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Seroepidemiology of Rubella in Primary School Students in Tehran, Iran

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This descriptive analytical prospective cross sectional study was performed with the aim to determine the prevalence of serological evidence of immunity to rubella in primary school students in the 19 educational sectors in Tehran and the prevalence of immunity in children with either documented or parentally reported immunization. Mean age was 9.17 ± 1.53 years and multistage sampling was performed. Standardized interviews obtained information on each child's reported (by parents) immunization status and documentary evidence of immunization was recorded from the Personal Health Record. Rubella Virus antibodies were measured by the quantitative chemiluminescent method. Sufficient blood for antibody testing was obtained from 1665 children, 975 (57%) were girls and 720 (43%) were boys, respectively. On the whole, 541 subjects (32.5%) had been vaccinated and 1124 (67.5%) had not been vaccinated at all. Among those vaccinated, 205 (38%) were seropositive and 336 (62%) were seronegative, respectively. Among those unvaccinated, 328 (29%) were seropositive and 796 (71%) were seronegative. Rubella immunization rates in Tehran are relatively low and most of these immunizations are provided by the private sector. Results indicated that the immunity produced by the rubella vaccine is not long-term. Thus rubella vaccination of infants does not decrease congenital rubella and it seems that the most certain time at which vaccination should be done to prevent congenital rubella syndrome, is premarital age in females.

Key words: Rubella, children, immunity, vaccination, antibody

INTRODUCTION

Rubella, caused by rubella virus, is a common contagious disease worldwide. Rubella virus normally causes a mild, self-limited disease characterized by rash, fever and lymphadenopathy. Rubella is often asymptomatic (Yvonne, 2004; James, 2004). It is more common among primary school children with 50% of cases occurring in the 5-14 year old age group (James, 2004; Gershon, 2004; Karakoc *et al.*, 2003; Modarress, 2000). It may go unnoticed to both the patient as well as to those close to them, thus leaving pregnant women at great risk of acquiring the infection. (Yvonne, 2004; James, 2004) public health importance of rubella is related to the effects on the fetus of primary rubella infection in pregnant women. During the first trimester of pregnancy, rubella infection can cause complications such as congenital rubella syndrome (CRS). Congenital rubella syndrome (CRS) can lead to deafness, heart disease, cataracts and a variety of other permanent manifestations (Gershon, 2000). Around half of rubella-infected pregnant women remain asymptomatic (Yvonne, 2004) and about 60% of newborns born to these mothers develop congenital deafness, 25% of which are progressive deafness (Yvonne, 2004; Gershon, 2000). The burden of disease from CRS is well documented in several developing countries, while data from many other countries suggest that they have a risk of CRS at least as high as that in industrialized countries during the prevaccination period (Cutts *et al.*, 1997).

Eradication of rubella can prevent 20% of all cases of perceptive deafness (Plotkin *et al.*, 1999). According to a WHO report, in developing countries the average annual incidence of CRS is 236,000 (Anonymous, 1991). In the year 2000, 77.4 cases of CRS were reported per 100,000 live births in the eastern Mediterranean region; most (175 cases) of which occurred in the US (Anonymous, 2000). With the aim to prevent CRS by controlling postnatal rubella, vaccination programs have been developed in many parts of the industrialized world. In those countries large rubella epidemics have stopped and the incidence of CRS declined (Plotkin *et al.*, 1999).

Different studies performed in Iran indicate the declining incidence of immunity to rubella such that it was 97% in women of fertile age in 1968 and fell to around 80% in 1986. In 1997, immunity rate was 78% in high school girls in Tehran (Eftekhar *et al.*, 2002). Choosing a suitable method of immunization needs compilation of basic information about the disease as well as about the complications of CRS through community epidemiologic studies. Since similar studies have not been performed in this age group as yet, we decided to determine the anti

rubella antibody titer among primary school children in Tehran in order to determine the incidence of rubella infection and to identify the optimum age of vaccination for prevention of CRS.

To estimate the prevalence of serological evidence of immunity to rubella in primary school students in Tehran, we conducted a cross-sectional sero-survey from September 2003 to September 2004.

MATERIALS AND METHODS

The survey was performed on 6-12 years old primary school students from 19 educational sectors of Tehran. The sample size was determined considering an expected prevalence of rubella virus antibodies of 70% with a worst acceptable error of 5% and a confidence interval of 95%. Multistage sampling was used. Overall, 1779 students were enrolled voluntarily and Informed consent was obtained from parents or legal guardians of students after informing them about the study.

