

Changes in epidemiological characteristics of varicella and breakthrough cases: Insights from Surveillance Data in Ningbo Spanning 2010 to 202

Xingqiang Pan, Yan Zhang, Xuefei Zhao, Dandan Zhang

Submitted to: JMIR Public Health and Surveillance
on: January 24, 2025

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Changes in epidemiological characteristics of varicella and breakthrough cases: Insights from Surveillance Data in Ningbo Spanning 2010 to 2023

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Abstract

Background: Varicella is a prevalent respiratory infectious disease. It is often inadequately managed in many regions, leading to an underestimation of its true incidence rate. The varicella vaccine remains the most effective measure for controlling the disease, and its widespread use has significantly reduced incidence rates. Additionally, non-pharmacological interventions during the COVID-19 pandemic have notably altered the epidemiological patterns of varicella. Continuous monitoring is therefore essential to understand these evolving patterns, aiding in the adjustment of immunization strategies and the development of prevention and control measures.

Objective: This study aims to monitor the epidemiological characteristics of varicella and the changes in breakthrough cases to inform adjustments in immunization strategies and enhance prevention efforts.

Methods: From 2010 to 2011, varicella incidence was monitored using active surveillance methods, and the immune history of patients was investigated. From 2012 to 2023, passive surveillance methods were employed. Data on varicella patients were obtained from the Chinese Center for Disease Prevention and Control's information system. The study period was divided into four intervals: 2010-2011, 2012-2013, 2014-2019, and 2020-2023, to analyze epidemiological characteristics and trends. A birth cohort of children born at surveillance sites from 2009 to 2013 was established to examine the epidemiological characteristics and trends of breakthrough cases.

Results: Between 2010 and 2023, 70,163 varicella cases were reported in Ningbo. Seasonal distribution indicated two incidence troughs before 2020, and only one from 2020 to 2023. The predominant age of onset was 10-14 years, accounting for 23.93% of cases. From 2010 to 2013, the highest incidence was among children aged 5-9; from 2014 to 2019, it shifted to those aged 10-14; and from 2020 to 2023, it was primarily among individuals aged 15-19. Following the introduction of a second vaccine dose (2014-2019), incidence among children under 10 decreased, notably by 59.54% in those aged 1-4. Conversely, incidence among individuals aged 10 and older increased, particularly by 123.78% in the 15-19 age group, with a significant upward trend (P trend <0.001). From 2020 to 2023, although incidence rates increased across age groups 15 and older, the rise was modest. The average annual incidence rate of breakthrough cases after one vaccine dose was 83.40/100,000 (range: 51.21-119.50/100,000), significantly higher than the 24.80/100,000 (range: 17.67-32.90/100,000) observed after two doses. However, the incidence of breakthrough cases after the first dose declined following the implementation of the two-dose program. The median time from vaccination to breakthrough case occurrence was 27 months (range: 17.5-48 months).

Conclusions: The epidemiological characteristics of varicella have changed significantly from 2010 to 2023, underscoring the necessity for continuous monitoring to effectively adjust immunization strategies and address emerging trends in breakthrough cases.

(JMIR Preprints 24/01/2025:71691)

DOI: <https://doi.org/10.2196/preprints.71691>

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Original Manuscript

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Abstract

Background: Varicella is a prevalent respiratory infectious disease. It is often inadequately managed in many regions, leading to an underestimation of its true incidence rate. The varicella vaccine remains the most effective measure for controlling the disease, and its widespread use has significantly reduced incidence rates. Additionally, non-pharmacological interventions during the COVID-19 pandemic have notably altered the epidemiological patterns of varicella. Continuous monitoring is therefore essential to understand these evolving patterns, aiding in the adjustment of immunization strategies and the development of prevention and control measures.

Objective: This study aims to monitor the epidemiological characteristics of varicella and the changes in breakthrough cases to inform adjustments in immunization strategies and enhance prevention efforts.

Methods: From 2010 to 2011, varicella incidence was monitored using active surveillance methods, and the immune history of patients was investigated. From 2012 to 2023, passive surveillance methods were employed. Data on varicella patients were obtained from the Chinese Center for Disease Prevention and Control's information system. The study period was divided into four intervals: 2010-2011, 2012-2013, 2014-2019, and 2020-2023, to analyze epidemiological characteristics and trends. A birth cohort of children born at surveillance sites from 2009 to 2013 was established to examine the epidemiological characteristics and trends of breakthrough cases. To assess the impact of non-pharmaceutical interventions (NPIs), a Recurrent Neural Network (RNN) model was constructed for deep learning analysis of incidence trends.

Results: Between 2010 and 2023, 70,163 varicella cases were reported in Ningbo. Seasonal distribution indicated two incidence troughs before 2020, and only one from 2020 to 2023. The predominant age of onset was 10-14 years, accounting for 23.93% of cases. From 2010 to 2013, the highest incidence was among children aged 5-9; from 2014 to 2019, it shifted to those aged 10-14; and from 2020 to 2023, it was primarily among individuals aged 15-19. Following the introduction of a second vaccine dose (2014-2019), incidence among children under 10 decreased, notably by 59.54% in those aged 1-4. Conversely, incidence among individuals aged 10 and older increased, particularly by 123.78% in the 15-19 age group, with a significant upward trend ($P_{\text{trend}} < 0.001$). From 2020 to 2023, although incidence rates increased across age groups 15 and older, the rise was modest. The average annual incidence rate of breakthrough cases after one vaccine dose was 83.40/100,000 (range: 51.21-119.50/100,000), significantly higher than the 24.80/100,000 (range: 17.67-32.90/100,000) observed after two doses. However, the incidence of breakthrough cases after the first dose declined following the implementation of the two-dose program. The median time from vaccination to breakthrough case occurrence was 27 months (range: 17.50-48 months). The RNN

model demonstrated high accuracy (MSE: 49.96) and indicated that implementation of emergency response and community lockdown measures in early 2020 correlated with a divergence between predicted and actual case numbers, suggesting an impact of NPIs on varicella transmission.

Conclusion: The significant shifts in varicella epidemiology between 2010 and 2023 highlight the importance of continuous monitoring and proactive immunization adjustments. We recommend for enhanced varicella surveillance focusing on adult populations, and a targeted increase in two-dose vaccine coverage, particularly in high-risk environments such as high schools and universities.

KEYWORDS

Varicella; breakthrough case; epidemiology; disease surveillance; infectious; monitoring; vaccine; Non-pharmacological interventions; Machine learning

Introduction

Varicella, a highly contagious disease caused by the varicella-zoster virus (VZV), is primarily transmitted through direct contact with the rash of varicella or herpes zoster, as well as by inhaling aerosolized droplets from the respiratory secretions of varicella patients[1]. While varicella is typically mild and self-limiting in healthy children, it can be life-threatening for immunosuppressed patients, pregnant women, and the elderly. In high-risk groups, varicella infection may result in severe complications such as pneumonia, encephalitis, hepatitis, organ failure, and acute cerebellar ataxia[2]. According to the World Health Organization (WHO), the annual global burden of varicella is estimated at around 140 million cases, leading to 4,200,000 harsh complications necessitating hospitalization, and resulting in 4,200 deaths[3]. Notably, China reported[4] a total of 3,047,715 varicella cases between 2016 and 2019, with an average annual incidence rate of 55.05 per 100,000. The incidence rate significantly increased from 35.50 per 100,000 in 2016 to 70.14 per 100,000 in 2019, surpassing other legally notifiable infectious diseases like measles and rubella. Since varicella is not a notifiable infectious disease in China, the actual incidence rate is probably higher than the reported rate. This underscores the pressing need for effective prevention strategies to tackle the significant public health impact of varicella infection.

