

INCREASE IN MEASLES CASES IN A CITY HOSPITAL, ISTANBUL, TURKEY

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SUMMARY

Objectives: Measles cases are increasing remarkably in our country as well as all over the world. In this study, it was aimed to examine the epidemiological and clinical characteristics of measles cases detected in our hospital, as well as the measles seroprevalence in our region.

Methods: A total of 7,452 individuals whose measles IgG and/or IgM antibodies were studied between December 2021 and March 2023 in the Medical Virology Laboratory in Başakşehir Çam and Sakura City Hospital were included in this retrospective study. Measles IgG and IgM antibodies were analysed by enzyme-linked immunosorbent assay. Demographic information, clinical symptoms and laboratory data of the participants were obtained from the hospital's electronic medical records.

Results: A total of 102 measles cases were identified between December 2021 and March 2023. Of these cases, 77 (75.5%) patients were ≤ 18 years old. Of the 73 measles cases with vaccination information, 90% were unvaccinated. The measles seroprevalence rate was 72.8%. The lowest seroprevalence rate (4.8%) among the age groups was found in 8–11-month-old babies, the highest cases rate (35.7%) was detected in this age group. It was determined that measles immunity increased with age ($r=0.276$, $p<0.001$) and was over 89.3% over the age of 30.

Conclusions: Measles immunity is insufficient in our region and measles remains an important public health problem until the age of 18. The recent increase in measles cases in our country and around the world shows that current vaccination programmes need to be implemented more decisively and strictly.

Key words: measles, vaccination, measles outbreak, seroprevalence, Istanbul

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INTRODUCTION

Measles, also known as rubeola, is an infectious disease that can be effectively prevented through vaccination. Nevertheless, it remains a significant global public health issue, contributing to both morbidity and mortality. However, there has been a recent surge in the number of reported cases. The measles virus, known for its high level of contagiousness (R_0 : 12–18), is transmitted via airborne spread from person to person (1, 2). The measles virus, a member of the genus *Morbillivirus* of the *Paramyxoviridae* family, has an enveloped, single-stranded, negative-polarized RNA genome (3). This virus has been divided into eight classes (A–H) that include 24 genotypes. Since 2018, only B3, D4, D8, H1 genotypes have been circulating globally. The vaccine strains used today (Moraten, Edmonston-Zagreb) are of genotype A (4). Because human is the only known host for the measles virus, it is a disease that can be eliminated by vaccination (1). According to the World Health Organisation (WHO), preventing the spread of measles requires the population to have at least 95% immunity. Therefore, high vaccination rates must be sustained (5).

The WHO aimed to eradicate measles in the Americas by 2000 and in Europe and the Eastern Mediterranean by 2010, with

the widespread introduction of the measles vaccination in 1980. This goal was met in the early 2000s, but measles outbreaks have re-emerged in these regions, particularly in our European neighbours, since 2017, due to a variety of factors including inadequate health education, a lack of access to medical care, inattention, and increased vaccine hesitancy (6–8). While the measles vaccination has been used in Turkey since 1970, the second vaccine dose was provided to primary school first grade students in 1998, and measles cases have been steadily decreasing since 2005, with no domestic measles cases detected in 2010. Since 2006, two doses of measles-rubella-mumps (MMR) triple vaccine have been delivered in our country as part of the national vaccination programme at 12 and 48 months (9–11). A measles epidemic occurred in our country in 2013 as a result of migration caused by the civil conflict in our border neighbour Syria, and it was brought under control. Similarly, our country was affected by the measles epidemics that began in our geographical neighbour Europe in 2017, with an increase in measles cases in 2019 (12) (Table 1).

The negative impact of the coronavirus disease 2019 (COVID-19) pandemic on vaccination programmes and the relaxation of pandemic control measures have resulted in an

Table 1. Measles – number of reported cases according to the World Health Organization*

