Preplanned Studies

Trends and Age-Period-Cohort Effect on Incidence of Varicella Under Age 35 — China, 2005–2021

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Summary

What is already known about this topic?

Varicella is an acute respiratory infectious disease primarily affecting children. However, recent studies have indicated an increasing susceptibility to varicella among older age groups.

What is added by this report?

The findings demonstrate a significant rise in the incidence rate among individuals aged 15–19. Males under 20 years old were found to have a higher risk compared to females, whereas males had a lower risk compared to females aged 20–35 years.

What are the implications for public health practice?

This study is the first comparative analysis using varicella data reported between 2005 and 2021 to examine the contributions of age, period, and birth cohort to varicella incidence in China. This study aims to provide a comprehensive analysis of the epidemiological characteristics of varicella in China and identify high-risk groups. The results of this study will contribute valuable information for the development of varicella prevention policies.

The incidence of varicella is primarily observed in children, although recent studies have shown an increasing incidence rate and proportion among the elderly population (*1*–*2*). Previous research has mostly focused on describing the epidemiological characteristics of varicella in specific provincial-level administrative division (PLAD) or cities in China (*3*–*4*). However, there is a lack of studies investigating long-term patterns of varicella incidence by gender, age, period, and cohort. Therefore, this study utilized age-period-cohort models to analyze the changing patterns of varicella incidence in China from 2005 to 2021, while also examining the effects of age, period, and cohort on incidence changes. Notably, the incidence rate of varicella significantly increased in the 15–19 and 10–14 age groups. Among males, the highest incidence risk was observed in the 15–19 age group, whereas the entire population and females reached peak incidence in the 25–29 age group. Males had a higher risk than females below the age of 20 but a lower risk between the ages of 20 and 35. Additionally, younger cohorts below the age of 20 exhibited a greater risk. These findings highlight the importance of implementing proactive measures to prevent varicella, particularly targeting gender differences and the elderly population. These insights can inform decision-makers in formulating appropriate prevention strategies.

From 2005 to 2021, a total of 4,108,983 male and 3,295,186 female varicella cases were reported in China across 31 PLADs. The cases were obtained from the Chinese Infectious Diseases Reporting System, which enables real-time dynamic monitoring of infectious disease epidemics at various administrative levels. Although varicella is not legally required to be reported, it is considered a key monitored infectious disease and follows the territorial management principle within the system. We calculated the crude incidence rates (CIR) by dividing the number of incident cases by the annual mean population of the same age and year. Additionally, the age-standardized incidence rates (ASIR) were determined using direct standardization with data from the seventh National Census in 2020 (http://www.stats.gov.cn/sj/pcsj/rkpc/7rp/indexch.Htm).

R software (version 4.2.2, R Foundation for Statistical Computing, Auckland, New Zealand) was utilized to analyze the incidence data. The Age Period Cohort (APC) Web Tool, provided by the National Cancer Institute of the United States, was used to study the epidemic characteristics of diseases through registry-based studies of incidence and mortality. We accessed the tool via the National Institute of Health website (https://analysistools.cancer.gov/apc/) to measure the age, period, and cohort effects. The intervention measures taken to control the coronavirus disease 2019 (COVID-19) from 2020 to 2021 had an impact on the outbreak of varicella (*5*). To avoid the interference of this unconventional policy on the trend change analysis model, we used the incidence data of varicella from 2005 to 2019 for APC analysis. For the APC framework, the age interval was aligned with the period interval. The varicella cases and population data were divided into three consecutive 5-year periods from 2005–2009 to 2015–2019. Age groups were defined in 5-year intervals, ranging from 0–4 to 30–34. This resulted in 9 partially overlapping birth cohorts, including individuals born from 1975–1979 to 2015–2019. The reference values were set as the age group of 0–4 years, the period of 2010–2014, and the cohort of 1995–1999. To assess the trend of incidence rate in each age group and the birth cohort effect, we used the Local Drift, which represents the annual percentage change (% per year) in incidence rate at a specific age. The overall time trend of the incidence rate, considering the period and cohort factors, was represented by the Net Drift, which is the annual percentage change (% per year) of the overall incidence rate. The significance of estimated parameters was assessed using the Wald chi-square test, with a two-sided test and a significance level of $P<0.05$.

