Seroprevalence of Rubella Antibodies and Effects of Vaccination among Healthy University Women Students in Korea

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Since the introduction of rubella vaccination in Korea in 1982, several outbreaks of rubella have occurred. In order to examine the current seroepidemiology of rubella virus infection in Korean women of child-bearing age, the healthy university women students of Yonsei University in Seoul aged 18~26 years were chosen as a model population. A survey was carried out in the time of routine annual physical check-up. Serum specimens of 242 volunteers of healthy women university students were randomly sampled for screening rubella-specific IgG/IgM antibodies by an automated enzyme immunoassay system (Vitek System VIDAS, bioMerieux Vitek, Inc., Lyon, France).

A total of 177 subjects were positive for rubella-specific IgG antibody, giving a prevalence of 73.1 %. The mean±standard deviation of rubella-specific IgG antibody was 99.3±95.3 IU/mL. In this study, the efficiency of a vaccination was about 88%. With such a relative high proportion of susceptibility (26.9%) among university women students in child-bearing age, a extensive rubella vaccination program should be enforced to prevent possible outbreaks of congenital rubella syndrome in the future.

Key Words: Rubella vaccination, rubella-specific IgG/IgM antibodies, enzyme immunoassay, congenital rubella syndrome

Rubella infection in pregnant women may cause congenital rubella syndrome, so it is now widely accepted that the vaccination should be offered to all susceptible women of child-bearing age. In Korea, however, the usual seroprevalence and titers of rubella antibodies among women of child-bearing age has not been yet clarified making it difficult for many obstetricians to serodiagnose the rubella infection in pregnant women.

The aim of this study was to estimate current seroprevalence among college students representing healthy adolescent women in Korea and to investigate serological changes after vaccination of seronegative individuals in order to gather a preliminary data to set up a vaccination policy of rubella virus for the school health program.

MATERIALS AND METHODS

Study population

The study subjects were chosen among the healthy women students of Yonsei University, Seoul, Korea. Each student was asked with a questionnaire consisting of some questions regarding her current health status and previous vaccination history. Two hundred and forty-two volunteers were recruited. Their

ages ranged from 18 to 26 years. Individuals with a rubella vaccination history were excluded.

Five mililiters of venous blood were collected and the sera were separated within two hours, frozen at −40℃, and tested for rubella-specific IgG and IgM assay.

Among the individuals with rubella-specific IgG negative or low positive results, sixty-three volunteers were vaccinated. Six and 12 months later, rubella-specific antibody tests were repeated in some volunteers.

Methods

Rubella-specific antibody tests were performed by enzyme-linked immunosorbent assay (ELISA) with VIDAS system (bioMerieux Vitek, Inc., Lyon, France). Vidas RUB IgG and IgM are automated assays which enable anti-rubella IgG and IgM in human serum to be quantitatively measured. The IgM antibodies are specifically detected after the capture of the sample IgM on the solid phase. These assays combine the indirect enzyme immunoassay method with a final fluorescent detection (ELFA). When the assay is completed, the results are analyzed automatically and the index (ratio of sample's fluorescent signal to the memorized standard signal) is calculated by the machine.

The assays were performed according to the manufacturer's procedure manual. Rubella-specific IgG level was quantitated as International Unit (IU)/mL. The results not greater than 20 IU/mL were reported as negative, while 30 IU/mL was taken as the positive cutoff value. Those results between 20 and 30 IU/mL were regared as low or borderline positive. The results of rubella-specific IgM test were reported negative when the ratio of sample fluorescent signal to standard signal was 0.8 or lower and positive when the ratio was 1.2 or higher. The results between the cutoff values were regarded as equivocal.

