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Changes in the epidemiology of varicella after the introduction of a universal vaccination program in the Republic of Korea

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ABSTRACT

Changes in the epidemiology of varicella after the introduction of a universal vaccination program in the Republic of Korea

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Introduction and Objective

Varicella (also known as chickenpox) is an acute and highly contagious disease caused by the varicella-zoster virus (VZV) and is a common childhood disease. The epidemiology of varicella has changed dramatically since introduction of the varicella vaccines that are highly effective in reducing the global incidence and burden of the disease. In the Republic of Korea, however, incidence of varicella has been increasing during 2006 to 2017 despite the implementation of a routine one-dose varicella vaccination program in 2005. This study was to investigate the changes in the epidemiology of varicella following the introduction of vaccination and to evaluate the vaccine effectiveness in Korea. The objectives are as follows:

(1) identify the effect of age, period, and birth cohort on increasing temporal trend of varicella incidence among children in Korea by conducting Age-Period-Cohort(APC) analysis.

(2) identify spatial patterns in varicella incidence and geographical risk factors of the disease by spatial analysis and fitting spatial regression model.

(3) evaluate the effectiveness of universal one-dose vaccination program on the incidence of varicella by performing a matched case-control study.

(4) assess the effect of varicella vaccination on disease severity despite that the vaccination might fail to protect against varicella incidence.

Methods

(1) Varicella incidence from January 2006 to December 2017 was obtained from the National Notifiable Disease Surveillance System data. Population statistics were available from the Korean National Statistics Office. The APC model was used to estimate the age, period, and cohort effects. APC analysis was conducted by the APC Web Tool proposed by Rosenberg.

(2) Varicella incidence of 250 districts (si-gun-gu) from January 2006 to December 2017 was also obtained from the National Notifiable Disease Surveillance System data. Sociodemographic data were available from the Korean National Statistics Office. Global (Moran's I) and local (LISA) spatial autocorrelation were calculated. Spatial regression analysis was performed to find sociodemographic predictors of varicella incidence to district level using spatial lag and spatial error model.

(3) The 537 cases and their individually matched controls were collected from the National Notifiable Disease Surveillance System. All confirmed cases were children with varicella in Seoul, Korea, between January 2013 and December 2013. To estimate the effectiveness of one-dose vaccination, conditional logistic regression analysis on the 1:1 matched pairs was performed after adjusting for the effects of possible confounders such as sex and age at vaccination. When calculating the effect of time since vaccination, we used conditional logistic models with dummy-coded variables.

(4) A total of 1,125 varicella cases reported as part of epidemiologic investigation of varicella from January 2015 to December 2017 in Seoul Metropolitan City were used. Data was provided by Korea Centers for Disease Control and Prevention (KCDC). Disease severity of patients was assessed by the number of skin lesions. Binary unconditional logistic regression analysis was performed to examine

the differences in disease severity between the two groups with factor of age controlled.

Results

(1) Varicella incidence and age-standardized incidence rates have shown a diagonally upward trend between 2006 and 2017. During the period, the incidence rate also increased for each age strata among children aged 0 to 12–year–old with age peak shifted from 4 to 6 years old. In the APC analysis, period and cohort curves showed similar increasing patterns.

(2) Local spatial clusters with high level of varicella incidence were initially confined to northeast region (Gangwon-do), rural and mountain area. In later, the 'hot spots' gradually spread to their neighboring districts and faded out over time, which led overall increase in incidence across the country. In spatial regression analysis, childhood percentage was risk factors on the incidence of varicella at district level while factors such as population density and number of hospitals have negative effect on the risk. Meanwhile, vaccine coverage rate was an insignificant factor on the incidence of varicella.

(3) In a matched case-control study, the overall effectiveness of one-dose varicella vaccination in preventing confirmed cases of varicella was

low (13%, 95% CI: -17.3–35.6) and the vaccine effectiveness sharply declined after the three year of vaccination due to waning of immunity. In specific, The fact that more than half of all vaccinees were immunized with the vaccine based on MAV strain, which only available in Korea, was distinct from the cases in other countries.

(4) Among a total of 1,008 varicella cases in Seoul, Korea, 869 cases (86.2%) were breakthrough cases and 139 (13.8%) were unvaccinated cases. The risk for severe illness was significantly decreased in breakthrough group than unvaccinated group. The risk for occurrence of moderate-to-severe disease in the breakthrough group was less than roughly half that of the unvaccinated group (OR = 0.570, CI: 0.365–0.890).

Conclusions

(1) The study describes the post-licensure epidemiology of varicella incidence with an aspect of time and age. The increasing trend in varicella incidence may be explained by vaccine failure. The age peak shifting could be associated with secondary failure, which relates to the waning of vaccine-induced immunity over time. The varicella vaccine is merely effective in the early years, but, in later, the incidence of breakthrough infection jumps as immunity rapidly wanes over time.

(2) The second study describes the post-licensure epidemiology of varicella incidence with an aspect of time and space. The result indicated that where have a low population density and a few healthcare providers and a high childhood percentage were vulnerable to varicella outbreak, while vaccine coverage showed no influence on the incidence due to its high vaccination rate. The overall increase in varicella incidence in Korea could be attributed by spread out of varicella from high incidence cluster to its neighboring districts.

(3) The third study was to evaluate the effectiveness of one-dose varicella vaccination program in Korea. A low effectiveness of vaccine and a rapid waning of immunity of administered vaccine in Korea suggested there is primary or/and secondary vaccine failure. This finding may provide a key to understand the increasing trend of varicella incidence following implementation of universal vaccination program in Korea. Due to an insufficient immunogenicity of the vaccine might have limited effectiveness to decrease in the incidence of varicella.

(4) The last study also assessed vaccine effectiveness with an aspect of effects on disease severity. The result suggested that one-dose vaccination was associated with the attenuation of disease severity in children varicella cases. Patients whose mild symptoms can also transmit varicella to others and often cause failure to isolation,

leading to outbreaks among those with close contacts in education facilities. Therefore, a recent increase in the incidence rate of varicella in Korea may be associated with a growing number of breakthrough cases

Key words : varicella, chicken pox, Age-period-cohort, case-control study, Spatial lag regression, Republic of Korea

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CHAPTER 1.

INTRODUCTION

1-1. Epidemiology of varicella and vaccine introduction

Varicella (also known as chickenpox) is an acute and highly contagious disease caused by the varicella-zoster virus (VZV) and is a common childhood disease. VZV is highly transmissible via respiratory droplets or direct contact with characteristic skin lesions of the infected person. Varicella is generally a mild disease, but severe complications may occur more often in adults, including infections of the lung (pneumonia) and neurological complications (e.g. encephalitis). Following primary infection, herpes zoster (also called shingles) may arise by reactivation of the same virus that remains latent in nerve cells. This usually occurs in adults aged 50 years or older and is accompanied by a painful rash.

The epidemiology of varicella has changed dramatically since introduction of the varicella vaccines that are highly effective in reducing the global incidence and burden of the disease [1]. The live attenuated vaccine was first developed based on the Oka VZV strain in 1974 and is now used widely in many countries. Although not universally adopted, WHO recommends that varicella vaccination should be introduced into routine immunization program. In December 2014, varicella vaccines were recommended 33 predominantly higher socioeconomic status countries [2].

The United States was the first country that adopted a universal varicella vaccination. In the US, routine one–dose vaccination of all children between the ages of 12 and 18 months was implemented in 1996 and has resulted in decreases in the incidence from 1.1–3.8 cases per 1,000 population between 1990 and 1994 to 0.3–1.0 cases between 1999 and 2001

[3]. The vaccine effectiveness of one-dose vaccination was estimated to be 85% (95% CI: 78–90%; p < 0.001) [4]. In Germany, where a routine varicella vaccination program was introduced in 2004, vaccination coverage between 2006 and 2011 was only 38–68%, whereas the number of cases decreased by 67%: from 6.6 per 1,000 patients in 2006–2007 to 2.2 in 2010 –2011 [5]. In Taiwan, implementation of a national free vaccination program led to an increase of vaccination coverage from < 10% before 2003 to 80% in 2004; in addition, there was a decrease in the age-standardized incidence rates from 7.2 in 2004 to 3.23 cases per 1000 person-years in 2008 [6]. In other countries where routine universal vaccination has been implemented, studies show significant reduction in the incidence of varicella [2].

In some countries, however, varicella vaccine still have not been adopted into their universal vaccination program due to cost-effectiveness of the vaccine and its negative impact on incidence of herpes zoster (HZ). In the United Kingdom, a study suggested when introducing a vaccine for routine childhood vaccination, there may an upward shift in age distribution of varicella, causing more severe disease burden [7]. In addition, a study suggested that implementation of universal varicella vaccination in children linked to an increased incidence of HZ in older populations [8].

1-2. Epidemiology of varicella and vaccination program in Republic of Korea

In Korea, varicella has become nationally notifiable since July 2005, by the time one-dose of varicella vaccine was introduced to national

immunization program and recommended for children aged 12-15 months old. Varicella vaccination was first started in private clinics for a high-risk group and some children after adoption of the vaccine in 1996. Considering an average of 600,000 doses per year was approved for market, about 480,000 to 1,280,000 person was estimated to have been administered varicella vaccine in private clinics. In January 2005, a one dose mandatory varicella vaccination was introduced to the national immunization program and was recommended for 12 to 15 month-old-infants. In 13th July 2005, varicella was listed on the national notifiable infectious disease, an approximate of 90,000 children from low-income families were administered a one-dose varicella vaccine by public health centers. With an assumption that the notification rate was 10 percent, a total of 210,000 were estimated to have varicella vaccination [9]. Since May 2009, the varicella vaccination program was implemented in private clinics providing subsidy of 30 percent of the vaccination cost. In 2014, a one-dose mandatory varicella vaccination becomes a totally free and universal program for all children aged 12 to 15 months old [10].

According to the National Notifiable Disease Surveillance System, incidence of varicella showed upward trend during 2006 to 2017 despite the implementation of a routine one-dose varicella vaccination. The incidence rate increased from 22.5 per 100,000 persons in 2006 to 154.8 in 2017 (Fig. 1-1). Given the vaccine coverage has reached up to 98.9% in 2012, this increasing trend raises doubt on the effectiveness of the vaccine.

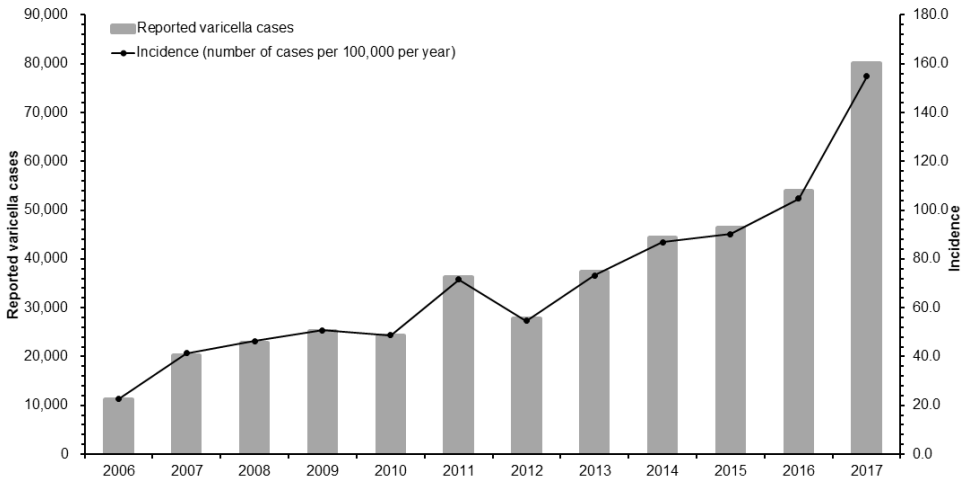


Figure 1-1. Reported cases of varicella and incidence rate to the National Notifiable Disease Surveillance System in the Republic of Korea

The data on the incidence rate of varicella and the vaccination coverage during the period before July 2005 when varicella was listed as a national notifiable infectious disease was unavailable. The pediatric sentinel surveillance, a sampling surveillance system for infectious disease among children, which was established in 2001, was a few available data covering the period before July 2005. The surveillance system was founded in June 2001 by voluntary participation of the 198 pediatricians and has been monitoring the incidence of infectious diseases which are common among children such as varicella. In the system, a private clinic was selected as sample with the ratio of 1 pediatrician per 100,000 population at a local level, which accounts for around 10 percent of the total number of pediatricians in the Korea and the reporting rate was maintained over 80 percent per annum; a sampled pediatrician voluntarily report to the infectious

disease surveillance team in the Korea Center for infectious Disease control and prevention through phone call, fax, or internet every week (until Tuesday) and even when having zero patient is reported. According to the surveillance system, the reported varicella cases and a part of the weekly reporting form is as follow (Fig. 1-2, Table 1-1) [9,11].

소아전염병 표본감시 주간보고서식														
1주일간 진료환자총수		( )명												
질병명 \ 연령		~6M	~12M	1세	2세	3세	4세	5세	6세	7세	8세	9세	10-14	15-19	20이상
수 두	남자														
	여자														

Figure 1-2. A part of the weekly reporting form in the pediatric sentinel surveillance

Table 1-1. Reported varicella cases and cases per 100 patients visits from the pediatric sentinel surveillance, 2001-2007

	2001	2002	2003	2004	2005	2006	2007
Varicella cases	6,370	9,244	14,296	13,257	15,165	13,779	14,119
Cases per 100 patient visits	0.30	0.25	0.28	0.28	0.29	0.26	0.27

Varicella is one of the national notifiable infectious disease and is monitored by mandatory surveillance system in which medical doctor, oriental medical doctor, and the head of the public health center or commander of a unit belonging to the Army, Navy, or Air Force are obliged to report when incidence of the disease. The obliged have to immediately report a confirmed or probable case to the head of competent public health center and then the case was finally reported to the Korea center for infectious Disease control and prevention through the web-based reporting system (http://is.cdc.go.kr). The mandatory surveillance system has a limitation of a reporting bias; The cases may be under-reported when the obliged do not fulfill their duty, and the cases may be over-reported when they report a similar symptom as varicella case due to health insurance coverage [12].