The introduction of the varicella vaccine has been crucial in disease control, significantly reducing the incidence, hospitalizations, and mortality rates associated with varicella[5,6]. The vaccine was first licensed for use in the United States in 1995. In 2006, a two-dose schedule was recommended for children, with the first dose given at 12-15 months and the second between 4-6 years of age[6]. This immunization strategy has also been adopted by Germany, Australia, and Canada. In contrast, China introduced the varicella vaccine in 1998 but did not include it in the national immunization program, opting a single-dose strategy targeting children aged 12-18 months. Starting in 2014, Ningbo implemented a two-dose vaccination strategy, with the first dose administered at 12-15 months and the second at age 3 and above. Vaccination in Ningbo is voluntary and self-funded, achieving a vaccination rate exceeding 90% for one dose and over 70% for two doses[7,8]. The use of the varicella vaccine in children has led to changes in the epidemiological characteristics of varicella, including a shift towards older age groups[3]. Non-pharmaceutical preventive measures for COVID-19 may also impact the epidemiological features of varicella. Studies indicated that the effectiveness of a single varicella vaccine dose diminishes over time, contrasting with the sustained effectiveness of the two-dose vaccine[9]. Even if vaccinated, breakthrough cases of varicella can still occur. Although usually less severe, these cases can contribute to the spread of varicella within a community.

The WHO emphasizes the need for thorough varicella surveillance to understand the disease's spread and to guide public health efforts in prevention and control. Since 2009, targeted

surveillance efforts have been implemented, establishing specific varicella surveillance points in Ningbo, China, to monitor disease incidence and spread. In 2012, the Ningbo Municipal Bureau of Health required all healthcare facilities to report varicella cases to the China Information System for Disease Control and Prevention (CISDCP) within 24 hours. And this measure enhanced the accuracy and promptness of data collection. This study aims to utilize both active and passive surveillance data to analyze the epidemiological features of varicella and breakthrough cases.

Methods

Setting

Ningbo, a sub-provincial city in Zhejiang province, East China, is one of the five state-planning cities in the country. Before 2016, Ningbo comprised six urban districts (Haishu, Jiangbei, Jiangdong, Zhenhai, Beilun, and Yinzhou), three satellite county-level cities (Fenghua, Yuyao, and Cixi), and two rural counties (Ninghai and Xiangshan). Following a regional restructuring in 2016, Ningbo now includes six urban districts: Haishu, Jiangbei, Zhenhai, Beilun, Yinzhou, and Fenghua; two county-level cities: Yuyao and Cixi; and two counties: Ninghai and Xiangshan. The city spans 9,816.2 km² of land and 8,355.8 km² of sea. As of the end of 2022, Ningbo had a population of 9.618 million permanent residents. Since 2005, the Ningbo Center for Disease Control and Prevention has operated the Ningbo Immunization Information System (NBIIS), a computerized system that maintains immunization data and demographic information on vaccines for the Ningbo region[10].

2010–2011, Active monitoring only

The varicella active surveillance project[10] was conducted in Yuyao City, Yinzhou District, and Ninghai County during 2010 and 2011, through a collaboration between the Yuyao CDC, Yinzhou CDC, Ninghai CDC, and Ningbo CDC. Yuyao City is located in the western part of Ningbo, on the southern bank of the Yangtze River Delta. Yinzhou is a central district of Ningbo, covering an area of 1,380 square kilometers. Ninghai County is situated to the south of Ningbo and spans approximately 1,931 square kilometers. The populations of Yuyao, Yinzhou, and Ninghai County were 830,000, 730,000, and 580,000, respectively.

Since mid-2009, local health providers and physicians in the varicella surveillance areas have been required to electronically report any diagnosed varicella case to CISDCP within 24 hours. The epidemiologic information recorded for each case includes age, sex, current home address, household registration, date of symptoms onset, date of diagnosis, vaccine history, and other relevant details. Public health doctors in the surveillance area were also responsible for actively identifying varicella cases in hospitals, community health service centers, schools, and kindergartens on a weekly basis. If an unreported varicella case was found, public health doctors would report them through CISDCP.

2012–2023, Passive Surveillance

Since 2012, under the requirement of the health administration department in Ningbo City, all medical institutions in the city are required to report varicella cases through CISDCP. The CDC conducted quarterly investigations on underreporting to improve the quality of reporting. (1) Varicella vaccine immunization strategy adjustment in 2014, Ningbo City implemented a 2-dose varicella immunization strategy. Children receive voluntary and self-paid varicella vaccination. The recommended timing for the first dose is at 1 year of age, and the recommended timing for the second dose is between 3–4 years of age. (2) Non-pharmaceutical intervention measures Starting from 2020, various non-pharmaceutical intervention measures (NPIs) have been implemented by the government to control the COVID-19 epidemic. These measures include maintaining social

distancing, wearing masks, school closures, and community lockdowns, which have had a significant impact on the transmission of other respiratory infectious diseases.

Diagnosis of Varicella and Breakthrough Cases

Varicella diagnostic criteria[11]: It is characterized by typical clinical manifestations, namely the presence of characteristic rashes that progress from macules to papules and then to vesicles before crusting. It is usually accompanied by fever and systemic symptoms such as malaise. If there are no typical clinical manifestations, diagnosis needs to be made in conjunction with epidemiological history. The incidence of varicella in Ningbo is determined by dividing the number of reported cases by the corresponding population size. Population data for each age group is sourced from the Ningbo Municipal Public Security Bureau.

A birth cohort was established for children born between 2009 and 2013 who received one dose of varicella vaccine at the surveillance sites. Their varicella incidence was monitored through CISDCP. Varicella vaccine administration information was obtained through Ningbo's Immunization Information System (NBIIS).

Breakthrough varicella is defined as the occurrence of clinically diagnosed varicella in individuals who present with characteristic symptoms and/or have a documented epidemiological exposure history (as previously described), with symptom onset occurring more than 42 days after vaccination[12]. Furthermore, the rate of breakthrough infections has been delineated as the ratio of breakthrough infections occurring in children who have undergone varicella vaccination.

Data extraction and analysis

The varicella cases recorded between the years 2010 and 2023 were sourced from the comprehensive infectious disease surveillance and CISDCP. According to the temporal onset of illness, the cases were stratified into four phases for the purposes of descriptive analysis: 2010-2011, 2012-2013, 2014-2019, and 2020-2023. In the context of regional distribution analysis, and owing to specific regional modifications in Ningbo, the interval from 2014 to 2019 was further subdivided into two distinct phases: 2014-2015 and 2016-2019. Chi-square statistical tests were employed to examine the variations in age and gender across the different phases, while trend chi-square tests were utilized to assess the evolving trends of various age cohorts within each phase.

