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Corresponding Author: Dr. day-yu chao, PhD

Corresponding Author's Institution: National Chung-Hsing University

First Author: Ie-Bin Lian

Order of Authors: Ie-Bin Lian; Yu-Zen Chien; Pi-Shan Hsu; day-yu chao, PhD

Abstract: The varicella vaccine has been available in the Taiwan market since July 1997. Beginning 1998-1999, Taipei City and Taichung City/County as the early launch areas included the varicella vaccine in their free pediatric vaccination programs. By contrast, the national free vaccination program was not implemented until 2004. We aim to investigate the changing epidemiology of varicella incidence through an analysis of age-period-cohort effects. With the greatest decrease in varicella incidence occurring in children aged below 6, the incidence of varicella shifted to older age groups as reflected in different birth cohorts. The current study provides important implications for the current vaccination policy.

Suggested Reviewers: Chwan-Chuen King
Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan
chwanchuen@gmail.com

Yin-Hen Hsieh
Department of Public Health and Institute of Biostatistics, China Medical University, Taichung, Taiwan 404
hsieh@mail.cmu.edu.tw

Wen-Chung Lee
Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.
wenchung@ntu.edu.tw

Mei-Shang Ho
Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.
homs@sinica.edu.tw

*Cover Letter

Dr. R.E. Spier, Editor, Vaccine
School of Biomedical and Life Sciences
University of Surrey
Guildford
Surrey GU2 7XH
UK
r.spier@surrey.ac.uk

Dear Dr. Spier:

We are submitting a manuscript entitled "**Age shift of varicella incidence after implementation of the one-dose varicella vaccination policy in Taiwan: an age-period-cohort analysis"** to be considered for publication in the "**Regular Research Articles"** section of **Vaccine** Journal

This article presents our finding that (1) the age-period-cohort three-way analysis of the incidence provided a unique way to investigate the changing epidemiology of varicella disease.; (2) with the greatest decrease in varicella incidence occurring in children aged below six years old, the incidence of varicella shifted to older age groups as reflected in different birth cohorts. The important finding in this study provide an important implication of immunity in these age groups and a catch-up vaccination or two-dose vaccination for susceptible older children and adolescents, particular female, is needed to prevent increased susceptibility and outbreaks in these groups in Taiwan.

This scientific paper has not been submitted or published elsewhere. Please send all correspondences to Dr. Day-Yu Chao at the following address. Your sincere assistance of this manuscript will be highly appreciated. If you have any question, please feel free to contact us.

Sincerely,

Dr. Day-Yu Chao, Ph.D.

Graduate Institute of Microbiology and Public Health
College of Veterinary Medicine
National Chung-Hsing University
250 Kuo-kuang Rd.
Taichung (402), Taiwan, Republic of China
TEL: 8864-22840694, FAX: 8864-22852186
E-mail: dychao@nchu.edu.tw

Abstract

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Age shift of varicella incidence after implementation of the one-dose varicella vaccination policy in Taiwan: an age-period-cohort analysis

Ie-Bin Lian[1], Yu-Zen Chien[1], Pi-Shan Hsu[2], Day-Yu Chao[3*]

1. Graduate Institute of Statistics and Information Science, National Changhua University of Education, Changhua, Taiwan (50058)
2. Department of family medicine, Taichung Hospital, Department of health, Executive Yuan, Taiwan, R.O.C
3. Graduate Institute of Microbiology and Public Health, College of Veterinary Medicine, National Chung-Hsing university, Taichung, Taiwan (401)

Reprint requests and correspondence to:

Day-Yu Chao, Ph.D.

Graduate Institute of Microbiology and Public Health, College of Veterinary Medicine

National Chung-Hsing university

Taichung, Taiwan (401)

TEL:886-4-22840694

FAX:886-4-22852186

EMAIL: dychao@nchu.edu.tw

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Running headline: age shift of incidence of varicella after varicella vaccination

Abstract

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1. Introduction

The implementation of a routine childhood varicella vaccination program in the United States in 1995 has resulted in a dramatic decline in morbidity and mortality related to varicella[1, 2]. Although one-dose varicella vaccine is highly effective in containing natural varicella cases, vaccine effectiveness decreases with time along with evidence of waning immunity[3]. Outbreaks of varicella in day care centers or primary schools continue to be reported, particularly among highly vaccinated populations[4, 5]. These breakthrough cases challenged the one-dose varicella vaccination policy as being unable to provide sufficient herd immunity levels to prevent outbreaks in school settings where exposure can be intense, put an end to varicella transmission among vaccinated children, and address the difficulty in the diagnosis of mild cases in vaccinated individuals and early recognition of outbreaks[6-10]. These are essential requirements for implementing control measures.

The varicella vaccine has been available in Taiwan since July 1997. In 1998, Taipei City included the varicella vaccine in its free pediatric vaccination programs for children over 12 months old. Taichung City/County followed suit in 1999. A 39%–52% range in vaccination rate was observed in 2000–2003, which soon increased to 82.93% after the implementation of the nationwide free varicella immunization program among children 12–18 months of age in 2004. For other areas in Taiwan, although the free varicella vaccination program for the public was not launched until 2004, people were still able to pay for a private varicella vaccination. A significant increase in vaccination rates was also observed from less than 10% before 2003 to 80% in 2004. Between 2005 and 2008, both Taipei and Taichung, as well as other areas in Taiwan maintained high vaccination coverage rates (nearly 94% according to a Taiwan-CDC personal communication). As a result, a significant decrease in varicella incidence among children 3–6 years old had been consistently observed in areas implementing the free vaccination policy[11-13].

Age-period-cohort (APC) analysis has been applied in infectious disease epidemiology to study the long-term effect of specific cohorts; APC is considered more appropriate than cross-sectional current-year studies[14-16]. Age, period, and cohort may have different implications for varicella incidence before and after the vaccination period. For example, an (pure) age effect of excessive morbidity underlines the importance of biological susceptibility in the specific age. A period effect of a sharp decline in morbidity after a particular year may be the hallmark of the success of a public health vaccination intervention program. The presence of a cohort effect raises the possibility that different antibodies waned, or that the increased exposure of unvaccinated cohorts experienced by different birth-cohorts may have a role in varicella morbidity. The APC model enables better characterization of these temporal factors in a unified framework.

With the success of the varicella vaccination program in reducing varicella incidence in children, monitoring the changing epidemiological patterns of varicella in different age groups in Taiwan has become crucial. The National Health Insurance (NHI) was initiated in Taiwan in 1995, and now covers 96.1% of the population that receives health care. It currently covers more than 95% of the population compared with healthcare providers nationwide. The NHI database becomes valuable for evaluating different kinds of health problems[17]. In this study, we evaluate the epidemiological characteristics of varicella from 2000–2008 as well as the effect of varicella vaccinations on the incidence rate of different birth cohorts, periods, and age groups in Taiwan. Through an age-period-cohort analysis model, the current study confirms that the nationwide varicella immunization in children resulted in an age shift, increasing the incidence rate of older children.