In the late 1980s, the Oka strain vaccine manufactured by Biken, Japan, was first imported and administered. In the mid 2000s, around the time a universal varicella vaccination program was adopted, there are four live attenuated vaccines are available; three (Varilrix by GSK, Varivax by MSD, Vari-L by Changchun) are imported and based on Oka strain, and one (Suduvax by Green Cross) is domestic and based on the MAV strain which is isolated from a 33-month-old Korean boy in 1989. Until recently, Suduvax and Vari-L predominantly used in the Korea and, in 2018, a domestic Oka strain based vaccine (Skyvaricella by SK Bioscience) was introduced. (Table 1-2)

Table 1-2. Varicella vaccines which are available in the Republic of Korea, 2006-2018

Year	Strain	Name of product	Manufacturer
2006	Oka	Varilrix	GSK
		Vari-L	Changchun Institute
		Sudu Vaccine	CJ
	MAV/06	Suduvax	Green Cross
Ref) The guidelines for varicella, 2006, KCDC			
2008	Oka	Varilrix	GSK
		Varivax	MSD
		Vari-L	Changchun Institute
	MAV/06	Suduvax	Green Cross
Ref) Varicella Vaccine, Hanyang Medical Reviews Vol.28.No.3.2008.			
2014	Oka	Vari-L	Changchun Institute
		Suduvax	Green Cross
Ref) The vaccines distributed on the domestic market (as of 2014.7.1), 2015, KCDC			
2018	Oka	Vari-L	Changchun Institute
		Skyvaricella	SK Bioscience
	MAV/06	Suduvax	Green Cross
Ref) The vaccines distributed on the domestic market (as of 2018.9.10.), KCDC (http://nip.cdc.go.kr)			

1-3. Study Objectives

This study was to investigate the changes in the epidemiology of varicella since the introduction of varicella vaccination and to evaluate the vaccine effectiveness of the national immunization program in Korea. The objectives are as follows:

First, identify the effect of age, period, and birth cohort on increasing temporal trend of varicella incidence among children in Korea by conducting APC analysis.

Second, identify spatial patterns in varicella incidence and geographical risk factors of the disease by spatial autocorrelation analysis and fitting spatial regression model.

Third, evaluate the effectiveness of universal one-dose vaccination program on the incidence of varicella by performing a matched case-control study if there is primary or secondary vaccine failure.

Finally, assess the effect of varicella vaccination on disease severity despite that the vaccination might fail to protect against varicella incidence.

The investigation of changes in epidemiology of varicella and evaluation of national varicella vaccination program may provide guidance for future epidemiological research and establish evidence for efficient vaccination policies.

CHAPTER 2.

Increasing varicella incidence rates among children in the Republic of Korea : An Age-Period-Cohort analysis

2-1. Introduction

Varicella is an acute infectious disease caused by the varicella-zoster virus. It is highly communicable, with secondary attack rates greater than 90% among susceptible individuals. The varicella vaccine, which became available in the early 1980s, conferred excellent immunogenicity against varicella infection. Countries such as the United States, Germany, and Taiwan where adopted varicella vaccination program experienced reduction in incidence rate of varicella [3,5,6].

In the Republic of Korea, one-dose of varicella vaccination was introduced to the National Immunization Program (NIP) in 2005. However, the incidence rate of varicella has yet to decline and, in fact, has been continuously rising, from 22.5 per 100,000 persons in 2006, to 154.8 in 2017 [13], despite the vaccine coverage has reached up to 98.9% in 2012 [14].

The age, period, and cohort (APC) effects may provide important epidemiologic clue to elucidate the current gap in immunity. Age effects are associated with different age groups, period effects affect all ages simultaneously over time, while cohort effects are related to changes among groups of individuals born in the same year. For instance, age effects imply the biological susceptibility of people of a specific age, period effects reflect environmental changes or diagnostic efficiency, and cohort effects represent early exposure to risk factors. The APC analysis has been used to study time trends in the incidence of infectious diseases [15-18]. The model separates time trends into the effects of age, period, and cohort.

In this study, we used APC model to obtain a better understanding of these effects on the incidence of varicella in Korea. The results might provide guidance for future epidemiological research and may implicate for better surveillance and vaccination policies.

2-2. Materials and Methods

Data collection

In Korea, varicella has become nationally notifiable since July 2005. In this study, to use full-year data on the annual varicella incidence, we obtained the National Notifiable Disease Surveillance System data from January 2006 to December 2017. Population statistics were available from the Korean National Statistics Office. The person-years of observation were tabulated into one-year classes for ages 0–12 and for the calendar period 2006–2017.

Statistical analysis

The APC model was used to estimate the age, period, and cohort effects. The standard APC model assumes that the observed number of varicella infections follows a Poisson distribution and that the incidence rates are a multiplicative function of age, cohort, and period, such that the logarithm of the rates is an additive function of the parameters [19-22]. The log age-specific rate λ (a,p) at age a in period p for people in cohort c=p-a, is as follows:

$$\log[\lambda(a,p)] = f(a) + g(p) + h(c)$$

where a, p, and c denote the mean age, period, and cohort, respectively, for the observational units and f, g, and h are parametric functions. The exact linear dependence of the regression variables (c=p-a) causes identifiability problem [22]. To decompose these three components into linear and non-linear parts and to obtain estimable functions such as the log-linear trend by period and cohort, we adopted the APC models proposed by Rosenberg [23], and conducted APC analysis by the APC Web Tool [24].

This online web tools provides “net drift”, indicates the annual percentage change of the expected age-adjusted rates over time (period and cohort); “local drift”, the annual percentage change of the expected age-specific rates over time; “longitudinal age curve”, the expected age-specific rates in reference cohort adjusted for period effects; “period (or cohort) rate ratio (RR)”, the age-adjusted relative risk in each period (or cohort) versus to reference one. And the corresponding Wald tests was used to determine significance.

2-3. Results

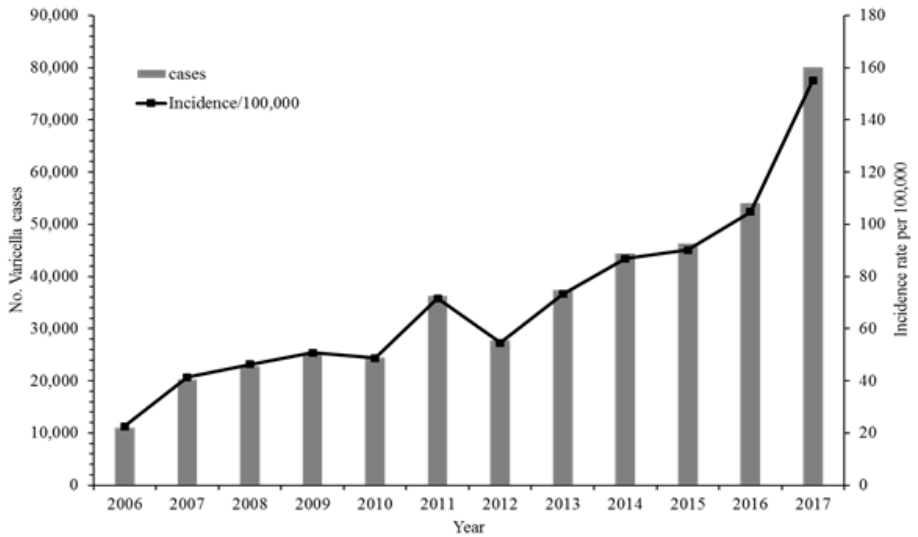
Descriptive data

Varicella incidence and age-standardized incidence rates have shown a diagonally upward trend between 2006 and 2017 (Fig. 2-1A). The incidence rate stratified by period also increased for almost all age groups (0 to 12–year–old). And the rates peaked between ages 4 and 6 years and we observed a drop-off in older ages (Fig. 2-1B).

An increasing tendency of higher varicella incidence rates with later

periods was determined for each age group (Fig. 2-2A). The age at which peak of incidence rate shifted from 4 years of age during 2006–2009, to 5 during 2010–2012, and to 6 during 2013–2017(except in 2016), which reflecting an age shift. The cohort curves also showed an increasing trend with later birth cohorts, especially, in ages 5 and 6 years (Fig. 2-2B). The age-specific rates were proportional to both period and birth cohorts.

(A)



(B)

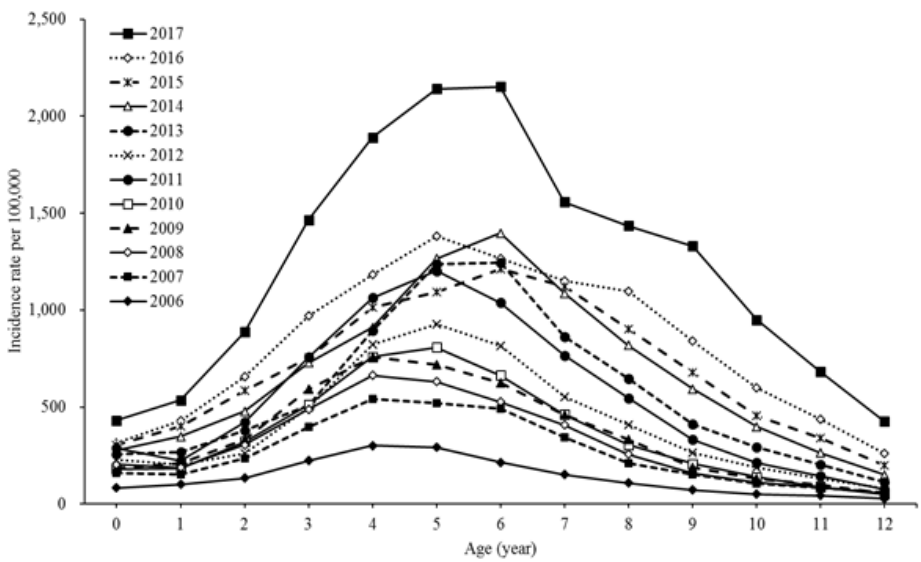
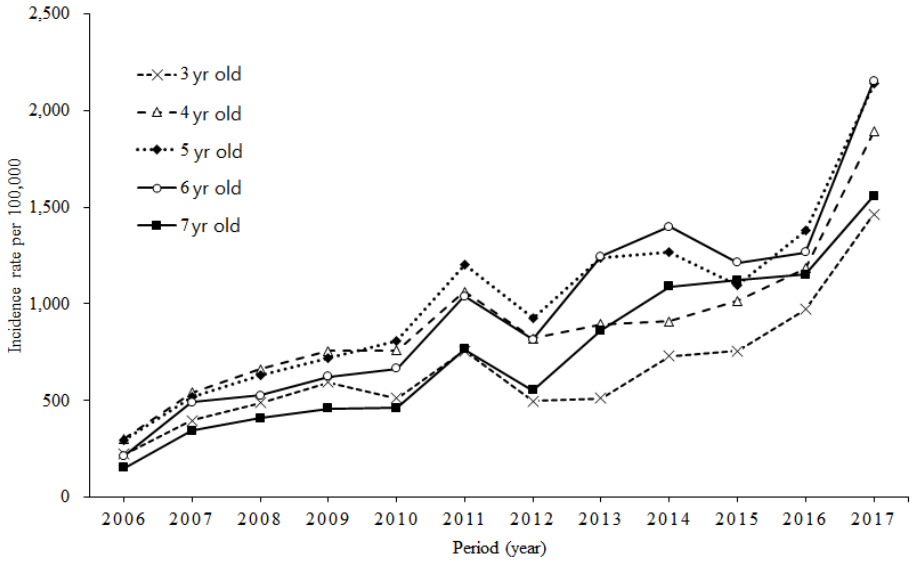


Figure 2-1. (A) Age-standardized incidence rates of varicella, 2006–2017 (B) Age-specific incidence rates of varicella, 2006–2017.

(A)



(B)

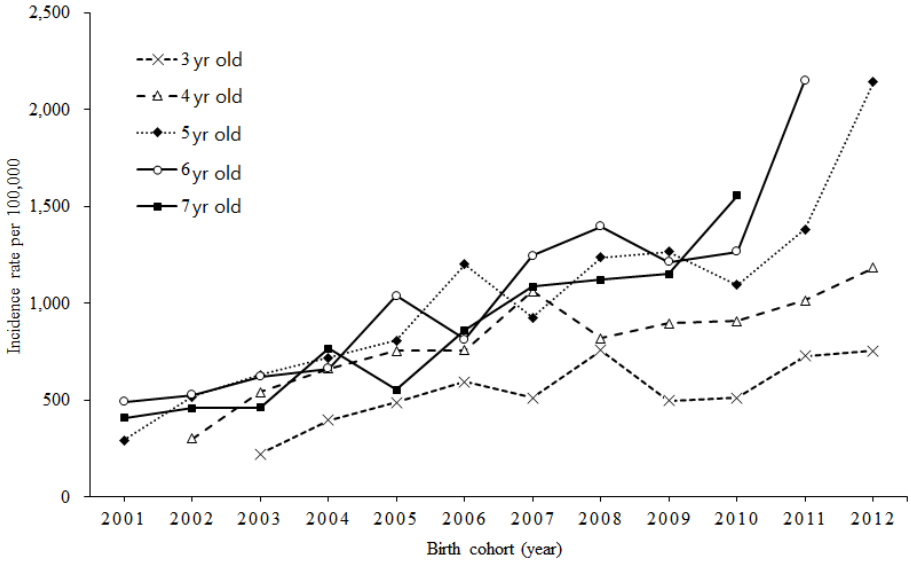


Figure 2-2. (A) Age-specific incidence rates of varicella by period, 2006–2017 (B) Age-specific incidence rates of varicella by birth cohort, 2001–2012.

Age-period-cohort analysis

The age, period, and cohort effects are presented in Fig. 2-3 and 2-4. The longitudinal age curve of varicella incidence rate displays the risk increased to peak at the ages 6–7 years and then declined thereafter (Fig. 2-3). The net drift, which indicate the annual percentage change of the estimated age-adjusted rates over time, was 17.4 and the curves of local drift, which reflect the annual percentage change of the estimated age-specific rates over time, showed upward trend with a peak at the age of 10–11 years.

The estimated period and cohort rate ratios (RRs) showed similar increasing patterns, however, period RR dramatically elevated in 2017 while cohort RR slightly decreased after the year 2015 (Fig. 2-4).

Wald tests suggested both period and cohort effects were statistically significant ($P < 0.05$ for all).