Figure 1A shows the overall upward trend of varicella incidence from 2005 to 2021 in China. The ASIR of varicella increased from 2.82 per 100,000 in 2005 to 71.51 per 100,000 in 2019, then it dropped to

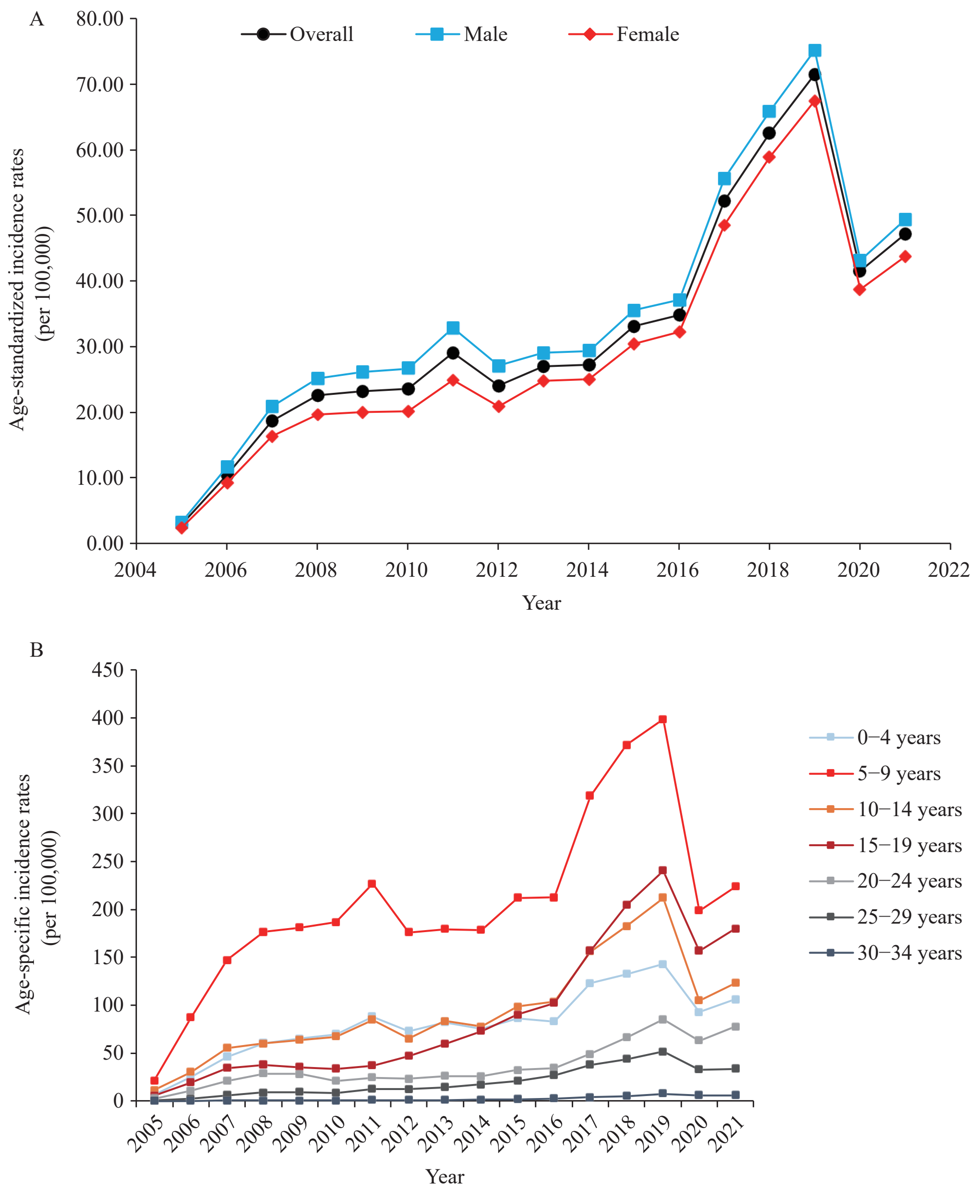

FIGURE 1. The trends of varicella incidence rate in China, 2005–2021. (A) Trends in the age-standardized incidence rates; (B) Age-specific incidence rates for varicella among individuals under 35 years of age.

