A SEROEPIDEMIOLOGY STUDY OF VARICELLA AMONG CHILDREN AGED 0-12 YEARS IN TAIWAN

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Abstract. The epidemiology pattern of varicella appears to vary among regions with different climates, population densities, and degrees of development. This study investigated the age-specific varicella zoster virus (VZV) seroprevalence in children aged 0 to 12 years in Taiwan and compared these seroprevalences between free and private vaccination areas. Residual sera were collected from 13 hospitals with 1,401 valid samples. Immunoglobulin G antibodies to VZV were measured by enzyme-linked immunosorbent assay. Parents of 656 children answered questions about the varicella incidence and varicella vaccination history of their children. In the 8-12 year-olds, the seroprevance ranged between 88.0-93.8% in northern, central, and eastern, while it was only 76.1% in southern Taiwan. The seroprevalence of children 0-5 years old were significantly different between free and private vaccination areas. Seropositive children who reported no history of varicella or receiving varicella vaccine accounted for 26.1-59.3% of the total positive cases. Our findings suggest the possible effects of climate, geographical conditions, and lifestyle on the seroepidemiology of VZV in Taiwan. The efforts of implementing a varicella vaccination program in Taiwan should focus on reaching high levels of coverage.

INTRODUCTION

Varicella, caused by varicella zoster virus (VZV), is a common contagious disease worldwide. The epidemiology pattern of varicella appears to vary among regions with different climates, population densities, and degrees of development (Fairley and Miller, 1996; Yawn *et al,* 1997; Gershon *et al,* 1999). It has been suggested that a trend towards lower seroprevalence of VZV with decreasing latitude is plausible because the age-related cumulative incidence of VZV in tropical climates is lower than in temperate zones (Garnett *et al,* 1993). In temperate regions, generally more than 90% of the population has acquired immunity to VZV during the first 15 years of life (Preblud, 1986; Wharton, 1996; Aebi *et al,* 2001). In the pre-vaccination era, the seroprevalence was 83% in the 11-15 year-old in Taiwan (Lin *et al,* 1996), and ranged between 51% to 70% in 10-14 year-old in Malaysia, Philippines, and Thailand (Barzaga *et al,* 1994; Khainullah *et al,* 1996; Migasena *et al,* 1997).

Although varicella is generally a mild disease, occasionally severe complications do occur. In addition, its very high incidence among healthy children gives rise to considerable morbidity. A live attenuated varicella vaccine developed from the Oka strain of VZV was approved for administration to children in Japan in 1986, in the United States in 1995, and in Taiwan in 1997. By the end of 2003, there have been more than 1 million varicella vaccine doses being imported in Taiwan. Except in two local areas (Taipei city and Taichung county/city), where free varicella vaccines have been provided to 12-month old children since October 1998, the varicella vaccines have been available only in the private markets in Taiwan.

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Since 2004, varicella vaccination has been included in the routine childhood vaccination program in Taiwan nationwide. The current study, which was conducted in 2003, described the age-specific VZV seroprevalence in children aged 0 to 12 years in Taiwan and compared the seroprevalences between areas where free varicella vaccines were provided and areas where vaccines were available in private markets only. The results of the epidemiological data are essential in evaluation of the efficiency of varicella vaccination strategies.

MATERIALS AND METHODS

Between August and December 2003, sera were collected from children aged 0 to 12 years old. These sera were residual specimens submitted to laboratories for other diagnostic purposes. There were total 13 hospitals participating in this research, including 3 in free vaccination areas and 10 in private vaccination areas. According to the geographical locations, the 10 hospitals in private vaccination areas were divided into 4 groups, including 2 in northern, 1 in central, 5 in southern, and 2 in eastern Taiwan. Out of the 1,423 sera tested, 22 gave inconclusive results and were excluded. The 1,401 valid samples included 514 from free vaccination areas (470 from Taipei City and 44 from Taichung County) and 887 from private vaccination areas. These 887 samples consisted of 252 from northern, 156 from central, 373 from southern, and 106 from eastern Taiwan.

In addition to estimating the age-specific seroprevalence, we asked parents of 656 children questions regarding the varicella incidence and varicella vaccination history of their children to further evaluate the proportion of possible sub-clinical infections. The age-specific proportion of sub-clinical infection was estimated by dividing the number of seropositive children who had no history of varicella and receiving varicella vaccine to the number of total respondents in each age group.

