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Original Article

Hospital-based seroepidemiological analysis of varicella antibodies in children without history of varicella disease

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Abstract

Introduction: There are no published studies on the anti-varicella zoster virus (VZV) IgG antibody status of children in Qingdao. Thus, the aim of the present study was to investigate anti-VZV antibody status in hospital-based children aged 0–13 years without a history of varicella disease.

Methodology: Children aged 0–13 years in Qingdao were included in the study population. The demographic data and vaccination histories of all the subjects were obtained from the Shandong Information System for Immunization Program. Varicella disease history data was obtained from the Chinese Information System for Disease Control and Prevention. Enzyme-linked immunosorbent assay was used for detecting anti-VZV IgG in serum samples, and the seropositivity rate and geometric mean concentration (GMC) of the antibody were analyzed.

Results: A total of 983 children were included in the study. The seropositivity rate was 55.04%, and the GMC was 121.74 mIU/mL. The seropositivity rate and antibody GMC were significantly higher in females than in males ($p < 0.05$) and significantly higher in children aged 4–6 years than in children aged < 4 years and 7–13 years ($p < 0.001$). The seropositivity rate and GMC in children increased with vaccine dose ($p < 0.001$). In contrast to the considerable decline in antibody levels 3–5 years after one dose of varicella vaccination, antibody levels observed at least 8 years after two doses of varicella vaccination showed no considerable decline.

Conclusions: Two-dose varicella vaccination is recommended for inclusion in China's national immunization program.

Key words: varicella; seropositivity; IgG; vaccine; antibody.

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Introduction

Varicella is an acute respiratory disease that is infectious and caused by the varicella-zoster virus (VZV). Varicella occurs mainly in winter and spring and is transmitted by contact with the respiratory secretions and skin blisters of patients with varicella [1–3]. The disease is common in children and is one of the leading causes of school-based public health emergencies [4–6].

The United States is the first country to initiate a routine childhood varicella immunization program. Since 1995, one dose of varicella vaccine has been administered to children older than 12 months [7]. The two-dose varicella vaccination schedule for children was introduced in 2006. The mean national incidence of varicella in the United States decreased by 88.6% after the implementation of this schedule, and the largest decreases were observed in children aged 5–9 years (95%) and 10–14 years (92%) [8].

The varicella vaccine was introduced in China in 1997. Initially, children aged 1–2 years were vaccinated with one dose of varicella vaccine at their own expense [9]. Following the results of intensive research on varicella vaccination from around the world, two-dose varicella vaccination is gradually replacing one-dose varicella vaccination. Although varicella vaccination has not yet been incorporated into the national immunization program in China, free varicella vaccination has been gradually introduced in some areas. Qingdao is one of the first regions in China to introduce free varicella vaccination. The first dose of varicella vaccination has been provided free of charge for children aged 1 year or older since 1 July 2013. The two-dose varicella vaccination has been provided free of charge to children aged 4 years or older since 1 July 2016. The implementation of free varicella vaccination in Qingdao has achieved remarkable results, and the incidence of varicella has decreased considerably [10].

A seroepidemiological study of antibody status to one-dose varicella vaccine was carried out in healthy children in Jiangsu Province, China, and showed that children vaccinated with one dose of varicella vaccine had 57.1% seropositivity rate and the level of antibody decreased with increasing time after vaccination [11]. However, there is no published data on the anti-VZV IgG antibody status of the children in Qingdao, and the advantage of two-dose varicella vaccination over the one-dose varicella vaccination in improving the anti-VZV IgG antibody status of children needs to be verified.

The purpose of this study was to investigate the distribution of anti-VZV IgG antibodies in hospitalized children aged 0–13 years, without a history of varicella disease. Children belonging to different age groups, gender, varicella vaccination doses, and times after vaccination were compared. Our aim was to explore the effects of varicella vaccination on the production of antibodies in children and to provide a reference for the optimization of varicella vaccination strategies.

