Comparison of varicella outbreaks in schools in China during different vaccination periods

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ABSTRACT
The purpose of this study was to investigate the outbreak trend of chickenpox and the epidemiological characteristics of outbreak related cases from 2017 to 2021, and compare the impact of voluntary self-funded single dose vaccination versus mandatory two-dose vaccine vaccination on varicella outbreaks. The data of varicella outbreaks in Jiangsu Province from 2017 to 2021 come from the national public health emergency management information system. We randomly chose 70 outbreaks from 2019 to 2020 for study in order to better understand the features and regularity of breakdown varicella (BV). In pilot cities with two doses of free VarV, the number of outbreaks decreased from 306 in 2017 to 123 in 2021, while the total number of cases related to the outbreak decreased by 64.6% (P < .01), the median size of the outbreak decreased from 24 cases (range: 6–146) to 21 cases (range: 10–93) (P < .01), and the incidence rate also decreased from 2.01/100 to 1.33/100. The proportion of cases with high fever, severe rash and complications in the BV group was lower than that in the primary varicella (PV), and the differences were statistically significant. The incidence rate of varicella among students who had post-exposure prophylaxis (PEP) activities was 1.42% (4/88/33,878), and 1.63% (2468/148,943) among those who did not (p = .005). The single-dose varicella vaccination was less effective in controlling the outbreaks, and the success of the full implementation of the routine two-dose varicella vaccination plan in the pilot cities provided a basis for implementation in the whole province, and long-term follow-up studies are needed to evaluate the effect of the new strategy in the future.

Introduction
Varicella is a highly contagious disease caused by varicella zoster virus. It can be transmitted to susceptible individuals through respiratory tract and direct contact with infected persons. The majority of varicella patients develop systemic herpes as well as a fever. It is a self limited disease, but it may have complications that necessitate hospitalization. Generally speaking, the incidence rate of preschool children is the highest, which can also cause outbreaks in schools. Vaccination is considered to be one of the most effective measures to prevent chickenpox. The live attenuated chickenpox vaccine (Oka strain) developed by Japan in 1974 has been shown to induce immune protection in human body with well safety. Up to now, varicella vaccine (VarV) has been included in routine childhood immunization in 36 countries and regions.

Many researches demonstrated that 1 doses of VarV can reduce morbidity and mortality, but outbreaks often occur among school students. Furthermore, when the varicella coverage rate improved, the proportion of cases in the vaccinated population increased. Two doses of VarV had been demonstrated to provide better protection in studies with a vaccine efficacy of 94–98%. A two-dose VarV vaccination schedule for children aged 4–6 years was suggested by the American Advisory Committee on Immunization Practice (ACIP) in 2007. Out of concern about cost-effectiveness, the two dose VarV vaccination program has not been implemented in China.

Prior to 2019, the VarV in Jiangsu Province was accessed voluntarily and at his own expense, and the average coverage rate in Jiangsu Province was close to 50%. Considering the breakthrough varicella after one dose of VarV, two doses VarV were included in the local routine immunization plan in seven pilot cities of Jiangsu Province (Nanjing, Suzhou, Changzhou, Yangcheng, Nantong, Zhenjiang and Wuxi) in early 2019 (the remaining six cities still maintain the mode of voluntary one-dose vaccination at their own expense). The first dose of VarV was given to children over the age of 12 months, and the second dose was given to children over the age of 48 months. At the same time, a temporary catch-up programme has been implemented. According to the Jiangsu Province Vaccination Program (2021 version), when 2 doses are administered, the recommended minimum interval between doses is 3 months for children (12 months to 12 years of age, inclusive) and 4 weeks for adolescents and adults (13 years of age and older).

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outbreak related cases from 2017 to 2021, and compare the impact of voluntary self-funded single dose vaccination versus mandatory two-dose vaccination on varicella outbreaks, and analyze the characteristics and rules of breakthrough cases in the outbreak, so as to provide information for further limiting varicella outbreaks and evidence for the implementation of two doses VarV plan in the whole province.

