

# Seroepidemiology of Varicella-Zoster Virus in Korea

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This study was designed to assess the immune status of the Korean population against varicella-zoster virus (VZV) through a seroepidemiologic study. Residual blood samples were collected from diagnostic laboratories throughout Korea. Samples were collected in October 2009 to March 2010 from persons 0-79 yr of age and were tested by ELISA (Enzygnost®; Dade Behring, Schwalbach, Germany). Total seroprevalence in subjects 1-79 yr of age was 89.6%. Seroprevalence increased as age increased from 67.3% in subjects 1-4 yr of age to 94.2% in subjects 10-14 yr of age and in subjects over 20 yr of age seroprevalence ranged from 98.0% to 100%. In children under 1 yr of age, passive immunity waned after birth with none of the subjects having antibodies from 7 months of age and over. Among subjects 1-79 yr of age, susceptible subjects to VZV were mainly under 20 yr of age. These results provide information in understanding the dynamics of varicella disease in Korea, which is important in building up strategies for disease control.

**Key Words:** Varicella-Zoster Virus; Seroprevalence; Seroepidemiology; Korean

## INTRODUCTION

Varicella-zoster virus (VZV) is an important cause of varicella (chickenpox) and herpes zoster. Varicella is a highly contagious disease with a household transmission rate up to 86% in susceptible individuals (1). Although varicella is often known as a mild illness in childhood, it can cause morbidity and mortality in otherwise healthy children and it is a more serious disease with higher rates of complications in adolescents, adults and immunocompromised persons (2).

Fortunately, varicella is a vaccine preventable disease and a live virus varicella vaccine has been available since 1974 (3). This vaccine was first introduced in Korea in 1988 and was initially recommended for high risk groups and healthy children on a private sector basis. In 2005, varicella vaccine was introduced into the national immunization program and routine vaccination was recommended for all children 12-15 months age. Regardless of the long vaccination history in Korea, data on the epidemiologic impact of the vaccine is limited. Also, outbreaks of varicella are still seen in the community. In several countries including the USA, Germany, Australia, Greece and Saudi Ara-

bia, a second dose of varicella vaccine has been recommended due to continuous varicella outbreaks (4, 5). With reports on primary or secondary vaccine failure after varicella vaccination (6), strategies to control varicella in the community are necessary. For this, an evaluation of the population immunity and vaccination rates along with assessment of the regional epidemiologic data is essential.

We conducted a seroprevalence study and measured immunity to VZV to assess the current immune status of the Korean population, find susceptible age groups and enhance comprehension of the dynamics of the epidemiology of varicella.

## MATERIALS AND METHODS

### Collection of serum samples

Residual serum samples after diagnostic testing, which would otherwise have been discarded were collected from two diagnostic laboratories located in Seoul, Korea. One laboratory has a network of laboratories located in provinces throughout Korea. Serum samples referred for the diagnosis of infectious diseases such as measles, mumps, rubella, varicella, hepatitis A and HIV

were excluded.

Samples were collected from October 2009 to March 2010. Subject information of each sample was deleted and serum samples were assigned with a new code number. The only demographic characteristics available were age, gender, district of laboratory and date of sampling.

Serum samples were collected from subjects aged 0-79 yr. Samples were stratified into the following age groups: < 1 month, 1-3 month, 4-6 month, 7-9 month, 10-11 month, 1-4 yr, 5-9 yr, 10-14 yr, 15-19 yr, 20-24 yr, 25-29 yr, 30-39 yr, 40-49 yr, 50-79 yr. Subjects < 10 yr of age were also analyzed in 1 yr interval.

### Anti-varicella antibody analysis

Anti-VZV IgG antibodies were evaluated by a commercial enzyme-linked immunosorbent assay (ELISA) kit (Enzygnost®; Dade Behring, Schwalbach, Germany). Samples with  $\Delta E < 0.100$  were determined as negative,  $0.100 \leq \Delta E \leq 0.200$  were classified as equivocal and  $\Delta E > 0.200$  were classified as positive. Equivocal results were repeated and reclassified if positive or negative. The ELISA was done at the Center for Vaccine Evaluation and Study, Medical Research Institute, Ewha Womans University School of Medicine, Seoul, Korea.