2. Materials and methods

2.1. Data collection

Taiwan began implementing its compulsory national health insurance system in 1995. Since then, the prevalence of health insurance coverage has increased from 56%–98% for the period ending 2007. During the period considered in this study, over 95% of its 23 million people are covered by health insurance. Clinics and hospitals had to register all treatments to apply for payment of expenses; thus, the accuracy of the databank is considerably reliable, especially after 1995 when the medical records of more than 95% of Taiwan's hospitals contracted with national health insurance were included into the database. The classification of the location of patients is based on the county/city of one's family register. Taipei City and Taichung

City/County have made the varicella vaccine available through their free pediatric vaccination programs for children over 12 months old since 1999, five years earlier than other areas in Taiwan. For this reason, Taipei City and Taichung City/County will be referred to as “early launch area” (ELA) hereafter for comparison with other areas in Taiwan.

2.2. Definitions

We analyzed the outpatient health care records from a sample of about 240,000 residents, randomly selected by the National Health Research Institute from those who attended the universal national health insurance. The sample comprises nearly 1/100 of the total population of Taiwan. The data include the diagnosis records of the International Classification of Diseases, 9th Revision; Clinical Modification (ICD-9-CM) codes related to varicella (052), and other codes related to each individual between 2000 and 2008. Demographic variables including the age, date of diagnosis, and residency were also considered. All the cases in the database were counted only once regardless of the number of times each case sought medical care because varicella is unlikely to re-occur in one year.

2.3. Statistical analysis

The age-standardized incidence rates (ASIR) of varicella and the corresponding 95% confidence interval (95% CI) were calculated based on the age distribution of the world standard population in 2000 from the World Health Organization. We also calculated a standardized morbidity ratio (SMR) for the ELA by dividing the observed incidence in ELA by its age-adjusted expected incidence based on the age distribution of the rest of Taiwan. An SMR value <1 indicates lower morbidity in ELA compared with the other areas of Taiwan.

The APC model under Poisson regression assumes a log-linear form for the morbidity from varicella incidence cases, that is,

$$\log\left(E(d_{ijk})/p_{ijk}\right) = \mu + a_i + t_j + c_k + \text{(interaction terms)}$$

where μ is a constant term representing the log-transformed "grand mean" of morbidity, and parameters a_i, t_j, and c_k represent the effects of age, period, and cohort, respectively. The interaction terms represent the interactions among the abovementioned variables, where d_{ijk} is the number of varicella cases, and p_{ijk} is the population cross-classified by age (indexed by i, i=1,2,…, I), period (indexed by j, j=1,2,..,J), and cohort (indexed by k, k=1,2,..,K). $E(.)$ denotes expectation. Here, a reference group with ages between 1–3 years old, over the years 2003–2005, and cohort of 1999–2001 for each of the three temporal variables is chosen and the corresponding parameter is set to zero. The exponentials of the parameters ($exp(a_i)$), $exp(t_j)$, $exp(c_k)$) are subsequently interpreted as the adjusted relative risks for the age, period, and cohort variables, respectively. Parameters for age, period, and cohort are not uniquely estimable because of the exact linear dependence of the regressor variables (cohort = period – age). The relationship creates an identifiability problem for the APC model so that parameters cannot be properly estimated without maneuvering around the linear dependency. We used the “individual records method” introduced by Robertson and Boyle (1986)[18, 19], which takes advantage of the data set with longitudinal records for each individual, to cope with the identifiability problem.

The actual calculation involves the matrices of the age-specific incidence rates from varicella cases for each of the three periods (2000–2002, 2003–2005, and 2006–2008) and each age group (1–3, 4–6, ..., 13–15). Based on these, 3 age groups, 5 period groups, and 15 cohort groups are defined. Dummy variables for age, period, and cohort were used throughout the Poisson regression analysis to avoid assumptions concerning the type of association between incidence rates and the dependent variables. A sequence of models was fitted separately for both the ELA and other areas, starting with the intercept-only model to the two-factor (age-period, age-cohort, period-cohort) models, and finally, to the three-factor (age-period-cohort) model. The Akaike information criterion (AIC) was used to choose the best-fit model. Parameter estimates with 95% CI were generated by the maximum-likelihood method. All the P-values are presented in two-sided test results. The modeling was carried out using the GENMOD procedure of SAS version 9.1.

3. Results

Table 1 shows the ASIR of varicella from 2000–2008 in the ELA and other areas in Taiwan. Consistent with the different starting years implementing the free vaccination policy, the varicella ASIR in the ELA was lower than those in other areas in Taiwan. The ASIR in the ELA decreased from 7.99 in 2000 to 2.76 cases per 1,000 person-years in 2008. The other areas in Taiwan also showed a mild decrease in varicella ASIR from 10.15 in 2000 to 8.01 cases per 1,000 person-years in 2003. The decline was particularly significant after the implementation of the nationwide free varicella vaccination program after 2004. From 7.2 in 2004, ASIR dropped to 3.23 cases per 1,000 person-years in 2008.

We used SMR to compare the risk between ELA and the rest of Taiwan (Fig. 1). The SMR of ELA was 0.8 times lower than that of the rest of Taiwan in 2000, and further dropped to 0.54 in 2005. However, the ratio gradually increased after the implementation of the nationwide free-vaccination program in 2004, and approached 0.9 in 2008, indicating that the deviance between the two areas had been narrowed.

Figure 2 shows the age-specific incidence rates of varicella in different areas of

Taiwan. The incidence rate peaked at the age group of 4–6 year-olds in the ELA and the rest of Taiwan, with the incidence rate of 54.21 cases per 1,000 person-years in other areas, which is higher than that in the ELA (32.91 cases per 1,000 person-years). The difference in incidence rates in both areas showed statistical significance ($p<0.05$). Moreover, the age at diagnosis of varicella gradually increased with time, and this increase was particularly significant after the implementation of the nationwide vaccination program in 2004. Figure 3 shows the average age at diagnosis of varicella in the ELA and other areas in Taiwan. In both areas, the average age increased slightly from about 5.4 years in 2000 to 6 years in 2004, and then escalated to 9 years in 2008. Using median age as an alternative, we can observe a similar incrementing effect of age at diagnosis of varicella. In the ELA, the median age of the incidence even increased to 11 years in 2008 (data not shown).