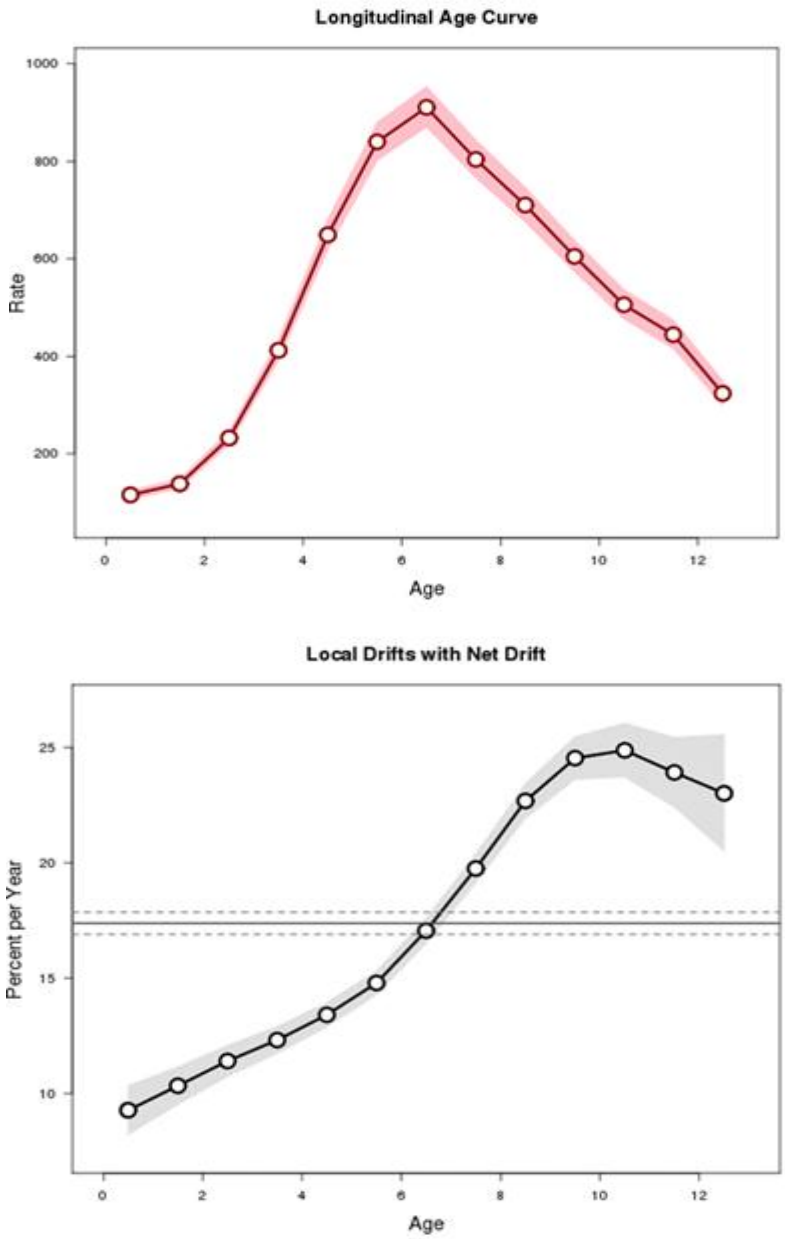


Figure 2-3. Longitudinal age curve and drifts(net drift and local drifts) obtained age-period-cohort analyses for the incidence rate of varicella and the corresponding 95% confidence intervals, 2006–2017.

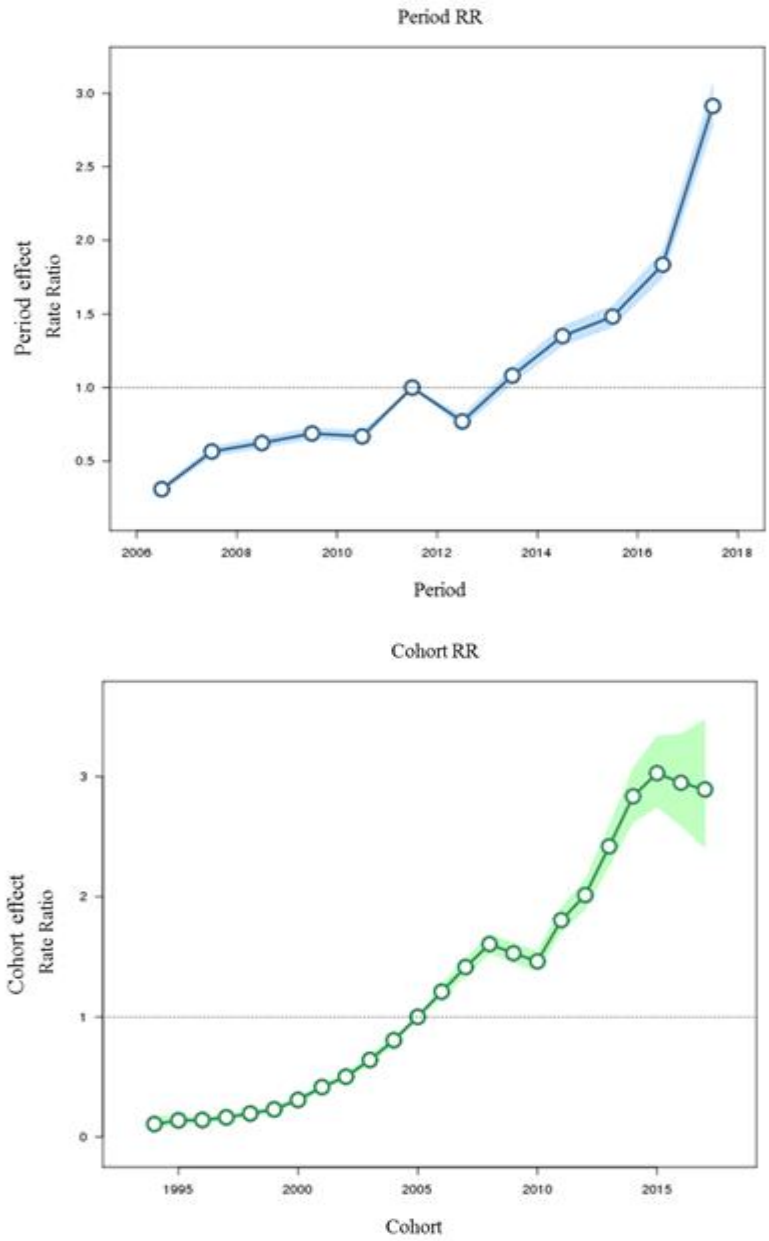


Figure 2-4. Period and cohort effects obtained age-period-cohort analyses for the incidence rate of varicella and the corresponding 95% confidence intervals, 2006–2017.

2-4. Discussion

Despite implementation of the universal varicella vaccination program in July 2005, there was an increase in the incidence rate of varicella between 2006 and 2017 in Korea. Our finding demonstrated that the period and cohort effects showed an upward trend over time except the age peak in the incidence rate shifting from 4 to 6 years old. This may indicate that a universal one–dose varicella vaccination in Korea has not been successful in preventing varicella zoster virus.

These the finding contradict to the observations in other countries. In the US, routine one–dose vaccination of all children between the ages of 12 and 18 months was implemented in 1996 and has resulted in decreases in the incidence from 1.1–3.8 cases per 1,000 population between 1990 and 1994 to 0.3–1.0 cases between 1999 and 2001 [3]. The vaccine effectiveness of one-dose vaccination was estimated to be 85% (95% CI: 78–90%; $p < 0.001$) [4]. Elsewhere, introduction of one–dose vaccine to the NIPs has led to decreases in the incidence even when vaccination coverage is suboptimal. In Germany, where a routine varicella vaccination program was introduced in 2004, vaccination coverage between 2006 and 2011 was only 38–68%, whereas the number of cases decreased by 67%: from 6.6 per 1,000 patients in 2006–2007 to 2.2 in 2010–2011 [5]. In Taiwan, implementation of a national free vaccination program led to an increase of vaccination coverage from < 10% before 2003 to 80% in 2004; in addition, there was a decrease in the age-standardized incidence rates from 7.2 in 2004 to 3.23 cases per 1000 person-years in 2008 [6].

Our data may be explained by primary or/and secondary vaccine

failure. Primary failure relates to the failed mounting of the immune system to produce antibodies initially [25]. A prospective case-based study conducted from 2006 to 2007 in Korea, showed almost no impact of varicella vaccine introduction, possibly due to insufficient immunogenicity [26]. The vaccine immunogenicity estimated in the case-control study was 54% (95% CI, 0.10–2.05), and the classical fluorescent antibody to membrane antigen (FAMA) assay revealed the seroconversion rate was 76.7%.

Secondary failure refers to the waning of vaccine-induced immunity over time [25]. Recent studies suggest that one-dose varicella vaccination have limited effectiveness to prevent outbreaks in mass gatherings or schools. In the U.S., after the introduction of varicella vaccine, there was a substantial difference in the vaccine's effectiveness in the first year after vaccination (97%) and in years 2 to 8 after vaccination (84%, P =.003) [27]. Another retrospective cohort study involving students attending elementary school suggested that 99% of one-dose vaccination coverage was not sufficient to prevent the varicella outbreak [28]. A longitudinal seroprevalence study in Korea showed a progressive decrease of the seropositivity rates following vaccination: 65% at age 1 year, 59% at age 2 years, 53% at age 3 years, and 49% at age 4 years [29]. The decreasing trend of antibody level may explain the continuing increase of varicella in all given cohorts despite the introduction of the vaccine into the national immunization program. According to Lee et al. [30] varicella vaccine effectiveness in Korea sharply declined after the three year of vaccination. Considering Korea’s high rate of vaccine coverage, most of the varicella

incidence is associated with breakthrough case. The age peak shifting detected in Korea, in spite of a rise in the incidence rate of varicella, could be associated with secondary failure. The age shift usually occurs with a decrease in the incidence rate because one-dose varicella vaccine applied to younger children about 12-18 months of age reduces exposure to circulating varicella zoster virus. The varicella vaccine, however, is merely effective in the early years, but, in later, the incidence of breakthrough infection jumps as immunity rapidly wanes over time.

Historical context is important in interpreting the data. In Korea, a varicella vaccine was first licensed and distributed in private market since 1988 [31]. There is no accurate data on vaccine coverage rate in the 1990s, but given the annual production volume over 500,000 doses, which is larger than the annual birth cohort of 400,000–500,000 the one dose coverage rate may have been sustained for more than decades. The first survey to measure vaccination coverage for varicella at regional rates was conducted in 2000 and was based on 850 children for whom vaccination record books were available. The survey revealed an overall varicella vaccination coverage of 72.5% [32]. In a subsequent coverage study, carried out in 2012 by face-to-face interview-based questionnaire survey among randomly selected 3,393 children aged 19-83 months, coverage with the one-dose varicella vaccine was 98.9% [33]. Given the high vaccination coverage in Koreans prior to the introduction to the NIP, the program may have not impacted in the incidence of varicella greatly.

Our study had a limitation that the period effect may have reflected registration bias. First, national surveillance of varicella was started in 2005,

by the time varicella vaccine was introduced to NIP; thus, the reporting system may not have been fully active during its initial stages, causing reporting bias. Second, given the nature of passive surveillance, a large portion of cases may be under reported especially those with mild breakthrough infections. In addition, lack of the incidence data before the implementation of one-dose varicella vaccine program made it hard to evaluate the exact effectiveness of the vaccination program. Despite these limitations, the present study is unique to evaluate the APC effects in a national varicella vaccination program. Our data indicate that individuals in the all cohorts, as well as more recently born cohorts have higher incidence of varicella infection, signaling a potential need for investigation on the gap of immunity.

In conclusion, there has been increase in the incidence of varicella among the Korean population with age peak shifting from 4 to 6 years old. Our data suggest the need for additional studies to address the current gap in varicella vaccination program in Korea.

CHAPTER 3.

Spatial epidemic characteristics and risk factor analysis of varicella in the Republic of Korea

3-1. Introduction

Varicella is an acute infectious disease caused by the varicella-zoster virus. The virus spreads mainly by touching or breathing in the virus particles that come from chickenpox blisters, and possibly through tiny droplets from infected people that get into the air after they breathe or talk, for example [34].

Countries such as the United States, Germany, and Taiwan where adopted varicella vaccination program experienced reduction in incidence rate of varicella [3,6,35]. The Republic of Korea, however, in spite of adoption of one-dose of varicella vaccination for children aged 12-15 month, its incidence rate showed an upward trend from 22.5 cases per 100,000 persons in 2006 to 154.8 cases in 2017 [36].

The geographic differences in varicella outbreak have not been assessed previously. As varicella tend to cluster geographically where susceptible population reside in close proximity, spatial analyses may provide better understanding to predict the incidence pattern of varicella. In this study, we used descriptive GIS methods and conducted spatial regression analysis to depict the spatial characteristics of varicella in Korea and to detect risk factors for varicella incidence at local level.

3-2. Materials and Methods

Data collection

The Republic of Korea is located in southern part of Korean Peninsula

and covers an area of 100,032km^2 with population of around 52 million in 2017. It consists of 17 provinces (si-do) divided into 250 districts (si-gun-gu). In this study, a total of 250 districts were included for spatial analysis.

In Korea, varicella has become nationally notifiable since July 2005. To collect the number of reported varicella cases at district level from January 2006 to December 2017, we used the National Notifiable Disease Surveillance System. Sociodemographic data on population density, childhood percentage, number of hospitals per 1,000 person, and vaccine coverage rate for each district were available from the Korean National Statistics Office. Direct standardization was used to derive varicella incidence rate for each districts.

Statistical analysis

An epidemic curve of monthly varicella cases during January 2006 to December 2017 was drawn to reveal the seasonal peaks and annual incidence was plotted to identify the annual trend during the periods.

To examine spatial distribution of incidence rates and their spatial autocorrelation, we visualized incidence rates divided into ten color scales between districts and calculated Moran's Index. To find local clusters such as 'hot spots' (high values next to high, HH), and 'cold spots' (low values next to low, LL), local indicators of spatial association (LISA) analysis was performed. Monte Carlo simulation was used to evaluate the p-value in conducting LISA analysis.

A spatial regression analysis was performed to find sociodemographic

predictors of varicella incidence to district level. The spatial lag and spatial error model is an extension of the traditional ordinary least square (OLS) regression model to include spatial dependency of variables or errors in the model. The spatial lag model takes the form:

$$Y = \rho WY + X\beta + \varepsilon$$

Where values of the dependent variable in neighboring locations (WY) are included as an extra explanatory variable. The spatial error model takes the form:

$$Y = X\beta + \lambda W\varepsilon + u$$

Where values of the residuals in neighboring locations ($W\varepsilon$) are included as an extra term in the equation. For the lack of predictors in 2017 and smoothing varicella incidence according to annual time trend, we focused on the last 6 years of the surveillance period (2012–2017).