TABLE 1. The age-specific incidence rates (per 100,000) of varicella in China, 2005–2021.

Groups	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
0–4 years																	
Overall	6.47	24.78	45.76	60.34	65.03	69.70	87.97	72.68	81.94	75.55	86.22	83.00	122.76	132.51	142.95	92.50	105.89
Male	7.08	27.24	49.55	65.62	71.41	76.44	98.17	80.66	88.39	80.29	92.20	87.70	129.35	137.80	149.08	93.26	108.43
Female	5.72	21.80	41.07	53.83	57.20	61.66	75.83	63.22	74.38	70.02	79.27	77.56	115.20	126.49	136.00	91.64	103.09
5–9 years																	
Overall	21.34	87.38	147.01	176.31	181.20	186.56	226.75	175.94	179.57	178.36	212.04	212.60	318.68	371.63	398.49	198.90	223.86
Male	23.27	91.92	157.52	189.44	195.41	202.98	248.92	193.56	188.30	187.57	223.00	222.74	334.23	386.41	415.51	202.83	231.33
Female	19.05	81.79	134.34	160.38	163.78	167.08	200.47	155.06	169.22	167.39	198.98	200.55	300.26	354.19	378.61	194.44	215.64
10–14 years																	
Overall	11.22	30.08	55.12	59.76	63.86	67.01	84.84	64.86	83.21	77.53	98.32	103.45	156.13	182.17	211.87	104.98	123.06
Male	11.81	31.35	59.12	63.63	67.49	72.50	91.27	70.51	84.17	80.48	102.61	109.42	161.99	191.78	225.32	117.49	136.65
Female	10.56	28.59	50.47	55.28	59.57	60.62	77.32	58.21	82.08	74.04	93.24	96.37	149.19	170.76	195.84	90.58	107.45
15–19 years																	
Overall	5.49	18.96	34.08	37.39	35.26	33.27	36.97	46.75	59.49	73.10	90.16	102.17	156.60	204.58	240.71	156.72	179.78
Male	6.59	20.90	37.83	40.63	42.63	39.94	40.58	50.40	62.75	77.80	95.85	108.41	166.29	214.82	251.90	164.04	192.99
Female	4.29	16.79	29.84	33.70	26.99	26.05	33.00	42.68	55.86	67.71	83.55	94.87	145.20	192.49	227.47	148.23	164.42
20–24 years																	
Overall	2.27	10.44	20.78	28.47	27.89	21.07	24.49	22.89	25.91	25.38	32.32	34.05	49.09	66.43	84.85	63.03	77.47
Male	2.09	11.81	20.93	30.18	30.34	22.23	24.30	23.77	25.31	23.11	28.13	32.83	43.15	55.93	72.94	60.16	73.68
Female	2.45	9.13	20.64	26.80	25.41	19.90	24.68	21.96	26.58	27.80	36.86	35.37	55.68	78.28	98.50	66.26	81.76
25–29 years																	
Overall	0.11	1.92	5.90	8.75	9.12	8.50	12.45	11.99	13.99	17.05	20.83	26.62	37.61	43.75	51.54	32.41	33.43
Male	0.08	2.23	5.95	9.34	8.52	8.56	12.38	10.21	11.42	14.91	18.80	21.16	32.19	35.49	39.18	27.46	27.60
Female	0.14	1.62	5.86	8.18	9.72	8.44	12.52	13.78	16.57	19.23	22.91	32.26	43.28	52.45	64.71	37.87	39.88
30–34 years																	
Overall	0.02	0.08	0.24	0.39	0.35	0.43	0.73	0.71	0.88	1.11	1.53	2.20	3.57	5.18	7.59	3.23	3.42
Male	0.03	0.11	0.30	0.48	0.37	0.42	0.84	0.66	0.94	1.09	1.45	1.97	3.23	4.75	6.97	2.86	2.91
Female	0.01	0.05	0.19	0.31	0.33	0.44	0.62	0.76	0.82	1.12	1.62	2.43	3.92	5.61	8.21	3.78	3.83