**Method**

**Description of Jiangsu**

Jiangsu is located in the east of China and consists of 13 cities (Nanjing, Suzhou, Changzhou, Yancheng, Nantong, Zhenjiang, Wuxi, Xuzhou, Yangzhou, Taizhou, Lianyungang, Huaian, Suqian). In 2021, the population was close to 85 million and the population aged 0–14 accounted for 15%, and the per capital gross regional product (PGDP) was close to US $20,000.

**Surveillance**

The data of varicella outbreaks in Jiangsu Province from 2017 to 2021 come from the national public health emergency management information system (a web-based computerized reporting system) and the on-site investigation data of staff handling the outbreaks. According to the date of onset of the first case, the outbreak is divided into three periods (2017–2018, 2019-Jun 2020 and July 2020–2021) according to calendar year to reflect the early, transition, and mature implementation of the 2-dose VarV plan, respectively. The varicella vaccination history of each student before the outbreak was obtained from Jiangsu Provincial electronic immunization registration system.

**Definitions**

The diagnostic criteria of varicella cases were based on epidemiological history, and the clinical manifestation was acute maculopapular vesicular rash without other obvious causes. The reporting standard of varicella outbreak was that 10 or more cases of varicella occurred in the same school, kindergarten and other collective units within 1 week. The occurrence of chickenpox in patients at least 42 days after vaccination is considered BV. A healthy person with no history of varicella vaccination who is infected after being exposed to a person with varicella was called a primary varicella (PV). PEP (post-exposure prophylaxis) refers to the measures taken to prevent infection after being exposed to varicella virus. According to the Jiangsu Province Varicella Emergency Vaccination Plan, once two cases of varicella are detected in the same class, a dose of VarV should be immediately offered to all unvaccinated students without varicella history.

**Clinical features of BV**

We randomly chose 70 outbreaks from 2019 to 2020 for study in order to better understand the features and regularity of BV. The working group was composed of professional investigators from Changzhou, Huaian, Nantong, Suzhou and Taizhou Centers for Disease Control and Prevention. Using a unified varicella case questionnaire to conduct on-site epidemiological investigations of chickenpox outbreaks in local kindergartens, primary and secondary schools and other collective units.

**Ethical statement**

This study was approved by the ethics committee of the Jiangsu Provincial Centers for Disease Control and Prevention, and conducted following the Declaration of Helsinki guidelines.

**Statistical analyses**

SPSS22.0 (IBM, Armonk, New York, USA) statistical software and Excel 2010 were used for statistical analysis. The $X^2$ test for trend was applied to analyze the number, scale and duration of outbreaks during 2017–2021. The qualitative data were described by rate and composition ratio, and the comparison of composition ratio adopts $X^2$ test. $P < .05$ was considered statistically significant.

**Result**

**Analysis on the characteristics of varicella outbreak and outbreak related cases**

A total of 981 chickenpox outbreaks occurred in schools, and 31,694 cases were confirmed to be related to the outbreak, including 18,064 cases (57.0%) were 5–9 years old and 3827 cases aged over 10 years (12.07%). In pilot cities with two doses of free VarV, the number of outbreaks decreased from 306 in 2017 to 123 in 2021, while the total number of cases related to the outbreak decreased by 64.6% ($P < .01$), the median size of the outbreak decreased from 24 cases (range:6–146) to 21 cases (range:10–93) ($P < .01$), and the incidence rate also decreased from 2.01/100 to 1.33/100. In addition, the duration of each outbreaks was shortened. The median duration of the outbreak was 35 days (range:2–131) during July 2017–2018 and decreased to 29 days (range:3–109) during July 2020–2021. In contrast, the scale and duration of varicella outbreaks increased over time in cities without pilot ($P < .01$). Over the three periods, only one outbreak involved less than 10 cases, and most outbreaks involved 10–49 cases (82.6%). Of the 981 cases of chickenpox in schools, 256 outbreaks occurred in kindergartens, 588 (59.9%) in primary schools and 137 (14.0%) in middle schools. In the pilot cities, the number of outbreaks in childcare institutions and primary schools decreased ($P < .01$), while the proportion of outbreaks in non pilot cities increased accordingly. In addition, the reported outbreaks in the pilot cities were mainly concentrated in 4–6 month (123/20.7%) and 10–12 month (413/69.6%) (Table 1).

