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Original

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Seroprevalence of measles, mumps, rubella, and varicella zoster virus antibodies among healthcare students: analysis of vaccine efficacy and cost-effectiveness

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ABSTRACT

Introduction. The aims of this study are to determine the seroprevalence for measles, mumps, rubella, and varicella zoster virus (VZV) in a cohort of nursing students, to evaluate vaccination response rates of nonimmune students, and to calculate the cost of vaccinating students based on seroprevalence screening.

Material and methods. A cross-sectional study was conducted August 2015–November 2016 among 326 healthy nursing students aged 14.1–18.1 years. Serum IgG antibodies were measured by ELISA. Results were analyzed by the Chi-square test; a p-value of < 0.05 was considered statistically significant.

Results. The number of seropositive participants (%) was 308 (94.5%) for rubella, 295 (90.5%) for VZV, 244 (74.9%) for measles, and 219 (67.2%) for mumps. A significant correlation was found between measles IgG and age. A relationship was also observed between VZV IgG and kindergarten attendance. Response rates to measles, rubella, VZV, and mumps vaccination were 96%, 92.3%, 87.5%, 78.8%, respectively. The total cost of vaccination after IgG screening was less than vaccination without screening.

Conclusions. In this study, participants' immunity to measles and VZV was low. Prevaccination serological screening was cost-effectiveness method for preventing measles, mumps, rubella, and varicella infections. We believe that administering booster measles, mumps, and rubella (MMR) vaccine doses or developing a special MMR vaccination strategy for at-risk groups may prevent MMR outbreaks.

Key words: Measles, mumps, rubella, varicella, seroprevalence, vaccine, cost-effectiveness

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Seroprevalencia de anticuerpos contra el sarampión, las paperas, la rubéola y el virus de la varicela zoster entre estudiantes de enfermería: Análisis de coste-efectividad de la vacuna

RESUMEN

Objetivos. Los trabajadores sanitarios con frecuencia están expuestos a agentes infecciosos mientras realizan sus tareas. Los objetivos de este estudio son determinar la seroprevalencia del virus de sarampión, paperas, rubeola y varicela zoster (VZV) en un grupo de estudiantes de enfermería, evaluar las tasas de respuesta de vacunación de estudiantes no inmunes y calcular el coste de vacunación de los estudiantes basándose en la detección de seroprevalencia.

Material y métodos. Se realizó un estudio transversal de agosto de 2015 a noviembre de 2015 entre 326 estudiantes de enfermería sanos de 14,1 a 18,1 años. Los anticuerpos IgG séricos se midieron por ELISA. Los resultados fueron analizados mediante la prueba de Chi-cuadrado.

Resultados. El número de participantes seropositivos (%) fue de 308 (94,5%) para la rubeola, 295 (90,5%) para el VZV, 244 (74,9%) para el sarampión y 219 (67,2%) para las paperas. Se encontró una correlación significativa entre la IgG del sarampión y la edad. También se observó una relación entre VZV IgG y asistencia a guardería. Las tasas de respuesta a la vacunación contra el sarampión, la rubeola, el VZV y las paperas fueron del 96%, 92,3%, 87,5%, 78,8%, respectivamente. El coste total de la vacunación después de la detección de IgG fue menor que la vacunación sin la detección.

Conclusiones. En este estudio, la inmunidad de los participantes al sarampión y al VZV fue baja. La detección serológica previa a la vacunación fue un método de coste-efectividad para prevenir las infecciones por sarampión, paperas, rubeola y varicela. Creemos que la administración de una dosis de la

vacuna triple vírica de refuerzo o el desarrollo de una estrategia especial de vacunación dosis de la vacuna triple vírica para grupos en riesgo puede prevenir los brotes de de sarampión, paperas y rubeola.