To evaluate the impact of non-pharmacological interventions (NPIs) on the incidence of chickenpox, we developed an advanced deep learning framework utilizing recurrent neural networks (RNNs). The model was trained on a dataset of chickenpox cases recorded between January 1, 2012, and December 31, 2018, and validated using data from January 1, 2019, to December 31, 2019. Predictions generated by the model were compared with actual incidence data from January 1 to June 30, corresponding to the implementation of Level 1 Emergency Response on January 22 and community lockdown measures introduced on February 2. The training process employed a sliding window technique to forecast future case numbers, and model performance on the validation dataset was evaluated using metrics such as mean squared error (MSE), root mean squared error (RMSE), and mean absolute error (MAE). The final model was then used to predict chickenpox incidence for the period from January 1, 2020, to June 30, 2020. These predictions were analyzed to assess the influence of NPIs by comparing the forecasted incidence with the observed data for the same timeframe.

The Python programming language facilitated the processes of data cleansing, analytical procedures, and data visualization. Two-sided P values were documented, adhering to a significance threshold of $P < 0.05$. All analytical procedures were conducted utilizing Python software 3.10[13].

Ethical Considerations

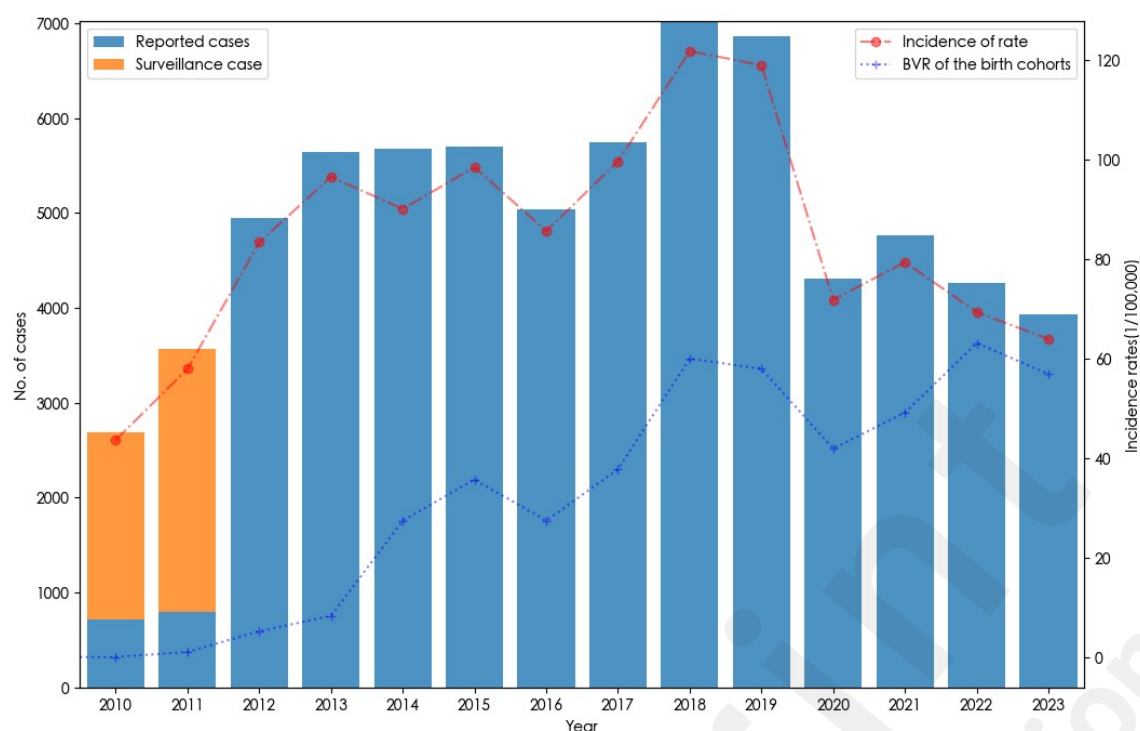
This study utilized secondary surveillance data on varicella cases obtained from the CISDCP. The study protocol was reviewed and approved by the Biological and Medical Ethics Committee of Ningbo Center for Disease Control and Prevention (Approval NO.: 202312), ensuring adherence to ethical guidelines for public health research. The original data collection involved informed consent procedures as per national regulations; the Ningbo CDC Ethics Committee specifically granted approval for this secondary analysis without requiring additional consent from individual patients. All data were fully anonymized and de-identified prior to access and analysis, protecting patient privacy and confidentiality. No personal identifiers were present in the dataset provided to the researchers. No compensation was provided to participants as this study involved the analysis of routinely collected surveillance data. The manuscript and supplementary materials do not contain any images of individual participants. We confirm that all data handling and analysis were conducted in compliance with relevant ethical standards and regulations for public health surveillance.

Results

Pathogenesis overview

Between 2010 and 2023, a total of 70,163 varicella cases were documented in Ningbo. Within the designated monitoring region, 4,753 cases were reported during 2010-2011. In the birth cohort from 2009 to 2013, there were 1,404 varicella cases, including 912 classified as breakthrough cases. The overall incidence rate for breakthrough cases was 47,149 per 100,000 individuals. The frequency of breakthrough cases increased over time post-vaccination, peaking in 2022 at 6,307 per 100,000. The annual incidence of varicella rose from 63.89 per 100,000 in 2010 to 98.42 per 100,000 in 2013. It remained relatively stable between 2014 and 2017, ranging from 85.58 to 99.60 per 100,000, before increasing to 121.75 per 100,000 in 2018. A significant decline began in 2020, with the incidence rate dropping from 71.79 per 100,000 to 6,389 per 100,000(Figure 1).

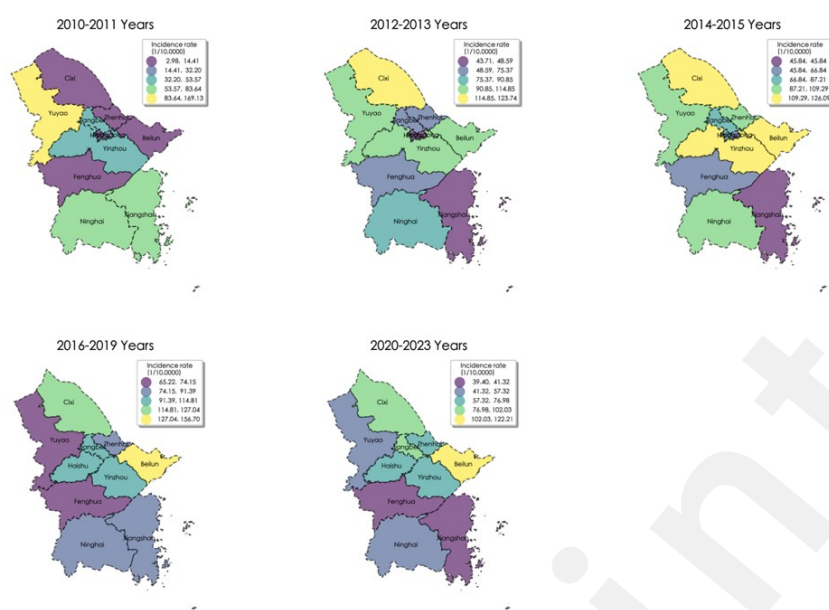
Figure 1. The prevalence of varicella in Ningbo, 2010-2023



Spatial Distribution

Between 2010 and 2023, the municipalities with the highest average annual incidence rates of varicella were Beilun District, Yinzhou District, and Cixi City, with rates of 113.44, 105.95, and 99.70 per 100,000, respectively. Figure 2 illustrates the trajectory of these rates across each county and city district. During the active surveillance period, Yuyao City recorded the highest average annual incidence rate of 169.13 per 100,000 in 2010-2011. In the subsequent periods of 2012-2013 and 2014-2015, Cixi City reported the highest rates, at 123.73 and 126.09 per 100,000, respectively. From 2016 to 2019 and 2020 to 2023, Beilun District had the highest rates, at 156.70 and 122.21 per 100,000, respectively.