To explore whether the age-increment effect was affected by different birth cohorts, the varicella incidence rates among different cohorts in 2000–2002, 2003–2005, and 2006–2008 were investigated separately in the ELA and other areas in Taiwan. These are shown in Figures 4A and 4B, respectively. For the ELA, which initiated the free pediatric vaccination policy for children older than 12 months in 1999, the 1996–1998 birth cohort showed two peaks of incidence rates of varicella both in 2000–2002 and 2003–2005. The peaks correspond to the age groups of 4–6 and 7–9 years. However, in other areas in Taiwan that did not implement the free pediatric vaccination policy until 2004, the two peaks were not observed until the periods 2003–2005 and 2006–2008 for the 1999–2001 birth cohort, reaching the ages of 4–6 and 7–9 years (Fig. 4).

Table 2 shows the results of the model building procedure for the APC analysis. Because of the limited number of strata, only one interaction was allowed in the model. In both the ELA and the rest of the areas, the final model was chosen based on the minimal-AIC criterion. As a result, the best model in both the ELA and the rest of the areas is age + period + cohort + period*cohort. The likelihood ratio tests based on the deviance indicate that the age, period, and cohort effects should all be taken into account. Adding the cohort effect resulted in the largest drop of both AIC and deviance.

The incidence rates among different age-cohort strata for the ELA and the other areas of Taiwan are shown in Figures 5A and 5B, respectively. The rates, which were estimated by the above mentioned APC model, were very similar to the observed rates. Both figures reconfirmed the age shift effect by showing the decrease in the incidence rates in the age groups 1–3 and 4–6 years. This is in contrast to the gradual increase in the incidence rate in the age groups 7–9 and 10–12 years through the progression of different birth cohorts. At the age group of 4–6 years old, we observed that in the ELA, the incidence rate began to rise from 27.6 per 1,000 person-years of 1993–1995 to 32.55 of the 1996–1998 cohort. Incidence rates started to drop to 22.6 of the 1999–2001 cohort and further down to 13.3 of the 2002–2004 cohort. In the other areas in Taiwan, the incidence rate also began to rise from the 1993–1995 cohort (35.08 per 1,000 person-years) to the 1996–1998 cohort (51.56 per 1,000 person-years). However, it remained at the high incidence of 43.5 per 1,000 person-years of the 1999–2001 cohort before the significant decrease to 34.05 of the 2002–2004 cohort. A similar decreasing effect was also observed for the age group of 1–3 years. By contrast, at the age group of 7-9 years old, the incidence rate gradually increased from 4.65 and 5.92 per 1,000 person-years of the 1990–1992 birth cohorts in the ELA and the other areas, respectively, to around 13 per 1,000 person-years of both 1993–1995 and 1996–1998 birth cohorts. This further increased to 16.91 and 24.18 per 1,000 person-years of the 1999–2001 birth cohorts in the ELA and other areas in Taiwan, respectively (Figure 5).

After controlling the birth-cohort effects by APC model, the 4-6 age groups still had the highest risk among all age groups during different time period from 2000 to 2008 in the early launch area (Table 3). The risk of acquiring varicella in the 4-6 age groups was 2.25 times higher than the 1-3 age groups in 2000-2002 and then decreased to 1.39 and 0.99 times in 2003-2005 and 2006-2008, respectively.

Interestingly, the risk of acquiring varicella in the 7-9 and 10-12 age groups gradually increased from 0.63 and 0.20 times in 2000-2003 to 0.69 and 0.36 times in 2006-2008 compared to that of the 1-3 age groups in 2000-2002 (Table 3). Similar trend was also observed in the other areas. It is also worth noting that the 7-9 age groups had become the second highest risk of acquiring varicella in 2003-2005 in the early launch area, which was 3 years earlier than the similar result observed in the other areas.

4. Discussion

Because of the overall incidence of varicella decline as a result of the success of the one-dose vaccination program in Taiwan, the risk of exposure to varicella continues to decrease. The accumulation of susceptible unvaccinated individuals may result in disease and outbreaks later in their lives, when varicella disease tends to be more severe. Our study confirms that the one-dose vaccination policy in place since 2004 had a strong impact on the decrease of incidence among children below 3 years of age. However, the impact also influenced the specific cohorts by accumulating the susceptible among the unvaccinated population, who possibly can contract the disease later in life.

The age-period-cohort three-way analysis of the incidence provided a unique way to investigate the changing epidemiology of varicella disease. Since the most significant decrease in varicella incidence occurred in children aged below 6, the median age for varicella cases has shifted from age 5–6 in 2000 to age 7–11 in 2006–2008. The age shift is also reflected in the different birth cohorts; that is, the 1999–2001 birth cohort presented two peaks of the incidence rate of varicella both in 2003–2005 and 2006–2008, which was at the ages of 4–6 and 7–9 years; the older birth cohort of 1996–1998 showed only one peak in 2000–2002, which was at the ages between 4–6 years. In the ELA, the 7–9 age groups had become the second highest risk group in relation to acquiring varicella in 2003–2005, which is 3 years earlier than similar results observed in the other areas. This changing epidemiology cannot be revealed by using cross-sectional current-year studies. Furthermore, this type of analysis can be used to assess the long-term protective effect of varicella vaccine on vaccination cohort populations in the future.

A concern exists as to whether the widespread childhood varicella vaccination may produce an upward shift in the peak age of the disease to the school-aged individuals, for whom varicella may be more severe. In particular, varicella vaccine effectiveness is only 80-85% and it might not provide sufficient levels of population immunity to prevent spread of disease even at high levels of vaccine coverage[20-24]. In the USA, a rise in the age of peak incidence of the disease is anticipated after the widespread introduction of varicella vaccination with a one-dose schedule from 3-6 years before 1995 to 6-9 years old in vaccinated children and 9-12 years old in unvaccinated children during 2004. However, the absolute number of cases in older children remained similar to that reported in the pre-vaccination era[3, 25]. In this study, the average age increased slightly from about 5.4 years in 2000 to 6 years in 2004, and then escalated to 9 years in 2008 after 5 years of the implementation of universal varicella vaccines. The result was consistent with the increase of hospitalization rate in the older age groups in Taiwan (data not shown). Therefore, vaccination of school-aged children is important in raising immunity and preventing school outbreaks in countries where the universal varicella vaccination program is initiated.