Methodology

Study population

Children aged 0–13 years who underwent medical examination between November 2019 and August 2020 were included in the study population. The inclusion criteria were as follows: (1) residency in the area for at least 3 months, (2) availability of complete information on varicella vaccination history, and (3) no history of varicella disease. The exclusion criteria were as follows: (1) refusal to provide venous blood samples, (2) suppressed immune system, and (3) chronic disease affecting the immune system.

Data collection

Demographic data and vaccination history of all the subjects were obtained from the Shandong Information System for Immunization Program. Information on varicella disease history was obtained from the Chinese Information System for Disease Control and Prevention (CISDCP). Serum samples were collected at a medical institution and frozen at −20 °C until testing.

Laboratory testing

Varicella-specific IgG antibodies were detected using enzyme-linked immunosorbent assay (ELISA). All the experiments were performed in the laboratory of the Qingdao Ming Qin Biological Technology Co., Ltd. All detection tests were performed by the same personnel using ELISA kits (batch number: EM0047, Virion\Serion Biotechnology Co. Ltd, Wurzburg, Germany) to avoid test bias.

Serum antibody positive determination

The samples were processed according to the manufacturer's instructions. Serum antibody concentrations ranged from 15 mIU/mL to 2000 mIU/mL. Samples with antibody concentrations of > 2000 mIU/mL were labeled as 2000 mIU/mL, and samples with antibody concentration of < 15 mIU/mL were labeled as 15 mIU/mL. IgG antibody concentrations were determined using the manufacturer's evaluation software. An antibody titer of > 100 mIU/mL was considered positive, a titer between 50 and 100 mIU/mL was considered equivocal, and a titer < 50 mIU/mL was considered negative [12]. In addition, equivocal results were retested using the same kits. If a retested sample resulted in values still in the equivocal range, then it was considered negative.

Statistical analysis

Data were analyzed using IBM SPSS 21.0 software (IBM Corp, Armonk, NY, USA) for statistical analysis. The average anti-VZV IgG antibody concentration status was represented by the geometric mean concentration (GMC). Seropositivity rates were compared between age groups, gender, and number of vaccine doses using the Chi square test, and antibody GMCs were analyzed using the t-test or analysis of variance (ANOVA). The vaccination group observed 0–2 years after varicella vaccination was the reference group. We used logistic regression models to analyze between-group differences in seropositivity rates after the administration of different doses of varicella vaccine. Given that the time grouping after varicella vaccination was a dummy variable, we coded for it and used linear regression models to analyze between-group differences in GMC after different doses of varicella vaccination. Age and gender were included as adjusted variables in all the models. A p *value* of < 0.05 was considered statistically significant.

Ethical approval

This study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the ethics committee of the Qingdao Center for Disease Control and Prevention (MR-37-23-043116). Written informed consent was provided by the parents or guardians of all enrolled participants.

Table 1. Distribution of anti-VZV IgG in children aged 0–13 years and without history of varicella from November 2019 to August 2020 in Qingdao, China.

Factor	N	Seropositive	Seropositivity rate (%)	*p* value	GMC (mIU/ml)	*p* value
Gender				< 0.01		< 0.01
Male	591	299	50.59		105.76	
Female	392	242	61.73		150.51	
Age group (years)				< 0.01		< 0.01
< 1	73	30	41.10		62.41	
1–3	232	113	48.71		90.84	
4–6	249	181	72.69		218.94	
7–13	429	217	50.58		113.67	
Vaccination dose				< 0.01		< 0.01
0	186	51	27.42		44.94	
1	473	237	50.11		113.24	
2	324	253	78.09		239.77	
Total	**983**	**541**	**55.04**		**121.74**	

GMC: geometric mean concentration.

Results

Characteristics of the study participants

A total of 983 children aged 0–13 (6.01 ± 3.87) years were studied; 591 (60.12%) were males and 392 (39.88%) were females. In addition, 73 (7.43%) children were of age < 1 years, 232 (23.60%) children were of age 1–3 years, 249 (25.33%) children were of age 4–6 years, and 429 (43.64%) children were of age 7–13 years. Of these children, 186 (18.92%) had no history of varicella vaccination, 473 (48.12%) had received one dose of the vaccine, and 324 (32.96%) received two doses of the vaccine (Table 1).

