turkish citizens and 26 (3.3%) were foreigners. While measles IgM positivity rates were 10.6% and 21.1% in Turkish and foreign patients respectively IgG positivity rates were 86.9% and 92.3% (p=0.32, p=1.00 respectively).

Out of 793 patients in this study, 80.1% were from Central Anatolia, 5.2% from Marmara, 3.9% from Aegean, 3.5% from Black Sea, 2.8% from Eastern Anatolia, 2.3% from Mediterranean and 2.3% from Southeastern Anatolia region. While measles IgG seropositivity rate was the highest in patients from Aegean region (96.8%) the lowest rate was found in Mediterranean region (70.6%) (p=0.33). Demographic characteristics of the patients were given in Table 1.

Table 1 Measles IgG antibody seroprevalence associated with demographic variables in 759 patients in Gulhane, Ankara.

Characteristic	Sample Size	Measles IgG Antibody Seroprevalence n (%)	P value
Gender			
Male	329	286 (86.9)	0.87
Female	430	375 (87.2)	
Age groups (years)			
0-18	112	87 (77.7)	0.002
19-40	500	448 (89.6)	
41-60	113	102 (90.3)	
>60	34	24 (70.6)	
Nationality			
Turkish	733	637 (86.9)	1.0
Others	26	24 (92.3)	
District type			
Black Sea	27	25 (92.6)	0.33
Central Anatolian	600	517 (86.2)	
Aegean	31	30 (96.8)	
Eastern Anatolian	26	23 (88.5)	
Mediterranean	17	12 (70.6)	
Marmara	40	38 (95)	
Southern Anatolian	18	16 (88.9)	
Year of collection			
2017	303	251 (82.8)	0.05
2018	197	175 (88.8)	
2019	259	235 (90.7)	

Discussion

While measles is the leading cause of vaccine-preventable child deaths in Africa and Asia it still causes outbreaks in industrialized countries [13]. Measles vaccine (Edmonston-B strain) was licensed in 1963 in the United States of America and began to be distributed in 1968 [15]. Global measles elimination has been a matter of debate since licensed measles vaccines [16]. Measles is still present in several countries of the world. By November 2019, there had been 413,308 confirmed cases reported to WHO by 187 member countries [17]. Democratic Congo Republic, Ethiopia, Georgia, Kazakhstan, Kyrgyzstan, Madagascar, Myanmar, Philippines, Sudan, Thailand and Ukraine are among the countries with present epidemics [18].

According to the results of our study, measles IgG seropositivity was 87.1%. Measles IgG seropositivity rates range from 45.7% to 99.7% in different geographical regions and different populations of our country [10,19-23]. Measles IgG seropositivity rates were between 94% and 99.7% among healthcare workers in Turkey, between 45.7% and 82.5% in pediatric age group and between 81.6% and 95.9% in general population [10,19-23]. In seroprevalence studies performed on general population in Central Anatolia, measles IgG seropositivity rates were reported between 81.6% and 82.5% [22,23]. Antibody prevalence in our study is consistent with those in regional studies. Seropositivity rates increasing by age were significant. Low seropositivity rate in pediatric age group in this study reveals that children have insufficient immune function. These low rates suggest that they are caused by vaccine refusal or insufficient vaccine dose. In our country, the number of parents who refuse to vaccinate their children has recently increased and while this number was 183 in 2011 it increased to 23,000 in 2018. In Turkey, vaccination rate which was 98% in 2016 regressed to 96% in 2017. However, measles elimination and vaccination strategies that have been used in Turkey since 2003 are the most determinant factors of higher IgG seropositivity rates compared to IgM seropositivity rates [24]. This anti-vaccination movement and vaccine-refusals are consistent with the data worldwide. After Adrew Wakefield, an English physician, published an article about the relationship between MMR vaccine and autism the debate on general vaccination accelerated in Europe. Although the article was removed from publication anti-vaccination movement continued. Even in a study in Ukraine, while the rate of second dose of MMR was 95% in 2008 it declined to 31% in 2016 [25]. Therefore, WHO detected the problems and published an evidence-based report on anti-vaccination and improvement of vaccination [26]. In case the number of vaccine-refusal cases reaches 50 thousands occurrence of an outbreak is highly possible. Main anti-vaccination statements in Turkey are as follows: Chemicals in the content of vaccines are hazardous on human health, profit anxiety of companies and their efficiency in scientific researches or it is also possible to avoid these diseases with natural ways by consuming some foods [24].

In this study, measles IgM positivity was 11.1%. Measles IgM positivity was higher in foreigners (21.1%) than in Turkish citizens (10.6%). After a vaccination program was initiated in 1970 and especially after the national vaccination campaign in 1985 the number of new cases considerably decreased in Turkey [27,28]. However, measles elimination program began to be implemented because the number of new cases increased again after 1987 and outbreaks were seen once in 3-4 years.19 While the incidence rate of measles was the highest (in a population of 100,000) in 2002 it was the highest (0.87) in 2018 among the years between 2014 and 2018 [29].

This increase was evaluated to be caused by migrations to different regions of our country, particularly Southeastern Anatolia Region, due to the civil war in Syria [30].

Annual measles outbreaks are typically seen in mild climates, at the end of winter and at the beginning of spring. They were determined in part by social contact patterns facilitating transmission (eg, congregation of children at school) and environmental factors favouring the viability and transmission of measles virüs [31].

In this study, a seasonal change was monitored in measles cases. Measles IgM seropositivity increased in December, November and January. However, cases with measles were also detected throughout the year.

Our study has some limitations. First of all, seropositivity rates in our study may not represent both national and regional population. Therefore, more comprehensive studies are needed. Due to retrospective nature of our study, vaccination status or infection history of the patients could not be described. Our results are based on some demographic characteristics of the patients and results of commercially sold instant ELISA test.

In conclusion, measles IgG seroprevalence in this study was 87.1%. This rate was found lower (77.7%) in pediatric age group. Although the rate of seropositivity increases with increasing age, the measles immunity rate in the whole study group is below the 95% immunity rate required to prevent outbreaks. According to data obtained from the study, the age group that should be targeted for immunization with vaccine is 0-18. Therefore, vaccination especially for this age group should be encouraged and awareness of the public should be raised about the benefits of immunization with all propaganda tools based on evidence. Moreover, national surveillance efforts should be featured in order to get more reliable information and primary targets for immunization should be mostly determined.

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