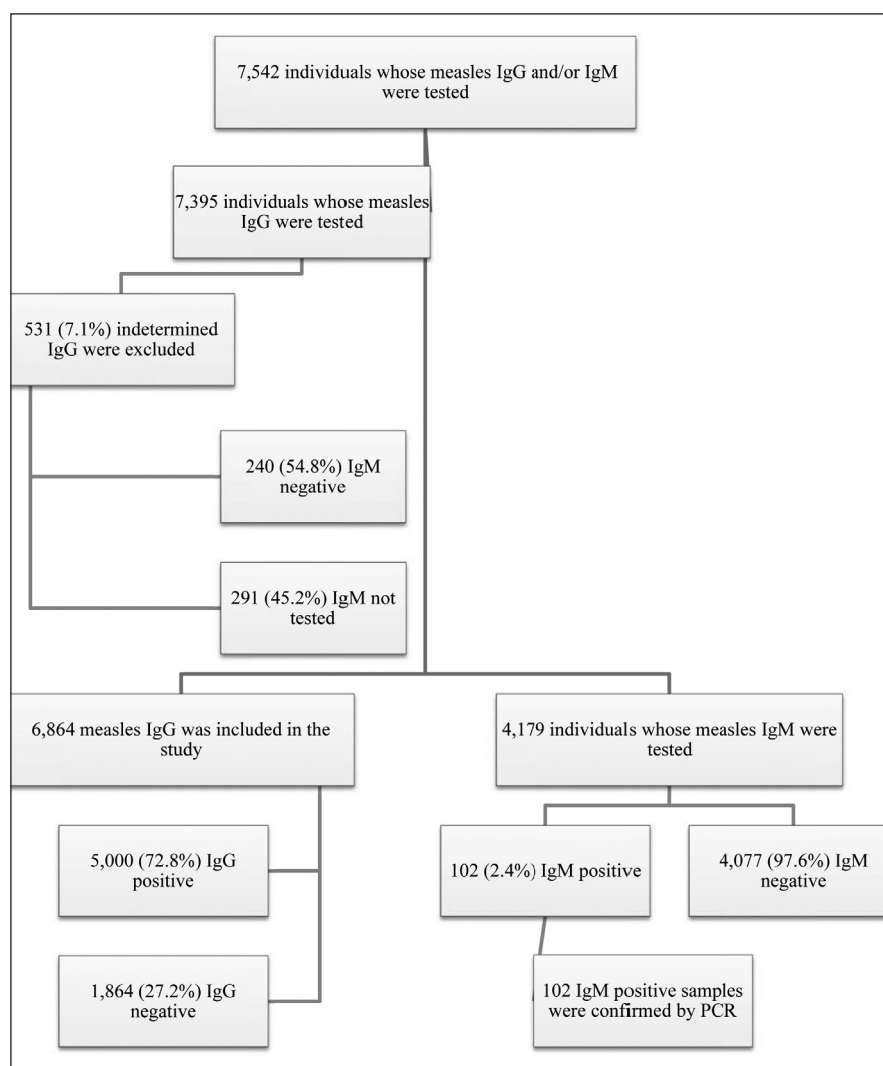
Location	2021	2020	2019	2018	2017	2016	2015	2014	2013
(WHO) Global	124,041	159,067	873,022	360,296	173,457	132,490	214,808	282,078	275,307
Africa	89,606	115,369	618,595	125,426	72,603	36,269	52,758	73,914	171,178
Americas	682	9,996	21,971	16,714	895	97	611	1,966	491
South-East Asia	6,514	9,389	29,389	34,741	28,474	27,530	48,888	42,899	24,564
Europe	89	10,945	106,130	89,148	24,356	4,440	25,957	14,176	26,346
Turkey			2,904	716	84	9	342	565	7,405
Eastern Mediterranean	26,089	6,769	18,458	64,764	36,434	6,275	21,418	18,080	20,884
Western Pacific	1,061	6,599	78,479	29,503	10,695	57,879	65,176	131,043	31,844

*Source: WHO (14); Turkey is part of the WHO Europa region.

increase in vaccine-preventable diseases such as measles (13). The increase in measles cases in Turkey after the COVID-19 pandemic is noteworthy. With a population of over 16 million, Istanbul is the most crowded city in our country with the highest population mobility and migration. In this study, we aimed to investigate the measles cases and the measles seroprevalence in the largest hospital in Istanbul.

MATERIALS AND METHODS

Cases whose measles IgG and/or IgM antibodies were studied between 17 December 2021 and 31 March 2023 in the Medical Virology Laboratory of our hospital were included in this retrospective study. Figure 1 shows the flow chart of the cases and their serological results included in the study. Our hospital is the

**Fig. 1. Flow chart of the cases and their serological results included in the study.**

largest hospital with 2,721 beds in Istanbul, a megacity with a population of over 16 million. As a tertiary healthcare institution, it mainly serves the population of the European side of Istanbul and also various provinces of Turkey. Approximately 11,000 health workers work in our hospital. When they are assigned to the hospital, serological screening tests such as measles IgG are routinely performed before they start working. This study included 7,452 people who were investigated for measles serology and 77.5% of them were healthcare workers. Demographic information, clinical symptoms and laboratory data of the participants included in the study were obtained from the hospital's electronic medical records. Persons with clinical findings consistent with measles, positive for measles IgM test and confirmed by PCR were defined as "measles case". Those with negative measles IgM and IgG tests were considered as "measles susceptible", while those with measles IgM negative and measles IgG positive were considered as "measles seropositive". This study was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital (Ref. no: 2023-256).