Antibody status in children by gender, age group, and vaccine dose

Among the 983 children, 541 were positive for anti-VZV IgG antibodies with seropositivity rate 55.04%, and GMC 121.74 mIU/mL. Antibody levels were significantly higher in females than in males ($p < 0.05$). The seropositivity rates of children in different age groups ranged from 41.10% to 72.69%, and the GMC ranged from 62.41 mIU/mL to 218.94 mIU/mL. Children in the 4–6-year age group had significantly higher antibody levels than the other age groups ($p < 0.001$). Antibody levels in children significantly differed between doses and gradually increased with dose ($p < 0.001$; Table 1).

Antibody status in children at different times after one dose of varicella vaccination

The seropositivity rate in children of age 0–2 years (58.18%) after one-dose varicella vaccination was significantly higher than that in children of age 3–5 years (42.86%, $p = 0.002$) and 6–12 years (43.20%, $p = 0.004$) after vaccination; and the GMC was significantly higher in the age group 0–2 years (127.95 mIU/mL) than in the age group 3–5 years (111.50 mIU/mL, $p = 0.04$), and 6–12 years (97.34 mIU/mL, $p = 0.007$) after one dose of varicella vaccination (Table 2).

Antibody status in children at different times after two-dose varicella vaccination

The seropositivity rate in children of age 0–2 years (82.87%) after two-dose varicella vaccination was not significantly different from that in children of age 3–5 years (68.89%, $p = 0.99$) and 6–8 years (66.67%, $p = 0.53$). In addition, the GMC in children of age 0–2 years (280.72 mIU/mL) after two-dose varicella vaccination was not significantly different from the GMC in children of age 3–5 years (163.13 mIU/mL, $p = 0.67$) and 6–8 years (247.89 mIU/mL, $p = 0.06$; Table 3).

Discussion

Varicella is a common infectious disease that tends to occur in clusters in primary and secondary schools. Establishing a durable and efficient immune barrier

Table 2. Antibody status of children at different times after one dose of varicella vaccination in Qingdao, China, from November 2019 to August 2020[a].

Time after one dose of varicella vaccination (years)	N	Seropositive	Seropositivity rate (%)	*p*[b]	GMC (mIU/mL)	*p*[c]
0–2	220	128	58.18	Reference	127.95	Reference
3–5	84	36	42.86	< 0.01	111.50	0.04
6–12	169	73	43.20	< 0.01	97.34	< 0.01

[a] Age and gender were included as adjusted variables in all models; [b] Logistic regression model was used to analyze differences in seropositivity rate between groups, with the group 0–2 years after one-dose of varicella vaccination as the reference; [c] Linear regression model was used to analyze differences in GMC between groups, with the group 0–2 years after one-dose of varicella vaccination as the reference; GMC: geometric mean concentration.

Table 3. Antibody status of children at different times after two-dose varicella vaccination in Qingdao, China, from November 2019 to August 2020[a].

Time after two dose of varicella vaccination (years)	N	Seropositive	Seropositivity rate (%)	*p*[b]	GMC (mIU/mL)	*p*[c]
0–2	216	179	82.87	Reference	280.72	Reference
3–5	90	62	68.89	0.99	163.13	0.67
6–8	18	12	66.67	0.53	247.89	0.06

[a] Age and gender were included as adjusted variables in all models; [b] Logistic regression model was used to analyze differences in seropositivity rate between groups, with the group 0–2 years after two-dose of varicella vaccination as the reference; [c] Linear regression model was used to analyze differences in GMC between groups, with the group 0–2 years after two-dose of varicella vaccination as the reference; GMC: geometric mean concentration.

through effective varicella vaccination is critical to the control and prevention of varicella.