Although the disease was generally mild among vaccinated children, varicella in vaccinated persons was as contagious as that in unvaccinated children. The high varicella vaccination coverage was not sufficient to prevent the outbreak and the risk factors for vaccine failure has been investigated[26-28]. In 2005, the Advisory Committee on Immunization Practices recommended the need for further prevention of varicella through improved vaccine-induced immunity with a routine two-dose vaccination program[29, 30]. The efficacy of two doses of varicella vaccine compared with one dose was assessed in a trial conducted among healthy children who were followed up for 10 years. The efficacy of the two-dose schedule was significantly higher than that of the one-dose system with 3.3-fold lower risk of developing varicella >42 days after vaccination in two- versus one-dose recipients[31]. Furthermore, the mathematical modeling on the impact of one-dose versus two-dose vaccination regimens suggested that the two-dose strategy can not only produce less natural varicella cases but also considerably fewer breakthrough varicella cases[32]. As the age-shift effect reported in this study and the breakthrough event published in previous studies[33, 34], the catch-up or two-dose vaccination should be considered in the paediatric vaccination program in Taiwan.

Five years after the implementation of the varicella vaccination program, vaccination coverage has increased to a great extent. Consequently, disease incidence has dramatically declined. To ensure the high immunity in all groups and prevent outbreaks among older children and adolescents in the future, implementing a policy that requires evidence of immunity for children who enter middle and high school is essential. This is important in relation to the view that varicella may result in serious complications and death in older age groups. A catch-up vaccination or two-dose vaccination for susceptible older children and adolescents, particular female, is needed to prevent increased susceptibility and outbreaks in these groups in Taiwan.

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Figure legends

Figure 1. Standardized morbidity ratios (SMR) and 95% CI of varicella in the early launch area compared to the rest areas in Taiwan.

Figure 2. Age-specific incidence rates of varicella in different areas of Taiwan.

Figure 3. The average age at diagnosis of varicella in the early launch area (ELA) and the other areas of Taiwan, respectively.

Fig 4. Incidence rate of varicella stratified by birth cohorts and year period in early launch area (ELA) (a) and the other areas of Taiwan (b)

Figure 5. Incidence rate of varicella among different age groups stratified by birth cohorts in early launch area (ELA) (a) and the other areas of Taiwan (b)

Table 1 Age-standardized-incidence rate (ASIR) of varicella during 2000-2008 in the early launch and other areas in Taiwan

Year	Early launch areas		Other areas	
	ASIR	95%CI	ASIR	95%CI
2000	7.99	(7.73,8.26)	10.15	(10,10.31)
2001	4.24	(4.09,4.38)	5.71	(5.62,5.79)
2002	5.08	(4.9,5.27)	9.05	(8.91,9.2)
2003	4.91	(4.73,5.09)	8.01	(7.88,8.14)
2004	3.8	(3.65,3.95)	7.2	(7.08,7.32)
2005	3.63	(3.48,3.77)	7.08	(6.96,7.2)
2006	3.78	(3.63,3.93)	5.89	(5.78,6)
2007	3.54	(3.37,3.7)	4.15	(4.08,4.23)
2008	2.76	(2.62,2.89)	3.23	(3.17,3.29)

Table 2. Model-fitting results for Age-Period-Cohort analysis for early-launch areas and other areas. The model with all main effects (A+P+C) was used as the reference, and the test of significance of an added interaction was based on the differences of deviance and degree of freedom between the new model and the reference model. The best model is chosen based on the smallest Akaike information criterion (AIC).

Model[1]	*Df*[2]	*Deviance*	*Likelihood ratio statistics (df*)*[3]	*P value*[4]	AIC
Early launch areas					
A+P	23	321.95	272.08(7)	<.0001	496.17
A+C	18	231.37	181.5(2)	<.0001	415.6
P+C	20	288.05	238.18(4)	<.0001	468.28
A+P+C	*16*	*49.87*	*Reference*	*Reference*	*238.09*
A+P+C+AP	8	38.15	11.72(8)	0.1645	242.38
A+P+C+AC	8	21.66	28.21(8)	0.0004	225.89
A+P+C+PC	8	6.82	43.05(8)	<.0001	211.05
Other areas					
A+P	23	1173.2	1094.13(7)	<.0001	1384.4
A+C	18	895.67	816.6(2)	<.0001	1116.9
P+C	20	1133.3	1054.23(4)	<.0001	1350.5
A+P+C	*16*	*79.07*	*Reference*	*Reference*	*304.34*
A+P+C+AP	8	55.97	23.1(8)	0.0032	297.24
A+P+C+AC	8	50.8	28.27(8)	0.0004	292.07
A+P+C+PC	8	14.09	64.98(8)	<.0001	255.36

1. A=age, P= period, C=cohort, AP=age*period, etc

2. df=degree of freedom;

3. df*=increase in df from the reference;.

4. P value: tail-probability of Chi-square distribution with df*.

Table 3. The relative risk between different age groups in different time periods under the average of birth cohort effects in early launch area and other areas in Taiwan

	Early launch areas			Other areas		
Age/Period	2000-2002	2003-2005	2006-2008	2000-2002	2003-2005	2006-2008
1-3	1.00	0.67	0.17	1.00	0.73	0.20
4-6	2.25	1.39	0.99	1.74	1.59	0.88
7-9	0.63	0.67	0.69	0.44	0.55	0.49
10-12	0.20	0.25	0.36	0.15	0.19	0.21
13-15	0.12	0.10	0.10	0.04	0.09	0.09

*the age group 1-3 years old and year of 2000-2002 were treated as the baseline in both areas

Figure(s)