Sera were maintained at -20ºC until serological analysis was performed by the laboratory in the Department of Medical Technology in Fooyin University (Kaohsiung, Taiwan). IgG antibodies to VZV were measured using an enzyme-linked immunosorbent assay kit, Enzygnost anti VZV/IgG (Dade Behring, Marburg, Germany), following the instructions recommended by the manufacturer. The test has a reported sensitivity of 99.3% and specificity of 100%. Sera were classified as negative if the optical density was less than 0.1 and as positive if higher than 0.2. Sera with optical density between 0.1 and 0.2 were classified as inconclusive. The inconclusive samples were not re-tested and the subjects were excluded from the study.

Age-specific as well as overall seroprevalences were compared with the chi-square test among 4 geographical regions and between free and private vaccination areas. All computations were performed in SPSS 10.0 for Windows (Chicago, IL, USA).

Table 1
Seroprevalence of VZV IgG antibodies among children living in private varicella vaccination areas.

Age	Areas							
	Northern		Central		Southern		Eastern	
	Positive/Total	%	Positive/Total	%	Positive/Total	%	Positive/Total	%
0	9/19	47.4	7/18	38.9	10/25	40.0	4/17	23.5
1[a]	2/14	14.3	8/14	57.1	7/23	30.4	2/19	10.5
2-3[a]	26/50	52.0	21/30	70.0	30/70	42.9	9/34	26.5
4-7	80/119	67.2	38/44	86.4	96/146	65.8	13/20	65.0
8-12	44/50	88.0	45/50	90.0	83/109	76.1	15/16	93.8
Total[a]	161/252	63.9	119/156	76.3	226/373	60.6	43/106	40.6

[a]$p<0.05$

RESULTS

Table 1 showed the results of the seroprevalence among children from private vaccination areas in Taiwan. The regional differences were significant in the age 1 and 2-3 years and when subjects of all ages were combined. In the age 0 group, seroprevalence was the lowest in eastern Taiwan, although not statistically significant. In the age 1-year group, the seroprevalences were lower than that of the age 0 group in all regions except in central Taiwan. In the 2-3 year-olds, the seroprevalence was also the lowest in eastern Taiwan. In the 4-7 year-olds, the seroprevalence was around 65% in northern, southern, and eastern, while reaching 86.4% in central Taiwan. In the 8-12 year-olds, the seroprevence increased to 88.0-93.8% in northern, central, and eastern Taiwan. The seroprevalence was only 76.1% in this age group in southern Taiwan.

Table 2 compared the seroprevalences in different age groups between free and private vaccination areas. The seroprevalence was significantly different between the 2 areas in the age 0 group (64.4% in free vaccination areas *vs* 38.0% in the private vaccination areas). In the 1-year olds, the seroprevalence decreased by around 20% from the respective age 0 group to 44.9% in the free vaccination areas. It decreased by approximately 10% from the respective age 0 group to 27.1% in the private vaccination areas. The seroprevalences in children 0-5 years old were significantly different between these 2 areas. Except in the 6 and 10-year olds, the seroprevalences were higher in the free vaccination areas than in the private vaccination areas, although not significantly after age 5 years.

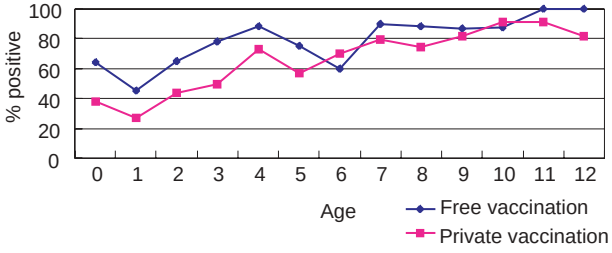

Fig 1–Comparison of seroprevalence of VZV IgG antibodies between children in free and private vaccination areas, Taiwan, 2003.

Table 2
Comparison of seroprevalence of VZV IgG antibodies between children living in free vaccination areas and private vaccination areas.