We used GeoDa software (version 1.12, The University of Chicago, IL, USA) to conduct spatial analyses and QGIS software (version 3.2.1) to visualize maps of incidence rates and local clusters.

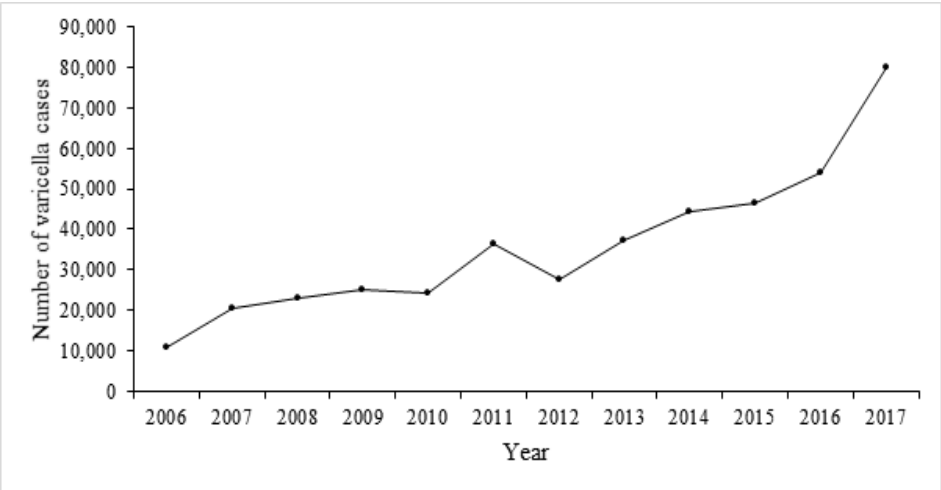
3-3. Results

Temporal trend

An increasing tendency of annual varicella incidence was observed during the whole 12-year period with a surge in 2017 (26,032 cases increased than the previous year) (Fig. 3-1A). During the period, varicella

incidence rapidly increased from 11,027 cases in 2006 to 80,092 cases in 2017 except small and large dips in 2010 (797 cases decreased than the previous year) and 2012 (8,486 cases decreased than the previous year), respectively. The monthly distribution of varicella cases showed a clear seasonal pattern with two peaks (Fig. 3-1B). The higher peak occurred in December and the lower peak occurred in May and the both of them fall into two regular semester (March-July, September-December).

(A)



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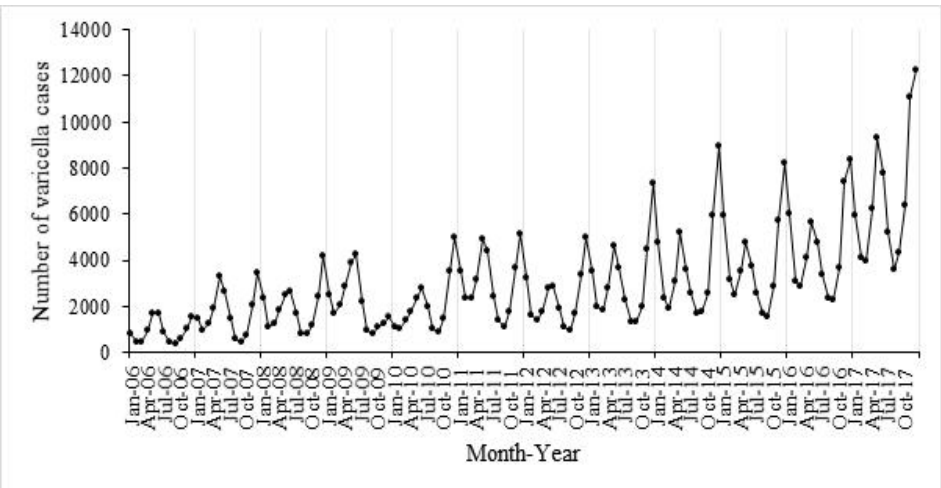

Figure. 3-1. Annual trend in varicella incidence during 2006-2017 and epidemic curve of monthly varicella cases in the Republic of Korea, between January 2006 and December 2017. (a) is for trend line, and (b) is for epidemic curve.

Spatial pattern

Varicella incidence cases distributed at 250 districts during the surveillance years were summerized in the following table (Table 3-1) being categorized into 17 provinces (si-do) (Fig. 3-2).

Table 3-1. Geographical distribution of varicella cases during 2006–2017 in the republic of Korea

Province	2006–2008		2009–2011		2012–2014		2015–2017	
(No. of districts)	N	(%)	N	(%)	N	(%)	N	(%)
Total(250)	50,967	(100.0)	81,641	(100.0)	106,979	(100.0)	179,920	(100.0)
Seoul(25)	4,390	(8.6)	8,032	(9.8)	11,641	(10.9)	21,864	(12.2)
Busan(16)	6,323	(12.4)	8,942	(11.0)	8,138	(7.6)	9,934	(5.5)
Daegu(8)	3,798	(7.5)	7,927	(9.7)	7,174	(6.7)	9,458	(5.3)
Incheon(10)	4,923	(9.7)	7,370	(9.0)	7,869	(7.4)	10,406	(5.8)
Gwangju(5)	1,005	(2.0)	1,917	(2.3)	2,828	(2.6)	5,532	(3.1)
Daejeon(5)	937	(1.8)	1,913	(2.3)	2,352	(2.2)	5,686	(3.2)
Ulsan(5)	2,677	(5.3)	3,112	(3.8)	3,760	(3.5)	5,525	(3.1)
Gyeonggi(42)	12,041	(23.6)	18,356	(22.5)	28,812	(26.9)	50,580	(28.1)
Sejong(1)	0	(0.0)	0	(0.0)	128	(0.1)	1,246	(0.7)
Gangwon(18)	6,228	(12.2)	7,945	(9.7)	6,339	(5.9)	5,397	(3.0)
Chungbuk(14)	1,010	(2.0)	2,039	(2.5)	1,807	(1.7)	4,008	(2.2)
Chungnam(16)	349	(0.7)	1,981	(2.4)	4,994	(4.7)	7,200	(4.0)
Jeonbuk(15)	1,556	(3.1)	1,087	(1.3)	4,946	(4.6)	7,851	(4.4)
Jeonnam(22)	1,210	(2.4)	2,408	(2.9)	4,059	(3.8)	8,130	(4.5)
Gyeongbuk(24)	2,203	(4.3)	3,011	(3.7)	3,753	(3.5)	8,707	(4.8)
Gyeongnam(22)	938	(1.8)	2,870	(3.5)	5,984	(5.6)	14,540	(8.1)
Jeju(2)	1,394	(2.7)	2,731	(3.3)	2,395	(2.2)	3,856	(2.1)

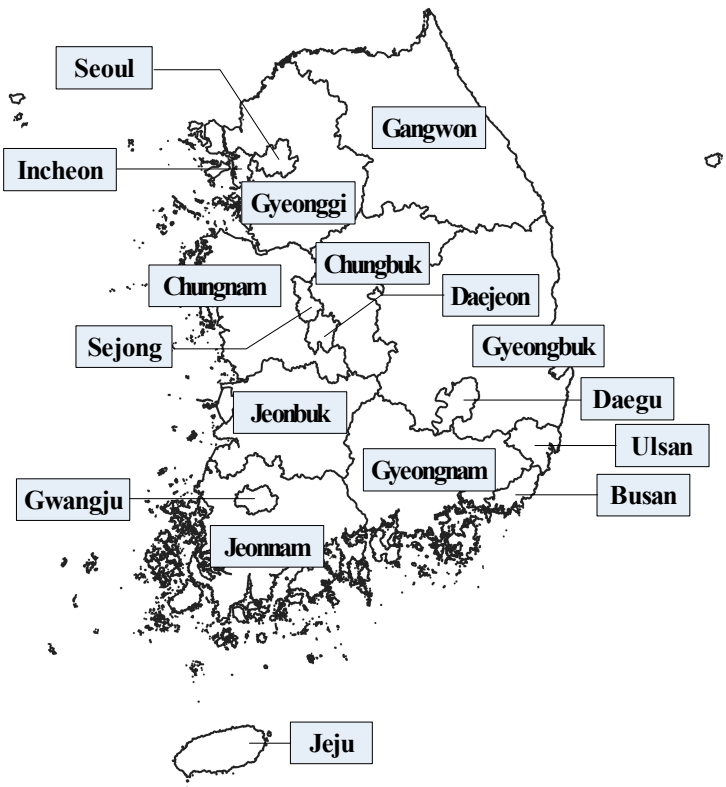

Figure 3-2. The map of 17 provinces in the Republic of Korea.

Varicella incidence rates of 250 districts according to surveillance years were described in color scaled maps with bold border line among 17 provinces (si-do) (Fig. 3-3). During the early surveillance periods of 2006–2008, there were concentrated regional distributions of outbreak in northeast (Gangwon-do) and south (Jeju-do) part of the country, where remote places from metropolitan city and located in rural area. During the second surveillance periods of 2009–2011, varicella incidence slowly spread out from northeast to its neighboring regions (Gyeonggi-do and Chungcheongbuk-do). During the third surveillance periods of 2012–2014, the increase of incidence rate was noted across the country. During the last surveillance periods of 2015–2017, a nationwide high incidence of varicella was reported and the high incidence region moved to central north (Yongin-si) and the edge of southwest (Mokpo-si) and southeast (Busan) part of the country.

The spatial pattern of clustering for varicella incidence rate was observed through global autocorrelation analysis (Table 3-2). A clear positive spatial autocorrelation was found within the varicella incidence rate during the whole periods of surveillance. Moran's Indices ranged from 0.1400 to 0.3210 and were all significant.

Local spatial clusters were shown in color categorized maps (Fig. 3-4). During the periods of 2006–2014, the High-High (HH) clusters were mostly confined to northeast region (Gangwon-do) and its neighboring districts (Yongin-si, Yeoju-si, Ichon-gun, Yangpyeon-gun in Gyeonggi-do). The neighboring districts also showed 'hot spot' clusters during the last surveillance periods of 2015–2017. The Low-Low (LL) clusters were mostly distributed southern part of the country during the surveillance periods. In the later periods, clusters gradually scattered and faded.

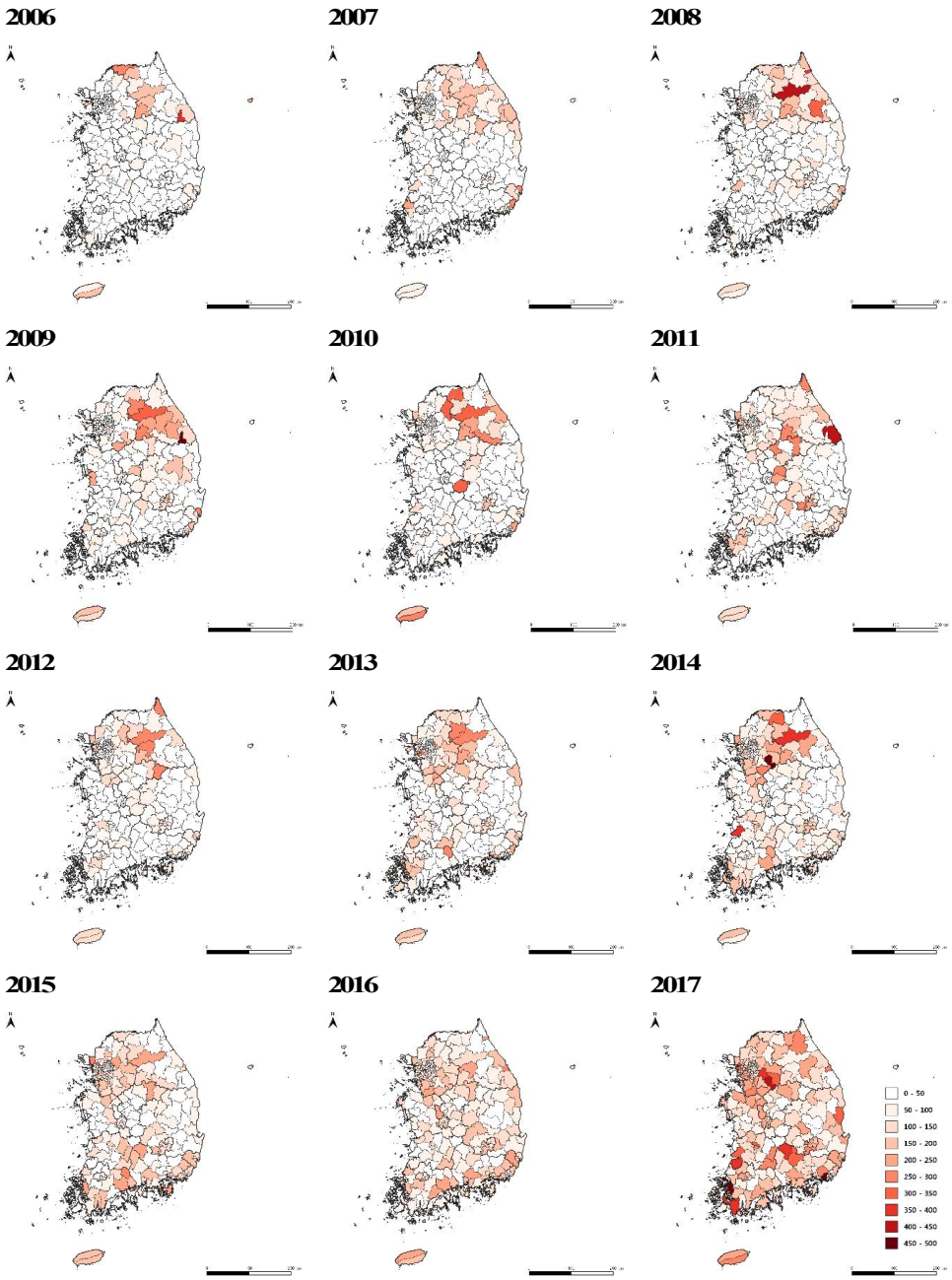

Figure 3-3. Incidence rate per 100,000/year of varicella in the Republic of Korea, 2006–2017.