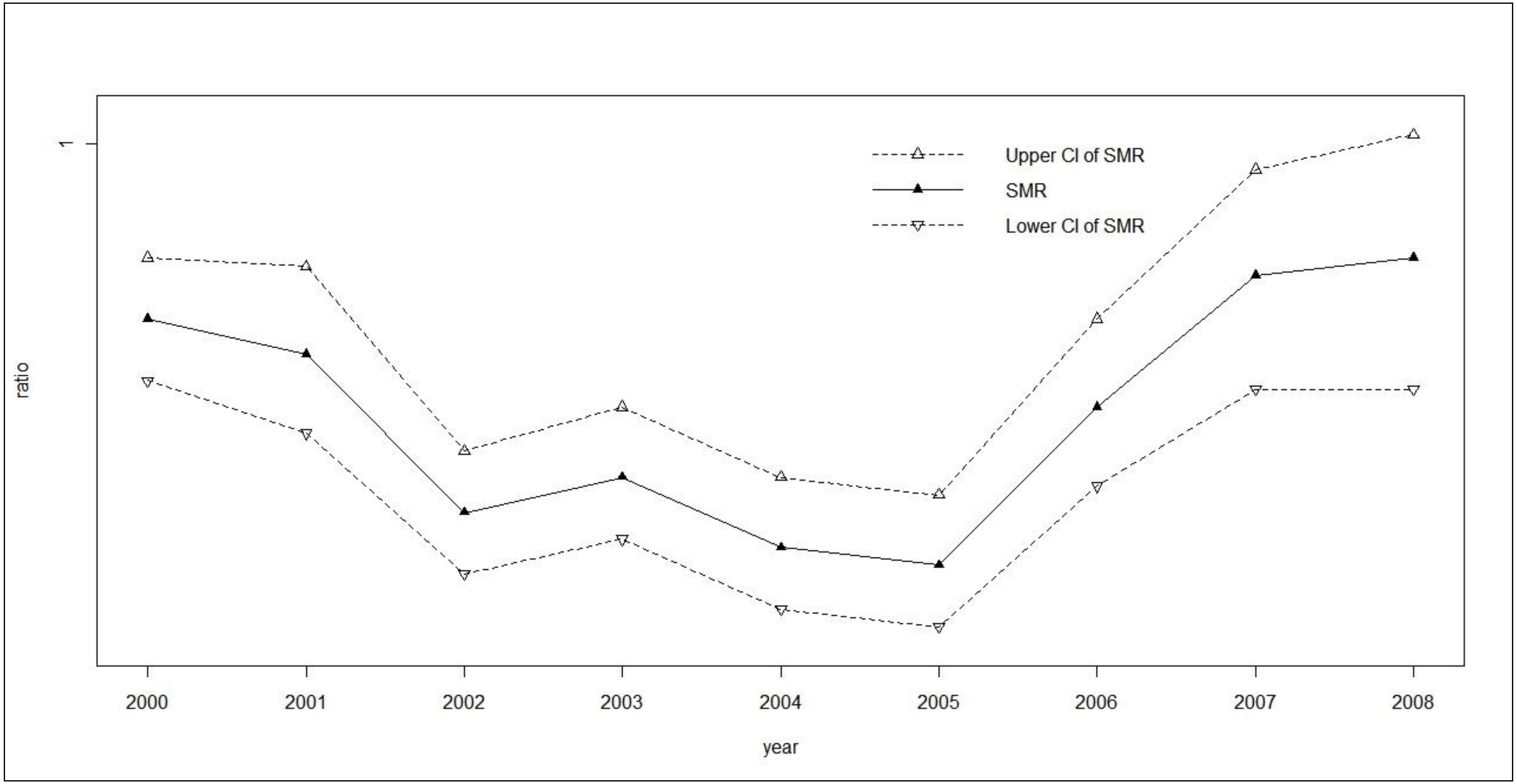


Figure 1. Standardized morbidity ratios (SMR) and 95% CI of varicella in the early launch area compared to the rest areas in Taiwan.