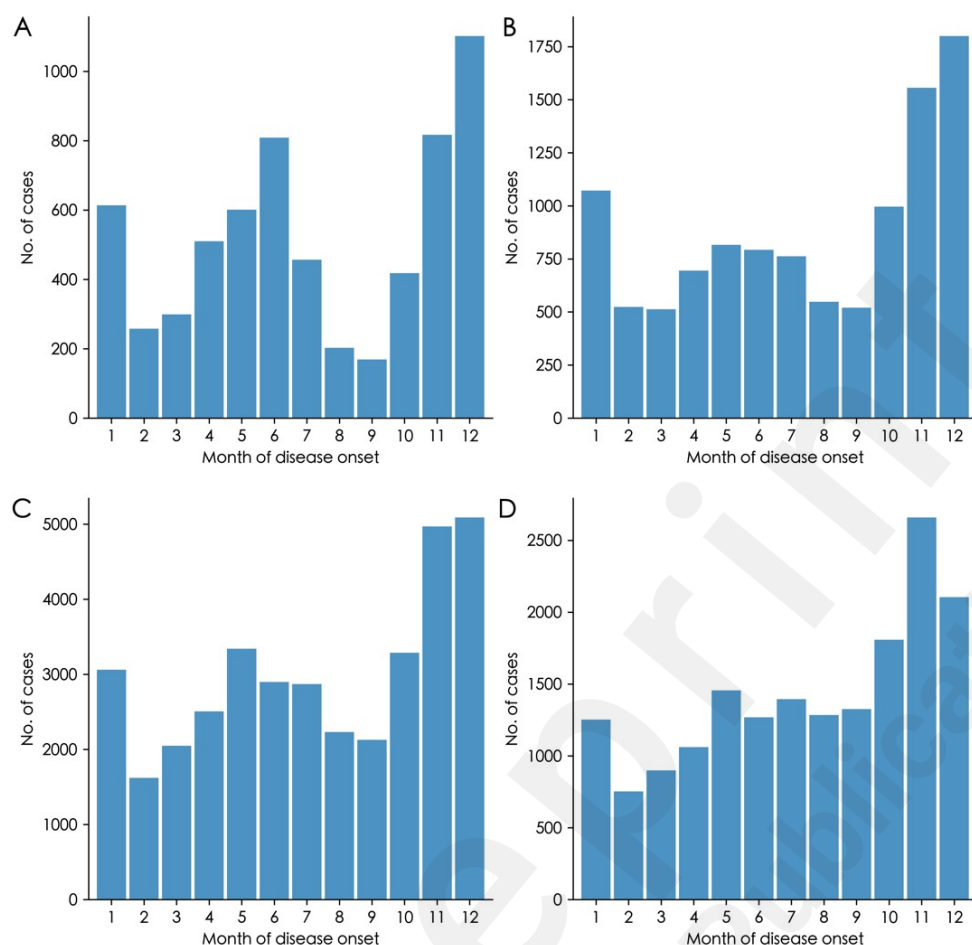
Figure 2. The spatial distribution of varicella in Ningbo, 2010-2023.



Temporal distribution

Between the years 2010 and 2023, there were documented instances of varicella cases on a monthly basis in the city of Ningbo. Figure 3 illustrates that during the periods 2010-2011, 2012-2013, and 2014-2019, two significant peaks in cases occurred: from May to July and from October to January of the following year. The incidence rates for May to July were 29.84% (1867/6257), 22.38% (2371/10595), and 25.27% (9108/36048), while the rates for October to January were 47.16% (2951/6257), 47.16% (2951/6257), and 45.51% (16406/36048), respectively. The months with the lowest incidence rates were February and September, with September accounting for 4.12% (258/6257), 4.95% (524/10595), and 4.49% (1620/36048), and February accounting for 2.70% (169/6257), 4.91% (520/10595), and 5.90% (2127/36048) across the respective years (see Figures A, B, and C). From 2020 to 2023, the incidence rates in August and September showed no significant variation, while the number of cases from October to January remained high, comprising 45.32% (7823/17263) of total cases (see Figure D).

Figure 3. Month of varicella onset in Ningbo. A The phase: 2010-2011; B The phase: 2012 - 2013; C The phase: 2014-2019; D The phase: 2020 - 2023.



Population distribution

Figure 3A shows that from 2010 to 2023, the age groups with the highest number of cases were primarily 10-14, 5-9, and 15-19 years, comprising 23.93% (16,795/70,163), 20.86% (14,639/70,163), and 17.42% (12,224/70,163) of the total cases, respectively. Notably, between 2010 and 2011, the 5-9 age group had the highest proportion, accounting for 40.10% (2,509/6,257) and 37.31% (3,953/10,595) of the total cases, respectively. In contrast, from 2014 to 2019, the 10-14 age group had the highest proportion, reaching 29.34% (10,577/36,048). From 2020 to 2023, the 15-19 age group had the highest proportion, accounting for 26.97% (4,656/17,263) of the total cases (Figure 3B).

From an analytical perspective on incidence rates, the age groups under 1 year and 5-9 years demonstrated a declining trend from 2012-2013 to 2020-2023, with reductions of 31.70% and 80.96%, respectively. In contrast, the 10-14 years age group experienced a significant increase of 72.68% from 2012-2013 to 2014-2019, followed by a decrease of 29.97% by 2020-2023. The age groups 15-19 years, 20-24 years, 25-29 years, and 30 years and above showed consistent upward trends from 2010-2011 to 2020-2023, with increases of 312.99%, 278.79%, 327.99%, and 575.62%, respectively. These trends were statistically significant, as determined by the trend chi-square test (all $P < 0.001$) (Figure 3C, Table 1).

Among the total cases, males constituted 54.90% (38,519/70,163), while females accounted for 45.10% (31,644/70,163), resulting in a male-to-female ratio of 1.22:1. From 2010-2011 to 2020-2023, the incidence rate for males increased by 146.72%, whereas the rate for females rose by 169.37% (Table 1).

Figure 4. The age distribution of varicella in Ningbo. A The number of cases by age groups; B The composition ratio of age by the phases; C The incidence rates by ages during the phases.

