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Varicella outbreak trends in school settings during the voluntary single-dose vaccine era from 2006 to 2017 in Shanghai, China

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ABSTRACT

Objective: To investigate varicella outbreak trends among schoolchildren during the voluntary single-dose varicella vaccine (VarV) era in Shanghai, China.
Methods: Trends in school varicella outbreaks from 2006 to 2017 were assessed using joinpoint regression models. The impacts of changes in single-dose VarV coverage among schoolchildren and implementation of post-exposure prophylaxis (PEP) strategies on outbreak trends were further analyzed.
Results: In total, 265 varicella outbreaks involving 3263 cases were reported in Shanghai from 2006 to 2017. The number of outbreaks showed an increasing trend from 2006 to 2017 (t = 2.62, p = 0.026), especially in kindergartens. The proportion of breakthrough varicella cases among all outbreak-related cases showed an increasing trend from 30.4% in 2008 to 85.7% in 2017 (t = 7.45, p < 0.001). Single-dose VarV coverage among schoolchildren was 88.1%, and showed a significant increase from the 1996 to the 2008 birth cohorts, followed by a non-significant decline from the 2008 to the 2014 birth cohorts. During school outbreaks in which PEP campaigns were conducted, the varicella attack rate was significantly lower than those in outbreaks without PEP campaigns (1.2% vs. 1.4%; Chi-square = 23.35, p < 0.001).
Conclusions: Even with high coverage, single-dose VarV is insufficient to prevent school outbreaks. The administration of VarV as PEP is an appropriate intervention for varicella outbreak control prior to implementing a two-dose VarV schedule.

Introduction

Most population-based epidemiological data on varicella originate from developed countries, with limited data available from low- and middle-income countries, including China (World Health Organization, 2014). Since 2006, clinicians have been required to register patient information in the National Infectious Disease Reporting System (NIDRS) within 24 h of a varicella diagnosis in Shanghai, China. A cross-sectional study conducted in three Chinese provinces in 2007 estimated that the incidence and prevalence of varicella in children aged ≤14 years were 183.7 cases per 10 000 individuals and 4.7 million cases, respectively, representing a high national burden (Yin et al., 2009). In addition, surveillance data from 2006 to 2007 demonstrated that more than 98% of outbreaks occurred in school settings (Cao and Xiang, 2009; Jin and Feng, 2007). Therefore, varicella outbreak control in school settings has become a major public health concern in China.

Students with varicella are considered infectious from 1 to 2 days prior to rash onset until all lesions have crusted over (5 to 7 days after rash onset) (Heininger and Seward, 2006). Students must be quarantined immediately after identifying a varicella rash, and this is the most common and practical measure to control school outbreaks. Therefore, clinical varicella case definitions are routinely used instead of time-consuming laboratory diagnosis in many parts of China to identify and isolate cases early (Cao et al., 2018; Shanghai Municipal Health and Family Planning Commission, 2016; Fu et al., 2010; Lu et al., 2013; Pan et al., 2018; Wang et al., 2013).

With the widespread use of varicella vaccine (VarV) worldwide, there has been a substantial reduction in the number of varicella

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cases (World Health Organization, 2014). A single dose of VarV has been recommended on a voluntary basis for healthy children in China since 1998. Although VarV is not included in the National Immunization Program in China, single-dose VarV coverage among children born in 2008–2012 was 73.6% in six provinces, and coverage was positively associated with economic development (Yue et al., 2017). Previous studies have shown that single-dose VarV performed satisfactorily in China, with vaccine effectiveness (VE) between 50.3% and 83.9% (Fu et al., 2010; Pan et al., 2018; Wang et al., 2013). However, in some cities with high economic productivity in China, such as Beijing and Shanghai, school outbreaks continue to occur despite high VarV coverage (Fu et al., 2015; Lu et al., 2012; Suo et al., 2017; Zhu et al., 2017). To contain varicella outbreaks, the administration of VarV has been recommended as a post-exposure prophylaxis (PEP) strategy in Chinese metropolitan cities, including Beijing (2006), Guangzhou (2012), and Shanghai (2013) (Cao et al., 2018; Li, 2013; Ma et al., 2009).