Table 3-2. Global spatial autocorrelation analysis of varicella incidence in the Republic of Korea, 2006–2017

	Moran's Index	Z	p value
2006	0.1400	2.6566	0.019
2007	0.2443	4.9754	0.001
2008	0.2245	4.6494	0.001
2009	0.1894	3.7468	0.003
2010	0.3210	6.258	0.001
2011	0.2102	4.0321	0.003
2012	0.2880	5.393	0.001
2013	0.2768	5.285	0.001
2014	0.2201	4.2282	0.001
2015	0.1921	3.7084	0.002
2016	0.1939	3.6515	0.002
2017	0.2491	4.7742	0.001

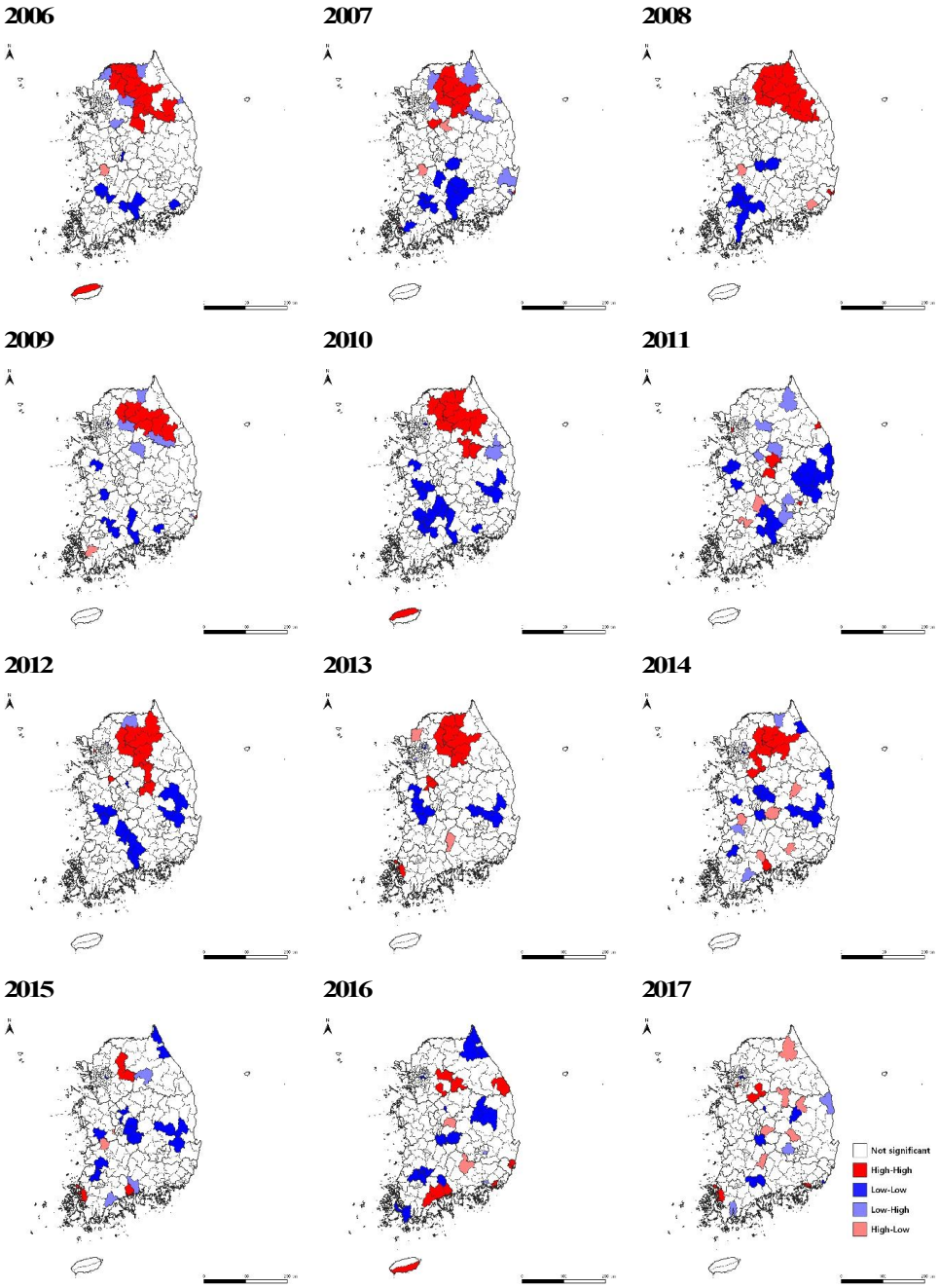

Figure 3-4. Cluster map of varicella incidence rate in the Republic of Korea, 2006–2017.

Spatial regression analysis

We assumed that sociodemographic factors such as population density, childhood (0 to 12-year-old) percentage, number of hospitals per 1,000 person, and vaccine coverage rate have influenced epidemics of varicella disease at district level (Table 3-3). Vaccine coverage rate of each provinces was over 96% and its geographical distribution was depicted in the map (Fig. 3-5). Using those variable as predictors, with annual varicella incidence as the dependent variable, we fitted a spatial regression model. Spatial error dependence resulted statistically significant and it could interpret 36.6% of the total variation (Table 3-4) while spatial lag dependence did not. Population density and number of hospitals per 1,000 person which is a proxy for local health infrastructure resulted having negative coefficient and the former was statistically significant. Childhood percentage had a positive coefficient and was statistically significant while vaccine coverage rate, which was categorized into four ordinal values by quartile of its distribution to avoid multicollinearity problem, resulted having positive coeffcient and statistically insignificant.

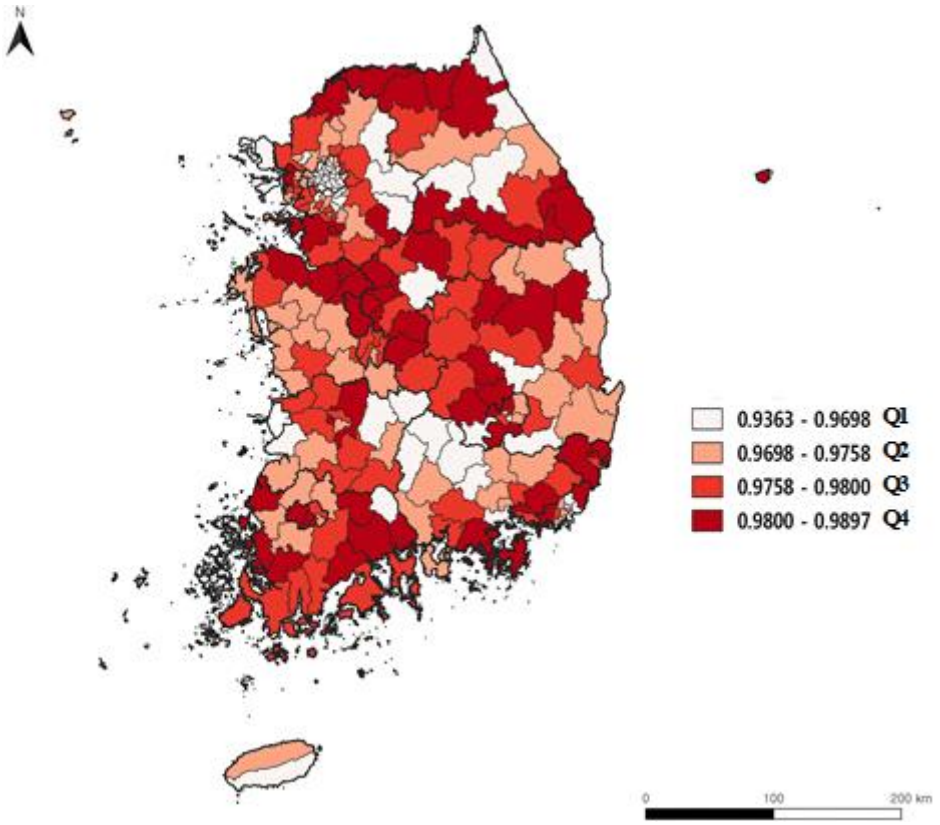

Figure 3-5. Map of average of vaccination coverage rates in the Republic of Korea, 2015–2017.

Table 3-3. Varicella incidence rate and sociodemographic predictors during 2012–2017 in the republic of Korea

Province (No. of districts)	Incidence rate (per 100,000)	population density (no. of person/㎢)	childhood percentage (%)	Number of hospitals (per 1,000)	vaccine coverage rate(%)
Total(250)	93.5	511.9	11.9	1.7	97.3
Seoul(25)	55.7	16653.8	10.4	2.1	96.2
Busan(16)	85.0	4571.9	10.0	1.8	96.8
Daegu(8)	111.0	2823.3	11.4	1.9	97.6
Incheon(10)	104.9	2765.7	12.2	1.4	97.7
Gwangju(5)	94.7	2936.8	13.4	1.8	98.2
Daejeon(5)	88.0	2824.8	12.9	1.9	97.7
Ulsan(5)	133.1	1096.7	13.0	1.5	98.4
Gyeonggi(42)	104.3	363.7	8.9	1.4	98.3
Sejong(1)	108.0	1217.2	13.2	1.5	97.4
Gangwon(18)	126.9	91.9	11.0	1.5	97.9
Chungbuk(14)	65.5	213.1	14.1	1.8	98.1
Chungnam(16)	98.2	251.2	12.5	1.6	98.0
Jeonbuk(15)	114.2	231.9	11.7	1.9	97.7
Jeonnam(22)	106.7	155.0	11.1	1.7	98.0
Gyeongbuk(24)	76.8	141.9	11.0	1.6	97.8
Gyeongnam(22)	102.2	317.8	12.6	1.4	97.7
Jeju(2)	168.8	330.0	13.6	1.7	97.0

Table 3-4. Spatial regression of sociodemographic predictors of varicella incidence in the Republic of Korea, 2012–2017

Variable*	Coeff.	S.E.	*P* value	AIC	R-squared
Constant	59.4212	12.5438	0.0000	2491.9	0.3658
Population Density	-0.0010	0.0005	0.0352		
Childhood Percentage	321.25	83.276	0.0001		
No. Hospitals per 1,000 person	-6.2536	3.6413	0.0859		
Vaccine Coverage Quartile†	4.3670	2.4043	0.0693		
Lambda	0.4731	0.0546	0.0000		

* Data of sociodemographic predictors in 2017 were missing and vaccine coverages were only available during 2015–2017. Spatial error model was fitted.

† Vaccine coverage quartile(min: 0.9363, Q1: 0.9697, Q2: 0.9758, Q3: 0.9800, max: 0.9897) was used to avoid multicollinearity problem.

3-4. Discussion

In this study, varicella epidemics varied over time and space. Our finding demonstrated that a temporal uptrend of varicella incidence in Korea from 2006 to 2017 and High-high positive spatial associations confined in northeast region (Gangwon-do) and their neighboring districts gradually spread and faded out over time, which led overall increase in varicella incidence across the country. In spatial regression analysis, childhood percentage has positive effect on the incidence of varicella at district level while population density and number of hospitals per 1,000 person have negative effect.

An upward trend in varicella incidence in Korea despite adoption of a universal one-dose vaccination is consistent with previous studies. Those studies suggested that an insufficient immunogenicity of the vaccine might have limited effectiveness to decrease in the incidence of varicella. In a population-based study, the effectiveness of the varicella vaccine was 13% (95% CI:-17.3–35.6) and the immunity rapidly waned three years after the vaccination [30]. Furthermore, a population-based study on effects of one-dose varicella vaccination on disease severity suggested one-dose varicella vaccination resulted milder symptoms leading to a failure to isolate patients and ended up outbreaks among those in close contact such as children in kindergarten or elementary school [37].

There was no study on spatial epidemic characteristics of varicella incidence at nation-wide scale. Nevertheless, an occurrence of local ‘hot-spots’ in remote areas such as Gangwon-do may be similar to the

results from other studies at province scale or focusing on other respiratory diseases like mumps and measles. In a spatio-temporal analysis of varicella in Valencia, Spain from 2008 to 2012, spatio-temporal clusters were identified where the population is economically disadvantaged or perhaps less educated and less aware of vaccination schedules [38]. In spatio-temporal analysis of measles [39] and mumps [40] in China, high-risk clusters were mainly distributed in the urban-rural transition zones or semi-urban areas because, with parents migrating to urban areas for employment opportunities, children were left in impoverished and remote area from vaccination clinics and became susceptible to disease.

The spatial regression results revealed that childhood percentage, which is population at high risk, had influence on the incidence of varicella. In the present study, childhood percentage showed vulnerability to varicella outbreak. This is in accordance with a previous study conducted APC analysis of varicella incidence in Korea [41], where the peak incidence was found at 4 to 6 years of age. In spatial analysis of mump in Korea, proportion of children population was a significant risk factor of mumps incidence because children were more susceptible than other age groups in population [42].

Number of hospitals per 1,000 person in district, considered as factor for health infrastructure in this study, also had effects on the incidence of varicella though statistically insignificant with p-value of 0.0693. The less healthcare providers had the district, the more had varicella incidence. This factor may be associated with low economic status of the district and be in line with the result of spatial analysis noted above.

The irrelevance of vaccine coverage rate to the incidence of varicella may be accounted by its value itself being higher than 90%, ranging from 92.3% to 100%. Given the high vaccination coverage in Koreans prior to the introduction of a universal one-dose varicella vaccination in 2005 and reached up to 98.9% in 2012, the vaccine may have not impacted in the incidence of varicella greatly.

Our study had several limitations. First, varicella cases were not collected from passive surveillance system, which cannot exclude reporting bias. A large portion of cases may be under reported especially those with mild breakthrough infections. Second, varicella cases were derived from aggregated data at district level not from individuals because of inaccessibility of personal information. Factors such as vaccination coverage, disease severity, and other socioeconomic status at individual level that may drive the varicella epidemic were not included in spatial regression model and have yet to be examined in detail. Finally, there might be multicollinearity among predictors of varicella incidence. We included popula tion density, childhood percentage, number of hospitals per 1,000 person, and vaccine coverage rate at once as independent variable. Thus, a flaw may exist in the interpretation of the causal relationship of the disease. Despite these limitations, this study is the first study to describe the spatial epidemiological characteristics of varicella by using spatial analysis at the district level in Korea and identified high-risk clusters and risk factors.

In conclusion, we intended to demonstrate the temporal and spatial pattern of varicella in the Republic of Korea during the past 12 years. Our study indicates that varicella incidence according to geographic regions vary

by population density, childhood percentage in the district and neighboring regions, suggesting the importance of community-level surveillance and monitoring strategy to prevent and control varicella incidence.

CHAPTER 4.