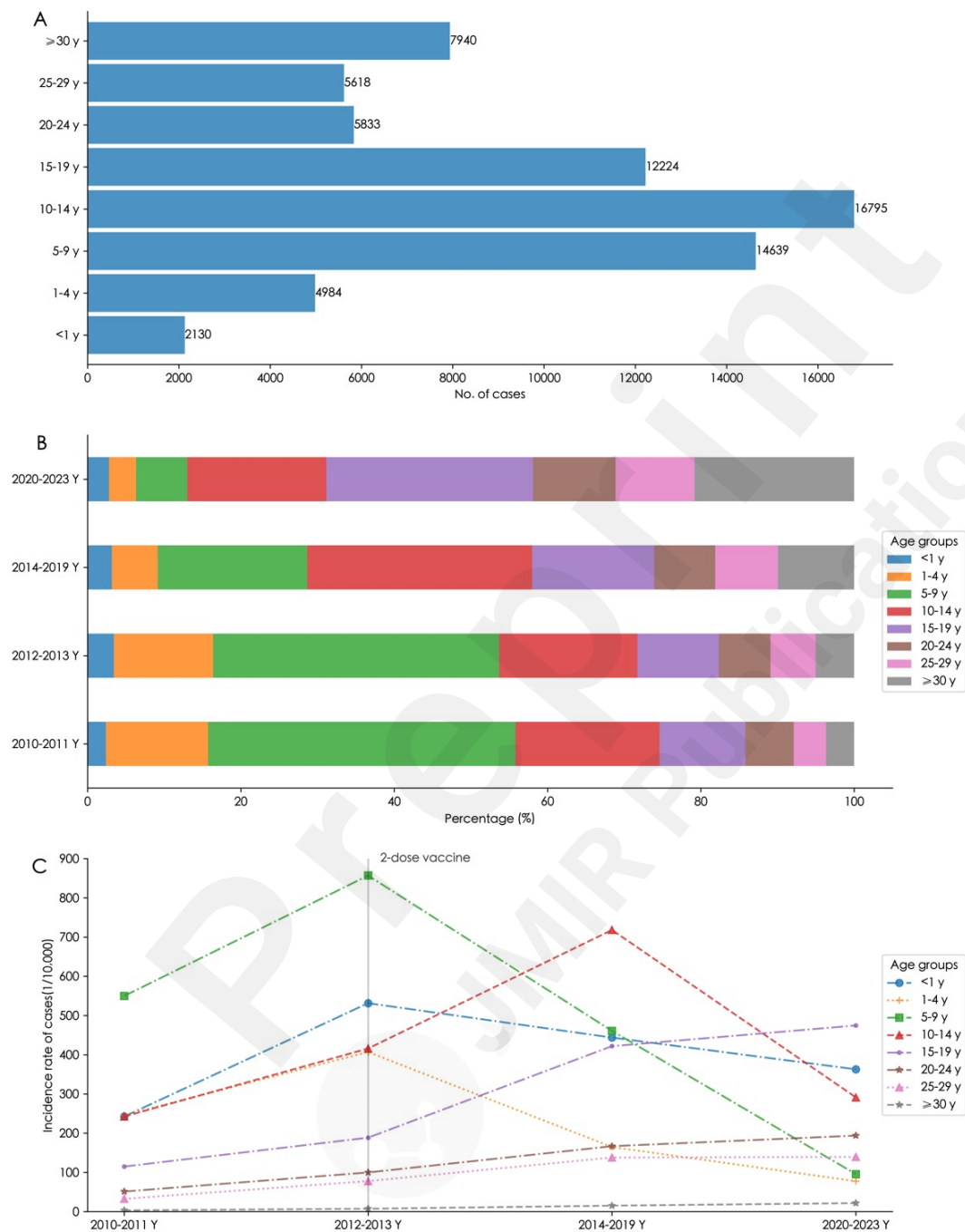


Table 1. The incidence rates of varicella by age and gender in Ningbo

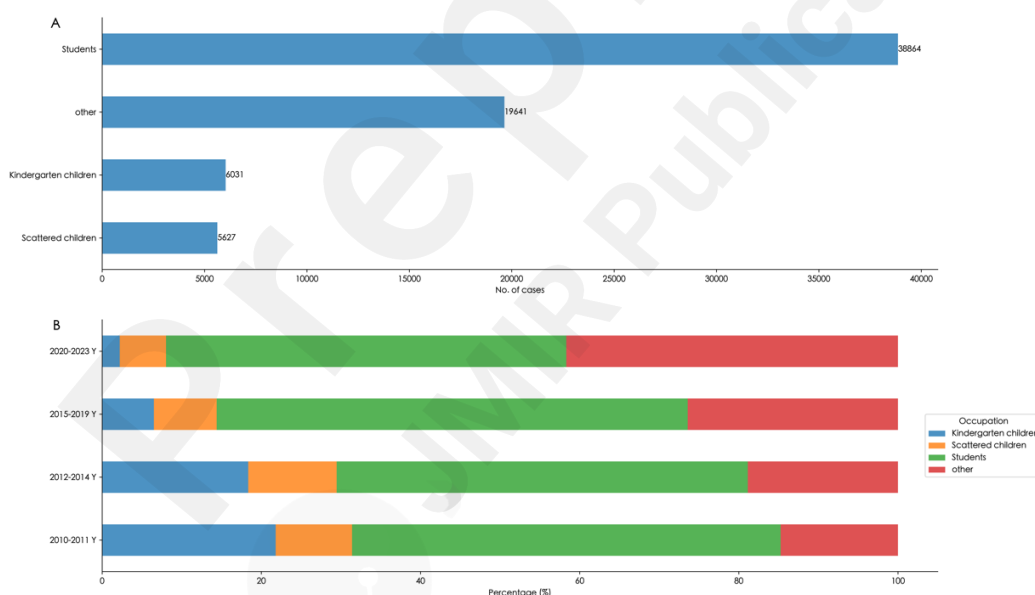
Characteristics		2010- 2011 Y	2012- 2013 Y	2014- 2019 Y	2020- 2023Y	D i f f e r e n c e 2 0 1 0 - 2 0 2 0 2020-2023 Y		D i f f e r e n c e 2 0 1 1 2 - Y 2 0 2 1 2014-2019 Y		D i f f e r e n c e 2 0 1 2 - Y 2 0 2 1 2020-2023Y		D i f f e r e n c e 2 0 1 3 0 - Y 2 0 2 1 2020-2023Y	
						%	P	%	P	%	P	%	P
Gender	Male	61.86	101.79	109.15	76.31	64.56	<0.001	7.23	<0.001	-25.04	<0.001	-30.09	<0.001
	Female	46.60	81.27	91.30	62.76	74.40	<0.001	12.34	<0.001	-22.77	<0.001	-31.26	<0.001
Age groups	<1 year	242.39	531.46	443.73	362.81	49.68	<0.001	-16.51	<0.001	-31.73	<0.001	-18.24	<0.001
	1-4 years	245.95	407.03	164.68	77.50	-68.49	<0.001	-59.54	<0.001	-80.96	<0.001	-52.94	<0.001
	5-9 years	549.74	856.84	460.81	95.44	-82.64	<0.001	-46.22	<0.001	-88.86	<0.001	-79.29	<0.001
	10-14 years	242.44	415.85	718.10	291.22	20.12	<0.001	72.68	<0.001	-29.97	<0.001	-59.45	<0.001
	15-19 years*	114.91	188.53	421.90	474.57	312.99	<0.001	123.78	<0.001	151.72	<0.001	12.48	<0.001
	20-24 years*	51.16	99.83	166.79	193.79	278.79	<0.001	67.07	<0.001	94.12	<0.001	16.19	<0.001
	25-29 years*	32.58	77.82	137.91	139.44	327.99	<0.001	77.22	<0.001	79.18	<0.001	1.11	<0.001
	≥30 years*	3.20	7.32	15.16	21.62	575.62	<0.001	107.10	<0.001	195.36	<0.001	42.61	<0.001
Total		50.76	90.53	104.11	70.13	78.35	<0.001	15.0	<0.001	-22.53	<0.001	-32.64	<0.001

*Chisq_test for trend :<0.001

Occupational distribution

Among the cases, here were 38,864 students (comprising 55.39%), 6,031 children in childcare (representing 8.60%), 5,627 children in disparate circumstances (accounting for 8.02%), and 19,641 instances classified as other non-children or students, which collectively constituted 28% (see Figure 5A). Figure 5B shows the distribution of cases by occupational classification. The proportion of children in childcare significantly declined ($P < 0.001$), from 21.80% in 2010-2011 to 2.21% in 2020-2023. Similarly, the percentage of children in disparate circumstances decreased from 9.61% in 2010-2011 to 5.82% in 2023 ($P < 0.001$). In contrast, the proportion of students remained relatively stable, with percentages of 53.84%, 51.67%, 59.19%, and 50.30% during the periods 2010-2011, 2012-2013, 2014-2019, and 2020-2023, respectively. Conversely, the proportion of other non-children or students increased significantly, from 14.75% in 2010-2011 to 41.67% in 2023 ($P < 0.001$).