47.19 per 100,000 in 2021, with higher incidence in males than in females. The highest incidence rate of varicella was observed in the 5–9 age group. The incidence rate significantly increased in the 15–19 age group and surpassed that in the 10–14 and 0–4 age groups, becoming the age group with the second highest incidence rate. Figure 1B shows that the incidence rate also significantly increased in the 20–24 and 25–29 age groups . Table 1 presents the incidence among different age groups by gender. The incidence rate of the 0–4, 5–9, 10–14, and 15–19 age groups was higher in males than in females. Conversely, the incidence rate of the 20–24, 25–29, and 30–34 age groups was higher in females than in males and increased over time.

The age-specific incidence risk of varicella showed a peak at 25–29 years and then decreased among all subjects and females. However, for males, the peak occurred at 15–19 years (Table 2). The local trends demonstrated an upward trend, with the highest annual percentage increase in the age group of 30–34 years. The Net Drift was 16.3, with males and females having Net Drifts of 15.1 and 17.7, respectively (Supplementary Table S1, available at https://weekly.chinacdc.cn/). The estimated period and cohort relative risks exhibited similar increasing patterns. In terms of cohort effects, there was an increase in the incidence rates of varicella for both genders in China. The cohort effects displayed a J-shaped pattern after adjusting for age and period effects, with younger birth cohorts experiencing a higher incidence risk (Table 3). Wald tests indicated that both period and cohort

TABLE 2. Age effects obtained from longitudinal age curves of varicella incidence rate (per 100,000) in China, 2005–2019.

Age groups (years)	Overall		Male		Female	
	Rate	95% *CI*	Rate	95% *CI*	Rate	95% *CI*
0–4	58.07	(37.79, 89.26)	64.52	(41.94, 99.25)	50.28	(32.71, 77.28)
5–9	230.88	(166.24, 320.65)	250.32	(179.74, 348.61)	207.50	(149.83, 287.36)
10–14	175.91	(132.19, 234.10)	188.05	(140.87, 251.02)	161.68	(121.92, 214.40)
15–19	283.32	(217.43, 369.19)	304.31	(232.66, 398.03)	258.73	(199.34, 335.82)
20–24	265.29	(195.68, 359.67)	239.31	(171.32, 334.29)	294.81	(224.03, 387.97)
25–29	322.94	(201.23, 518.26)	245.92	(146.31, 413.34)	417.04	(270.74, 642.40)
30–34	68.44	(36.21, 129.33)	52.20	(26.06, 104.56)	88.57	(49.60, 158.15)

Abbreviation: *CI*=confidence interval.

TABLE 3. Period and Cohort effects obtained from Age-Period-Cohort analysis for the varicella rates in China, 2005–2019.