It appears that varicella outbreak trends among schoolchildren have not been examined extensively during the voluntary single-dose VarV era in Shanghai, China. The aim of this study was to investigate varicella outbreak trends and the epidemiological characteristics of cases in school settings in Shanghai from 2006 to 2017. The impacts of changes in single-dose VarV coverage among schoolchildren and of the PEP strategy implemented since 2013 on outbreak trends were further analyzed. The data from this study provide empirical evidence to inform prevention and control measures for varicella outbreaks, as well as to enable the implementation of a two-dose VarV schedule in provinces of China where this has not yet been adopted.

Materials and methods

Participants and study design

All students enrolled in kindergartens (aged 4–6 years), primary schools (aged 7–11 years), middle schools and high schools (aged 12–18 years) in Xuhui District, Shanghai, China, were eligible participants. The study was conducted in three parts (Figure 1). The first was to describe trends in school varicella outbreaks from 2006 to 2017 (Figure 1). The second was to assess the impact of changes in VarV coverage among schoolchildren on school outbreak trends. In this part, two cross-sectional studies in the 2011/2012 (with relatively low VarV coverage) and 2017/2018 (relatively high VarV coverage) school years were conducted (Figure 1). The interval of 6 years between the two surveys was selected to ensure that the initial cohort of students had graduated and to avoid repeated sampling. A multistage randomized cluster sampling method was used to select participants. Four of the 13 streets in Xuhui District were randomly selected, and one kindergarten, one primary school, and one middle school were randomly selected on each street. In total, 12 school settings were randomly selected. Two classes of each grade were randomly selected from each school, and all of the students in these classes made up the study population. In the third part, the impacts of PEP campaigns on varicella outbreaks were assessed (Figure 1). Since 2013, the Shanghai government has recommended that unvaccinated students and students who have received single-dose VarV more than 5 years previously receive one-dose VarV as PEP to control school outbreaks. The workflow for PEP campaign implementation has been described previously (Wu et al., 2019).

Definitions

A clinical case of varicella was defined as the development of an acute generalized maculopapulovesicular rash, as diagnosed by a clinician, following exposure to varicella. Varicella occurring more than 42 days after VarV vaccination was defined as breakthrough varicella (BV). An outbreak was defined as five or more epidemiologically linked varicella cases occurring within 21 days in a school setting.

Field epidemiological investigations

The Xuhui District Center for Disease Control and Prevention (CDC) actively searched for varicella cases among schoolchildren through the NIDRS to identify school outbreaks. Case information including demographic characteristics, time of varicella onset, and VarV immunization history during school outbreaks from 2006 to 2017 was collected through field epidemiological investigations. School nurses were also involved in controlling each outbreak, performing referrals, reporting and follow-up of varicella cases. In the early stages of varicella outbreak management, information on case vaccination history was sporadically collected due to inadequate identification of BV cases. Since 2008, the Xuhui District CDC has adopted a new management model for varicella outbreaks (Zhang et al., 2014a), and the collection of case information, including vaccination status, has become more standardized. Therefore, analyses of the epidemiological characteristics of BV were restricted to outbreaks from 2008 to 2017. Starting in 2013, timely PEP campaigns were conducted after the identification of outbreaks when vaccine stocks were sufficient.

Assessment of VarV coverage using questionnaires

Questionnaire sheets (including questions on informed consent, demographic information, varicella history, and VarV immunization status) were distributed to parents of schoolchildren during the 2011/2012 and 2017/2018 school years. VarV status was verified by school nurses through school immunization records. Students from high schools were not included in the survey because these schools did not retain their immunization records.

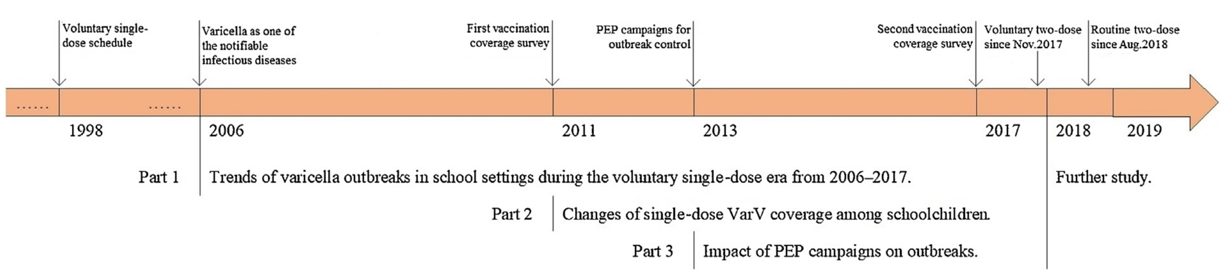

Figure 1. Changes in varicella vaccine control strategy in Shanghai and workflow for this study. Abbreviations: PEP, post-exposure prophylaxis; VarV, varicella vaccine.