Measles specific IgM and IgG antibodies were studied by the Next Level Alisei (Milan, Italy) device with the enzyme-linked immunosorbent assay (ELISA) method using the NovaLisa kit (NovaTec Immundiagnostica GmbH, Germany). Internal quality controls were added to each study. Sample (mean) absorbance value \times 10/cut-off ratio and NTU (NovaTec Unit) value were obtained. The results obtained were considered negative if <9 , with 9–11 indeterminant and >11 positive. Samples with indeterminant values and positive for measles IgM were studied twice. Results that were found to be indeterminant were excluded from the study. Samples found positive for measles IgM were confirmed by measles PCR testing at the National Public Health Laboratory.

In this study, the age groups were defined according to the measles vaccination schedule in Turkey, where measles-mumps-rubella (MMR) vaccine is administered in two doses at 12 and 48 months. The ≤ 7 months group was defined to observe the effect of maternal antibodies, the 8–11 months group to observe children with reduced maternal antibodies who had not yet received the first dose of the vaccine, the 1–4 years group to observe children who had received the first dose but not the second dose, and the 5–18 years group to observe children who had received both doses of the vaccine.

Statistical Analysis

Statistical analysis was performed with SPSS version 22.0. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether or not they are normally distributed. Quantitative variables were compared using the Mann-Whitney U test, and qualitative variables were compared using the Pearson's chi-squared test. Correlation coefficients and statistical significance for the relationships between variables were calculated with Spearman's rank correlation coefficient test. Results with a p value below 0.05 were considered statistically significant.

RESULTS

This study included 7,452 individuals whose measles serology was investigated. The median age of the participants was 25 (interquartile range – IQR: 22–28), 65.1% were females, 9% were 18 years old and younger, and 2.6% were foreign nationals (Table 2). The study included 5,772 (77.5%) healthcare professionals

Table 2. Demographic, laboratory, and clinical data of the study population

	Total, n (%)	≤ 18 years, n (%)	> 18 years, n (%)	p-value
Number	7,452	668 (9)	6,784 (91)	
Age, median (interquartile range)	25 (22–28)	11.5 (4–18)	25 (23–28)	
Gender				
Male	2,543 (34.1)	274 (41)	2,269 (33.4)	
Female	4,909 (65.1)	394 (59)	4,514 (66.6)	
Nationality				
Turkish	7,261 (97.4)	590 (88.3)	6,671 (98.3)	
Foreigner	191 (2.6)	78 (11.7)	113 (1.7)	
Measles IgG Positive	5,000 (72.8)/6,864	290 (49.2)/590	4,710 (75.1)/6,274	<0.001
Measles IgM Positive	102 (2.4)/4,179	79 (17.3)/457	23 (0.6)/3,722	<0.001
Symptoms				
Fever	97 (99)	74 (99)	23 (100)	0.58
Koplik's spot	59 (60)	48 (64)	11 (48)	0.17
Maculopapular rash	94 (96)	73 (97)	21 (91)	0.20
Conjunctivitis	63 (64)	51 (68)	12 (52)	0.17
Cough	79 (81)	65 (87)	14 (61)	0.006
Pneumonia	6 (6)	5 (7)	1 (4)	0.69
Diarrhoea	20 (20)	16 (21)	4 (17)	0.68

whose median age was 25 (IQR: 23–28), and 68.3% were women. Figure 1 shows the flow chart of the cases and their serological results. The first measles case was identified in our hospital in February 2022, and by the end of March 2023, a total of 102 measles cases were detected. Although a total of four measles cases were seen in different periods in 2022, the number of cases increased by the fourth week of 2023 (Fig. 2). The median age of the measles cases was 8 (IQR: 1–17), 53% were females and 29 (28.4%) were foreign nationals. The ratio of IgM positivity in women was statistically higher than in men ($p=0.011$). Measles IgM positivity was detected in 77 (75.5%) cases, aged 18 years and younger. Figure 3 displays the positive ratio within each age group. The coexistence of measles IgM and IgG positivity was detected in 12 measles cases. Sixty-six (90.4%) of the 73 measles cases with vaccination information were unvaccinated, while

seven (9.6%) were vaccinated with two doses. Clinical data was available in 98 of the measles cases. In these cases, fever (99%) and maculopapular rash (96%) were the most frequent symptoms. Only six (6%) of the patients developed pneumonia. Cough was found to be significantly higher in children compared to adults ($p=0.006$). Clinical findings are given in Table 2.