Figure 5. The occupational distribution of varicella in Ningbo. A Number of cases by occupations□B Composition ratio of occupations by the phases.



The incidence and number of varicella breakthrough cases

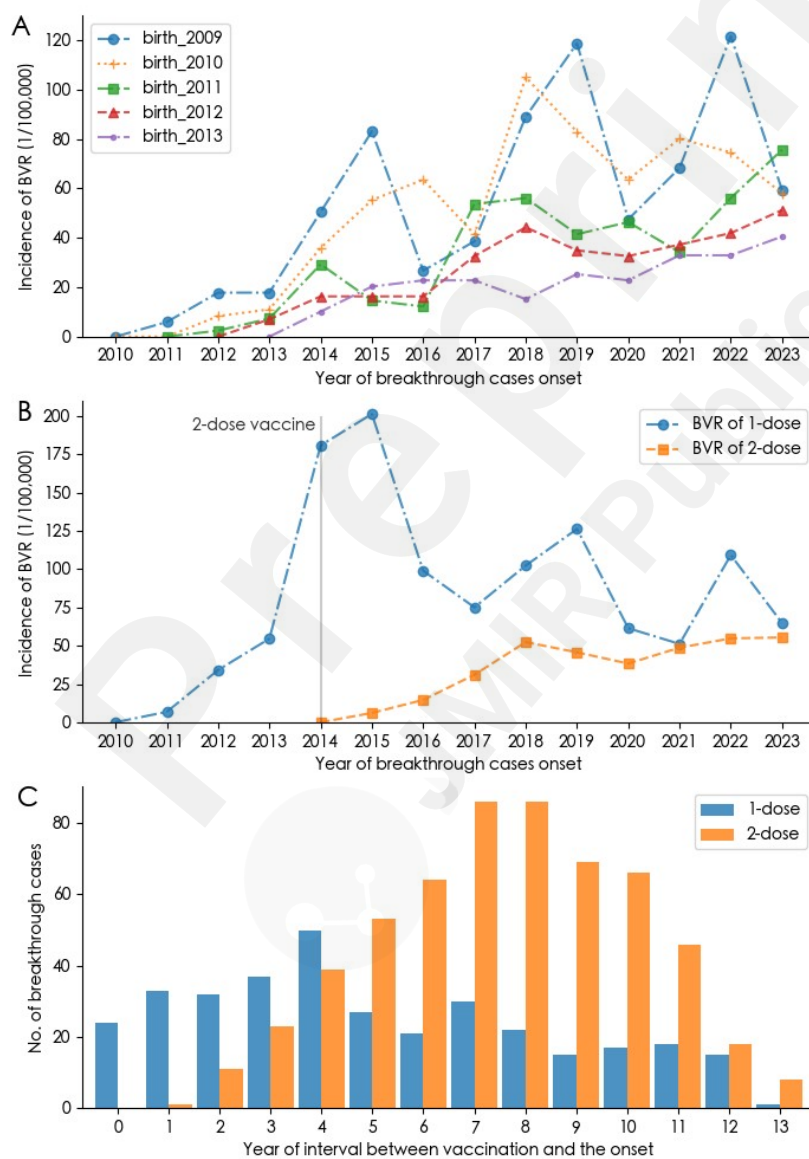
Figure 6A presents the annual incidence of breakthrough varicella infection among different birth cohorts from 2009 to 2013, spanning the years 2010 to 2023. The mean annual breakthrough varicella incidence rate (BVR) has shown a downward trend in cohorts with more recent birth years compared to those with earlier birth years. Specifically, the BVR was 53.16 per 100,000 individuals (range: 29.66–80.07 per 100,000) in 2009, 48.52 per 100,000 (range: 27.62–71.80 per 100,000) in 2010, 30.64

per 100,000 (range: 14.63–48.76 per 100,000) in 2011, 23.60 per 100,000 (range: 9.31–39.56 per 100,000) in 2012, and 17.53 per 100,000 (range: 5.06–32.91 per 100,000) in 2013.

The average annual incidence of breakthrough cases following a single dose of the varicella vaccine was 83.40 per 100,000 (range: 51.21–119.50 per 100,000), significantly higher than the incidence after two doses, which was 24.80 per 100,000 (range: 17.67–32.90 per 100,000). Notably, after the implementation of the two-dose immunization protocol, the incidence rate of breakthrough cases following the first dose showed a downward trend (Figure 6B).

The median time from vaccination to the occurrence of breakthrough cases was 27 months (range: 17.50–48 months). For individuals who received a single dose, the median interval was 23 months (interquartile range: 17.25–31.50 months), whereas for those who received two doses, it was 46 months (interquartile range: 18–66 months), as depicted in Figure 6C.

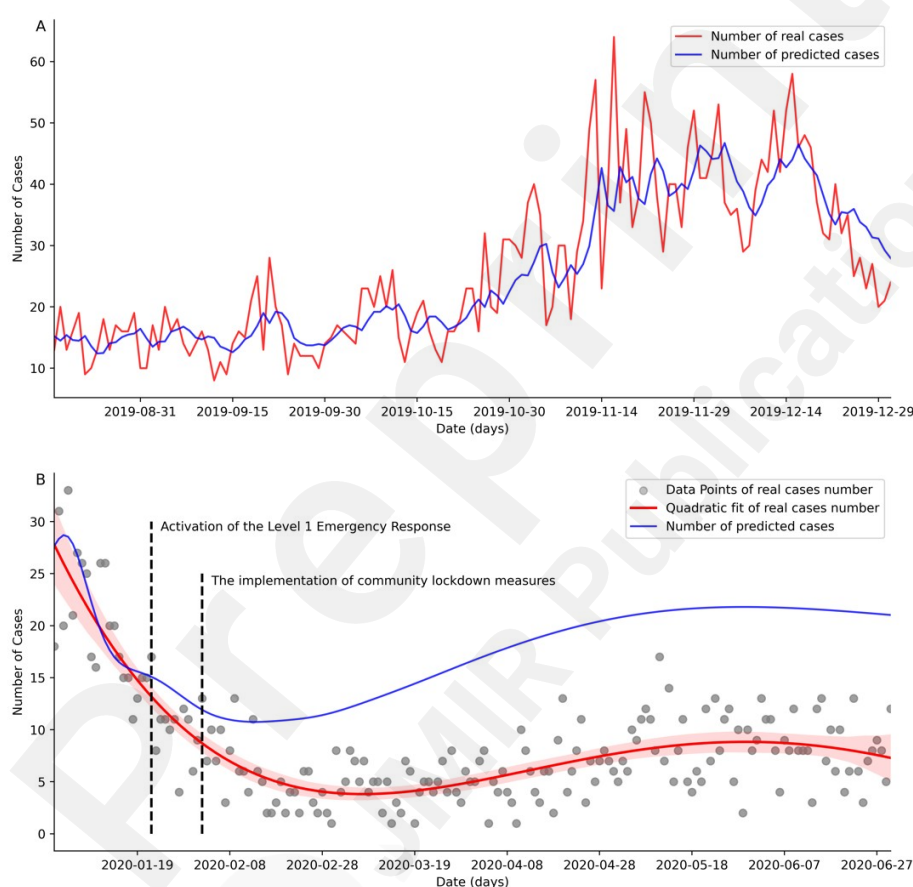
Figure 6. The incidence and number of varicella breakthrough cases in Ningbo. A The annual incidence of breakthrough cases by birth cohorts. B The annual incidence of breakthrough cases by 1-dose and 2-dose varicella vaccination. C The number of breakthrough cases by the year of interval between vaccination and the onset.