Age	Areas				Significance
	Free vaccination		Private vaccination		
	Positive/Total	%	Positive/Total	%	
0	125/194	64.4	30/79	38.0	0.00
1	22/49	44.9	19/70	27.1	0.05
2	32/49	65.3	40/91	44.0	0.02
3	32/41	78.0	46/93	49.5	0.02
4	30/34	88.2	83/114	72.8	0.06
5	30/40	75.0	47/83	56.6	0.05
6	18/30	60.0	58/83	69.9	0.32
7	17/19	89.5	39/49	79.6	0.49
8	23/26	88.5	44/59	74.6	0.15
9	13/15	86.7	48/59	81.4	0.63
10	7/8	87.5	43/47	91.5	0.56
11	3/3	100.0	30/33	90.9	1.00
12	6/6	100.0	22/27	81.5	0.56
Total	358/514	69.6	549/887	61.9	0.00

Table 3
Estimation of varicella infection among children reported no history of varicella and receiving varicella vaccine.

Age group	Seropositive		Total number of subjects	Proportion of B/A (%)
	All (%) (A)	No varicella and vaccination history (%) (B)		
0	20 (54.1)	19 (51.4)	37	95.0
1-2	46 (34.1)	12 (8.9)	135	26.1
3-4	68 (53.1)	19 (14.8)	128	27.9
5-6	74 (67.9)	26 (23.8)	109	35.1
7-8	65 (70.7)	29 (31.5)	92	38.7
9-10	72 (81.8)	36 (40.9)	88	50.0
11-12	59 (88.1)	35 (52.2)	67	59.3
Total	414 (63.1)	176 (26.8)	656	42.5

Table 3 estimated the proportion of seropositive subjects who reported no history of varicella and no history of receiving varicella vaccine to all seropositive cases and to total respondents. Fifty-one percent of the infants were seropositive with no history of varicella and vaccination, accounting for 95% of the total positive in this age group. The proportions of seropositive children who reported no history of varicella and vaccination steadily increased from 8.9% in the 1-2 year-olds to 52.2% in the 11-12 year-olds, accounting for 26.1% to 59.3% of the total positive cases.

DISCUSSION

Our study is the first nationwide varicella seroepidemiology study in Taiwan. Since it is difficult to obtain blood samples from young children, we used residual sera from hospitals instead of from randomly sampled subjects. It is likely that using random samples would not necessarily improve the representativeness in children with such young age because of the possible low response rate in the community. Kelly *et al* (2002) have found that a random cluster survey and a convenient sampling give comparable estimates of immunity to vaccine preventable diseases like varicella in children of school age in Australia. These authors further suggested that the collection of a convenience sample of sera from diagnostic laboratories is an appropriate sampling strategy to provide population immunity data (Kelly *et al,* 2002).

The different epidemiology of primary varicella infection between tropical and temperate countries is well established. It is postulated that high ambient temperature and humidity in the tropics could reduce VZV transmission by inactivating the virus in the cutaneous lesions (Lokeshwar *et al*, 2000). Except southern Taiwan, which is located in the sub-tropical to tropical regions, the rest parts of Taiwan are located in the temperate to sub-tropical regions. The monthly average temperature is approximately 3ºC higher in southern than in the rest parts of Taiwan. The comparison of seroprevalence among private vaccination areas in our study indicated a smoother increase and a smaller extent of infection in southern Taiwan. The seroprevalence was around 90% in 8-12 year-old children in the temperate to sub-tropical regions, whereas it was only 76% in the sub-tropical to tropical regions.

Our results were consistent with the findings from other temperate countries. In the United States, studies have reported 100% seropositivity by the age of 13 years (Munech and Nassim, 1986) or only 6% susceptible in 11 to 19 year-old teenagers (Wharton, 1996). Similarly, in the United Kingdom, over 90% of individuals were infected by the age of 15 years (Fairly and Miller, 1996). VZV seroprevalence reached over 90% among 8 to 9-year-old children in Germany (Watzler *et al,* 2002) and 91.8% among 10 to

14-year-old in Spain (Salleras *et al,* 2001). In Belgium, the seroprevalence was 92.5% in 9 year-old children (Thiry *et al,* 2002). In Switzerland, VZV seroprevalence was 97.7% at age 10 years (Aebi *et al,* 2001) and 96.6% in 13 to 15-year-old adolescents (Heininger *et al,* 2001).

The seroprevalence in children 8-12 years old in southern Taiwan fell between those in temperate and tropical regions. A Turkish study reported a VZV seroprevalence of only 90% in the 15 to 19 year-olds (Kanra *et al,* 2002). An Italian study indicated that VZV seroprevalence only reached 91.8% in the 20 to 39 year-olds (Gabutti *et al,* 2001). This study reported that about 17% of Italian 10 to 19 year-olds lacked immunity to VZV. Authors of these two studies attributed the lower seroprevalences to climatic conditions. In tropical countries like India, the seroprevalence was 71.7% among the 11 to 15 year-olds (Lokeshwar *et al,* 2000). The seroprevalences in children aged 10-14 years in Thailand, Malaysia, and Philippines were 70, 50.8, and 57%, respectively (Barzaga *et al,* 1994; Khainullah *et al,* 1996; Migasena *et al,* 1997.