Indeterminant results were observed in 7.1% of 7,395 samples investigated for measles IgG and these were excluded from the study. Of the remaining 6,864 samples, 72.8% were found to be IgG positive (Fig. 1). In 2,685 of these samples, IgM was not studied because seropositivity without clinical symptoms was not explored. The median age of measles IgG positive subjects was 26 (IQR: 23–30) and 65.1% were females. There was no statistically significant difference between the genders in terms of IgG positivity ($p=0.086$). Measles IgG results by age groups

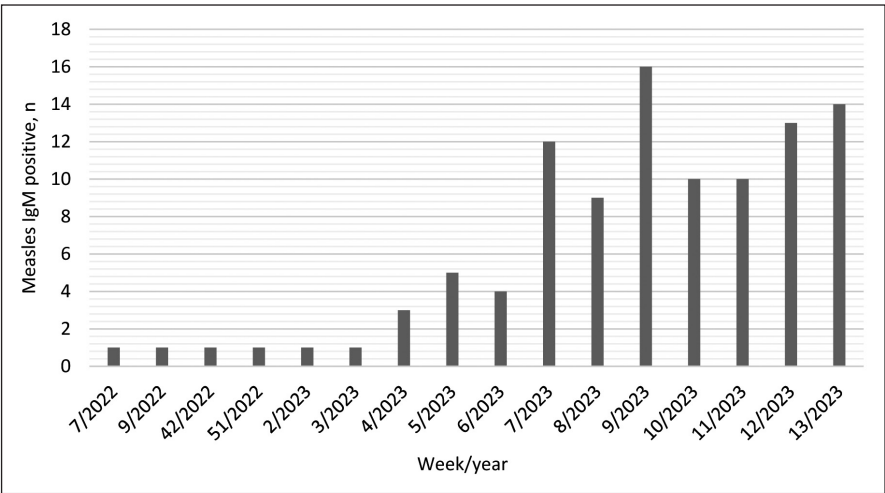


Fig. 2. Distribution of measles IgM positivity by weeks.

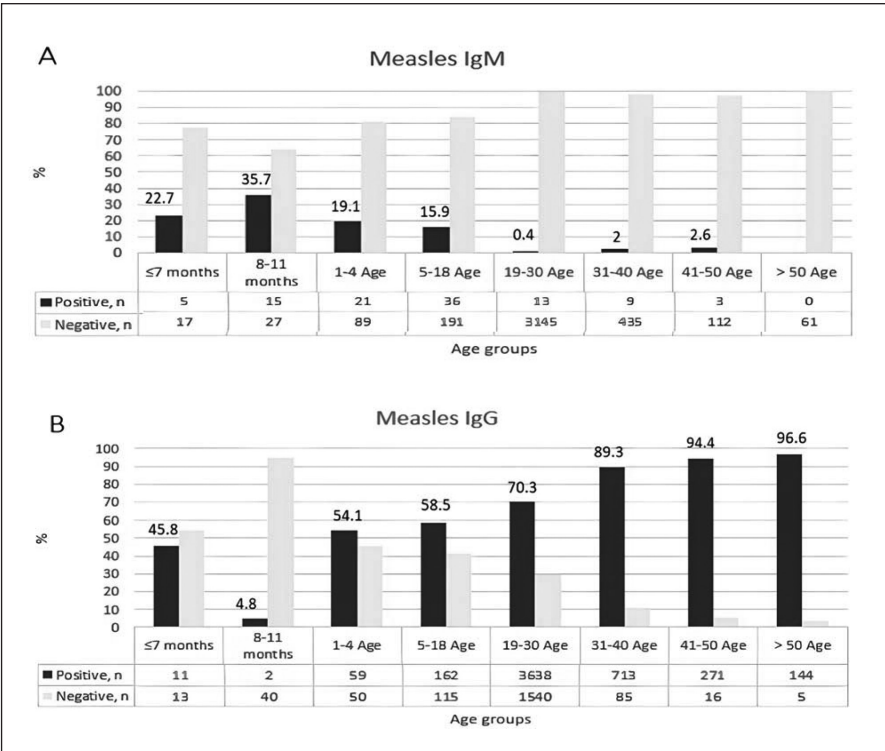


Fig. 3. Measles IgM (A) and measles IgG (B) positivity by age groups.