### Statistics

Seroprevalence data for genders and age groups were analyzed as percentages with 95% confidence intervals (95% CI). The chi-square test was used to compare differences between gender or age groups. A value of  $P < 0.05$  was considered as statistically significant.

### Ethics statement

The study proposal was reviewed and approved by the institutional review board at Ewha Womans University Mokdong Hospital in Seoul, Korea (ECT 203-2). Informed consent was exempted by the board.

## RESULTS

### Seroprevalence against varicella-zoster virus

Among 1,302 samples, 1,117 samples were positive, 54 samples were equivocal, 131 samples were negative, with a total seroprevalence of 85.8% for subjects 0-79 yr of age (Fig. 1). After excluding subjects < 1 yr of age, seroprevalence against VZV was 89.6% in Korea. Seroprevalence was 67.3% in subjects 1-4 yr of age, and increased steadily as age increased with a seroprevalence of 78.0% in subjects 5-9 yr of age, 94.2% in subjects 10-14 yr of age, 94.4% in subjects 15-19 yr of age and 98.0%-100.0% in subjects over 20 yr of age. In comparison of seroprevalence between male and female subjects according to age group, there was no significant difference between gender groups in all age groups from subjects 1-79 yr of age (data not shown).

In subjects < 1 yr of age, seroprevalence for varicella was 27.5%. The seroprevalence pattern can be seen in Fig. 1. All subjects < 1 month had anti-VZV IgG antibodies. Seroprevalence decreased dramatically afterwards, from 66.7% of subjects 1-3 months of age to 15.0% in subjects 4-6 months of age and none of the subjects 7-11 months of age had anti-VZV IgG antibodies.

To enhance comprehension of dynamics of VZV infection in the community, seroprevalence was evaluated by 1 yr unit among subjects under 10 yr of age (Fig. 2). Seroprevalence ranged from 57.5% to 95.0% and was lowest in subjects 3-5 yr of age. Seroprevalence showed a steady increase as age increased in subjects 5-9 yr of age and remained > 90% in subjects up to 10-19 yr of age (Fig. 1).

In this study, seroprevalence estimation was based on positive results. Among 1,302 samples, 54 samples were equivocal and 98.1% (53/54) were under 20 yr of age. A gap between positive versus positive + equivocal results was widest in subjects 3-5 yr of age (Fig. 2). The gap decreased in subjects 6-9 yr of age, which could possibly suggest an increase in immunity against varicella in these age groups.

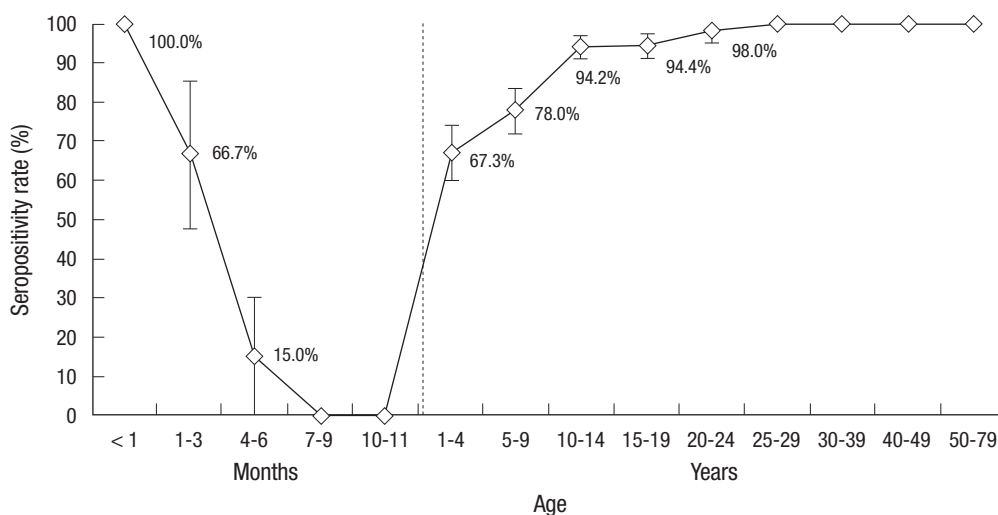


Fig. 1. Age specific seroprevalence against varicella-zoster virus in Korea. Bars indicate 95% confidence interval.