Samples of 2 mL venous blood were taken from each subject and the serum was separated and frozen at -20°C. Rubella Virus specific antibody titer (IgG) was estimated using LIAISON Rubella IgG (310720) kit, by the quantitative chemiluminescent method, with a specificity of 97.03-100% and a sensitivity of 99.27-100%. (The LIAISON[®] Rubella IgG assay uses chemiluminescent immunoassay (CLIA) technology for the quantitative determination of specific IgG antibodies to rubella virus in human serum or plasma samples. Strada per crescentino -13040 saluggia (vercelli) -italy).

Using this kit, IgG titers <9 IU/mL, 9-11 IU/mL and >11 IU/mL were considered as negative, borderline and positive, respectively. Data analysis was carried out with SPSS 11.5 using chi square and Fisher tests.

RESULTS

Of the 1779 students selected, 114 were excluded from the study due to inadequate amount of blood, hemolysis of blood, or absence of a questionnaire. Thus 1665 subjects were enrolled, 945 (57%) of whom were girls and 720 (43%) were boys. Mean age was 9.17±1.53 years.

Anti rubella antibody titer was negative, borderline and positive in 1128, 12 and 525 subjects, respectively. Borderline cases were also considered seronegative. Rubella virus antibodies were detected in serum samples from 525 (31.5%) of the 1665 subjects studied (Table 1).

Overall, 525 subjects (31.5%), seropositive, 1128 (67.5%), Seronegative and 12 (1%), were borderline. Among the 945 girls enrolled, 663 (70%) and 6 (1%) had borderline antirubella antibody titer. Among the 720 boys,

Table 1: Prevalence of antirubella virus antibodies by sex in Tehran

Serology	Girls		Boys		Total	
	No.	%	No.	%	No.	%
Negative	663	70	465	64	1128	67.5
Borderline	6	1	6	1	12	1.0
Positive	276	29	249	35	525	31.5
Total	945	100	720	100	1665	100.0

Table 2: Prevalence of antirubella virus antibodies by age group in Tehran

Serology age group	Negative		Borderline		Positive		Total	
	No	%	No	%	No	%	No	%
6	30	88	-	-	4	12	34	100
7	199	76.5	-	-	61	23.5	260	100
8	211	71	4	1	82	28	297	100
9	218	65.5	2	0.5	113	34	333	100
10	220	67	2	0.5	107	32.5	329	100
11	213	61	3	1	131	38	347	100
12	37	57	1	1.5	27	41.5	65	100

Table 3: Prevalence of antirubella virus antibodies by geographical group in Tehran

Serology	Northern		Western		Eastern		Southern	
	No	%	No	%	No	%	No	%
Negative	369	72	322	72.5	218	68	356	67
Positive	145	28	125	27.5	101	32	173	33
Total	514	100	447	100	319	100	529	100

Table 4: Prevalence of antirubella virus antibodies by history of vaccination against rubella in Tehran

Serology	Vaccinated		Unvaccinated		Total	
	No	%	No	%	No	%
Negative	336	62	796	71	1132	68
Positive	205	38	328	29	533	32
Total	541	100	1124	100	1665	100

249 (35%), seropositive, 465 (65%), seronegative and 6 (0.8%), were borderline. There were no statistically significant differences in seropositivity rate with regard to gender 249 of 720(35%), in males and 276 of 945 (29%), in females; (p = 0.054).

The percentage of seropositive subjects increased with age. Antirubella antibody titer increased with increasing age such that the lowest titer (7%) occurred in 6 years old and highest titer (44%) occurred in 12 years old. This finding was statistically significant (p<0.001) (Table 2).

The rate of seropositivity was lowest (28%) in the northern educational sector of Tehran and the rate higher in the western (29%), eastern (32.5%) and southern (35%) educational sectors. These differences were not statistically significant (p = 0.238) (Table 3).

Overall 541 subjects (32.5%) had been vaccinated while 1124 subjects (67.5%) had not been vaccinated. Among the vaccinated individuals, 205 (38%) were seropositive and 336 (62%) were seronegative and among those who had not been vaccinated, 328 (39%) and 796 (71%) were seropositive and seronegative, respectively (Table 4).

DISCUSSION

In our study on 1665, 6-12 year old primary school children in Tehran, antibody titer was positive in 276 (29.5%) and negative in 669 (70.5%) of girls. Among the 720 boys enrolled, 249 (35%) were seropositive and 471(65%) were seronegative. However, there was no significant statistical difference according to gender (p = 0.054).

Other studies show similar results based on the prevalence of disease or antibody titer and gender in all age groups (Eftekhari *et al.*, 2002).

Seroprevalence usually increases with age (Gomwalk and Ezeronye, 1985; Lawn *et al.*, 2000), this is similar to our study results. In our study, rubella antibody titer rose with increasing age such that the prevalence was lowest (12%) in 6 years old and highest (41.5%) in 12 years old. This difference was statistically significant (p = 0.001) (Table 2). In a similar study in 5-9 years old group, 25.5% were seropositive and 74.5% were seronegative while in the 10-14 years old age group, 61% were seropositive and 39% were seronegative; none had history of rubella vaccination (Eftekhari *et al.*, 2002).