are shown in Figure 3. IgG positivity was detected in 45.8% of 24 infants aged seven months and younger in whom maternal antibodies could be detected. Immunity ratio was the lowest in the 8–11-month age group in which maternal antibodies disappeared. A low, highly significant positive correlation was found between seroimmunity ratios and age ($r=0.276$, $p<0.001$). Measles IgG positivity was found in 3,928 (68.1%) healthcare personnel, but IgM positivity was not observed.

DISCUSSION

The first measles case in our hospital, which was opened in May 2020, was diagnosed in February 2022. Subsequently, in the fourth week of 2023, there was a notable rise in the incidence of measles, with a total of 102 cases detected by the 13th week. According to WHO data, measles cases peaked in Turkey in 2019, similar to the rest of the world (Table 1) (14). However, data on the number of measles cases in our country since 2020 was unavailable. An increase in the number of measles cases has been reported in different countries around the world. According to the September 2022 – February 2023 CDC data, the country with the highest number of cases was India with 61,562 cases, followed by Yemen with 10,046 cases, and Ethiopia with 4,388 cases (15).

Outbreaks occurring within countries characterised by populations with high mobility have the potential to facilitate the dissemination of infectious diseases across international borders. Of the 336 measles cases reported in the USA up to 2018, 40 were imported from Europe, of which 12 resulted in local USA outbreaks (16). In our study, 29 (28.4%) of 102 measles cases, and especially the cases who were first diagnosed with measles, were foreign nationals. With the implementation of a highly effective measles elimination programme in Turkey, the incidence of measles cases remained consistently low, with no more than 15 reported cases between the years 2007 and 2010. However, since 2011, serious increases in the number of cases started and epidemics occurred (9). The rapid influx of refugees from Syria to Turkey suggests that it contributed greatly to the increase in cases (9, 14). It was determined that 76.6% of 2,827 Syrian children under temporary protection in Turkey had no MMR vaccine (17). Global instability, migration, and the rise of people who are reluctant or unwilling to receive vaccinations are all factors that are contributing to an increase in measles incidence. The number of Turkish families who refused to vaccinate their children was assessed to be 18 in 2011, 980 in 2013, 5,400 in 2015, 12,000 in 2016, and 23,000 in 2018 (18). Measles incidence increased tenfold from 0.01 per 100,000 people in 2016 to 0.10 per 100,000 population in 2019 (18). In addition to vaccine rejection, immunocompromised persons who are unable to produce a protective antibody response, as well as those younger than the immunisation age also contribute to the increase in measles incidence (18, 19).

In our study, 75.5% of those diagnosed with measles were under the age of 18. In a similar research conducted in Korea, 75% of measles cases were reported to be infants and children (13). In a study carried out in Spain, however, measles cases were predominantly discovered (68.9%) in those aged 20 and above (20). The cause for these disparities could be related to countries' immunisation rates and mobile demographics.

The seroprevalence rate for measles was determined to be 72.8% in this study involving 6,864 individuals from Istanbul's largest hospital. The majority of the study participants (77.5%) were healthcare workers, and the seroprevalence of measles among them was even lower (68.1%). Similar to this research, a study conducted in Istanbul in 2022 found a seroprevalence of 70% for measles among 8,654 participants (21). This study also supports that the low measles immunity found in our study was already low in Istanbul in recent years. In a study conducted in a province in the Aegean Region in Turkey in 2014, the measles seroprevalence rate was found to be 82.2% in 1,250 participants over the age of 2 (12). In investigations conducted in Korea in 2017 and 2019, the rate of measles immunity was determined to be 71.5% and 74.9%, respectively (22, 23). In a study conducted in Italy in 2020, this rate was 77.2% (24). According to the WHO, preventing the spread of measles requires the population to have at least 95% immunity (5). It is seen that the measles seroprevalence in our region is far behind the community immunity with a rate of 72.8%. These studies show that measles immunity is insufficient in various countries and even reaches levels that can lead to epidemics.