Varicella appears to affect in later childhood in eastern region than in other parts of Taiwan since only 26.5% of the 2-3 year-old children in this area is immune to VZV. Eastern Taiwan has much more mountainous area and lower population density than western (including the northern, the central, and the southern) Taiwan, where most population live in larger urban and industrial cities. The different geographic condition and lifestyle in eastern Taiwan have probably changed the epidemiology of VZV. The smaller kindergarten and pre-school attendance rate among eastern young children has delayed the spread of highly infectious airborne childhood infections like VZV (Fairley and Miller, 1996; Yawn *et al,* 1997; Brisson *et al,* 2001). Similar observation has been made in Thiry *et al*'s study comparing VZV seroprevalences at 2 to 4 year-olds in Belgium, Switzerland, Germany, and Italy (Thiry *et al,* 2002).

Free varicella vaccines were provided to 1 year-old children after October of 1998 in Taipei city and Taichung city/county. Therefore, children aged between 1 and 5 years in 2003 living in these areas were eligible to receive free varicella vaccine. Our results indicated that the seroprevalence in children aged 0-5 years were significantly higher in free vaccination areas than those in the private vaccination areas. The higher seroprevalence among children aged less than 1 year in the free vaccination areas is probably due to the higher seroprevalence among pregnant women in the city. In their study during 1992 and 1994, Lin *et al* (1996) have reported that the varicella seroprevalence was about 85% in Taipei city. We have no way, however, to examine the assumption since no other varicella seroepidemiology study has ever been done in the rest parts of Taiwan. Likewise, given the fact that the seroprevalence in 1-year-old children reduced in both free and private vaccination areas, the higher seroprevalence observed in this age group in free vaccination areas is probably due to the residual maternal antibodies instead of the effect of vaccination.

Although the vaccine is free, we suspected that the acceptance of the newly introduced vaccine is probably lower than expected, especially in younger children. In our other investigation, the seroconversion rate of VZV vaccine in children reached at least 91%. However, none of the seroprevalence in the age groups under 6 years in the free vaccination areas was over 90%.

Our results showed that the seroprevalence among children aged 1 to 12 years who reported no history of varicella and receiving varicella vaccine ranged between 8.9% and 52.2%. Lieu *et al* (1998) also reported that children without a clear history of varicella have seroprevalence ranging from 9 to 68%, depending on age and clinical history. The proportion of seropositivity among children without history of varicella and vaccination to all seropositivity increased from 26% to 60% as the age increases. That is, we could estimate that 1 out of 4 seropositive children aged 1 to 2 years has been infected subclinically. Similarly, 3 out of 5 seropositive children aged 11 to 12 years old have been infected sub-clinically. The increment of the proportion of sub-clinical infection remained relatively stable, ranging from 6% to 11% for every 2 years increase in age. If we assume that the population is stable and there has been no particular variation in varicella epidemiology during the past

12 years, we could estimate that the occurrence of sub-clinical infection ranges approximately 3-5% each year for children under 12 years in Taiwan.

As with any other mass pediatric vaccination programs, the consequences of the extensive use of varicella vaccine must be thoroughly evaluated from an epidemiological point of view. Our results indicated a lower extent of VZV infection in southern Taiwan and a later infection in eastern Taiwan among children aged under 13 years. These findings suggested the possible effects of climate, geographical conditions, and lifestyles on the seroepidemiology of VZV in Taiwan. Cost-benefit analysis of vaccination against chickenpox in Taiwan has shown that routine childhood vaccination program is worthwhile from the societal perspective (Hsu *et al,* 2003) and it has been included as one of the routine vaccination items nationwide since 2004. Efforts of implementing this program should focus on reaching high levels of coverage since fail to do so could lead to a possible increase in the mean age of acquisition of the infection, which should be avoided for communicable diseases in general (Anderson and May, 1990) and especially for varicella. In addition, given the estimate that about 60% of the 12 year-old children without a history of varicella and vaccination are seropositive, the use of serologic testing for varicella before vaccination in adolescents needs to be further evaluated.

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