RESULTS

The results of rubella-specific antibody tests among healthy university students
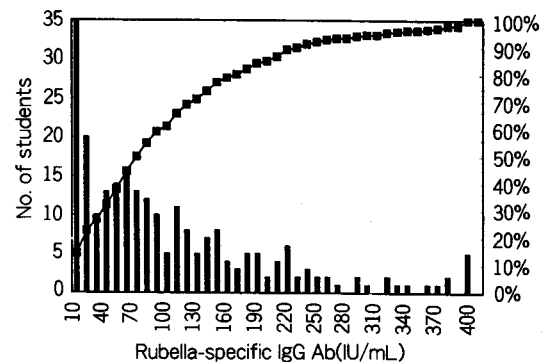
The mean rubella-specific IgG level of 242

Fig. 1. *Distribution of the rubella-specific IgG antibody levels (IU/mL) among 242 healthy women students of Yonsei University in Korea. Bars represent the number (frequency) of students and line means cumulative percentage of the level.*

Table 1. The results of five students who showed positive or equivocal positive for rubella-specific IgM antibody among 242 healthy university women students

Age	Rubella-specific IgG Ab		Rubella-specific IgM Ab	
	IU/mL	Result	Ratio[a](Sample/Standard)	Result
18	113	positive	1.67	positive
20	124	positive	5.11	positive
18	129	positive	0.84	equivocal
21	147	positive	0.87	equivocal
19	284	positive	0.95	equivocal

[a]: Ratio means sample's fluorescent signal to the standard signal.

healthy individuals was 99.3 ± 95.3 IU/mL and the distribution is shown in Fig. 1. Sixty-five participants seemed not to have sufficient immunity for rubella virus (55 negatives and 10 low positives) and vaccination was recommended, of which 63 were actually immunized

Table 2. The changes in the rubella-speific antibodies of thirty-three students' paired sera after vaccination

Student's Name	Rubella-specific IgG Ab (IU/mL)		Rubella-specific IgM Ab Ratio[a](Sample/Standard	
	6 month	12 month	6 month	12 month
KGS	276	231	0.07	0.06
KGH	71	93	0.1	0.09
KNM	33	37	0.12	0.11
KMH	63	110	0.14	0.11
KSA	11	9	0.09	0.07
KSJ	80	95	1.1[b]	0.68
KSO	98	126	0.08	0.07
KEH	35	63	0.1	0.09
KJE	150	185	0.13	0.15
KHG	53	44	0.15	0.12
PSW	28	42	0.08	0.08
BHG	165	141	0.06	0.06
BSJ	400	400	0.08	0.11
BEK	40	36	0.09	0.07
STE	27	372	0.08	0.1
SER	41	46	0.11	0.13
SEJ	63	121	0.37	0.31
SJS	129	190	0.11	0.11
SMS	128	221	0.09	0.08
OSN	270	233	0.11	0.11
RKI	64	64	0.48	0.43
YSI	129	176	0.53	0.35
LSY	95	81	0.12	0.1
LEK	105	100	0.45	0.07
LJS	400	353	0.2	0.16
LJE	238	178	0.35	0.37
LHH	55	37	0.12	0.12
LAK	154	107	0.13	0.13
JMY	130	77	0.39	0.3
JJH	159	140	0.55	0.28
CJY	49	12	0.25	0.24
HMJ	35	35	0.22	0.11
HKS	298	80	0.09	0.08
Total	123.4 ± 104.2[c]	128.3 ± 101.3	0.22 ± 0.22	0.17 ± 0.14

[a] : Ratio means sample's fluorescent signal to the standard signal.

[b] : Equivocal (all the results of rubella-specific IgM Ab in this table except this one were negative).

[c] : Mean $\pm$ S.D

with rubella vaccine. Meanwhile, rubella-specific IgM revealed two positives and three equivocal positives, whose rubella-specific IgG levels ranged from 113 to 284 IU/mL (Table 1). The majority of the participants (97.9%) were IgM-negative.

The results of rubella-specific antibody tests six months after vaccination

Forty-two individuals were subjected to follow-up test six months after vaccination. The rubella-specific IgG level ranged from 11 to 400 IU/mL, on the average 120.4 IU/mL. Thirty-seven (88.1%) showed seroconversion while two were still negative and three were in the range of low positivity. Among 42 women, two showed IgM equivocal positive results whose IgG level was 80 and 116 IU/mL respectively.