The age distribution of the outbreak-related cases in the pilot cities had changed during the three periods. The age of outbreak-related cases <5 years old accounted for 32.2%, 5–9 years old accounted for 57.0%, while those over 10 years old accounted for only 10.7% during July 2017–2018. However, 49.0% of outbreak-related cases were aged 5–9, while more
Table 1. Reported varicella outbreaks during 2017–2021.

| Region                      | 2017–2018 | 2019–2020.6 | 2020–2021 |
|-----------------------------|-----------|-------------|-----------|
| Outbreaks, no.              | 306       | 126         | 164       |
| Outbreak-related cases, no. | 962       | 4091        | 5489      |
| No. per outbreak, median (range) | 24(6–146) | 25(10–127)  | 24(10–136) |
| No. of schoolchildren       | 476,954   | 256,108     | 299,653   |
| Incidence                   | 2.01/100  | 1.59/100    | 1.83/100  |
| Outbreak size, no. (%)      |           |             |           |
| <10 cases                   | (0.3)     | (0.0)       | (0.0)     |
| >50 cases                   | 51(16.7)  | 26(20.6)    | 28(17.1)  |
| Outbreak setting, no. (%)   |           |             |           |
| kindergarten                | 74(24.2)  | 24(19.0)    | 48(29.3)  |
| primary school              | 193(63.1) | 91(72.2)    | 89(54.3)  |
| middle school               | 39(12.7)  | 11(8.7)     | 27(16.5)  |
| Duration of outbreak, median (range), days | 35(2–131) | 23(3–133) | 35(4–133) |
| case patients, no. (%)      |           |             |           |
| <1 year                     | 125(1.3%) | 49(1.2%)    | 82(1.5%)  |
| >4 years                    | 2983(31.0%) | 1330(32.5%) | 1482(27.0%) |
| >5 years                    | 5486(57.0%) | 2316(56.6%) | 2909(53.0%) |
| >10–14 years                | 703(7.3%) | 2867(70.0%) | 664(11.0%) |
| >15–19 years                | 308(3.2%) | 1012(5.5%) | 395(7.2%) |
| >20 years                   | 19(0.2%)  | 90(2.0%)    | 16(0.3%)  |
| Quarter, no. (%)            |           |             |           |
| 1–3 month                   | 10(3.3%)  | 11(0.8%)    | 12(7.3%)  |
| 4–6 month                   | 61(19.9%) | 30(23.8%)   | 36(22.0%) |
| >7–9 month                  | 181(9.9%) | 75(6.5%)    | 106(1.6%) |
| >10–12 month                | 217(70.9%) | 88(69.8%)   | 106(66.4%) |
| VarV immunization, no. (%)  | yes (BV cases) | 4494(46.7%) | 2017(49.3%) |
|                             | no        | 5130(53.3%) | 2074(50.7%) |

than 30.0% were aged >10 from July 2020–2021. At the same time, there was no such change in non-pilot cities (Table 1).

Analysis of clinical characteristics of outbreak

A total of 31,694 varicella cases were reported in the outbreak from July 2017 to 2021, with 16,086 (50.8%) of those who had received VarV being classified as BV (based on the final report for each outbreak). The proportion of BV cases in outbreaks showed an upward trend from 46.7% in 2017 to 63.2% in 2021 ($P < .001$). In order to better understand the difference between the clinical manifestations of BV cases and PV cases, 70 outbreaks from 2019–2020 were selected for analysis, as the final reports of outbreaks were relatively rough and it could not fully reflect the whole situation of each varicella case. The results showed that there were 1233 BV cases and 1723 PV cases. The ratio of male to female cases was 1.18:1. The average age of onset was 7.44 ± 2.12 years. The age of onset was mainly 5–9 years in the BV and PV case group. Among 2956 varicella cases, the proportion of BV cases and PV cases with high fever (>39°C) was 5.4% and 23.5% respectively, and the difference was statistically significant ($P = .000$). Compared with the severity of rash, the proportion of severe rash in the PV case group (80.6%) was significantly higher than that in the BV case group (49.9%). Furthermore, there were 153 cases of complications in the PV case group and only 18 cases (1.5%) in the BV case group, the difference was statistically significant ($P = .000$). The complications of 18 cases were pneumonia (7 cases), encephalitis (3 cases) and skin bacterial infection (8 cases). At the same time, hospitalizations and the whole course were lower in the BV group than in the PV group. In addition, we found that 14 outbreaks of PEP strategy occurred in 70 outbreaks. The incidence rate of varicella among students who had PEP activities was 1.42% (488/33,878), and 1.63% (2468/148,943) among those who did not ($P = .005$). Simultaneously, the scale and duration of varicella outbreaks also decreased ($P < .01$) (Table 2).