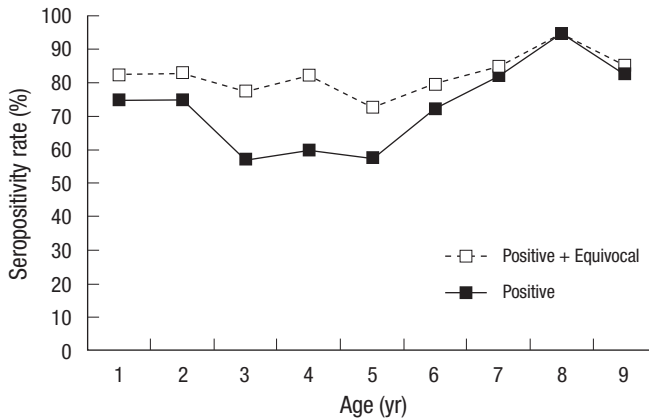


Fig. 2. Seroprevalence against varicella-zoster virus among children under 10 yr of age in Korea.

## DISCUSSION

Total seroprevalence against VZV in subjects 1-79 yr of age was 89.6% in Korea. Seroprevalence increased with age and almost all subjects over 20 yr of age had anti-VZV IgG antibodies. In reverse, most of the subjects susceptible to VZV were under 20 yr of age. Among subjects 1-4 yr of age, 32.7% were susceptible to VZV, followed by 22.0% of subjects 5-9 yr of age. The susceptible proportion dropped to 5.6%-5.8% subjects 10-19 yr of age.

When analyzing subjects under 10 yr of age by 1 yr interval, we found that the seroprevalence decreased from 75.0% in subjects 1 yr of age to 57.5% in subjects 5 yr of age. This could reflect waning of immunity after vaccination, which has been reported in clinical settings (7). However in subjects 5 yr of age and older, seroprevalence increased as age increased and also a gap between positive and positive + equivocal seroprevalence patterns decreased in subjects 6-9 yr of age, which could possibly suggest infection or booster immunity due to spreading of VZV in population. This exposure to of VZV could mean clinical disease or subclinical infection. Nonetheless with the increase in seroprevalence we suggest that there is some amount of exposure to wild-type VZV in children under 10 yr of age.

Equivocal antibody levels were mainly found in subjects under 20 yr of age. Based on the fact that VZV vaccine was first introduced in Korea approximately 20 yr ago and is currently done in subjects 12-15 months of age, equivocal antibody levels could possibly reflect the weaker immune status in vaccinated population compared with populations with acquired natural immunity. However, up to date there is no absolute way to discriminate antibodies elicited by natural immunity versus vaccine-induced immunity.

Although data in the prevaccine era is limited, there are two studies recently performed in Korea regarding the seroprevalence to VZV. Choi et al. (8) reported the seroprevalence in subjects < 1 yr of age to over 75 yr of age and the results were similar to our study. Another study was performed in subjects over

40 yr of age using fluorescent antibody to membrane antigen test (FAMA) and the results showed seropositivity of 98.6% in that age group (9). According to age groups, our results showed seroprevalence of 67.3% in subjects as early as 1-4 yr of age. This is higher than studies done in other countries such as Australia and Italy, which reported seroprevalence 20%-35% and 10%-30% in these age groups, respectively (10-12). Seroprevalence was also higher in Korea among subjects 5-19 yr of age compared with these countries. Studies done in these countries were performed with serum samples collected before introduction of varicella vaccine, therefore this difference in young children may reflect the effect of vaccination in Korea. Although there would be differences in local epidemiology, comparing seroprevalence with these prevaccine studies give us a glimpse into the impact of the vaccine.

There are some limitations to this study. The seropositivity against VZV was determined by ELISA. Compared with the golden standard FAMA, sensitivity in subjects of natural immunity and in the vaccinated population was reported as 83% and 78%, respectively (13). Specificity in both groups was 100%. However, much effort has been done to evaluate the adequacy of the ELISA method for detecting anti-VZV IgG antibodies and standardization of assays in seroepidemiology studies of VZV (14). Also, the FAMA is a tedious and labor intensive method, which requires experience and interpretation of the results can be subjective. In contrast, the ELISA is a widely used method with less inter- and intra-personal variability. The results obtained in a seroepidemiology study reflect the general immune status of the population in contrast with situations of clinical diagnosis which need a high sensitivity and specificity. Based on these characteristics, ELISA is the most widely used method for VZV seroprevalence studies.