The results of rubella-specific antibody tests twelve months after vaccination

Forty-nine individuals were subjected to follow-up test twelve months after vaccination. The IgG level ranged from 12 to 400 IU/mL, on the average 129.8 IU/mL. The seroconversion rate was 87.8% (43/49). Four were IgG-negative and two were low positive. Only one student showed IgM-positive whose IgG level was 327 IU/mL.

The results of rubella-specific antibody tests who participated in both follow-up tests at sixth and twelfth months after vaccination

The number of participants joined both follow-up serological tests sixth and twelfth months after vaccination was thirty-three. The paired samples showed increases in IgG levels and decreases in IgM ratios with time. The average IgG level at the sixth month after vaccination was 123.4 IU/mL and that at the twelfth month was 128.3 IU/mL, respectively (paired t-test, $p < 0.05$). And the average IgM ratio at the sixth month after vaccination was 0.22 and that at the twelfth month was 0.17, respectively (Table 2). The values after 6 month and 12 month were significantly different.

One individual who showed IgM-equivocal result at six months after vaccination turned negative another six months later, and her IgG level increased from 80 to 95 IU/mL during that time.
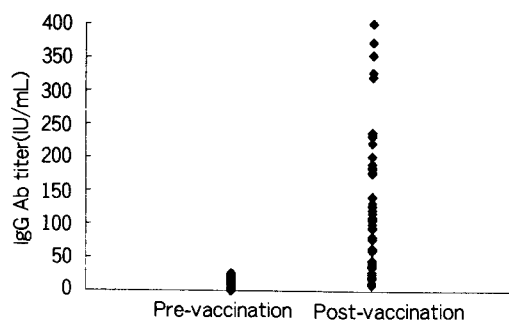

Fig. 2. *Changes in rubella-specific IgG Ab titers before and after vaccination.*

Table 3. Rubella-specific antibodies after vaccination

Rubella-specifc antibodies	Patients' Group	Six-month after vaccination(n=42)	Twelve-month after vaccination(n=49)	Overall (n=91)
Rubella-specific	Overall	120.4± 97.4[b]	129.8± 10.8	125.5±102.3
IgG Ab(IU/mL)	Follow-up[c](n=33)	123.4±104.2	128.3±101.3	
Rubella-specific	Overall	0.23± 0.22	0.21± 0.26	0.22± 0.24
IgM Ab(Ratio[a])	Follow-up(n=33)	0.22± 0.22	0.17± 0.14	

[a] : Ratio means sample's fluorescent signal to the standard signal.

[b] : Mean ±S.D.

[c] : Follow-up means the group of paired serum samples.

Overall results of rubella-specific antibody tests after vaccination

Among the 63 volunteers vaccinated for rubella virus, 53 individuals were tested for rubella-specific antibody tests either six or twelve months after vaccination. Thirty-three were joined at both times, nine were only at the sixth month, and sixteen were only at the twelfth month. Their serological findings are summarized in Table 3.

Fig. 2 shows the rubella-specific IgG antibody levels of 63 subjects before vaccination and 49 subjects after vaccination (12 months post-vaccination). As is shown in the figure, the rubella-specific IgG antibodies after vaccination significantly increased.

DISCUSSION

Rubella (German measles) is a common contagious disease with mild constitutional symptoms and generalized rashes, but exposure during the first trimester of pregnancy may result in congenital defects (Chernesky and Mahony, 1995; Ekblad, 1995). The triad of anatomic abnormalities including cataracts, neurosensory deafness and congenital heart disease has been referred to as the congenital rubella syndrome (Ewert *et al.* 1992; Fogel *et al.* 1996). Thus, serological tests to determine the immune status in women and tests to diagnose recent rubella virus infection in pregnant women are of great importance (Ahmed, 1992; Chernesky and Mahony, 1995). The epidemiology of rubella infection has been studied in many areas of the world (Ahmed, 1992; Fraser *et al.* 1993; Garcia *et al.* 1993; Leogrande, 1993; Lin and Chen, 1993; Pelissero *et al.* 1993; Lin and Chen, 1994; Miller *et al.* 1994; Souza *et al.* 1994; Janes, 1995; Saldanha and Azevedo, 1995), and mass immunization programs conducted in many countries have successfully decreased the infection with a concurrent reduction in congenital rubella syndrome (ACOG, 1993; Condon and Bower, 1993; Gay *et al.* 1994; Szilagyi *et al.* 1994; Ferson, 1995; Matter *et al.* 1995).