Impact of non-pharmaceutical interventions

To further analyze the impact of non-pharmaceutical interventions on the incidence of varicella, we constructed a Recurrent Neural Network (RNN) model for deep learning. This model features a three-layer neural network architecture with a total of 469,633 trainable parameters. Figure 7A illustrates the comparison between the actual and predicted case numbers in the validation dataset, demonstrating the model's effectiveness and accuracy in identifying varicella incidence trends. The model achieved a Mean Squared Error (MSE) of 49.96, a Root Mean Squared Error (RMSE) of 7.07, and a Mean Absolute Error (MAE) of 5.36. Figure 7B presents a comparison of the predicted and actual varicella case numbers from January 1 to June 30, 2020. The results indicate that after the implementation of the Level 1 Emergency Response on January 22, the predicted case numbers gradually exceeded the actual case numbers. Following the implementation of community lockdown measures on February 2, the discrepancy between predicted and actual case numbers significantly increased.

Figure 7. Using Recurrent Neural Network to analyze the impact of non-pharmacological interventions on varicella incidence. A The comparison between the actual and predicted case numbers in the validation dataset B The comparison of the predicted and actual varicella case numbers from January 1 to June 30, 2020.



Discussion

In China, varicella is not a legally regulated infectious disease, and the varicella vaccine, as the most effective control measure, is administered voluntarily and at personal expense. Varicella monitoring sites were established to conduct proactive monitoring in Ningbo City. Subsequently, health authorities required online direct reporting according to the requirements for reporting Class C infectious diseases. Compared to other studies based largely on voluntary case reporting[14–16], this method can more accurately reflect epidemiological characteristics. This study

examined the epidemiological characteristics of varicella from 2010 to 2023, revealing significant changes. The administration of two doses of the varicella vaccine and non-pharmaceutical interventions had a substantial impact on the epidemiological characteristics.

Previous studies have consistently demonstrated a decline in varicella incidence following the introduction of the varicella vaccine[17–19]. However, our research presents a contrasting trend, revealing an overall increase in varicella incidence from 2010 to 2019. This observation, mirrored by the rising incidence reported in Anhui province from 2012 to 2019 [15], suggests that vaccine impact can be complex and influenced by local epidemiological factors. While our data show a 15.0% increase in varicella incidence following the implementation of a 2-dose immunization strategy, this overall trend masks important age-specific effects. Notably, we observed a significant decrease in varicella incidence among children under 9 years old, with the most substantial decline (59.54%) in the 1 to 4 age group. This finding aligns with reports from Shi et al. [17], who documented a similar reduction in incidence among children aged 0-4 in Minhang District, Shanghai, and supports the efficacy of the vaccine in this young age group. However, the contrasting trend of increasing incidence among individuals aged 10 and above warrants further investigation. This divergence from the findings of Marin et al. [18], who reported declines across all groups, highlights the potential for waning immunity or incomplete vaccine coverage in older populations. Shi et al.'s report of a 54.09% reduction in incidence among children aged 5-19 [17] further underscores the age-specific nature of vaccine effectiveness. Several factors may explain these discrepancies. The timing of 2-dose vaccination programs differs considerably between regions. The United States implemented a routine 2-dose program in 2007, with the second dose administered relatively early at ages 4-6, while our study area implemented the program in 2014. Shanghai's program, beginning in 2017 and integrated into the local immunization plan by August 2018 with over 80% coverage for the second dose [17], demonstrates the importance of both program timing and achieving high vaccination rates. Our continued observation of increasing incidence among those aged 10-19 suggests that lower overall varicella vaccination rates in this cohort may be a key driver.

The optimal timing of the second dose also remains a point of discussion. While the US and Shanghai recommend it at age 4, Ningbo City administers it at age 3. Sero-epidemiological studies offer conflicting insights: Sun et al.[15] suggest a three-year interval between doses maximizes antibody concentration, while Zhang et al. [16] indicate higher seropositivity rates with earlier administration (ages 3-6). These findings emphasize the need for further research to refine immunization strategies and tailor them to local epidemiological contexts. Ultimately, understanding these nuanced interactions between vaccination programs, age-specific immunity, and population-level factors is crucial for optimizing varicella control and preventing future outbreaks.

During the COVID-19 pandemic, NPIs have demonstrated significant efficacy in controlling varicella outbreaks[20,21]. Originally intended to contain COVID-19,

these interventions inadvertently reduced the incidence of other respiratory infectious diseases, such as varicella, due to similar transmission pathways[21]. Measures such as social distancing, mask-wearing, and enhanced hygiene practices led to a notable decline in varicella cases, underscoring their effectiveness in managing respiratory infections. In Xi'an, China, the incidence of varicella decreased by 43.18% in 2020 compared to 2019, attributed to the implementation of COVID-19 NPIs[14]. A European study also suggests that these infection control measures during the pandemic may have curtailed the spread of varicella[22]. Research by Wang et al. [23] indicated that the actual number of varicella cases was 93.37% lower than expected, as predicted by the ARIMA model, highlighting a significant reduction in varicella activity due to COVID-19 NPIs. Our study revealed that the incidence of chickenpox decreased by an average of 32.64% during the COVID-19 pandemic. Among individuals aged 15 years and older, the rate of increase in chickenpox cases continues to rise; however, this rate is significantly lower compared to the trends observed between 2014 and 2019. Additionally, predictions generated using the LSTM model demonstrated that prior to the implementation of COVID-19 prevention and control measures, the predicted number of chickenpox cases closely aligned with the actual reported cases. Following the adoption of these measures, the predicted case numbers consistently exceeded the actual reported cases. Notably, after the introduction of community closure management, the discrepancy between predicted and actual case numbers widened further. These findings suggest that non-pharmaceutical interventions implemented to curb the spread of COVID-19 also contributed to the prevention and control of chickenpox. Additionally, between 2020 and 2023, the low incidence of varicella from August to September was not significant. This finding aligns with the results of Sabale et al.[22], indicating that infection control measures during the pandemic may have altered the seasonal transmission patterns of varicella and reduced its incidence rate.