Palabras clave: Sarampión, paperas, rubeola, varicela zoster , vacuna, coste-efectividad

INTRODUCTION

Measles and varicella zoster virus (VZV) are transmitted from person to person through an airborne route, while mumps and rubella are transmitted through respiratory droplets [1]. Measles and VZV can cause outbreaks [2–4]. Because health care workers (HCW) can be infected during outbreaks and because infections among HCW can also lead to outbreaks, the immune status of HCW is vital from the perspective of community health. In addition to an HCW-associated VZV outbreak in 2004 in Thailand, HCW-associated measles outbreaks have occurred in 2008 in the United States and in 2015 in Mongolia [2–4]. The Centers for Disease Control and Prevention (CDC) recommends measles, mumps, and rubella (MMR) and VZV vaccinations for all HCW [5]. In order to control these infections, regular seroprevalence screening and vaccination programs must be implemented.

In Turkey, measles vaccination (live attenuated vaccine; 0.5 ml) was given between 1998 and 2006 to children at nine months and seven years of age. MMR vaccination (live attenuated vaccine; 0.5 ml) has been given since 2006 to children at one and seven years of age. VZV vaccine has been included in the childhood vaccine schedule since 2013 as one dose given at the age of twelve months. Updating the vaccination schedule in 2006 might have increased MMR immunity; however, published studies that examine the long-term impact of this update are few.

Measles, mumps, rubella, and VZV (chicken pox) are vaccine-preventable viral diseases. Prevaccination screening and mass vaccination are the most commonly used vaccination methods. In the past, studies have demonstrated that prevaccination screening can be cost-effective [6, 7]. However, prices of both vaccines and the ELISA kits used in screening have changed in recent years. For this reason, a cost-effectiveness analysis using current pricing is needed.

The aims of this study were to determine the seroprevalence for measles, mumps, rubella, and VZV (MMRV) in a cohort of nursing students, to evaluate vaccination response rates of nonimmune students, to calculate the cost of vaccinating students based on seroprevalence screening, and to gain a better understanding about relationships between factors that can affect seroprevalence.

MATERIAL AND METHODS

Izmir is the largest city in western Turkey. A total of approximately 400 students are studying at the nursing high school in Izmir, Turkey. As part of their studies, students work with healthcare personnel. A cross-sectional study was conducted August 2015–November 2015 among 326 healthy nursing students aged 14.1–18.1 years.

Informed written consent was obtained from a parent or guardian of each participant. Age; gender; epidemiological data; history of measles, mumps, rubella, and chickenpox; the status of participants' vaccination; and adverse events from vaccine administration were recorded retrospectively. Costs for vaccines and ELISA kits were calculated. Blood samples of approximately 10 ml were obtained from each participant. Serum was separated and kept refrigerated at 4ºC until testing. Serum samples were assayed for measles-specific IgG (Alegria® Test Strips, Orgentec Diagnostika, Germany), mumps-specific IgG (Alegria® Test Strips, Orgentec Diagnostika, Germany), rubella-specific IgG (Alegria® Test Strips, Orgentec Diagnostika, Germany) and VZV-specific IgG (Alegria® Test Strips, Orgentec Diagnostika, Germany) by ELISA at the microbiology laboratory. Serological tests results were interpreted according to the manufacturer's instructions. Equivocal values of antibody levels were considered as seronegative. Participants with a seronegative status were informed and vaccination was offered. Two doses of MMR vaccination was administered in one-month apart. Priorix brand (0.5 ml, subcutaneous) vaccine was used for MMR vaccination and Varivax brand (0.5 ml, subcutaneous) vaccine was used for VZV vaccination. Two doses of VZV vaccination was administered in one-month apart. The preferred injection site for participants is the posterior triceps aspect of the upper arm. Participants' antibody levels were measured from serum collected two months after the second vaccination. The cost of two doses of VZV vaccine is $72, and two doses of MMR vaccine costs $16. The costs of ELISA kits were as follows: VZV IgG, $4; rubella IgG, $3; measles IgG, $2; mumps IgG, $2. Costs are current as of November 2015 prices for vaccines and ELISA kits purchased in Turkey.