Rubella infections can be transmitted from mother to fetus resulting in so-called congenital rubella syndrome. When the pregnant woman has sufficient immunity to the rubella virus, the congenital infection can be prevented (Weber *et al.* 1993). So, the vaccination for rubella virus is now included in a regular vaccination program. Vaccine is given to girls routinely at fifteenth month after birth and at the age of three. In Korea, however, the nation-wide vaccination program was started at 1982, so at the present time, most adolescent and young women of child-bearing age (over 16 years old) did not have the chance to be vaccinated for the rubella virus. In order to analyze risk factors for seronegativity to rubella and to assess the efficacy of a rubella screening and vaccination in women of child-bearing ages, we analyzed rubella serology and the effects of a vaccination in healthy women university students.

Our study revealed that 26.9% of the healthy women from 18 to 26 years old were needed a vaccination because they did not have sufficient immunity for rubella virus. They had negative or low positive anti-rubella IgG levels.

The postvaccination seroconversion rate was 88.1% and 87.8% after 6 and 12 months respectively. These findings suggest that serological follow-up and decision making whether or not to offer reinforcing vaccination should be an essential part in the vaccination program for rubella virus (Marsack *et al.* 1995).

From the current viewpoint of diagnostic virology, there are now a variety of methodologies available (Ahmed, 1992; Chernesky and Mahony, 1995). As well as commonly performed serological detection methods of antiviral antibodies, various approaches to detect viral antigens from viral culture techniques to molecular biological methods such as polymerase chain reaction have been developed (Bosma *et al.* 1995). Nevertheless, even such a highly sophisticated method does not give physicians satisfaction with regard to diagnostic sensitivity or specificity, namely, diagnostic accuracy. Moreover, such modalities are not easy to perform and expensive as well to be used as a routine diagnostic test. Thus, the

serological tests for specific antiviral antibodies are still the first-line choice for the diagnosis of viral infection because they represent the functional immune status of the host and have advantages such as simple procedure, standardization, and cost-effectiveness.

Until now, the vaccine was not recommended for boys or men in Korea. In temperate climates, rubella is endemic throughout the year, but there is a regular seasonal peak between March and May (Horstmann, 1989). Before the widespread use of the vaccine, rubella was most commonly found among children, but many susceptible adolescents and young adults were also infected (Horstmann, 1982). After 1977, a change in the epidemic pattern of rubella was identified. The regular cycle of rubella epidemics no longer existed. The change deserves further investigation with the current seroprevalence of rubella infection being examined.

From this study, the titer of rubella-specific IgG antibody was increased and turned positive in 88% of the test subjects after 6 months of vaccination. And after 12 months, the positive rate was similar to the 6 months' data but the titer of rubella-specific IgG antibody more significantly increased ($p < 0.05$). We concluded that the rubella vaccination program should be extended to include seronegative women of reproductive age.

REFERENCES

ACOG: Immunization during pregnancy. ACOG Technical bulletin number 160--October 1991. *Int J Gynaecol Obstet 40: 69-79, 1993*

Ahmed MU: IgM and IgG antibidies specific to rubella in child bearing women. *J Pakistan Med Assoc 42: 121-122, 1992*

Bosma TJ, Corbett KM, Eckstein MB, O'Shea S, Vijayalakshmi P, Banatvala JE, Morton K, Best JM: Use of PCR for prenatal and postnatal diagnosis of congenital rubella. *J Clin Microbiol 33: 2881-2887, 1995*

Chernesky MA, Mahony JB: Rubella virus. *In Manual of Clinical Microbiology. 6th ed. Washington DC, American Society for Microbiology, 1995, 968-973*

Condon RJ, Bower C: Rubella vaccination and congenital rubella syndrome in western australia. *Med J Aust 158: 379-382, 1993*