Statistical analyses

Data were entered into EpiData 3.1. Differences between groups were assessed using Pearson's Chi-square test or the Student *t*-test, as appropriate. Joinpoint regression models (Kim et al., 2000) were used to identify temporal trends from 2006 to 2017 in the incidence of outbreak-related varicella and the numbers, size, and duration of varicella outbreaks. These factors were standardized by grouping schools by type, from 0 to 1 according to percentile rank, and the data were further represented as thermodynamic diagrams using Microsoft Excel. Trends in VarV coverage among schoolchildren born in 1996–2014 were analyzed using joinpoint regression models. IBM SPSS Statistics (version 18) and Joinpoint (version 4.7.0) were used for the data analysis. Values of $p < 0.05$ were considered statistically significant.

Results

Varicella outbreaks

There were 265 varicella outbreaks in school settings in Shanghai, China, from 2006 to 2017. The mean outbreak size was 12.5 cases and the average outbreak duration was 75.5 days (Table 1). The number of outbreaks showed an increasing trend over time from 18 in 2006 to 42 in 2017 ($t = 2.62$, $p = 0.026$) (Table 2, Figure 2). The size and duration of varicella outbreaks were maintained at perennially stable levels from 2006 to 2017 (Figure 2). Reported outbreaks were concentrated in the second and fourth quarters of each year, which accounted for 24.2% and 59.2% of all outbreaks, respectively (Table 1).

Of the 265 varicella outbreaks in school settings, 34 occurred in kindergartens (12.8%), 133 occurred in primary schools (50.2%), and 98 occurred in middle/high schools (37.0%) (Table 1). The number of outbreaks occurring in kindergartens showed an increasing trend from 2006 to 2017 ($t = 2.25$, $p = 0.048$), but no increasing trends were identified in primary schools or middle/high schools (Figure 2).

More than half of the outbreaks (54.0%) involved 5–9 cases, with the remaining 122 (46.0%) involving ≥10 cases (Table 1). The proportion of outbreaks involving ≥10 cases varied significantly in kindergartens, primary schools, and middle/high schools (17.6%, 52.6%, and 46.9%, respectively; Chi-square = 13.39, $p = 0.001$).

Table 1
Characteristics of school-based outbreaks and cases.

Characteristics	Number of outbreaks $n = 265$ (%)	Number of cases $n = 3263$ (%)
Type of school		
Kindergarten	34 (12.8)	245 (7.5)
Primary school	133 (50.2)	1792 (54.9)
Middle school	98 (37.0)	1226 (37.6)
Size of students		
5–9 cases	143 (54.0)	924 (28.3)
≥10 cases	122 (46.0)	2339 (71.7)
Quarter		
First quarter	29 (10.9)	265 (8.1)
Second quarter	64 (24.2)	726 (22.3)
Third quarter	15 (5.7)	220 (6.7)
Fourth quarter	157 (59.2)	2052 (62.9)
PEP campaign		
Yes	68 (25.7)	773 (23.7)
No	197 (74.3)	2490 (76.3)
VarV immunization		
Yes		1650 (50.6)
No		1613 (49.4)
Age (years) (mean ± SD)		10.84 ± 3.54
Size (mean ± SD)	12.5 ± 11.9	
Duration (mean ± SD)	75.5 ± 21.0	

PEP, post-exposure prophylaxis; VarV, varicella vaccine.

Schools with more than 800 students were more likely to report outbreaks involving ≥10 cases than those with fewer students (53.5% vs. 37.2% of outbreaks; Chi-square = 7.02, $p = 0.008$).