Effectiveness of varicella vaccination program in preventing laboratory-confirmed cases in children in Seoul, the Republic of Korea

4-1. Introduction

Varicella is an acute contagious disease caused by the varicella-zoster virus (VZV). A live attenuated varicella vaccine was first developed in 1974 and is now used widely in many countries including the United States, Germany, China, Taiwan, and Republic of Korea [43-47]. In a recent meta-analysis of global varicella vaccine effectiveness, varicella vaccine was reported to be effective in preventing varicella [48]. In specific, the United States where a universal two-dose varicella vaccination program was adopted since 2006 experienced declines in the incidence of the disease, the hospitalization of infected patients, and disease outbreaks [49].

In Republic of Korea, the varicella vaccination has been recommended for children in high-risk groups since 1988. Following the introduction of universal varicella vaccination by the National Immunization Program (NIP) in 2005, one-dose varicella vaccine has been recommended for all children aged 12–15 months. Four live attenuated varicella vaccines are available; three are based on the Oka strain, and one is based on the MAV strain. However, the incidence of varicella has yet to decline and, in fact, has been continuously rising, from 22.5 per 100,000 persons in 2006 to 73.2 in 2013 [50].

The objective of this study was to evaluate the effectiveness of one-dose varicella vaccination program in Republic of Korea by performing a matched case-control on children in Seoul.

4-2. Materials and Methods

We performed a matched case-control study on children who were younger than 12 years of age in Seoul, Republic of Korea. Relevant data were collected from the National Notifiable Disease Surveillance System (NNDSS). The NNDSS, which was established in 2001, consists of case-based national infectious disease data collected via a surveillance system; nationally notifiable diseases such as varicella must be reported by all local public health centers in the country. The varicella case data in the NNDSS include demographic and clinical details such as patient name, date of birth, gender, address, date of disease onset, laboratory confirmation, and vaccination status.

All cases were children with varicella identified in Seoul between January 2013 and December 2013. Cases were composed of confirmed and possible cases and we only use the former to avoid misclassification bias. We excluded cases born prior to universal varicella vaccination adopted in 2004 or after 2012, because varicella vaccination is recommended for children aged 12–15 months. In order to estimate the exact effectiveness of varicella vaccine, we also excluded subjects who developed varicella within 42 days after vaccination (the so-called “wild-type” varicella) and who were vaccinated twice.

We aimed at selecting controls to represent the source population from which varicella cases arose. From the same NNDSS data, mumps and scarlet fever were considered appropriate as controls for the following reasons; 1) mumps and scarlet fever are infectious diseases independent of varicella, 2)

age distribution in incidence of mumps or scarlet fever is similar to that of varicella.

In recruiting age-matched controls who had suffered from mumps or scarlet fever but had no history of varicella were identified in Seoul between January 2013 and December 2013 in the same NNDSS population where cases were reported. We matched each control by date of birth to a 1-month interval centered on the birth date of each case; a single control was randomly chosen if more than one candidate seemed appropriate. Ultimately, we created a list of 1:1 individually matched controls.

The effectiveness of a vaccine was estimated as follows; we calculated vaccine effectiveness by substituting the matched overall risk (OR) for the relative risk (RR) (1–RR); this approximates the RR in a case-control study [51].

Statistical analysis

The X^2test was used to compare the groups in terms of categorical variables, and the paired t-test was used to compare them with regard to continuous variables. To estimate the effectiveness of one-dose vaccination, we performed conditional logistic regression analysis on the 1:1 matched pairs after adjusting for the effects of possible confounders such as sex and age at vaccination; we then calculated matched odds ratios with 95% confidence intervals (CIs). When calculating the effect of time since vaccination, we used conditional logistic models with dummy-coded variables [52]. A two-sided P value < 0.05 was considered statistically significant. All data were analyzed with the aid of SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

4-3. Results

Subjects

In 2013, a total of 3,622 cases were reported. Of the 3,622, we excluded 2,807 possible varicella cases. Of the remaining 815 cases, we also excluded 278 cases; 230 had been born before June 2004, 27 had been infected within 12 months of birth, 5 had wild-type varicella, 16 had received two doses of vaccine (Fig. 4-1). Finally, we included 537 varicella cases in the study.

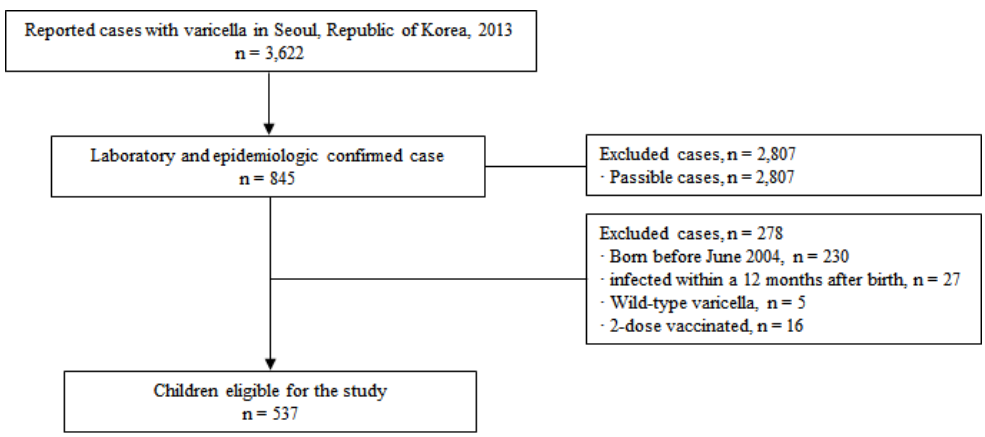

Figure 4-1. Subject recruitment procedures for 1:1 matched case-control study.

Characteristics of cases and controls

The 537 cases and their individually matched controls were similar in terms of both age and gender. The proportions of vaccinated cases and controls were similar, at 407 (75.8%) and 419 (78.0%), respectively (Table 1).

Of those who were vaccinated, 379/407 (93.1%) cases and 366/419 (87.4%) controls were vaccinated before 15 months of age, as recommended by the national vaccination policy. The proportion of cases vaccinated was significantly higher than the proportion of controls vaccinated ($P < 0.002$).

More than half of all vaccinated cases (241/407; 59.2%) and 227/419 (54.2%) of the controls received vaccine A; the proportions of the other vaccines used were as follows: Unknown (20.4% of cases and 19.1% of controls) > vaccine B (13.0% and 10.0%, respectively) > vaccine C (5.9% and 11.7%, respectively) > vaccine D (1.5% and 5%, respectively). However, the proportions of the vaccines used were significantly different between the groups ($P = 0.001$). Thus, both age at vaccination and type of vaccination were entered into the conditional logistic model.

Table 4-1. Characteristics of children with varicella and matched controls

Characteristics	Cases	Controls	p-value
Age(month)			0.967
Mean±SD	68.6±22.7	68.5±22.7	
Median(range)	70 (55-85)	70 (54-85)	
Gender(no,%)			0.297
Male	289 (53.8)	306 (57.0)	
Female	248 (46.2)	231 (43.0)	
MMR vaccine status(no,%)			<.0001
Unvaccinated	97 (18.1)	13 (2.4)	
Received MMR vaccine	440 (81.9)	524 (97.6)	
No. of varicella vaccination within 28days of MMR vaccine	1 (0.19)	3 (0.56)	
Vaccination status(no,%)			0.385
Unvaccinated	130 (24.2)	118 (22.0)	
Vaccinated	407 (75.8)	419 (78.0)	
Age at vaccination(month)			0.002
≤15	379 (93.1)	366 (87.4)	
> 15	28 (6.9)	53 (12.6)	
Type of vaccination			0.001
A	241 (59.2)	227 (54.2)	
B	53 (13.0)	42 (10.0)	
C	24 (5.9)	49 (11.7)	
D	6 (1.5)	21 (5.0)	
Unknown	83 (20.4)	80 (19.1)	

* Number of who received varicella vaccine at age younger than 12 months was 5 in control.

† MMR=measles-mumps-rubella.

Effectiveness of varicella vaccination

According to the conditional logistic regression analysis of the data for matched pairs, the overall effectiveness of one-dose varicella vaccination was 13% (95% CI, -17.3–35.6). The unadjusted estimate of vaccine effectiveness was 11.8% (95% CI, -17.1–33.6, P = 0.385) (Table 4-2).

Table 4-2. Overall effectiveness of varicella vaccine

Cases	Matched control		VE(95%CI)	*p*-value
	Vaccinated	Unvaccinated		
Vaccinated	327	80	13.0(-17.3–35.6)	0.361
Unvaccinated	92	38		

* When unadjusted for matched pairs, vaccine's effectiveness(1-OR) was 11.8%(-17.1%–33.6%, *p*-value=0.385). In addition, when using relative risk(RR) obtained from age controlled poisson regression model with robust standard errors, VE(1-RR) was 0.47%(-3.77%–6.75%, *p*-value=0.8863). When using excess relative risk(ERR), VE was 12.2%(-18.9%–30.0%, not significant under α=0.05).

† VE=vaccine effectiveness(1-matched OR), CI=confidence interval, OR=overall risk.

Conditional logistic regression analysis of vaccine effectiveness by each of the four vaccine manufacturers showed that the effectiveness of different vaccines varied (Table 4-3). Only vaccine C exhibited statistically significant effectiveness (88.9%; 95% CI, 52.1–97.4). The vaccine effectiveness were -5 % (95% CI, -61.9–31.9) for vaccine A, -100% (95% CI, -700–50.1) for vaccine B, 71.4% (95% CI, -37.5–94.1) for vaccine D, and -16.7% (95% CI, -101–32.4) for the vaccine of an unknown manufacturer.

Table 4-3. Effectiveness of varicella vaccine by manufacturers

Vaccine	Vaccinated cases with unvaccinated controls	Unvaccinated cases with vaccinated controls	VE(95%CI)		*p*-value
A	42	40	-5	(-61.9–31.9)	0.825
B	6	3	-100	(-700–50.0)	0.327
C	2	18	88.9	(52.1–97.4)	0.003
D	2	7	71.4	(-37.5–94.1)	0.118
Unknown	28	24	-16.7	(-101–32.4)	0.580

Overall, the effectiveness of a one-dose varicella vaccination was 75.8% (95% CI, 22.8–92.4) in the first year after vaccination. Thereafter, effectiveness decreased, falling to zero (or below) in the fourth and the sixth years. When adjusted for sex, age at vaccination and measles-mumps-rubella (MMR) vaccination within 28 days of birth, the effectiveness of varicella vaccine was not significant even in the first year after vaccination (Table 4-4).

Table 4-4. Overall effectiveness of varicella vaccination by time since vaccination

Time since vaccination(year)	No.of Vaccination		Unadjuste VE (95% CI)	*p*-value	Adjusted VE (95% CI)	*p*-value
	case	control				
1	19	31	75.8 (22.8–92.4)	0.017	67.1 (-12.0–90.3)	0.075
2	39	41	60.4 (-49.2–89.5)	0.171	49.5 (-96.0–87.0)	0.323
3	37	42	57.9 (-24.5–85.7)	0.118	52.1 (-45.7–15.8)	0.195
4	84	80	-7.2 (-130.9–50.2)	0.859	-15.7 (-153.6–47.2)	0.716
5	83	88	8.6 (-59.5–47.6)	0.752	-10.0 (-75.2–44.1)	0.973
6	86	68	-58.3 (-184.1–11.8)	0.124	-59.8 (-188.9–11.6)	0.120
7	37	41	13.2 (-56.0–51.7)	0.636	-10.9 (-60.5–50.6)	0.700
8	22	28	26.8 (-37.2–60.9)	0.091	25.3 (-40.4–60.2)	0.366

* VE=vaccine effectiveness, CI=confidence interval, MMR=measles-mumps-rubella.

† Results are adjusted for sex, MMR vaccination within 28 days, age at vaccination.

4-4. Discussion

The results of this study show that the overall effectiveness of one-dose varicella vaccination in preventing confirmed cases of varicella was low and insignificant (13%; 95% CI, -17.3–35.6). Specifically, the vaccine effectiveness of vaccine A, which was used in more than half of all vaccinations, was -5% (95% CI, -61.9–31.9), whereas vaccine C was highly effective (88.9%; 95% CI, -52.1–97.4). Vaccination was effective for only 1 year (the estimate of 75.8% fell to 67.1% after adjustment for confounders).

These results are consistent with those of a recent clinical case-control study assessing the effectiveness of an MAV strain-based varicella vaccine in Republic of Korea [26]. The estimated effectiveness was statistically insignificant (54%; 95% CI, -0.10–2.05) and the vaccine may not have alleviated clinical symptoms. In contrast, studies in other countries have shown that single-dose varicella vaccination was highly effective in terms of both reducing the prevalence of varicella and alleviating the symptom severity [45,53-55]. Oka strain-based varicella vaccines have been 87% effective in the United States [4,27], 86% effective in Germany [53], and 84% effective in China [45]. In other studies, varicella vaccination remained quite effective over time, although some waning was evident after the first year [27]. However, vaccine effectiveness then rebounded and persistent immunity was evident in some studies.

In Republic of Korea, more than half of all vaccinees were immunized with vaccine A, derived from an MAV/06 strain of varicella isolated from a 33-month-old Korean boy in 1989 [57,58]. An immunogenicity study and a

prelicensing safety study [58-60] showed that the strain was highly immunogenic and safe, with a post-vaccination geometric mean titer (GMT) of 173.7 and seroconversion rate of 100%. However, two clinical trials [61,62] and a recent clinical case-control study [26] showed that the vaccine did not ameliorate disease severity and was poorly immunogenic. A recent immunogenicity study on MAV and Oka (Vari-L) vaccine showed that the MAV vaccine generated higher seropositivity rates and antibody titers than the Oka vaccine and provided immunity against VZV, despite waning of immunity observed [29]. Not all Oka vaccine in this study, however, were effective against VZV, so it cannot directly be interpreted that MAV vaccine is effective.

The age at vaccination may also affect effectiveness, and our cases and controls differed significantly in this regard. In the United States, children vaccinated at younger than 15 months were at increased risk of breakthrough infection of varicella [27]. The proportion of children vaccinated at ages younger than 15 months was higher in the case group. Nevertheless, when we entered age at vaccination in our conditional model, using a dummy variable for time, age was not significant.

This study had several limitations. Selection bias may have been operating when we created our list of controls. The proportions of cases and controls who received MMR vaccinations differed, as it was lower in cases (81.9%) than in controls (97.6%). However, as Republic of Korea operates a universal health insurance system and as MMR vaccination is included in that system, the difference between cases and controls is unlikely to have introduced any substantial bias. Second, the severity of disease was not

recorded. To assess vaccine effectiveness, it is appropriate to ask if the vaccine alleviates severity of symptoms aspects of disease, such as fever, rash, and number of lesions. Again, we lacked such data. However, this is the first community-based matched case-control study on cases confirmed both epidemiologically and in the laboratory who underwent one-dose varicella vaccination in the Republic of Korea.