Participants were excluded from the study based on the following criteria: absence of vaccination card, having immunodeficiency or acute febrile illness, having a history of vaccine allergy, or a history of receiving a blood transfusion. In addition we excluded smokers because the number of cases was insufficient for a statistical study.

The study was approved by the Ethics Committee of the İzmir Tepecik Training and Research Hospital. The study was conducted according to the principles of the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, amended in October 2013).

Data management and statistical analysis were performed by using SPSS (Statistical Product and Service Solutions) for Windows (version 22.0) (IBM, Armonk, NY, USA). Statistical correlations for the effects of sex, age, kindergarten history, and vaccination on seroprevalence was calculated by the Chi-square test. The percentage of participants with positive results for MMRV was calculated with a 95% confidence interval (CI) and p-values < 0.05 were considered statistically significant.

RESULTS

A total of 326 students were enrolled as study participants, of which 245 (75.1%) were female. Mean age of all participants was 16.46 ± 0.03 years and ranged from 15 to 18 years.

Based on recollection by study participants or their family members, 119 (36.5%) had measles, 66 (20.2%) had mumps, 37 (11.3%) had rubella, and 208 (63.8%) had VZV during childhood. None of the participants had been vaccinated for VZV. All participants aged 16.1–18.1 years received measles vaccine at the age of nine months and seven years and no MMR vaccine. Of the participants aged 14.1–16.1, 181 (55.5%) received one dose of measles vaccine at the age of ninth months and one dose MMR vaccine at seven years.

The number of seropositive participants (%) was 295 (90.5%) (95% CI 87.3–93.7) for VZV, 244 (74.9%) (95% CI 70.2–79.6) for measles, 308 (94.5%) (95% CI 92.0–97.0) for rubella, and 219 (67.2%) (95% CI 62.1–72.3) for mumps. Correlation of age and gender groups to seroprevalence was found to be significant only between measles IgG and age (p<0.001) (table 1).

Fifty-three (16.2%) of the study participants attended kindergarten. The serological profile of those who did and did not attend kindergarten was compared. Only VZV IgG and kindergarten attendance were found to be related (p=0.039) (table 1).

Measles, mumps, and rubella vaccination was recommended to 172 (52.7%) of the participants and VZV vaccination to 31 (9.5%). The serology results of the 172 participants who were recommended for MMR vaccination were distributed as follows: 76 (23.3%) participants were negative for only mumps IgG, 53 (16.2%) participants were negative for only measles IgG, 8 (2.4%) participants were negative for only rubella IgG, 6 (1.8%) participants were negative for both rubella and mumps IgG, 25 (7.6%) participants were negative for both measles and mumps IgG, and 4 (1.2%) participants were negative for both rubella and measles IgG. No participants were negative for rubella, measles, and mumps IgG.

The vaccination rejection to the MMR vaccine (40.1%) vaccine was higher than to the VZV vaccine (22.5%). Two months after the second vaccine administration, seroconversions were detected in 12 (96.3%) (95% CI 86.0–100) participants for rubella , 48 (96%) (95% CI 90.6–100) participants for measles, 12 (87.5%) (95% CI 74.3–100) participants for VZV, and 56 (78.8%) (95% CI 69.3–88.3) participants for mumps (figure 1). Vaccine side effects were examined three days after the MMR vaccine administration and 2 (1.7%) participants had swelling and pain at the injection site. One participant (0.8%) had subfebrile fever eight hours after the vaccination. No side effects were observed in participants who received the VZV vaccine.

The cost of two doses of MMR vaccine plus two doses of VZV vaccine without the serological screening for MMRV at the time of this study was $28,688 (table 2). After the serological screening, the cost of vaccination for only those participants who were seronegative was $8,570 (table 2).