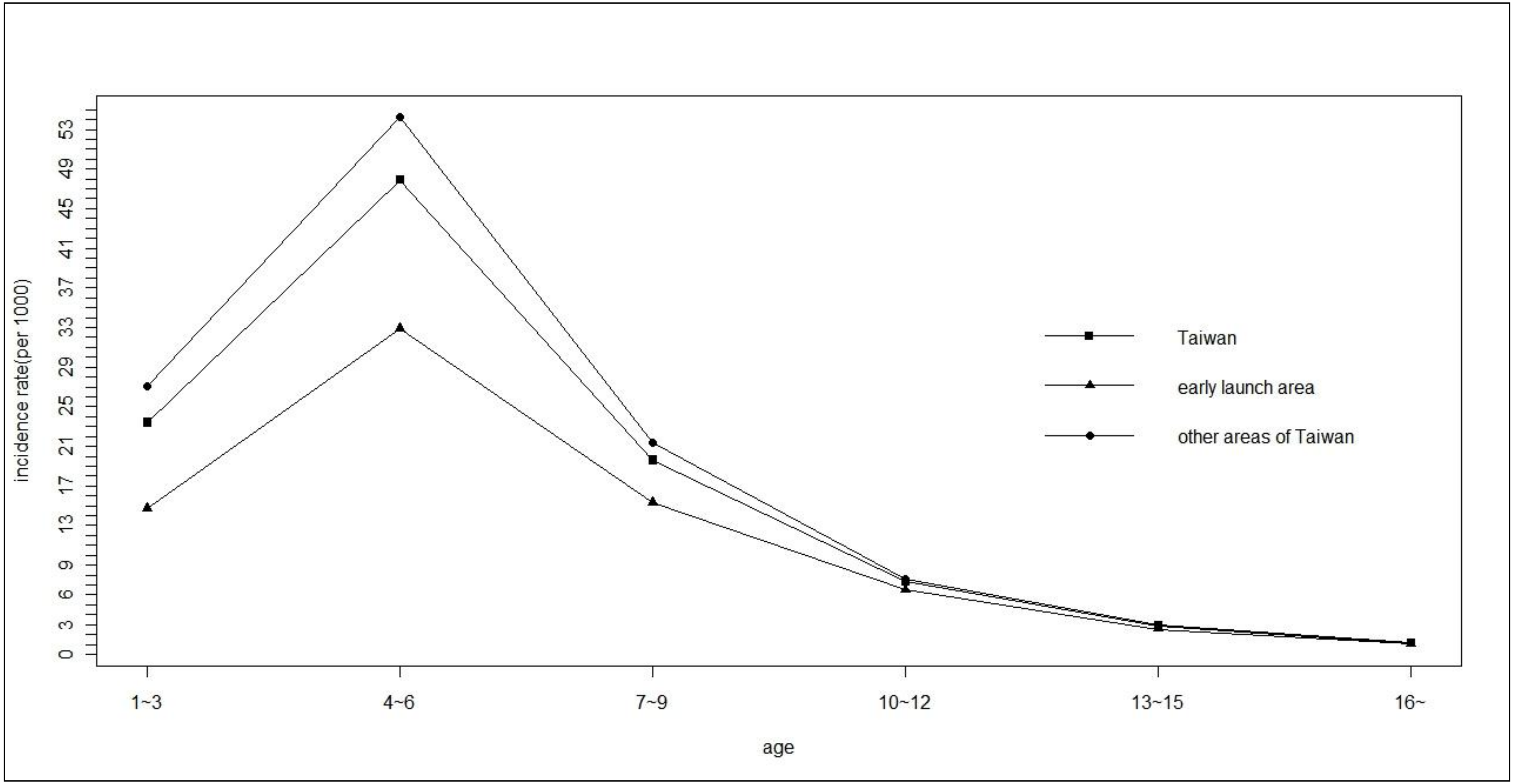


Fig 2. Age-specific incidence rates of varicella in different areas of Taiwan

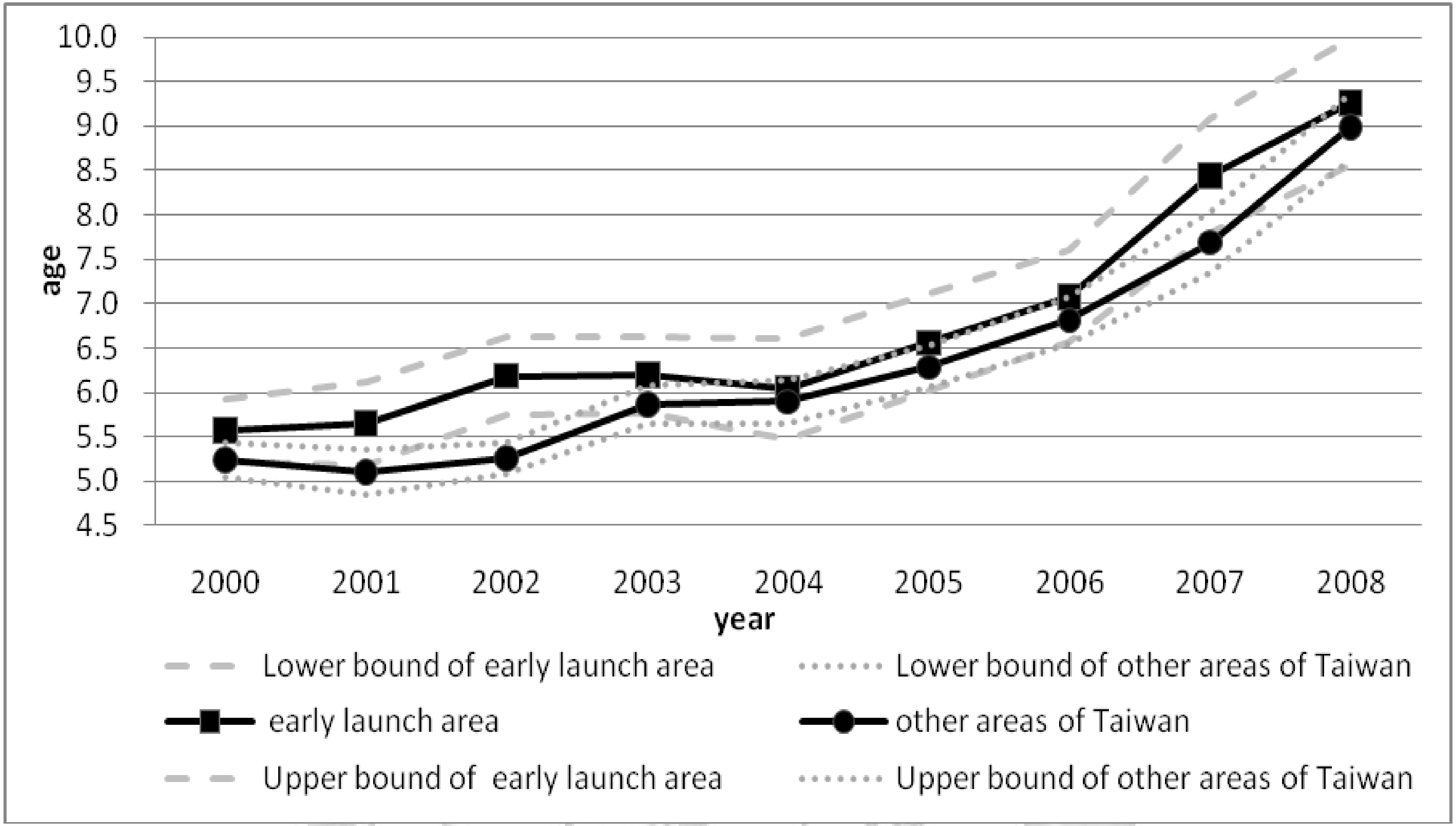
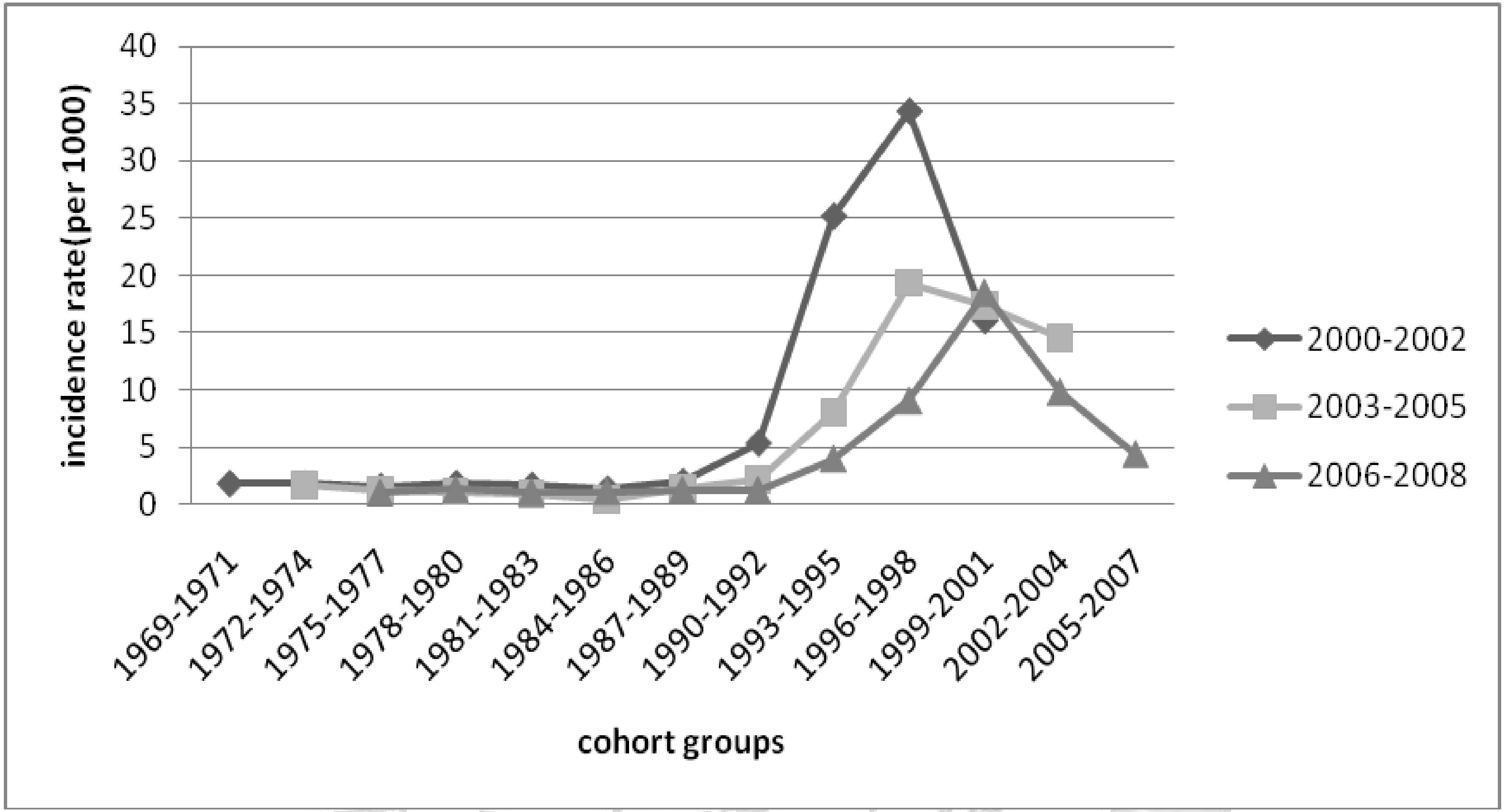