Ekblad U: Biological agents and pregnancy. *J Occup Environ Med 37: 962-965, 1995*

Ewert DP, Frederick PD, Mascola L: Resurgence of congenital rubella syndrome in the 1990s, Report on missed opportunities and failed prevention policies among women of child-bearing age. *JAMA 267: 2616-2620, 1992*

Ferson MJ: Another vaccine, another treadmill? *J Paediatr Child Health 31: 3-5, 1995*

Fogel A, Barnea BS, Aboudy Y, Mendelson E: Rubella in pregnancy in Israel: 15 years of follow-up and remaining problems. *Isr J Med Sci 32: 300-305, 1996*

Fraser V, Spitznagel E, Medoff G, Dunagan WC: Results of a rubella screening program for hospital employees: A five-year review (1986~1990). *Am J Epidemiol 138: 754-764, 1993*

Garcia DG, Ewert DP, Mascola L: A survey of hospital postpartum and postabortion rubella vaccination policies in Los Angeles County, 1992. *Infect Control Hosp Edidemiol 14: 513-516, 1993*

Gay NJ, Valambia S, Galaski D, Miller E: Selective rubella vaccination programmes: A survey of districts in England and Wales. *Commun Dis Rep CDR Rev 4: R77-79, 1994*

Horstmann DM: Rubella. *Clin Obstet Gynecol 25: 585-597, 1982*

Horstmann DM: Rubella. In Viral Infections of Humans, Epidemiology and Control. *New York, Plenum Medical Book Co., 1989, 617-631*

Janes R: Assessment of rubella immunity in women born in 1959-74 in a solo rural general practice. *N Z Med J 108: 384-385, 1995*

Leogrande G: The epidemiology of rubella virus infections in a large city of southern Italy. *Int J Clin Lab Res 23: 151-154, 1993*

Lin DB, Chen CJ: Current seroepidemiology of rubella virus infection among female residents in Taiwan. *J Med Virol 41: 174-178, 1993*

Lin DB, Chen CJ: Seroepidemiology of rubella virus infection among female residents on the offshore islets of Taiwan. *J Trop Med Hyg 97: 75-80, 1994*

Marsack CR, Alsop CL, Kurinczuk JJ, Bower C: Pre-pregnancy counselling for the primary prevention of birth defects: Rubella vaccination and folate intake. *Med J Aust 162: 403-406, 1995*

Matter L, Bally F, Germann D, Schopfer K: The incidence of rubella virus infections in Switzer-

land after the introduction of the MMR mass vaccination programme. *Eur J Epidemiol 11: 305-310, 1995*

Miller E, Tookey P, Morgan-Capner P, Hesketh L, Brown D, Waight P, Vurdien J, Jones G, Peckham C: Rubella surveillance to June 1994: Third joint report from the PHLS and the National Congenital Rubella Surveillance Programme. *Commun Dis Rep CDR Rev 4: R146-152, 1994*

Pelissero C, Marena C, Aguzzi F, Bevilacqua M, Rebasti F: Seroepidemilogy, morbidity and vaccination strategies against rubella infection. Eight years experience in Oltrepo Pavese. *Eur J Epidemiol 9: 322-326, 1993*

Saldanha MJ, Azevedo A: Congenital rubella. Still with us. *Acta Med Port 8: 319-322, 1995*

Souza VA, Moraes JC, Sumita LM, Camargo MC, Fink MC, Hidalgo NT, Pannuti CS: Prevalence of rubella antibodies in a non-immunized urban population, Sao Paulom Brazil. The Division of Immunization, CVE. *Rev Inst Med Trop Sao Paulo 36: 373-376, 1994*

Szilagyi PG, Rodewald LE, Humiston SG, Hager J, Roghmann KJ, Done C, Cove L, Fleming GV, Hall CB: Immunization practices of pediatricians and family physicians in the United States. *Pediatrics 94: 517-523, 1994*

Weber B, Enders G, Schlosser R, Wegerich B, Koenig R, Rabenau H, Doerr HW: Congenital rubella syndrome after maternal reinfection. *Infection 21: 118-121, 1993*