DISCUSSION

Measles is endemic throughout the world [7]. Although measles has been eradicated in some developed countries, it can still cause serious health problems in developing countries. Measles seroprevalence rates were 54.0% in United Arab Emirates, 72.7% in Luxembourg, 87.8% in Germany, 90% in France,

Table 1 **Age, gender, and kindergarten history distribution of measles, mumps, rubella, varicella IgG seroprevalence**

	Measles IgG n (%) (%95 CI)	VZV IgG n (%) (%95 CI)	Rubella IgG n (%) (%95 CI)	Mumps IgG n (%) (%95 CI)	Total
Female	177 (72.3) (66.7–77.9)	220 (89.8) (86.0–93.6)	231 (94.3) (91.4–97.2)	166 (67.8) (61.9–73.7)	245
Male	67 (82.8) (74.6–91.0)	75 (92.6) (86.9–98.3)	77 (95.1) (90.4–99.8)	53 (65.5) (55.1–75.9)	81
14.1 < age < 16.1	150 (82.8) (77.3–88.3)	165 (91.2) (87.0–95.3)	169 (93.4) (89.8–97.0)	118 (65.2) (58.3–72.1)	181
16.1 < age < 18.1	94 (64.9) (57.1–72.7)	130 (89.7) (84.8–94.6)	139 (95.9) (92.7–99.1)	101 (69.7) (62.2–77.2)	145
Attended kindergarten	45 (84.9) (75.3–94.5)	52 (98.1) (94.4–100)	49 (92.4) (85.3–99.5)	38 (71.6) (59.5–83.7)	53
Did not attend kindergarten	197 (72.2) (66.9–77.5)	243 (89.0) (85.3–92.7)	259 (94.8) (92.2–97.4)	181 (66.3) (60.7–71.9)	273

CI: confidence interval

Table 2 Cost of vaccination with or without screening

	Cost for vaccination after screening method of susceptible students	Cost for vaccination without screening method	Cost difference
MMR	326 x 7[a] + 16[b] x 172[c] = 5,034 $	326 x 16[b] = 5,216 $	182 $
Varicella	326 x 4[d] + 31[e] x 72[f] = 3,536 $	326 x 72[f] = 23,472 $	19,936 $

[a]Price of MMR ELISA kit for one serum sample: 7$ (rubella IgG= 3$, measles IgG= 2$, mumps IgG= 2$)

[b]Price of two dose MMR vaccine: 16$)

[c]Amount of total planned MMR vaccine [(only mumps IgG negative) 76 + (only measles IgG negative) 53 + (only rubella IgG negative) 8 + (both rubella and mumps IgG negative) 6 + (both measles and mumps negative) 25 + (both rubella and measles negative) 4 = 172 case]

[d]Price of VZV IgG ELISA kit for one serum sample: 4$

[e]Amount of total planned VZV vaccine

[f]Price of two dose VZV vaccine: 72$

91% in India, 91.7% in Czech Republic, 95.5% in Japan, 95.6% in Israel, and 98.6% in Turkey [7–15]. The seroprevalence of measles in our study is consistent with other studies; however, some differences between the results of these studies stand out. We believe that regional differences such as living conditions and rates of vaccination may cause this variation.

One dose of MMR vaccine provided 93% immunity against measles and two doses of MMR vaccine provided 97% immunity [16]. The low measles immunity observed in this study may be due to a decrease in measles IgG levels with age or to not receiving two doses of MMR vaccine. In our study, a significant difference was found between the seroprevalence for measles IgG in the younger group, who had one dose of measles vaccine and one dose of MMR vaccine, and the older group, who had two doses of measles vaccination ($p < 0.05$). One interpretation of these data is that the MMR vaccine containing three viruses is more effective in eliciting immunity than vaccination with the measles virus alone. Serological screening of HCW who were vaccinated with two doses of measles during childhood and then administering MMR vaccine only to those who are seronegative can prevent the infection of those individuals in the future and lower the risk of measles outbreaks.