In conclusion, the one-dose varicella vaccination program did not clearly protect against varicella. Therefore, it is necessary to further investigate why we had reduced effectiveness of varicella vaccine in the Republic of Korea.

CHAPTER 5.

Effects of one-dose varicella vaccination on disease severity in children in Seoul, Republic of Korea

5-1. Introduction

Since the introduction of a universal varicella vaccination program, countries such as the United States, Germany and Taiwan has experienced reduction in incidence rate of varicella [63-65]. However, in the Republic of Korea–where one-dose of varicella vaccination recommending for all children aged 12-15 months was introduced to the National Immunization Program (NIP) in 2005 and the coverage has reached up to 98.9% in 2012 [33] the incidence rate of varicella has been continuously rising from 22.5 per 100,000 persons to 154.8 from 2006 to 2017 [66]. Previous study demonstrated that the vaccine immunogenicity may be not sufficient to provide effective immunity against varicella infection [26,30].

To our knowledge, there has been no population-based study to assess disease severity of varicella cases after adoption of a universal one-dose varicella vaccination to the NIP. In this study, we aimed to investigate the effect of vaccination on disease severity of varicella.

5-2. Materials and Methods

In this study, 1,125 varicella cases reported as part of epidemiological investigation of varicella from January 2015 to December 2017 in Seoul Metropolitan City were used. Data was provided by Korea Centers for Disease Control and Prevention (KCDC). According to the KCDC guidelines, an epidemiological investigation is re-quired if varicella outbreaks including index cases occur in more than 5% of students in a classroom within a 3-week period in schools, kindergartens or day care centers. When varicella

outbreak reported, public health centers should conduct an epidemiological investigation within 3 days, collecting data from the patient's parent with the help of school health teacher. The information includes the name, gender, date of birth, date of diagnosis, vaccination status, and related clinical symptoms such as of rash (the number skin lesion), fever, headache and arthralgia (Fig. 5-1). Varicella-related symptoms were determined by the clinical practitioners through physical examination of the patients. Disease severity of patients was assessed by the number of skin lesions as used in previous study [4,53,67,68]. Mild cases were defined as those having less than or equal to 50 skin lesions; moderate cases were defined as those having 51-249 skin lesions; severe cases were defined as those having more than or equal to 250 skin lesions.

We excluded 117 cases: 3 cases were excluded for infected before 12 months of age; 12 cases for having varicella within 42 days after vaccination (breakthrough varicella in infection with VZV occurring in a vaccinated person more than 42 days after vaccination); 4 cases for being 2-dose vaccinated; and 98 cases for being born before 2004.

We used t-test and Chi-square were to compare the difference in distribution in general characteristics, clinical symptoms and disease severity in the vaccinated (breakthrough) group and unvaccinated group. Binary unconditional logistic regression analysis was performed to examine the differences in disease severity between the two groups with factor of age controlled.

All statistical analyses were implemented by using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA). $P<0.05$ was considered significant and all tests of statistical significance were two-sided.

[5-3] 수두 (의사)환자 역학조사서

집단발병 코드 정보

집단발병 관리번호	집단번호		발병사례 번호	
☛ 집단번호은 관할지역에서 집단발병이 발생한 순서대로 아라비아숫자로 번호를 부여하고, 발병사례번호 역시 동일 집단내에서 발병한 순서대로 아라비아숫자로 번호를 부여하되, 발병여부가 나중에 확인된 학생은 확인된 순서대로 번호를 부여하도록 함. 전산상으로는 해당년도-보건소명-□□-□□□, 으로 확인되게 됨				

기관정보

해당보건소		작성자		작성일		연락처	( ) -
신고법의원		담당의사		소재지		연락처	( ) -

환자인적사항

환자성명		성별	□ 남 □ 여	생년월일		연령	세 개월
국적	□ 내국인 □ 외국인 ☛ 외국인은 국적 추가 입력 (국적:)					생존여부	□ 생존 □ 사망
주소		보호자성명				연락처	( ) -
실거주지							
소 속	□ 학교 □ 유치원(어린이집) □ 군부대 □ 회사 □ 장기요양시설 □ 요양병원 □ 기타 ( ) □ 없음	소속기관명		▪학생인 경우 학년/반 추가기입		소속기관 연락처	
소속집단 인원	1) 전체 층 명, 2) 해당 학급 인원 수: 명 ※어린이집, 유치원, 학교 등의 경우 소속집단의 반 인원과 전체 층인원 기재						

고위험군 추가 조사

고위험군 여부	□ 예 □ 아니오 ☛ 예(고위험군)인 경우 해당 고위험군 사항 체크 □ 수두백력이 없거나 접종력이 없는 면역저하자 (HIV 감염포함) □ 면역력이 없는 임신부 □ 분만 전 5일부터 분만 후 2일 내에 수두에 걸린 임신부에게 태어난 아기 □ 면역력이 없는 모체에게 재태연령 28주 이상으로 태어나 입원중인 미숙아 □ 모체의 수두면역력과 상관없이 재태연령 28주 미만, 출생체중 1,000g 이하의 입원중인 미숙아

임상 증상 및 경과 (해당 사항에 모두 V 표시)

주요 증상	□ 발열 □ 발진 □ 두통 □ 관절통 ☛ 발진 시작일 월 일 ☛ 발진 시작부위 □ 얼굴/목 □ 몸통 □ 팔/다리	신고기관 진단일	월 일
		수포 병변 갯수	□ <50 □ 50-249 □ 250-499 □ ≥500
합병증 유무	□ 예 ☛ 합병증 종류 : □ 피부/연조직 감염 □ 소뇌염/실조 □ 혈소판감염증 □ 뇌염 □ 탈수 □ 폐렴 □ 아니오		
항생제(항바이러스제) 치료여부	□ 예 (기간 :) □ 아니오		

발진발생 3주 전부터 조사 시점까지 의료기관 이용력 : □ 유 □ 무

진료 상황	의료기관		진료날짜	격리입원 기간
	기관명	연락처		
□ 외래			월 일, 월 일	
□ 입원			월 일 ~ 월 일	월 일 ~ 월 일 / □ 해당없음

▪ 격리입원 : 1인실 입원, 다인실 1인 사용, 코호트 격리

실험실적 검사

검체 종류	검체 채취일	검사 종류	검사 결과
가피 □ 미실시	월 일	PCR	□ 양성 □ 음성 □ 진행중
수포액 □ 미실시	월 일	PCR	□ 양성 □ 음성 □ 진행중
인두도찰 □ 미실시	월 일	PCR	□ 양성 □ 음성 □ 진행중
혈청 □ 미실시	월 일	IgM	□ 양성 □ 음성 □ 진행중
		IgG	□ 양성 □ 음성 □ 진행중

예방접종력

①	년 월 일	접종장소	□ 병의원 □ 보건소	백신명	등록된 백신의 이름
②	년 월 일	접종장소	□ 병의원 □ 보건소	백신명	등록된 백신의 이름
접종 추가 확인 내역	년 월 일	접종장소	□ 병의원 □ 보건소	(접종력 확인원) □ 아기수첩 □ 환자·보호자 기억 □ 기타( )	

감염원 조사

발진발생 전 3주간 유사증상자 접촉력 □ 예 □ 아니오

☛ 예인 경우 선행 유증상자 정보 작성

성 명	연령	소속	연락처	관계	발병일	환자구분	수두 접종력
					__월__일	□ 확진 □ 의사	□ 접종( ) 회 □ 안함 □ 모름
					__월__일	□ 확진 □ 의사	□ 접종( ) 회 □ 안함 □ 모름
					__월__일	□ 확진 □ 의사	□ 접종( ) 회 □ 안함 □ 모름

* **감염원 중 확진자가 신고 안된 경우 역학조사서 작성하여 신고**

접촉자 조사

(별도의 서식을 작성하지 않으나 환자의 동일 소속집단인 가족, 학교 등에서의 유증상 여부를 1주일 단위로 모니터링 하며, 최종환자 발생 후 잠복기의 2주기에 해당되는 5주 기간 까지 추가환자 발생이 없는 경우 종료함)

수두(의사환자 관리 점검표

점검 항목	확인란
1. 환자 관리 (유행확산 방지 및 고위험군 관리)	
1) 학교, 직장, 공공장소 등 외출제한 및 가택격리 지도	□ 실시
2) 환자 주변에 고위험군이 있는 경우 접촉하지 않도록 지도	□ 실시
2. 감염원 조사 (유행 규모 및 원인 규명)	
1) 환자 발진 발생전 3주간 접촉자 중 발진이 있었던 자 파악	□ 실시
3. 접촉자 관리 (유행 차단)	
1) 접촉자 조사	□ 실시
2) 접촉자 대상 수두 발병 감시와 접촉자 중 환자 발생 시 가택 격리 지도	□ 실시
3) 감수성자 예방접종 권장	□ 실시
4) 접촉자 또는 보호자 대상 교육 및 홍보 실시 - 가정통신문, 예방접종 안내문 등 배포	□ 실시
4. 의료기관 및 지역사회 홍보	
1) 의료기관에 수두 의심환자 방문 시 지체없이 신고하도록 조치	
2) 수두 증상이 비전형적인 경우 신속한 검사 의뢰 요청	
3) 관할지역 내 수두 유행 현황에 대한 정보 제공	
4) 수두 예방접종 필요성 등에 대한 정보 제공	
5) 외출 후 손 씻기 등 개인위생 강화 안내	

☛ **유행종료 시 유행 역학조사 결과보고서와 함께 유행종결보고를 실시하도록 함**

* 시/군/구에서는 굵은 테두리 안 항목에 빠짐없이 기입하여 시도 및 질병관리본부에 지체없이 보고 바랍니다.

Figure 5-1. Varicella epidemiological investigation reporting form.

5-3. Results

Among a total of 1,008 varicella cases in Seoul, Korea, 869 cases (86.2%) were breakthrough cases and 139 (13.8%) were unvaccinated cases. The mean age for breakthrough cases was younger than unvaccinated cases (7.72 y vs 8.82 y; $P<0.0001$). No significant differences were observed in gender and report source distributions in the two groups. Of those cases, about a half were male or female and 83 to 88% cases were elementary school students.

There was no difference in the clinical symptoms between the two groups. Among patients, rash was the most common in breakthrough group and unvaccinated group (99.5 and 100%, $P=0.4229$) and rash onset on mostly on the body (54.1% and 43.7%, $P=0.0008$); fever was the second (33% and 36.7%, $P=0.5095$); headache was the third (7.3% and 10.1%, $P=0.2448$); arthralgia was the rare (1.2%, only in the breakthrough group).

Disease severity differed between the two groups. In the breakthrough group, the proportion of cases with moderate-to-severe symptoms was less than that in the unvaccinated group (14.6% vs 25.8%, $P=0.0016$). The risk for occurrence of moderate-to-severe disease in the breakthrough group was less than roughly half that of the unvaccinated group (OR=0.570, CI: 0.365–0.890).

Table 5-1. Comparison of the epidemiology and disease severity between the breakthrough cases and unvaccinated cases

	Breakthrough cases (N=869)		Unvaccinated cases (N=139)		OR (95%CI)	*P*-value
Age(year)						
Mean±SD	7.72 ± 1.86		8.82 ± 2.04			<.0001
Gender(no, %)						
Male	478	(55.0)	72	(51.8)		0.4807
Female	391	(45.0)	67	(48.2)		
Report Source(no, %)						
Kindergarten	131	(15.1)	13	(9.4)		
Elementary School	724	(83.3)	122	(87.8)		
Unknown	14	(1.6)	4	(1.6)		
Clinical symptoms(no, %)[a]						
Rash	865	(99.5)	139	(100.0)		
Affected part of rash onset						
Face and neck	333	(38.5)	56	(40.3)		
Body	468	(54.1)	60	(43.2)		
Arms and legs	64	(7.4)	23	(16.5)		
Fever	294	(33.8)	51	(36.7)	0.888 (0.602–1.309)	0.5095
Headache	63	(7.3)	14	(10.1)	0.975 (0.517–1.838)	0.2448
Arthralgia[b]	10	(1.2)	0	(0.0)	–	0.4178
Severity(no, %)						
Mild(<50)	742	(85.4)	104	(74.8)	0.570 (0.365–0.890)	0.0016
Moderate to severe(≥50)	127	(14.6)	35	(25.8)		
Moderate(50-249)	114	(89.8)	32	(91.4)		
Severe(≥250)	13	(10.2)	3	(8.6)		

* Detected every clinical symptoms were recorded

† Continuity adjusted chi-square test was used because one of the cell frequency was equal to zero.

5-4. Discussion

The results of the present study showed that one-dose vaccination was associated with the attenuation of disease severity in children varicella cases. We found that the risk for severe illness was significantly decreased in breakthrough group than unvaccinated group (14.6% vs. 25.8%; OR=0.570). In other words, the vaccine effectiveness (=1–OR) of one-dose of varicella vaccine administered at 12-15 months of age was 43% (95% CI: 11.0–63.5%) against moderate-to-severe varicella.

This finding is consistent with results from previous studies reported elsewhere. The odds ratio that the illness was more severe than mild in breakthrough cases than in unvaccinated cases was noted in Germany (12.5% vs. 68.2%; OR=0.183)10, the United States (14.3% vs. 52.4%; OR=0.273)9 and in China (25.6% vs. 44.8%; OR=0.446) [68].

Our data may be contrasted to the results from studies on varicella vaccine effectiveness suggesting the insufficient immunogenicity of the vaccine in Korea. In a clinical-based study, the effectiveness of one varicella vaccine product (Suduvax, Green Cross, South Korea) was estimated 54% (CI: 0.10–2.05) by case-control study and the seroconversion rate was 76.67% by the classical fluorescent antibody to membrane antigen (FAMA) assay [26]. In a population-based study in Seoul, Korea, the effectiveness of the varicella vaccine was 13% (CI: -17.3–35.6) and the vaccine-induced immunity rapidly decreased after three years since vaccination, suggesting waning of immunity [30].