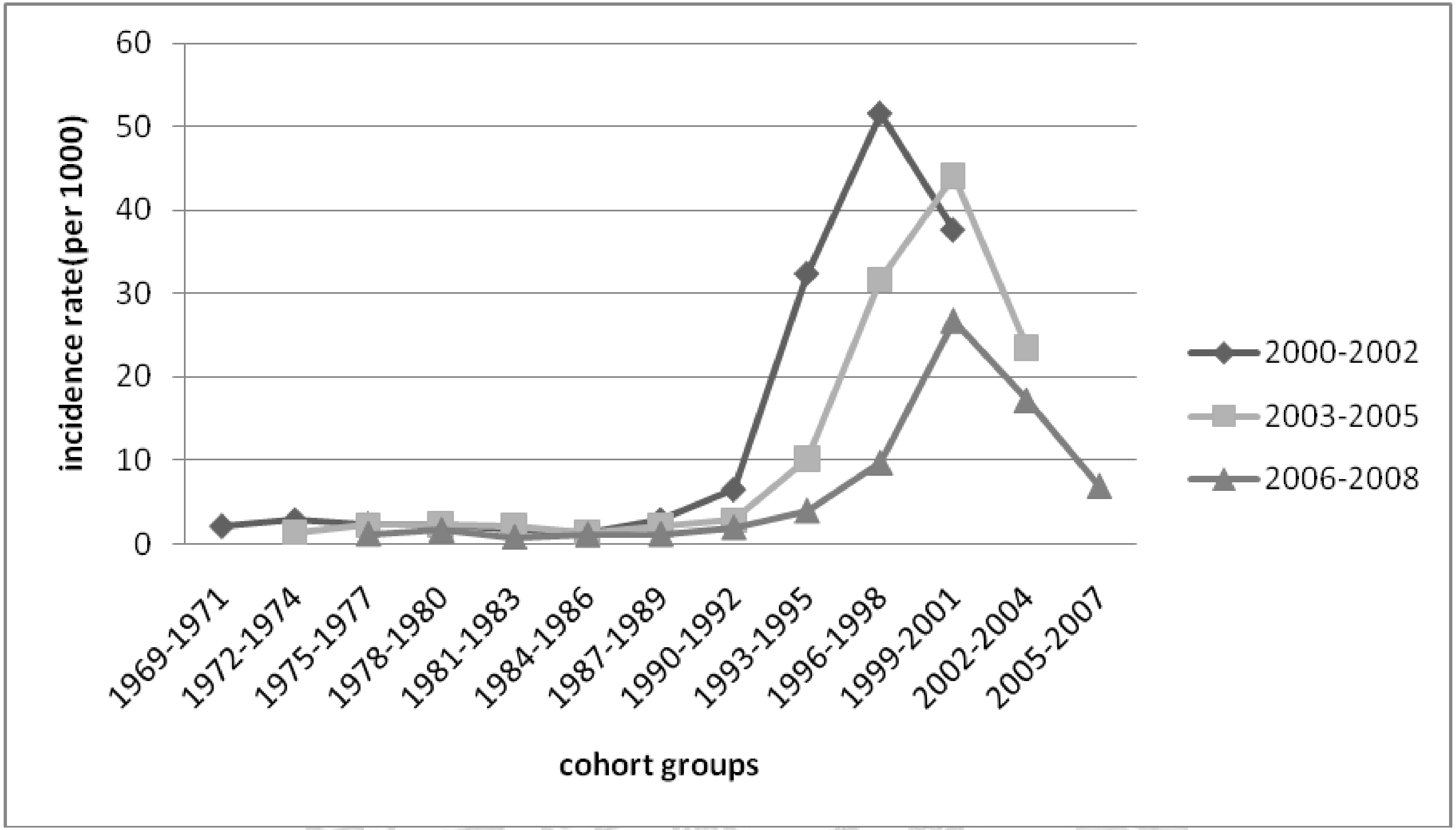
Fig 3. The average age at diagnosis of varicella in the early launch area (ELA) and the other areas of Taiwan, respectively.

Fig 4. Incidence rate of varicella stratified by birth cohorts and year period in early launch area (ELA) (a) and the other areas of Taiwan (b)

(a)