Seroprevalence studies should be assessed in concordance with vaccination policies and vaccination rates. Up to date, varicella vaccine is included in the national immunization policy in Korea, and is recommended as 1 dose for children 12-15 months of age. Recent reports of varicella vaccination rates were 96.2% in a study done in 2008 among children 16-72 months (15). An investigational seroprevalence study collecting vaccination or disease history, possibly targeted for subjects under 20 yr of age, would enhance comprehension towards the role of the vaccine in these subjects.

Each country has a different position regarding the policy towards varicella vaccination. Up to 2009, among 194 countries, 19 countries introduced varicella vaccine for national immunization or selected vaccination for high risk groups and a proportion of these countries including Australia, Canada, Germany, Greece, Korea, Saudi Arabia, Uruguay, Latvia, Luxembourg, Brazil and the USA recommend routine immunization for children (5). The World Health Organization recommends routine childhood immunization against varicella to be considered in coun-

tries where varicella is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85%-90%) and sustained vaccine coverage can be achieved. This assertion was based on the concern that childhood immunization with lower coverage could theoretically shift the epidemiology of the disease and increase the number of severe cases in older children and adults (16). In Korea, data of varicella in the prevaccine era is limited. However, according to data from the National Health Insurance Corporation (NHIC), 96.9%-97.8% of all varicella disease was seen in subjects < 20 yr of age each year and 88%-90% of these cases were under 10 yr of age throughout 2001-2009. In this seroepidemiology study, we did not find a shift to older age groups of susceptible population. In the USA, varicella vaccine is recommended as a 2-dose schedule for routine immunization in children. Despite a great reduction in incidence of varicella disease, this policy was established due to continuous outbreaks throughout 2001-2005 in schools with high varicella vaccination coverage (range 96%-100%) indicating that the 1-dose vaccination program could not prevent varicella outbreaks completely (4, 17, 18). Also, index cases occurring among vaccinated subjects with mild or sub-clinical disease can lead to asymptomatic spread of the virus in the community. Other countries including Germany and Luxembourg have included a second dose of varicella vaccine in relation with the introduction of the measles-mumps-rubella-varicella (MMRV) combination vaccine (19). With outbreaks in the community and changes in policies among many countries, there has been an increasing concern towards the need of adopting a second dose of varicella for routine immunization in Korea. However such a decision should be based on the disease burden, nationwide varicella vaccination rates, cost-effectiveness or cost-benefit studies of a 2-dose policy, reassessment of the vaccine delivery and performance system and immunogenicity studies of current varicella vaccines used in Korea, along with seroprevalence studies which reflect the immunity of the population.

Varicella vaccine has been used in Korea for more than 20 yr and it was introduced in the national immunization program in 2005. Varicella was not a reported disease until 2005 and data collected by the NHIC of number of patients claimed for medical examination at hospitals throughout the country are available since merely 2001. Also, there are no seroprevalence studies on VZV in the prevaccine era, therefore it is difficult to estimate the impact of the vaccine. Seroprevalence, evaluated by ELISA, does have limitations in sensitivity and specificity of the method. Also, how effective the antibody detected by ELISA will work in actual disease prevention in terms of direct contact vs casual contact in the general population is also important. Therefore caution is warranted in interpretation in aspects of actual immune protection. However the data from this study is meaningful in that it can reflect the pattern of seroprevalence for VZV

and give us a view into the target age groups or susceptible population and the degree of susceptibility. According to this study, the overall seroprevalence in subjects 1-79 yr is 89.6% in Korea, and susceptible subjects to VZV are mainly under 20 yr of age. Seroprevalence is lowest in subjects 1-4 yr of age by 67.3%, and steadily increases with age. Considering that vaccination is recommended in subjects 12-15 months, this steady increase in seroprevalence with age increase could suggest the possibility of natural boosting due to continuous exposure to the virus. Further studies on the incidence of actual disease and disease burden are warranted. With a high burden, we could consider the need of a second dose of vaccine to better control varicella disease.

These results provide information in understanding the dynamics of varicella disease in Korea, which is important in building up strategies for disease control.

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