Congenital rubella syndrome can be prevented by rubella IgG screening in women during their reproductive years and by immunizing those who are seronegative. One dose of MMR vaccination provides 97% rubella immunity [17]. According to our study, 95.9% of rubella immunity was observed in participants with no prior MMR vaccination while 93.4% immunity was observed in participants who had received one dose of vaccine. No significant difference was observed between the participants who had received one dose of MMR vaccine and those who did not ($p > 0.05$). These results may be explained by a faster reduction of antibody levels after MMR vaccination than after rubella virus infection [18]. Rubella seroprevalence was found to be 76% in Finland, 82.5% in Kuwait, 88% in India, 90.4% in Luxembourg, 96.1% in France, and 97.2% in Turkey [9, 12, 15, 19–21]. The seroprevalence of rubella in our study is consistent with other studies. Based on these results, it can be interpreted that MMR vaccination should be administered at one and seven years of age and that one dose MMR vaccine at only seven years of age does not sufficiently contribute to immunity because it does not adequately stimulate immunity.

One dose of MMR vaccine provided 78% immunity against mumps and two doses of MMR vaccine provided 88% immunity [22]. According to our study, no significant difference was observed in mumps immunity between the participants who received one dose of MMR vaccine and those who did not ($p > 0.05$). Mumps seroprevalence rates were 56.4% in Luxembourg, 57.4% in Japan, 61.8% in Austria, 72.6% in Czech Republic, 82% in Thailand, 88.3% in Spain, 89% in Italy, and 92.2% in Turkey [7 ,9, 14, 23–27]. Regional differences in seroprevalence may be attributable to differences in childhood vaccination schedules in each country. Mumps immunity was found to be low in our study, which is consistent with other studies [9, 14, 23, 24]. Low mumps immunity may lead to outbreaks among HCW in the future. We believe that administering booster MMR vaccine doses or developing a special MMR vaccination strategy for at-risk groups may prevent mumps outbreaks.

In public places, infections transmitted by respiratory droplets can spread rapidly from person to person. Celik et al. did not observe a significant relationship between MMR seroprevalence and kindergarten attendance [28]. In our study, measles seroprevalence was higher in those who went to kindergarten; however, the relationship was not statistically significant ($p = 0.052$). Significant differences in VZV seroprevalence were found between participants who attended kindergarten and those who did not ($p = 0.039$). This result may be explained by the fact that VZV is highly contagious and is transmitted by an airborne route. In other studies, VZV seroprevalence was higher than that observed in our study: Koivisto, et al. [19], González-Escalada et al. [26], and Kimura et al. [29] observed seroprevalences of 93%, 92.8%, and 92–98%, respectively. The lower seroprevalence observed in our study may be explained by the fact that none of the participants in our study had received prior VZV vaccination.

Measles, mumps, rubella, and VZV are usually reported in childhood and the incidence of MMRV was observed to be similar between genders [26,28,30]. Although there was no statistical difference, seroprevalence of measles was lower in