Our study reveals a notable shift in the age distribution of varicella incidence. While consistent with previous reports demonstrating a significant decline in cases among young children [19][24,25], we observed a gradual increase in varicella among individuals aged 10-14 between 2010 and 2019, followed by a subsequent rise in cases among those aged 15-19 between 2020 and 2023. This contrasts with findings from studies conducted in largely vaccinated populations [26], which have not reported a similar shift towards older age groups. The 95.5% decrease in incidence among children under 10 reported by Moek et al. [19], highlights the effectiveness of childhood vaccination programs, but also underscores the potential for a displacement of incidence to older, unvaccinated or incompletely vaccinated populations. Our finding of increasing incidence among adults aged 20 and above further supports this hypothesis. The observed epidemiological pattern, with students representing the primary incidence group and a decline in cases among children in childcare, suggests that the implementation of the two-dose vaccination strategy for children aged 3 and above is successfully shifting the primary locus of transmission away from early childhood settings like kindergartens. This pattern is consistent with the concept of

'herd immunity' waning in older, unvaccinated cohorts, leading to increased susceptibility and transmission within these groups. Further research is needed to investigate the long-term implications of this age-related shift and to inform targeted vaccination strategies for adolescents and adults.

Our initial observations, supported by extensive literature, indicate that the two-dose varicella vaccine provides substantial epidemiological protection [8,10,27–29] and generally achieves a high vaccination rate. However, breakthrough cases of varicella continue to occur. Lin et al.[30] reported that among 6,961 varicella cases in Qingyang, China, 28.4% were breakthrough cases. Similarly, Zhu et al.[31] documented an increase in the proportion of breakthrough cases during outbreaks, rising from 21.5% in 2008 to 86.1% in 2014, indicating an upward trend. Our findings also demonstrate an increasing incidence of breakthrough cases over time following vaccination. Notably, the incidence of breakthrough cases with the two-dose vaccine is lower than with a single dose. Furthermore, the implementation of a two-dose immunization strategy significantly reduced the incidence of breakthrough cases associated with a single dose. The median interval between breakthrough cases was 23 months after a single dose and 46 months after two doses. This suggests that while breakthrough cases still occur after two doses, the two-dose regimen is more effective than a single dose. It not only extends the duration of immune protection but also plays a crucial role in mass immunization efforts.

While the two-dose varicella vaccine demonstrably provides substantial epidemiological protection and achieves high vaccination rates [8,10,27–29], recent data highlight the ongoing occurrence of breakthrough cases, a phenomenon increasingly recognized in the post-vaccination era. Studies from China, such as those by Lin et al. [30] (28.4% breakthrough rate among 6,961 cases) and Zhu et al. [31] (increasing from 21.5% in 2008 to 86.1% in 2014), corroborate a growing trend of breakthrough infections, potentially linked to factors such as waning immunity or the emergence of vaccine-escape viral strains. Our findings align with this trend, demonstrating an increasing incidence of breakthrough cases over time following vaccination. Importantly, our data confirm the superior protection offered by the two-dose regimen compared to a single dose, a finding consistent with established immunological principles regarding vaccine-induced immunity and memory cell development[32]. The significant reduction in breakthrough cases associated with the two-dose strategy underscores its critical role in sustaining population immunity. The observed median interval of 23 months post-single dose versus 46 months post-two doses suggests that the second dose not only enhances initial protection but also extends the duration of immunity, a key consideration for long-term public health strategies. Further research is needed to investigate the factors contributing to breakthrough infections, including viral genetics, host immune responses, and the potential need for booster doses to maintain robust protection.

This study has certain limitations. First, the identification of chickenpox cases in

Ningbo primarily relies on clinical assessments. Cases with atypical presentations require evaluation in conjunction with epidemiological histories. However, when cases lack both characteristic clinical features and relevant epidemiological context, accurate identification becomes challenging. As vaccination coverage increases, breakthrough chickenpox cases often present with mild symptoms. Without comprehensive epidemiological investigations, such cases are likely to be overlooked. Furthermore, since 2012, chickenpox surveillance in Ningbo has predominantly relied on passive monitoring. This approach depends on healthcare providers voluntarily reporting diseases, symptoms, or health events, and it involves compiling data from existing medical records and self-reports from the public. Passive surveillance may lead to diagnostic inaccuracies, such as misclassifying non-chickenpox cases as chickenpox [33]. Additionally, it may result in underreporting, thereby underestimating the true incidence rate. The shift from active to passive monitoring introduces potential biases, particularly in terms of the completeness and representativeness of reports, which can obscure temporal trends and geographic distribution patterns in the data. Active monitoring, while more comprehensive, requires significant labor and time resources, making its consistent implementation across the city challenging. As a result, passive monitoring is widely adopted as a cost-effective alternative for tracking the epidemiological characteristics of infectious diseases over extended periods. To address the limitations of passive monitoring, implementing quality improvement measures is essential. For example, since 2012, Ningbo has integrated chickenpox case reporting into the management framework for Class C statutory infectious diseases. Disease control agencies at various levels are required to conduct regular audits to identify underreporting and provide feedback to improve surveillance accuracy. Based on monitoring outcomes, the system has not indicated significant underreporting of chickenpox cases. Third, LSTM have demonstrated clear advantages in predicting long-term trends, they remain unable to accurately model the overall spread of chickenpox during the COVID-19 pandemic. Consequently, the LSTM method is insufficient for evaluating the long-term impact of non-pharmaceutical interventions on chickenpox incidence when vaccine effects are excluded.

Through extensive longitudinal surveillance of varicella, we have identified significant changes in its epidemiological characteristics. These include the elimination of the seasonal incidence trough, a shift in the age of onset, and an increasing trend in adult morbidity. These findings highlight the critical need for ongoing epidemiological monitoring and underscore the importance of adapting vaccination strategies to address evolving epidemiological patterns, particularly in the context of post-pandemic public health measures. Our investigation further revealed that the incidence of breakthrough cases was markedly lower among individuals who received the two-dose varicella vaccination regimen compared to those who received only one dose. This emphasizes the importance of completing the full vaccination series to achieve higher levels of individual protection and herd immunity. Additionally, the application of machine learning algorithms has demonstrated

significant potential in predicting chickenpox incidence. These algorithms enable more effective analysis of the impact of NPIs on disease incidence, providing evidence that NPIs have substantially reduced the burden of chickenpox. The growing use of machine learning in disease surveillance allows researchers to identify previously undetectable patterns and trends, improve predictive accuracy, and facilitate timely interventions. This, in turn, supports the development of more effective disease control measures. In summary, continuous epidemiological surveillance remains essential. We recommend enhanced monitoring of varicella in adults, increased vaccine coverage among individuals aged 15 years and older, and the implementation of two-dose vaccination programs in high-risk settings such as high schools and universities. For individuals who have received only one dose, it is strongly advised to complete the second dose promptly to ensure optimal protection.

Acknowledgments

This research was supported by Ningbo Science and Technology Program(2023S042), Zhejiang Province Medical and Health Science and Technology Program (2023KY1130), Ningbo Top Medical and Health Research Program (No.2023020713) and Science and Technology Program for Disease Prevention and Control in Zhejiang Province (No.2025JK277).

Authors' Contributions

XP and DZ designed the primary components of the study. XP, YZ, and XZ were responsible for data collection and manuscript preparation.

Conflicts of Interest

None declared.

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Supplementary Files