Outbreak-related varicella cases

A total of 3263 clinically confirmed varicella cases (excluding 39 teachers) were reported during the 265 outbreaks, but no cases were hospitalized (Table 1). The average age of outbreak-based varicella cases showed an increasing trend from 2006 to 2010 ($t = 3.14$, $p = 0.016$), followed by a decreasing trend from 2010 to 2017 ($t = -4.20$, $p = 0.004$). The average age of cases was older during the 2006–2010 period compared with the 2011–2017 period (11.4 years vs. 10.5 years; $t = 7.35$, $p < 0.001$). During the 2006–2010 period, 29 (2.3%), 778 (60.9%), and 470 (36.8%) cases were reported in kindergartens, primary schools, and middle/high schools, respectively. By contrast, in 2011–2017, 216 (10.9%), 1014 (51.1%), and 756 (38.1%) cases were reported in kindergartens, primary schools, and middle/high schools, respectively. The difference in the proportions of outbreaks occurring in different school types between these two periods was statistically significant (Chi-square = 90.80, $p < 0.001$).

The average outbreak-related varicella incidence was 28.6 cases per 10 000 individuals. Varicella incidence showed a perennially stable trend from 2006 to 2017 ($t = 0.92$, $p = 0.379$) (Figure 2). Over the period from 2006 to 2017, the average outbreak-related varicella incidence in kindergartens, primary schools, and middle/high schools was 9.4 cases, 46.9 cases, and 26.4 cases per 10 000 individuals, respectively. Varicella incidence in kindergartens showed an increasing trend from 2006 to 2017 ($t = 3.69$, $p = 0.004$), but no such trend was observed in primary schools or middle/high schools (both $p > 0.05$) (Figure 2).

Epidemiological characteristics of BV

A total of 2794 varicella cases were reported during 2008–2017, and 1579 (56.5%) cases who had previously received single-dose VarV were classified as BV. The average age at vaccination among BV cases was 21.9 months and the average interval from vaccination to BV infection was 7.7 years. The time elapsed from vaccination to infection among BV cases showed an increasing trend from 2008 to 2017 ($t = 2.34$, $p = 0.047$).

The proportion of BV cases among all outbreak-related varicella cases showed an increasing trend from 30.4% in 2008 to 85.7% in 2017 ($t = 7.45$, $p < 0.001$) (Table 2, Figure 2). The proportion of BV cases among all outbreak-related cases in kindergartens, primary schools, and middle/high schools was 83.4% (191/229), 70.1% (994/1418), and 34.4% (394/1147), respectively (Chi-square = 403.13, $p < 0.001$). Except for kindergartens ($t = -0.37$, $p = 0.722$), both the proportions of BV cases among primary school students ($t = 5.49$, $p = 0.001$) and among middle/high school students ($t = 6.22$, $p < 0.001$) showed increasing trends from 2008 to 2017 (Figure 2).

VarV coverage and VE

During the 2011/2012 and 2017/2018 school years, 2494 and 2702 questionnaires were distributed to parents, respectively, from which 2328 (93.3%) and 2539 (94.0%) valid responses were collected, respectively. The demographic characteristics of schoolchildren are shown in the **Supplementary Material**. Among the 4867 students sampled, 580 (11.9%) were unvaccinated and 4287 (88.1%) had previously received single-dose VarV. Single-dose VarV coverage during the 2017/2018 school year was slightly higher than during the 2011/2012 school year (91.8% vs. 89.0%, $p < 0.001$). The joinpoint regression model detected two joinpoints in the 2000 and 2008 birth cohorts. Single-dose VarV coverage

Table 2
Outbreak-related varicella incidence among schoolchildren in Shanghai from 2006 to 2017.

Year	Outbreaks	Cases	Number of BV cases (%)	Number of schoolchildren	Incidence[a]
2006	18	346	58 (16.8)	95 534	36.2
2007	13	123	13 (10.6)	90 098	13.7
2008	19	217	66 (30.4)	89 335	24.3
2009	23	280	82 (29.3)	88 930	31.5
2010	18	311	66 (21.2)	90 518	34.4
2011	18	174	70 (40.2)	91 632	19.0
2012	24	294	168 (57.1)	92 695	31.7
2013	19	193	124 (64.2)	94 777	20.4
2014	21	177	118 (66.7)	96 675	18.3
2015	30	447	308 (68.9)	99 504	44.9
2016	20	231	174 (75.3)	105 138	22.0
2017	42	470	403 (85.7)	107 098	43.9
Average	22	272	138 (50.7)	95 161	28.6
Total	265	3263	1650 (50.6)	1 141 934	28.6

BV, Breakthrough varicella.
[a] Incidence unit: cases per 10 000 individuals.