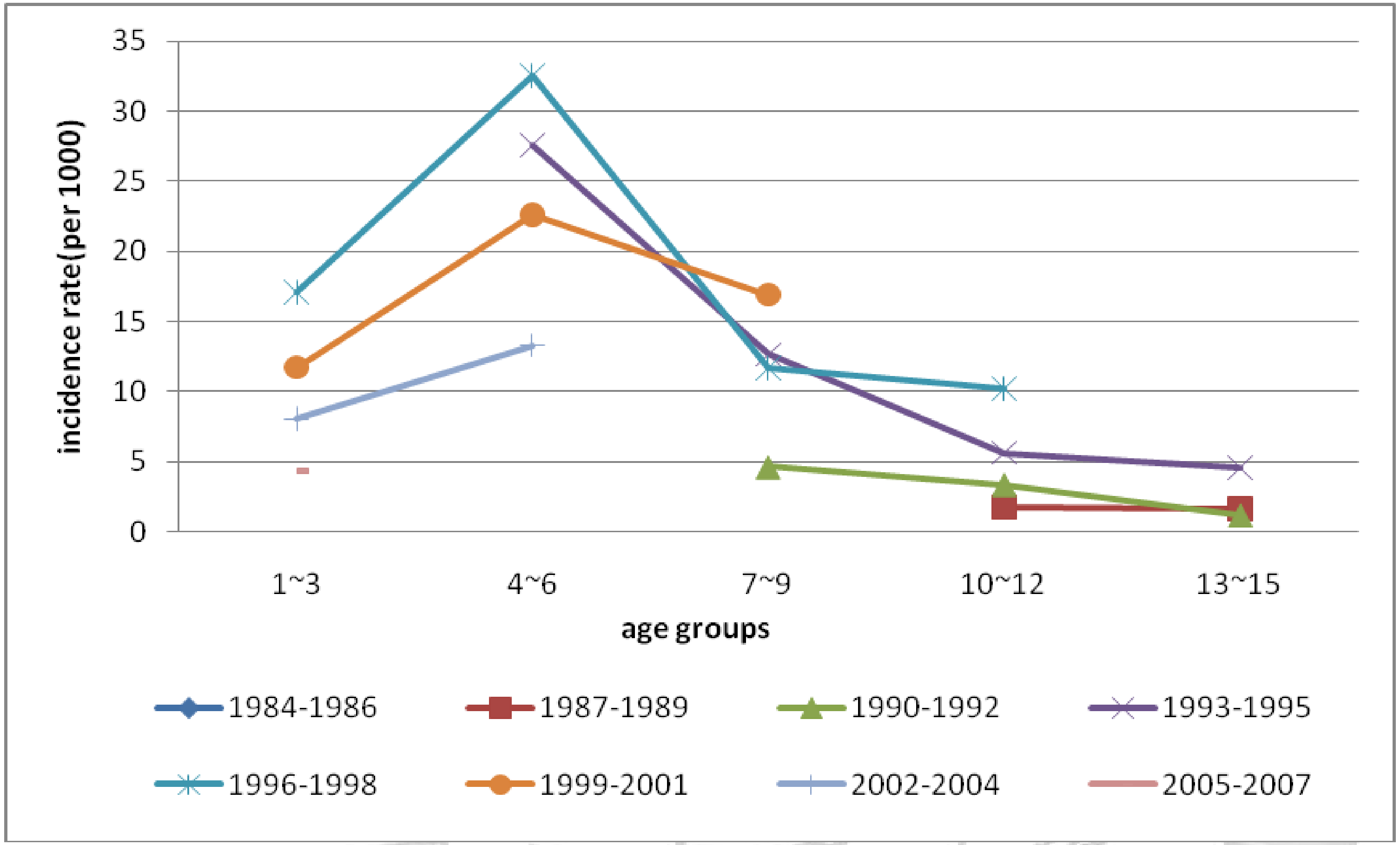
(b)



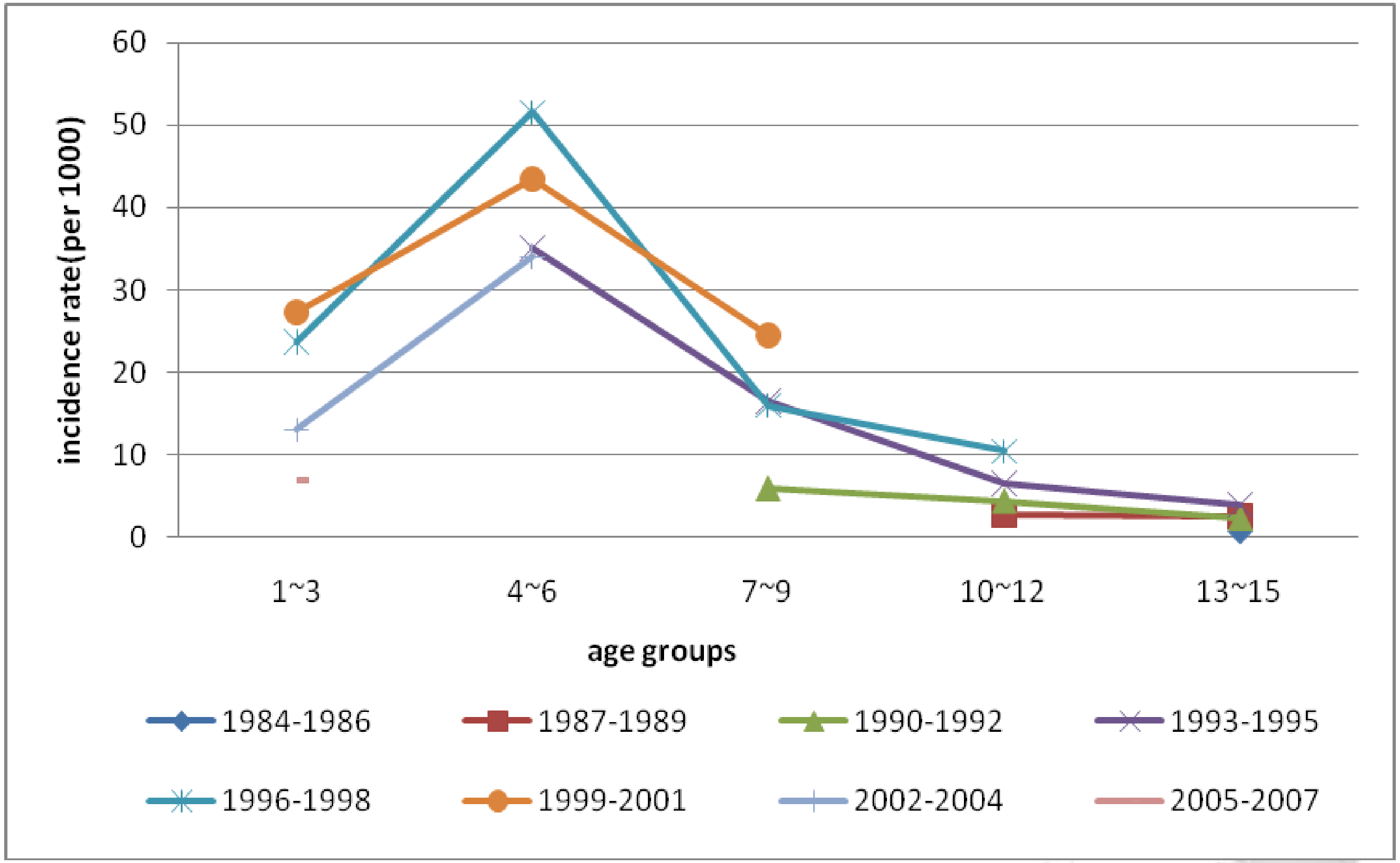
incidence rate(per 1000)
60
50
40
30
20
10
0
1969-1971
1972-1974
1975-1977
1978-1980
1981-1983
1984-1986
1987-1989
1990-1992
1993-1995
1996-1998
1999-2001
2002-2004
2005-2007
cohort groups
2000-2002
2003-2005
2006-2008

Figure 5. Incidence rate of varicella among different age groups stratified by birth cohorts in early launch area (ELA) (a) and the other areas of Taiwan

(a)



(b)



60
50
40
30
20
10
0
incidence rate(per 1000)
1~3
4~6
7~9
10~12
13~15
age groups
1984-1986
1987-1989
1990-1992
1993-1995
1996-1998
1999-2001
2002-2004
2005-2007