From these findings, we could suggest that a universal one-dose

varicella vaccination program may have limited effectiveness to decrease in the incidence rate of varicella but have positive effect in attenuation of disease severity in children varicella cases. Two clinical studies on the severity of varicella in Korea demonstrated that milder pattern of rash was observed in breakthrough group than in unvaccinated group [69] and the number of lesions detected were significantly lower in breakthrough group than in unvaccinated group [62]. From the perspective of a vaccinated patient, milder symptoms by attenuation of disease severity are benefit. Contrarily, from the perspective of a population health care management, pat ients with breakthrough varicella can also transmit varicella to others despite that they generally have a lower rate of infectivity than those who are unvaccinated. Mild symptoms often lead to a failure to isolate patients and lead to outbreaks among those in close contact such as children in kindergarten or elementary school.

Our study had several limitations. A relatively small number of unvaccinated cases due to a high level of vaccine coverage may cause selection bias. A tendency that a patient who is infected with varicella in later years develops severe disease could be confounded in our study data because the mean age in the unvaccinated group is significantly higher than that in the breakthrough group (8.82 y vs 7.72 y). To alleviate this selection bias, however, we employed age as a confounder in the logistic model. There could be also recall bias because the reporter would fill out the epidemiological survey depending on his or her memory. In addtion, in the epidemiological survey form, the questionnaire about the number of lesions only request the range of the number with a broad bracket(<50, 50-249,

250-499, ≥500) rather than a concrete number of lesions, which makes unavailable to precisely distinguish disease severity from another. Case definition may affect the findings of this study because the data did not distinguish between clinical cases and laboratory-confirmed cases. Unlike laboratory-confirmed cases, probable cases are likely to include patients who have similar symptoms like rash but are not infected with varicella. Considering a high vaccine coverage rate, probable cases could be categorized into breakthrough group than unvaccinated group. This may have resulted in an underestimation of disease severity in breakthrough group. The exact impact of a universal one-dose varicella vaccination on disease severity could not be assessed due to a lack of previous population-based data on varicella vaccination and its effect on severity before adoption of the universal vaccination. Furthermore, we could not either estimate changes in disease severity over time because there was no data on annual incidence of varicella cases categorized by disease severity. Despite these limitations, the present study is the first population-based study to assess a universal one-dose varicella vaccination on disease severity in Korea and to provide an explanation on the recent increase in the incidence rate of varicella after introduction of the national varicella vaccination program.

In conclusion, our study suggest that universal one-dose varicella vaccination may have a significant effect on attenuation of disease severity in children. Additional prospective study is necessary to assess the longitudinal effect of the varicella vaccination program on disease severity of varicella in Korea.

CHAPTER 6.

Discussion and Conclusion

6-1. Increasing varicella incidence rates among children in the Republic of Korea: An Age-Period-Cohort analysis

The study describes the post-licensure epidemiology of varicella incidence with an aspect of time and age. There was an increase in the incidence rate of varicella between 2006 and 2017 in Korea. During the period, the incidence rate also increased for each age strata among children aged 0 to 12–year–old with age peak shifted from 4 to 6 years old. Period and cohort curves showed similar increasing patterns.

The result may be explained by primary or/and secondary vaccine failure. The former relates to the failed mounting of the immune system to produce antibodies initially and the latter relates to the waning of vaccine-induced immunity over time. The age peak shifting could be associated with secondary failure. The varicella vaccine is merely effective in the early years, but, in later, the incidence of breakthrough infection jumps as immunity rapidly wanes over time. Historical context that high vaccination coverage prior to the introduction of varicella vaccine into national immunization program in Korea may affect the result.

6-2. Spatial epidemic characteristics and risk factor analysis of varicella in the Republic of Korea

The second study describes the post-licensure epidemiology of varicella incidence with an aspect of time and space. During the surveillance periods of 2006–2017, local spatial clusters with high level of varicella incidence

were initially confined to northeast region (Gangwon-do), rural and mountain area. In later, the 'hot spots' gradually spread to their neighboring districts and faded out over time, which led overall increase in varicella incidence across the country. In spatial regression analysis, childhood percentage was risk factors on the incidence of varicella at district level while factors such as population density and number of hospitals have negative effect on the risk. Meanwhile, vaccination coverage rate resulted to have nothing to do with varicella incidence.

This may indicate that a district where has a low population density and a few healthcare providers and more childhood percentage was vulnerable to varicella outbreak.

6-3. Effectiveness of varicella vaccination program in preventing laboratory-confirmed cases in children in Seoul, the Republic of Korea

The third study was to evaluate the effectiveness of one-dose varicella vaccination program in Korea by performing a matched case-control on children in Seoul to investigate if there is primary or/and secondary vaccine failure. The result showed that the overall effectiveness of one-dose varicella vaccination in preventing confirmed cases of varicella was low (13%, 95% CI: -17.3–35.6) and the vaccine effectiveness sharply declined after the three year of vaccination due to waning of immunity. In specific, The fact that more than half of all vaccinees were immunized with the vaccine based on MAV strain and only available in Korea was distinct from the cases in other countries where adopted routine varicella vaccination and experienced

substantial decrease in incidence of varicella.

This finding may provide a key to understand the increasing trend of varicella incidence following implementation of universal vaccination program in Korea. Due to an insufficient immunogenicity of the vaccine might have limited effectiveness to decrease in the incidence of varicella.

6-4. Effects of one-dose varicella vaccination on disease severity in children in Seoul, the Republic of Korea

The last study also assessed vaccine effectiveness with an aspect of effects on disease severity. The result suggested that one-dose vaccination was associated with the attenuation of disease severity in children varicella cases despite the vaccination failed to protect against varicella incidence. The risk for severe illness was significantly decreased in breakthrough group (vaccinated group) than unvaccinated group (14.6% vs. 25.8%; OR=0.570).

This implicates that a universal one-dose varicella vaccination program may have limited effectiveness to decrease in the incidence rate of varicella but have positive effect in attenuation of disease severity in children varicella cases. In addition, patients whose mild symptoms can also transmit varicella to others and often cause failure to isolation, leading to outbreaks among those with close contacts in education facilities. Therefore, a recent increase in the incidence rate of varicella in Korea may be associated with a growing number of breakthrough cases.

6-5. Implications for varicella vaccination policy and future researches

It has been more than a decade since the implementation of universal one-dose varicella vaccination. Nevertheless, incidence of varicella has been continuously rising and spatially spreading out across the country. Meanwhile, the overall effectiveness of vaccine and vaccination policy have not been properly examined.

In conclusion, an increase in incidence of varicella was attributed to vaccine failure. Insufficient immunogenicity of the vaccine for a low vaccine effectiveness and a rapid waning of immunity have failed to prevent from incidence of varicella. The vaccine's positive effect in attenuation of disease severity also might cause a growing number of breakthrough cases as being unsuccessful in isolating patients with mild symptoms.

In this regard, to prevent and control of varicella incidence and to reduce the disease burden in Korea, enhancing the effectiveness of the vaccine is important. Moreover, varicella vaccine is a live attenuated vaccine so that distribution and storage of vaccine, so called 'cold-chain system', should be carefully managed by healthcare providers. Unless the vaccine failure be overcome, introducing of a routine two-dose vaccination is merely a secondary issue.

Further researches should be conducted on herpes zoster along with varicella because they are both infectious disease caused by the same VZV virus and exogenous boosting by VZV exposure may play a role in HZ incidence by maintain cell-mediated immunity. Developing a mathematical model to predict incidence of both varicella and HZ by comparing multiple

vaccination strategies is consider to be a meaningful work in establishing an evidence-based vaccination policy.

Varicella is a preventable disease when administerd vaccine works properly. Through continuous monitoring and evaluation of vaccination policies against varicella using national surveillance system, we could develop more effective approaches for more effective control and prevention of varicella transmission in the Republic of Korea.

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국문초록

연구의 배경과 목적

수두는 전염력이 매우 높은 급성 감염 질환으로 수두-대상포진바이러스가 원인이며, 영유아에 흔한 질병이다. 수두역학은 수두백신 도입 이후 극적으로 변화하였으며, 수두백신은 세계적으로 질병발생과 질병부담을 감소시키는데 아주 효과적이다. 그러나 한국에서는 2005년부터 수두백신 1회 국가예방접종을 실시했음에도 불구하고 2006년부터 2017년 동안 수두발생이 계속 증가하고 있다. 이 연구는 한국에서 수두백신 도입 이후 수두역학의 변화를 살펴보고 백신효과를 평가하는 것을 목적으로 한다. 세부적으로는,

(1) 연령, 기간, 코호트 효과가 시간에 따른 국내 영유아 수두발생 증가에 어떠한 영향을 미쳤는지 연령-기간-코호트 분석을 통해 알아본다.

(2) 수두발생의 공간적 패턴과 지리적 위험요인을 공간분석과 공간회귀모형 적합을 통해 알아본다.

(3) 수두백신 1회 국가예방접종이 수두발생에 미친 효과를 환자-대조군 연구를 통해 평가한다.

(4) 수두백신이 감염 시 질병 중증도에 미치는 영향을 평가한다.

연구 방법

(1) 국가감염병감시시스템에서 수집된 2006년 1월부터 2017년 12월까지 신고 된 수두발생 자료와 통계청 인구자료를 활용하였다. 연령, 기간, 코호트 효과를 평가하기 위해 연령-기간-코호트 분석을 사용하였으며, 분석은 Rosenberg가 개발한 APC Web Tool을 통해 실시하였다.

(2) 국가감염병감시시스템에서 수집된 2006년 1월부터 2017년 12월까지 신고된 250개 시군구 수두발생 자료와 사회인구학적자료는 통계청 자료를 활용하였다. 전체 및 부분공간자기상관은 Moran's I 및 LISA를 통해 측정하였다. 수두발생의 사회인구학적 요인을 탐지하기 위해 시군구 수준에서 공간회귀분석을 실시하였으며, spatial error 모형을 이용하였다.

(3) 국가감염병감시시스템에 환자로 신고 된 537명 수두환자와 개별매칭된 537명 대조군 자료를 이용하였다. 수두환자는 2013년 1월부터 2013년 12월까지 서울특별시에서 발생한 확진환자이다. 수두백신 1회 접종의 효과를 평가하기 위해 1:1 매칭 짝(pair)에 대하여 conditional logistic 회귀분석을 실시하였으며, 성별 백신접종연령과 같은 잠재적 교란변수를 포함시켜 보정하였다. 백신접종이후 시간에 따른 효과를 측정하기 위해 이를 가변수로 코딩하여 모형에 포함시켰다.

(4) 질병관리본부가 제공하는 수두환자 역학조사 자료를 이용하였으며, 연구대상은 2015년 1월부터 2017년 12월까지 역학조사를 통해 보고된 서울시 거주 1,125명의 수두환자이다. 질병 중증도는 수포개수로 분류하여 정의하였다. 수두접종 및 미접종 집단에 대하여 중증도를 알아보기 위해

unconditional logistic 회귀분석을 실시하였으며, 모형에서 연령을 보정하였다.

결과

(1) 2006년부터 2017년까지 수두환자 발생 수와 연령표준화된 발생률은 우상향하는 경향성을 보였다. 수두발생률은 0-12세 영유아의 모든 연령대에서 증가하였고, 다발연령(age peak)은 4세에서 6세로 이동하였다. APC분석에서 기간 및 코호트 그래프는 모두 유사한 증가양상을 보였다.

(2) 수두발생수가 높은 지역적 공간군집은 초기에 농어촌 산악지역인 북동부 지역(강원도)에만 국한되어 나타났다. 시간이 지남에 따라 '핫스팟'은 인근지역으로 점차 확산되어 사라졌으며, 전국적으로 전체 수두발생수가 증가되는 결과를 초래하였다. 공간회귀분석 결과 인구밀도와 의료기관 수는 수두발생에 음(-)의 효과를 영유아수의 비율은 양(+)의 효과를 갖는 것으로 나타났으며, 백신접종률은 유의하지 않았다.

(3) 짝짓기된(matched) 환자-대조군 연구에서 확진환자 예방과 관련된 수두백신 1회접종의 백신효과는 낮은 수준이었으며 (13%, 95% CI: -17.3 -35.6), 백신효과는 접종 3년 이후 부터 면역감소로 인해 급격하게 감소하였다.

(4) 서울시 거주 1,008명의 환자 중 869명(86.2%)은 돌파감염자이고 139명(13.8%)은 백신미접종자였다. 중증도 위험은 돌파감염군(백신접종군)에서 백신미접종군보다 유의하게 감소하였다. 돌파감염군에서 중증도가

moderate-to-severe하게 발생할 위험은 백신미접종군보다 약 절반가량 낮게(OR = 0.570, CI: 0.365-0.890) 나타났다.

결론

(1) 첫 번째 연구는 수두백신 도입 이후 시간과 발생 연령 측면에서의 수두 역학을 기술하고 있다. 수두발생의 증가 양상은 백신실패로 설명할 수 있을 것이다. 다발연령 상승은 시간이 지남에 따라 면역이 감소되는 백신의 2차실패와 연관이 있는 것으로 보인다. 수두백신은 접종 초기에만 예방효과가 있을 뿐 이후에는 백신에 의한 면역력이 급감함에 따라 돌파 감염수가 급증하게 된다.

(2) 두 번째 연구는 수두백신 도입 이후 시간과 공간 측면에서의 수두역학을 기술하고 있다. 연구결과에 따르면 우리나라의 전반적 수두발생 증가는 수두발생률이 높은 클러스터로부터 주변지역으로의 확산에 따른 것으로도 볼 수 있다. 인구밀도가 낮으며 의료기관 수가 적은 가운데 수두 위험군인 영유아의 수가 많은 경우 수두 유행에 취약한 것으로 나타났다.

(3) 세 번째 연구는 한국의 수두백신 1회 접종 정책의 효과를 평가하고 있다. 백신효과가 낮고 접종 이후 면역이 급감하는 것으로 볼 때 1, 2차 백신실패가 존재함을 알 수 있다. 이는 백신정책 도입 이후에도 수두발생이 증가하고 있는 현상을 이해하는 데 핵심이 된다. 백신에 의한 면역력이 충분하지 못함에 따라 수두발생을 감소시키는 데 있어 수두백신 효과가 제한됨을 알 수 있다.

(4) 네 번째 연구는 수두백신이 질병 중증도에 미치는 효과를 평가하고 있다. 연구 결과 수두백신 1회접종은 영유아의 수두 중증도를 완화시키는 것으로 나타났다. 다만 증상이 미약한 환자는 타인에게 수두를 전파시킬 수 있음에도 격리가 제대로 되지 않아 보육시설의 근접 접촉자들에게 수두 유행을 야기할 수 있다. 따라서 최근 한국의 수두발생률의 증가는 이에 따른 돌파감염의 증가와 연관이 있는 것으로 볼 수 있다.