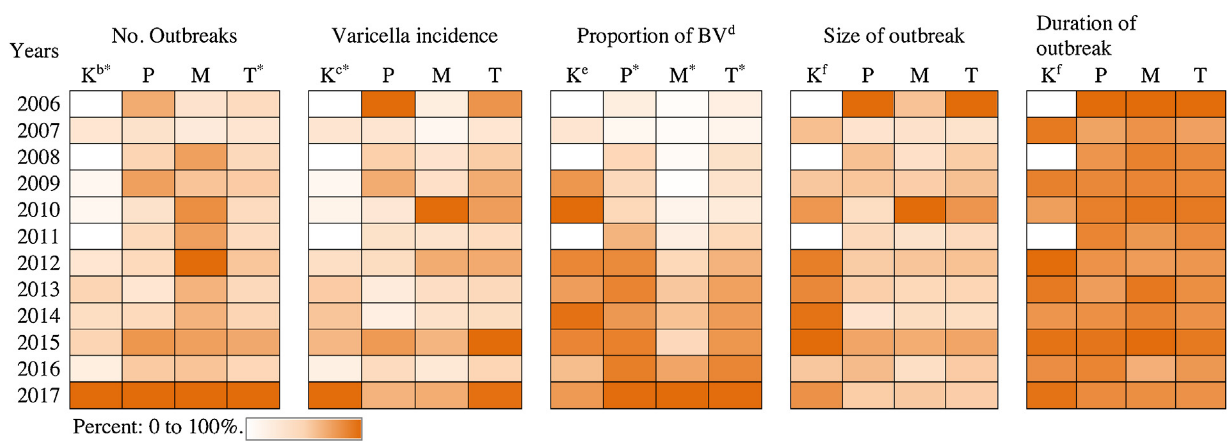

Figure 2. Trends in varicella incidence and the numbers, size, duration, and proportion of breakthrough varicella in varicella outbreaks in Shanghai, from 2006 to 2017[a]. Abbreviations: K, kindergarten; P, primary school; M, middle school; T, total; BV, breakthrough varicella.
[a]In each column, we divided the values for each year by the maximum value of the column to yield a standardized score from 0 to 1, and then represented these data as thermodynamic diagrams. *After joinpoint regression analysis, there was a yearly increasing trend ($p < 0.05$). [b]We substituted 0 with 1 outbreak in 2006, 2008, and 2011 for joinpoint regression analysis. [c]In 2006, 2008, and 2011, we substituted 0 with 5 cases to calculate varicella incidence. [d]Analyses of trends in BV cases were restricted to outbreaks from 2008 to 2017. [e]In 2008 and 2011, we substituted 0 with an average of 2 years around 2008 and 2011, respectively. [f]Joinpoint regression was not conducted in kindergartens.

increased significantly by 9.2% per year of age between the 1996 and 2000 birth cohorts ($t = 3.31$, $p = 0.007$), followed by a steady and significant increase until the 2008 birth cohort (2000 to 2008 birth cohort: 1.2%; $t = 3.91$, $p = 0.002$). A non-significant decline of 1.0% per year of age was observed between the 2008 and 2014 birth cohorts ($t = -2.14$, $p = 0.055$) (Figure 3).

A total of 380 (7.8%) varicella cases were reported among these 4867 students. The prevalence of varicella among unvaccinated students was higher than that among students who had received single-dose VarV (26.4% vs. 5.3%; Chi-square = 315.51, $p < 0.001$). Compared with unvaccinated students, the VE for students who had received single-dose VarV was 84.4% (95% confidence interval 80.4–87.6%). There was no significant difference in VarV coverage between students without siblings and students with siblings (88.1% vs. 87.7%; Chi-square = 0.07, $p = 0.799$), but the VE of VarV among students in single-child families was higher than that among students with siblings (85.0% vs. 79.3%). The proportion of students without siblings was significantly lower during the 2017/2018 school year than during the 2011/2012 school year (86.0% vs. 94.2%; Chi-square = 90.93, $p < 0.001$).