Variable	Overall		Male		Female	
	Rate ratio	95% *CI*	Rate ratio	95% *CI*	Rate ratio	95% *CI*
Period						
2005–2009	0.52	(0.41, 0.66)	0.54	(0.43, 0.68)	0.51	(0.40, 0.61)
2010–2014	1.00	1.00	1.00	1.00	1.00	1.00
2015–2019	2.38	(1.96, 2.90)	2.21	(1.81, 2.71)	2.58	(2.14, 3.11)
Cohort						
1975	0.02	(0.00, 0.10)	0.02	(0.00, 0.16)	0.01	(0.00, 0.06)
1980	0.07	(0.03, 0.16)	0.09	(0.04, 0.23)	0.05	(0.02, 0.12)
1985	0.28	(0.17, 0.48)	0.34	(0.19, 0.60)	0.24	(0.15, 0.38)
1990	0.49	(0.34, 0.71)	0.52	(0.35, 0.77)	0.45	(0.32, 0.64)
1995	1.00	1.00	1.00	1.00	1.00	1.00
2000	2.54	(1.90, 3.40)	2.51	(1.87, 3.38)	2.58	(1.94, 3.44)
2005	4.19	(3.04, 5.78)	4.13	(2.99, 5.71)	4.28	(3.11, 5.88)
2010	6.50	(4.52, 9.35)	6.31	(4.37, 9.10)	6.79	(4.73, 9.73)
2015	9.42	(5.66, 15.68)	8.96	(5.37, 14.97)	10.18	(6.14, 16.90)

Abbreviation: *CI*=confidence interval.

effects were statistically significant (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

DISCUSSION

This study investigates the long-term trend of varicella incidence among individuals under 35 years old in China from 2005 to 2021, focusing on gender differences and changes in age groups. First, we observed a continuous increase in the incidence rate of varicella in China, but there was a significant decline in 2020 due to the intervention measures taken during the COVID-19 pandemic. Second, the incidence rate of varicella among individuals under 20 years old and between 20–35 years old exhibited opposite gender differences: males had a higher incidence rate than females among individuals under 20 years old, but this difference reversed among those between 20 and 35 years old. Third, there were gender differences in the specific high-risk age groups for varicella within different populations. Furthermore, all population groups exhibited similar and elevated period and cohort effects. These findings highlight the importance of developing targeted varicella prevention strategies for high-risk groups. Consistent with previous literature (*1–4*), our study demonstrates that the highest incidence rate of varicella still occurs in the 5–9 age group. This high incidence rate is mainly attributed to the incomplete development of the immune system, making the body susceptible to varicella infection through direct or indirect contact (*6*). However, our study reveals new findings compared to previous research. It shows a rapid increase in the incidence rate among the 10–14 and 15–19 age groups in China, as they did not previously receive the varicella vaccine and lacked population immunity (*7*). Among varicella cases under 20 years old, males experienced a higher disease burden, potentially due to increased outdoor activities and involvement in crowd-intensive gatherings. Conversely, females had a higher disease burden among varicella cases aged 20–35 years, possibly due to higher pressures in college life, family, and work settings.

The increased incidence of varicella can be attributed to several factors. First, there has been an improvement in the diagnosis of varicella, leading to a decrease in misdiagnosis and missed diagnosis cases. Standardized diagnostic procedures have played a crucial role in achieving this (*8*–*9*). Additionally, certain regions have heightened their management of varicella cases to ensure accurate reporting and a more representative incidence level (*2*,*4*). Furthermore, the impact of global warming on the risk of varicella cannot be overlooked. A study conducted in Guangzhou City, Guangdong Province found that the relative risk of varicella was highest [1.11; 95% confidence interval (*CI*): 1.07, 1.16] at lag 21 days, with a mean temperature of 31.8 °C (*10*). This highlights the influence of meteorological factors such as temperature, humidity, precipitation, and air pressure on varicella incidence.

The cohort effect, on the other hand, primarily reflects the influence of social changes on specific generations. The elevated risk of varicella among young cohorts can be attributed to the coverage rate of varicella vaccination. In most areas of China, the varicella vaccine is administered once after the age of 12 months, offering protection to the 0–4 age group. This contributed to a relatively stable incidence rate prior to 2016. However, the significant increase in the number of newborn children since the implementation of the universal two-child policy in 2016 has led to a rise in the incidence rate among the 0–4 age group since 2017. Moreover, the lack of subsequent booster immunization has resulted in insufficient vaccine protection for the 5–9 age group. Additionally, the current rate of one dose of varicella vaccine in China falls short of achieving population immunity (*7*), leading to a persistently high incidence rate among younger cohorts. It is worth noting that vaccination procedures often limit the age of vaccination to under 12 years old, leaving a gap in vaccination strategies for older age groups. This especially affects high-school and college students, potentially causing a shift in the peak incidence of varicella (*5*). As a result, future policy research should prioritize the immunization of varicella among older children and adults.