Analysis on the characteristics of BV cases, the time interval and dose of vaccination

Among the 1233 BV cases, 1212 cases (95.6%) received one dose VarV, and 21 cases (4.4%) received two doses VarV (Table 2). The average time from one dose VarV to the onset was 5.74 ± 0.82 (95%CI:5.69–5.79) years, while the second dose VarV was 6.16 ± 0.52 (95%CI:5.94–6.35) years, the difference was statistically significant ($P = .023$). In addition, differences in the temperature, the rash count and the course were also statistically significant.

Discussion

Chickenpox is a highly contagious disease. About 60% of the 400 outbreaks in Jiangsu Province of China occur every year. The disease burden caused by chickenpox is quite serious. Although countries have begun to implement universal chickenpox vaccination plan and also reached some achievements, the outbreaks still occur frequently in schools, especially in some areas where single dose vaccination had been implemented. Therefore, the use of two doses VarV plan is a key consideration for all
countries and regions. Even in economically developed areas of Beijing and Shanghai, only two doses of VarV are recommended for school-age children, which was not included in the local immunization plan. VarV was first licensed in 1998 in China, and it is a self-funded vaccine. Children can receive one dose at the age of 12 months. However, the incidence rate of chickenpox in Jiangsu province was still on the rise. Therefore, the 7 pilot cities included 2 doses VarV into the local immunization program (Nanjing, Wuxi, Suzhou, Changzhou, Nantong, Yancheng and Zhenjiang) with the vigorous promotion of local governments.

The number of outbreaks and outbreak-related cases in these seven pilot cities has decreased dramatically since the adoption of a routine 2-dose varicella immunization program, which is consistent with other studies. However, the number and scale of outbreaks increased in 6 non-pilot cities that did not implement the plan. In addition, the primary schools were the most common site of outbreaks in both pilot and non-pilot cities. The age distribution of outbreak-related cases in 7 pilot cities was changing, the proportion of 5–9 years old cases decreased from 57.0% to 49.0%, while the proportion of cases among 10-year-olds increased from 10.7% to 30.0%. The initiation of a two-dose varicella immunization strategy could be the key explanation. It’s also possible that the globe was suffering from the COVID-19 pandemic in 2020–2021, and the time for the resumption of primary school was relatively late according to standard of the Education Department. The majority of the time, children could receive online instruction at home, which helps to prevent the spread of diseases transmitted through contact.

However, we did not find such a phenomenon in the six non-pilot cities, and the proportion of 5–9 year old cases increased from 56.6% to 65.0%. This increase may be due to the low coverage of VarV caused by socio-economic differences, or the large increase in the number of school-age children and schools as a result of the two-child policy that began in 2015 in China. Varicella was known to be more dangerous in older children and adults. The risk of natural infection has decreased dramatically as VarV coverage has improved. Many persons who are vulnerable to varicella may become infected later in life. By 2021, about 40% of school-age children had not been vaccinated with VarV, we know that the level of antibody protection induced by VarV decline over time, and the results of studies by Francesco Paolo Bianchi and Pasquale Stefanazzi found that booster dose was effective and safe in achieving seroconversion. In addition, the safety profile of measles, mumps, rubella and varicella (MMRV) vaccine have been confirmed by post-market adverse event surveillance data, which can eliminate the concerns of some children’s parents about the long-term immunogenicity and safety of VarV and improve the compliance of vaccination. Meanwhile, the research evidence in the United States showed that the school outbreak still accounts for a certain proportion in the era of two doses VarV. Therefore, the coverage rate may need to be higher in the high exposure environment, other strategies such as continuous monitoring of outbreak, compliance of vaccination, implementation of PEP activities and enrollment requirements of two doses VarV remain important.