In the ages above than 15 years, rubella antibody titer rose with increasing age reaching almost 70% (Eftekhari *et al.*, 2002; Terada, 2003; Zanetta *et al.*, 2003; Vameghi and Fatemi, 2000; Amin Zadeh *et al.*, 1976; Behzadi, 1994). This is important to notice that rising of seroprevalence with age, does not necessarily mean that rising of age cause seroprevalence rising and Cohort effect must be considered.

Similar studies have not been performed as yet on 6-12-year-old children in Iran but it has been done in high school girls which showed a 16-21% seronegative towards the rubella virus (Modarress, 1988).

Lowest seropositivity (28%) occurred in the northern educational sector of Tehran and highest infectivity was seen in the western (29%), eastern (32.5%) and southern (35%) sectors. These findings were not statistically significant ($p = 0.238$) (Table 3).

In a different study performed in different geographical regions in Tehran, the incidence of infection was 73% in 1986 in northern Tehran and the antibody titer was 89% in western Tehran. In 1997, the rate of rubella infection was lowest (72.5%) in northern and highest (88.5%) in southern Tehran, which indicates an increasing rate of infection with advancing age in southern Tehran (Vameghi and Fatemi, 2000). On the average, 64% of vaccinated individuals were seronegative and a statistically significant difference was not found between different geographical regions in Tehran ($p = 0.238$).

In our study only 37.5% of primary school children, who had been vaccinated at 15 months or above, were seropositive. In another study performed in Japan, in which rubella vaccination was not compulsory, 27% of under 18-years-old girls were seronegative which can warn us about the risk of Congenital Rubella Syndrome in the future (Terada, 2003). In a study performed in Brazil, 78% of 6-8 years old children who had been vaccinated at 15 months of age were seropositive (Zanetta *et al.*, 2003). The difference between these results seems to be due to the age of study subjects.

The difference between these two results seems to be due to the age groups studied, in that our study antibody titer decreased with increasing age, which means that the rubella antibody titer produced by the vaccine had gradually declined. Furthermore, repeated contact with the virus, as seen by the high rubella infection rate in these regions, has resulted in high titers to still remain.

Although rubella vaccination at 15 months produces immunity in 99% of cases (seroconversion) (Kohler *et al.*, 2003) and regarding that in one study 90% of cases were seropositive 6 months after mass vaccination (Zanetta *et al.*, 2003), but the gradual decline in IgG antibody titer following vaccination

leads to decreased immunity such that it had fallen to 76%, 6-8 years after vaccination of 15-month-old children (Zanetta *et al.*, 2003; Mossong *et al.*, 2004). In our study, anti rubella virus antibody reached 37.5% for 6-12 years old children and in another study, it had fallen to 85%, 8 years after vaccination (Zanetta *et al.*, 2003). Thus it can be concluded that although the stability of the vaccine differs in different geographical regions worldwide, but the gradual decline in rubella antibody IgG titer after vaccination is seen in all cases worldwide (Zanetta *et al.*, 2003; Mossong *et al.*, 2004). Therefore, considering that the rate of immunity in children, who were vaccinated at 15 months or above, was 37.5% in our study, it seems that vaccination at this age does not produce adequate immunity in 12-years-old. On the contrary, around 29% of unvaccinated primary school children were seropositive and the incidence of infection increased with advancing age reaching 72% in 12-44 years-old. These values are clearly lower (80%) than acceptable values (Eftekhari *et al.*, 2002; Terada, 2003; Zanetta *et al.*, 2003). In a study performed to eradicate rubella infection, it was suggested that mass vaccination of adults should take place with high rubella vaccination coverage in order to prevent CRS (Irons *et al.*, 2000). Further investigations show that mass rubella vaccination of adults produced more than 95% vaccination coverage in areas which previously had 80% vaccination coverage (Castillo-Solorzano, 2004). Comparing the results of the two suggested methods for preventing CRS, namely the vaccination of young girls and women after delivery with that of giving a double vaccine dose; first at 18 months and next at 12 years, it was seen that both methods were successful in decreasing CRS such that the annual number of CRS cases occurring before 1974 in Sweden, was 14 cases which fell to 2 cases between 1975-85 and none have been reported since 1985 (Bottiger and Forsgren, 1997).

CONCLUSIONS

Considering the results derived from the above studies, as well as our study, it seems that vaccination during childhood is not adequate for eradication of CRS and it is important to vaccinate young girls and women before marriage and, if possible, to estimate the rubella antibody titer before marriage or pregnancy and to vaccinate all seronegative cases.

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