Studies examining measles seroprevalence by age groups have been conducted in various countries. In a study of 239 travelling people from the Netherlands, the overall measles seroprevalence was 82%, with the lowest seroprevalence reported in children aged 12–18 (72%). In contrast, seroprevalence was 100% in travellers born before 1965 (25). In a study of 1,690 people in India, the overall seroprevalence rate was reported as 94%, with the lowest seroprevalence in the 6–10 age group (86%) (26). In a study of 4,598 people in Mongolia, general seroprevalence was reported 94%, with the lowest seroprevalence (47%) in the 6–11-months age group (27). In a study conducted with 1,250 participants over the age of 2 in Turkey, the lowest seroprevalence was found in the 10–19 age group with 48.7% (12). In this study, the lowest measles IgG seroprevalence rate (4.8%) was seen in 8–11-month-old babies among the age groups, and the highest case rate (35.7%) was in this age group. It is known that maternal antibodies help protect the baby from measles up to a certain level for the first 6 months (28). The reason for the highest case rate in this age group can be explained by the fact that this group is below the vaccination age and that protective maternal antibodies are usually no longer available. The second age group with the highest incidence was ≤ 7 months old babies. Measles IgG positivity rate was 45.8% in infants ≤ 7 months of age who were expected to have protective maternal antibodies. This suggests that despite the potential of maternal antibodies to protect infants from infection, these infants are largely born to seronegative mothers. The rate of measles was found to be 19.1% in the group aged 1–4 years, who did not receive second dose vaccines according to the vaccination schedule of our country, and whose measles seroprevalence rate was relatively low (54.1%). The high number of cases in this age group can be attributed to inadequate vaccination or not being vaccinated. In this study, it was observed that humoral immunity increased with age and was above 89.3% especially over the age of 30. However, no measles cases over 50 years of age have been observed. In a similar study conducted in Istanbul, it was found that immunity increased with age and the measles seroprevalence rate was approximately 90% in those aged 29 and above (21).

The most common prodromal symptom in measles cases is fever. Nsubuga et al. (29), in their study of 30 measles cases reported fever, rash and conjunctivitis in all cases, and cough and cold in 90% of the cases. So et al. (13) reported rash in 90% of 20 measles cases, fever in 80%, cough and runny nose in 50%, and conjunctivitis in only 5%. In our study, the most common symptoms were fever (99%), maculopapular rash (96%) and cough (81%). Cough was found to be significantly higher in children compared to adults ($p=0.006$). Conjunctivitis was seen in 64% of the cases, diarrhoea in 20% and pneumonia in 6% of the cases. Therefore, in the diagnosis of measles, conjunctivitis and diarrhoea should not be ignored, as well as the most common prodromal symptoms.

Measles vaccine was first introduced in Turkey in 1970, but a consistent and routine vaccination programme was not established until 1985. After this year, widespread administration of measles vaccine contributed to a significant decrease in the viral load circulating in the community and increased community immunity. As a result, the incidence of measles infection decreased at an early age (10). In our study, 73 measles cases had vaccination information. Only 9.6% of these cases had a history of vaccination. This vaccination rate was consistent with other studies. In an Italian study, 5.5% of 604 measles cases were vaccinated with one or two doses (30). In the study of López-Perea et al. (20) carried out in Spain, 9.4% of 863 cases with vaccination information were single-dose vaccine cases and 14% were vaccinated with two doses. In another study, it was reported that 2–10% of vaccinated individuals did not develop protective antibody titres (31). Despite the availability of a highly effective and safe vaccine for preventing measles infection, there remains a possibility of infection even among individuals who have been vaccinated.

Limitations of the Study

The fact that the majority of the sample population consists of healthcare professionals may have affected the age distribution. Vaccination information was available only for some cases of measles. It was not possible to obtain vaccination information from the mothers of seronegative infants. The seropositivity rate was determined without distinguishing between vaccination and previous infection. Additionally, cellular immunity had to be ignored because it could not be measured.

CONCLUSIONS

In this study, it was determined that herd immunity was insufficient for measles, with a seroprevalence rate of 72.8% in our region. The fact that 75.5% of measles cases were clustered under the age of 18 shows that measles is still an important public health problem in this age group. The vaccination status of refugees who have entered our country in large numbers in recent years should be questioned and unvaccinated people should be identified and vaccinated to prevent measles outbreaks. The fact that measles cases continue to increase in our country and in the world shows that existing vaccination programmes should be implemented more decisively and strictly not only on a national basis but also worldwide.

Conflicts of Interests

None declared

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