The study had several limitations. First, our observations were made at the group level, which makes it susceptible to ecological fallacies. Second, the data range imposed limitations on our ability to estimate earlier period and cohort impacts. Third, we only analyzed age, period, and cohort effects, and did not consider other environmental factors or vaccination status as covariates in this study. Lastly, varicella is a non-legally reported infectious disease, which introduces the possibility of underreporting of varicella cases.

In this study, we conducted a comprehensive analysis of the epidemiological characteristics of varicella in China from 2005 to 2021. We utilized data from the infectious disease monitoring system to evaluate the age, period, and cohort effects of varicella in China for the first time. These findings enhance our understanding of the epidemiological characteristics of varicella in China, providing a basis for promoting the vaccination of children with two doses of varicella vaccine and conducting research on strengthening immunization with adult varicella vaccine.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Local Drifts with Net Drifts obtained by age-period-cohort analyses for the incidence rate of varicella in China, 2005–2019.

Variable	Overall		Male		Female	
	Percent per year	95% *CI*	Percent per year	95% *CI*	Percent per year	95% *CI*
Local Drifts						
0–4 years	8.43	(4.05, 12.99)	8.06	(3.68, 12.62)	9.06	(4.67, 13.64)
5–9 years	9.85	(7.08, 12.69)	9.65	(6.88, 12.49)	10.15	(7.38, 13.00)
10–14 years	15.41	(11.76, 19.18)	15.24	(11.56, 19.04)	15.64	(12.02, 19.38)
15–19 years	17.93	(13.33, 22.71)	17.05	(12.42, 21.88)	19.00	(14.45, 23.74)
20–24 years	13.51	(7.70, 19.63)	11.44	(5.29, 17.95)	15.57	(10.12, 21.29)
25–29 years	21.88	(12.19, 32.42)	19.21	(8.97, 30.40)	24.30	(15.23, 34.08)
30–34 years	33.67	(11.67, 60.01)	30.18	(8.74, 55.84)	37.60	(14.86, 64.83)
Net Drifts	16.35	(13.28, 19.50)	15.10	(11.95, 18.34)	17.67	(14.67, 20.75)

Abbreviation: *CI*=confidence interval.

SUPPLEMENTARY TABLE S2. Wald tests of APC model parameters of varicella incidence rate (per 100,000) in China, 2005–2019.

Group	Model parameter	χ^2	*df*	*P*-value
Overall				
	Net drift = 0	123.22	1	<0.0001
	All age deviations = 0	121.26	5	<0.0001
	All period deviations = 0	1.72	1	0.1896
	All cohort deviations = 0	20.38	7	0.0048
	All period RR = 1	133.82	2	<0.0001
	All cohort RR = 1	179.69	8	<0.0001
	All local drifts = Net drift	20.30	6	0.0025
Male				
	Net drift = 0	98.64	1	<0.0001
	All age deviations = 0	119.39	5	<0.0001
	All period deviations = 0	1.10	1	0.2936
	All cohort deviations = 0	17.31	7	0.0155
	All period RR = 1	105.03	2	<0.0001
	All cohort RR = 1	160.67	8	<0.0001
	All local drifts = Net drift	17.20	6	0.0086
Female				
	Net drift = 0	152.56	1	<0.0001
	All age deviations = 0	128.87	5	<0.0001
	All period deviations = 0	2.57	1	0.1092
	All cohort deviations = 0	24.55	7	0.0009
	All period RR = 1	169.55	2	<0.0001
	All cohort RR = 1	205.42	8	<0.0001
	All local drifts = Net drift	24.50	6	0.0004

Abbreviation: APC=age-period-cohort; RR=relative risk; *df*=degree of freedom.