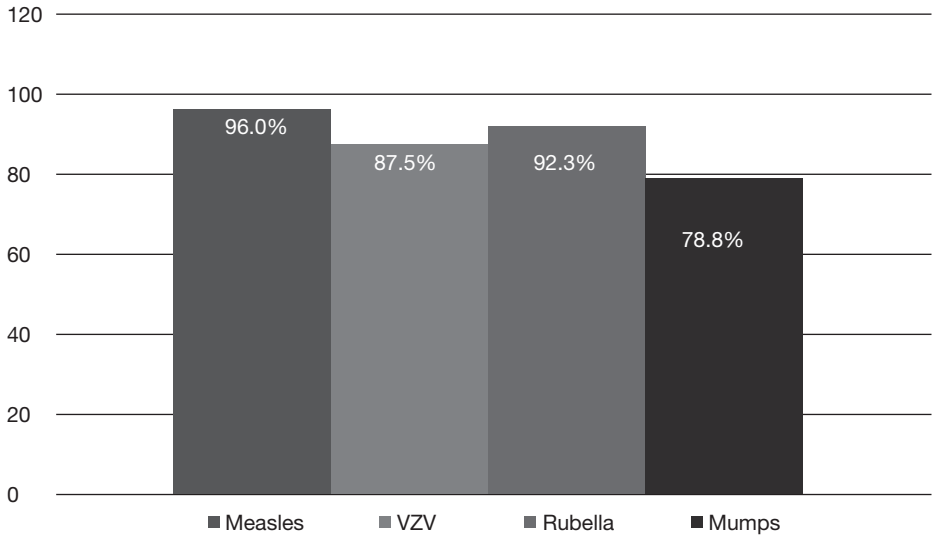

Figure 1 | **Participants vaccine response rates after two months of completion of two dose vaccination**

female gender. A similar result was obtained for measles in a study conducted in our country by Aypak et al [21]. As a personal opinion, we estimate that this situation may be caused by behavioral factors such as boys' engaging in social activities more in Turkish society.

In previous studies, measles, mumps, rubella, and VZV vaccine response rates were 88.5–98.9%, 64.4–71.8%, 70–95.2%, 72.2–79.2%, respectively [14, 31]. The rate of MMR vaccine response observed in this study was similar to that observed in other studies; however, our VZV vaccine response rate was slightly higher. This result can be explained by the absence of prior VZV vaccination in our study population. Although free vaccination was provided to MMRV seronegative participants, the vaccination rate remained below the targeted level. The low vaccination rate; it represents the damage caused by false beliefs in media reports that attempt to link certain vaccines to diseases such as autism. We estimate that the refusal of vaccination by healthcare personnel who are in constant contact with infected patients may cause a hospital-acquired outbreak in the future. This situation poses a significant risk for both their health and public health.

It is estimated that a hospitalized patient with an uncomplicated MMR infection will incur costs of $300–400 and a patient with an uncomplicated VZV infection will incur costs of $500–600 to the social health insurance system in Turkey. The cost increases since ELISA kits are used in the method which is according to the results of serological screening. However, vaccination without serological screening uses a large number of vaccines. Our study found that vaccinating only those participants who were found to be seronegative during screening saved $20,118 compared to the cost of vaccination without screening. In other studies, costs for vaccine and ELISA kits were low, but age and seroprevalence were high [6, 7]. A prevaccination screening was also found to be more cost-effective than mass vaccination for preventing VZV infection [6, 7]. Both Celikbas et al. [7] and we have demonstrated that screening before MMR vaccination costs less than mass vaccination. However, Alp et al. [6] determined that screening before MMR vaccination was not cost-effective compared to mass vaccination. The major reason for the difference is that in our study we have identified seronegative cases for two viruses. We found that it was sufficient to vaccinate these participants with two doses of MMR vaccine. In the study of Alp et al. [6], they calculated total four doses of MMR vaccine for these cases. Thus, we found prevaccination screening to be more cost-effective than mass vaccination despite low seroprevalence and high costs for both ELISA kits and vaccines.

We believe our study contributes to the literature because we evaluated differences in measles vaccination, measured seroprevalence approximately eight to nine years after receiving one dose of MMR vaccine, determined MMRV seroprevalence, and analyzed the cost-effectiveness of MMRV immunization strategies. One limitation of our study is the narrow age range of our study population. Other limitations of our study; the inability to calculate expenses related to consumables, preparation of serums, medical interpretation, health care and loss of labour due to vaccine side effects. Finally, the study was conducted in Izmir, Turkey and its population may not be representative of other parts of the country.

In conclusion, we believe that HCW are particularly at risk for mumps and measles, that one dose of MMR vaccination at seven years of age is insufficient to provide MMR immunity, and that kindergarten attendance can contribute to VZV seroprevalence.

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None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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