Currently, varicella vaccination is mainly administered as one- or two-dose varicella vaccination. Our results showed that children vaccinated with two doses of varicella vaccine had significantly higher seropositivity rates and GMC than those vaccinated with one dose. Although one dose of varicella vaccine may provide some protection, vaccination with one dose of varicella vaccine may lead to immune failure [5,13–15]. Two doses of varicella vaccine reduced the likelihood of immune failure and played an important role in increasing resistance to varicella infection and reducing the incidence of moderate-to-severe varicella [16–20]. Rieck *et al.* showed that the risk of varicella in unvaccinated individuals in areas with 68% coverage of two doses of varicella vaccine was significantly lower than in areas with 25% coverage [21]. Therefore, two-dose varicella vaccination and increased vaccine coverage are currently the most effective among measures for protecting the population against varicella infection [22,23].

This study showed significant differences in seropositivity rate and GMC between male and female children: the females showed significantly higher values. Other vaccine-related studies have reported similar results [24–26]. In the present study, the percentage of females with a history of varicella vaccination was slightly higher than that of males (83.4% vs. 79.5%). This finding may be one of the reasons for the higher seropositivity rate and GMC in females. However, a study in Jiangsu Province showed that the varicella seropositivity rate of females was significantly higher even when the vaccination rate of males was higher than that of females in the same area [11]. This result may be attributed to factors, such as difference in hormone production in males and females and varied immune system effects. In fact, estrogens enhance immune response, and androgens reduce immune response; strengthening initial humoral immune response and slowing down the waning of varicella immunity in females as compared with males after varicella vaccination [27–31].

The results grouped by age showed that children aged 4–6 years had significantly higher rates of anti-VZV IgG seropositivity and GMC than the other age groups. The potential reason is that the 4–6-year age group had the highest proportion of children with a history of varicella vaccination (97.2%) and the highest proportion of children who had received two doses of varicella vaccine (65.1%). The varicella vaccination policy in Qingdao City stipulates that the varicella vaccine can only be administered at the age of > 1 year, and thus the group of children aged < 1 year in this study were unvaccinated children. The seropositivity rate and GMC in children aged < 1 year can be attributed to maternal antibodies. However, owing to the limited sample size of children in this group, analyzing trends in the levels of varicella antibodies carried by their mothers over time was impossible after the children were born.

Our study showed significant decreases in seropositivity rate and GMC 3–5 years after one-dose varicella vaccination. Seropositivity rate decreased to 42.86%, and GMC decreased to 111.50 mIU/mL. This result is consistent with the findings of many studies that show that the protective effect of one-dose varicella vaccination begins to wane 3–5 years after vaccination [7,9,19,32,33]. By contrast, no significant decline in antibody levels was observed 8 years after the two-dose varicella vaccine. Notably, 6–8 years after the two-dose varicella vaccination, the seropositivity rate was still as high as 66.67%, and the GMC was 247.89 mIU/mL. This result may be due to the fact that the two doses of varicella vaccine improve protection and that two doses of varicella vaccine are administered when a child enters kindergarten or school life. Continued stimulation by external pathogens and acquired immunity provided by the vaccine allows the immune system to develop long-term immunity.

This study had several limitations. First, owing to the limited sample size, our study only analyzed changes in antibody levels in different time groups after vaccination and failed to explore in detail changes in antibody levels in each year after varicella vaccination. Second, this cross-sectional study could only suggest a

possible relationship association, and not prove causal relationship. Third, hospital-based sampling was not representative of the entire population of the area. Patients who seek medical advice may be different from the rest of the population. Patients who refused blood sampling may have refused to receive injectable vaccines. Finally, our study may have included a small number of asymptomatic children with varicella who did not go to the hospital and therefore could not be enrolled in the CISDCP.

Conclusions

Our study analyzed the antibody status of children aged 0–13 years without a history of varicella in Qingdao. Anti-VZV IgG antibody levels in children increased substantially with increasing dose of varicella vaccine. In contrast to the substantial decline in antibody levels 3–5 years after one-dose varicella vaccination, antibody levels after two-dose varicella vaccination showed no substantial decline at least 8 years. Thus, requiring children to receive two doses of varicella vaccine 3 years after the first dose is reasonable. We recommend that two doses of varicella vaccine be included in the national immunization program.

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Conflict of interests

No conflict of interests is declared.

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