Our research demonstrated that the proportion of BV cases in outbreaks was increasing, owing to better VarV coverage, which was consistent with research from Shanghai and the United States. The results of 2956 cases of 70 outbreaks collected in this study show that the clinical manifestations of patients with either 1 dose or 2 doses were relatively mild and the proportion of serious complications was low. It was consistent with international literature. The total number of vesicular rash in patients who received two doses VarV was less than in patients who received one dosage VarV, according to Kuter et al. and the same result was founded in our investigation. Meanwhile, this study also found that patients who received 2 doses VarV had relatively fewer complications and shorter course of treatment. The average time from one dose VarV vaccination to the onset was 5.74 ± 0.82 (95% CI:5.69–5.79) years, while the second dose VarV was 6.16 ± 0.52 (95%CI:5.94–6.35) years. Some studies have found that the incidence of VarV 5 years after vaccination was 2.6 times of that within 5 years. Due to the problem of sample size, the

\[ \text{Table 2. Comparison of clinical manifestations of varicella outbreaks in Jiangsu Province in 2019–2020.} \]

| Symptoms          | Primary case group | BV group | P Value | 1dose       | 2dose       | P Value |
|-------------------|--------------------|----------|---------|-------------|-------------|---------|
|                   |        |          |         | 328(26.6)  | 1(0.1)      |         |
|                   |        |          |         | 817(66.3)  | 20(1.7)     |         |
|                   |        |          |         | 67(5.4)    | 0(0.0)      |         |
|                   |        |          |         | 598(48.5)  | 20(1.6)     |         |
|                   |        |          |         | 614(49.8)  | 1(0.1)      |         |
|                   |        |          |         | 1195(96.9) | 20(1.6)     |         |
|                   |        |          |         | 17(1.4)    | 1(0.1)      |         |
|                   |        |          |         | 1212(98.3) | 21(1.7)     |         |
|                   |        |          |         | 269(21.8)  | 0(0)        |         |
infectivity and clinical manifestations and the average time of onset of the BV cases after two doses VarV are not clear. Further research and long-term monitoring are needed to evaluate the effectiveness of the two doses of varicella vaccination plan. At the same time, policymakers in countries and regions that have implemented the two-dose varicella vaccination plan should pay close attention to the so-called exogenous enhancement hypothesis, which cannot effectively control the phenomenon of herpes zoster due to the reduction of the natural infection proportion of the general population caused by increasing of the coverage rate, and timely modify the current vaccination strategy.

This study had several limitations. First, the analysis was based on aggregated data from the final reports of each outbreak, so we could not observe the individual characteristics of cases. Second, with the increase of VarV coverage rate, the misclassification of BV cases could have occurred because of atypical symptoms. Third, we selected 70 outbreaks from 2019 to 2020 which was a transitional period, so we were unable to collect enough BV cases after two VarV doses.

In conclusion, the single-dose varicella vaccination strategy was less effective in controlling outbreaks, the full implementation of the routine two-dose varicella vaccination plan in the pilot cities seems to significantly reduce the number and scale of outbreaks. The primary schools were still the main sites of chickenpox outbreaks, but outbreaks were beginning to affect middle schools as well. Improving coverage of 2-dose varicella vaccination and expanding school entry requirements, were likely to affect the incidences of disease and outbreaks. The clinical manifestations of BV cases after two doses VarV may be milder than those vaccinated with one dose, but further research was needed to confirm. The evidence provided the basis for a province-wide implementation of a 2-dose varicella vaccination strategy. However, long-term monitoring of the impact of this vaccination policy was required.

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No potential conflict of interest was reported by the author(s).

Author contributions statement
X.S.: Conceptualization, Methodology, Software, Data curation, Writing—original draft, Visualization, Supervision, Validation, Writing—review & editing. Y.H.Z and H.S.: Conceptualization, Methodology, Data curation, Investigation. Y.X.: Data curation, Investigation. L.Z.: Data curation, Investigation. Z.G.W.: Data curation, Investigation.

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