Impacts of PEP campaigns on varicella outbreaks

PEP campaigns were conducted in a total of 68 school outbreaks after 2013. The attack rates of varicella among students during outbreaks in which PEP campaigns were conducted and during outbreaks in which PEP campaigns were not conducted were 1.2% (792/67 292) and 1.4% (2510/176 171), respectively (Chi-square = 23.35, $p < 0.001$). The average number of cases per outbreak was lower during outbreaks in which PEP campaigns were conducted than in outbreaks in which PEP campaigns were not conducted, but this difference was not statistically significant (11.6 vs. 12.7 cases per outbreak; $t = -0.65$, $p = 0.514$). No differences in outbreak duration were observed between outbreaks in which PEP campaigns were or were not conducted.

Discussion

Although single-dose VarV coverage among students in this study was higher than that recommended in a World Health Organization position paper (88% vs. 80%) (World Health Organization, 2014), varicella outbreaks continued to occur

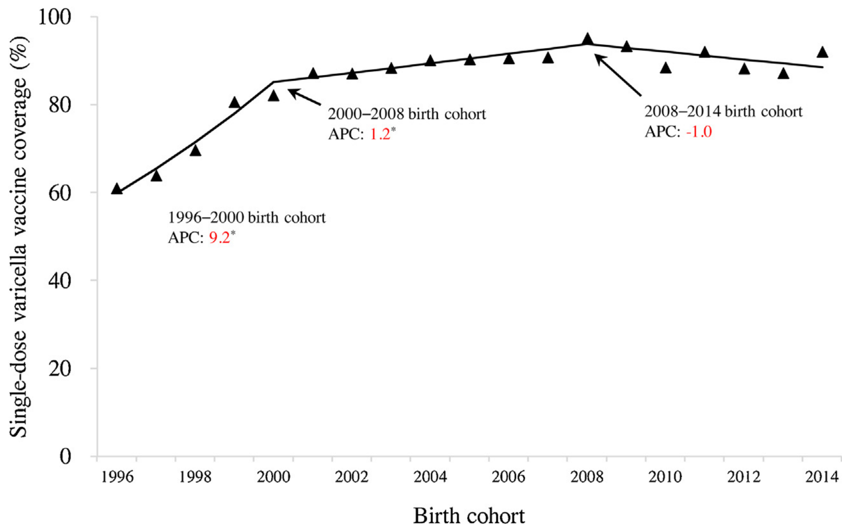

Figure 3. Joinpoint analysis of varicella vaccine (VarV) coverage trends among schoolchildren born in 1996–2014 in Shanghai, China.
Annual percent changes (APCs) are depicted from joinpoint analysis of single-dose VarV coverage trends. In this study, APC represented the changes in VarV coverage for every 1 year advancing age among schoolchildren. *APC $p < 0.05$, two-tailed.

frequently in schools (87.2%). The outbreak-related varicella incidence was 28.6 cases per 10 000 individuals. The results of this study confirm those in previous reports that single-dose VarV is insufficient to prevent school varicella outbreaks (Lopez et al., 2006; Marin et al., 2007; World Health Organization, 2014).

It was found that in the voluntary single-dose VarV era, the number of school outbreaks in Shanghai increased between 2006 and 2017, especially in kindergartens. There are several possible explanations for this increase. Firstly, China's one-child policy has gradually changed since 2007; it was replaced with the universal two-child policy starting in 2015 (Zeng and Hesketh, 2016). With an increase in the numbers of schoolchildren and school settings (**Supplementary Material**), school varicella outbreaks are more likely to occur. The proportion of varicella cases occurring in kindergartens during the 2011–2017 period was significantly higher than that during the 2006–2010 period (10.9% vs. 2.3%). It was found that the prevalence of varicella was higher and the VE was lower among students with siblings than among students without siblings. Therefore, students with siblings are more likely to acquire varicella infection, and the spread of varicella among siblings may increase the risk of transmission in school settings. Secondly, the participation rate for extracurricular student training reached 48.3% in 2017 (Wang, 2018), which is also likely to increase the spread of varicella between schools. Thirdly, Shanghai's population increased from 18 million in 2006 to 24 million in 2017, mainly due to migration (five million individuals) from poorer economic areas. Inequalities of immunization coverage due to socio-economic differences exist in China and other countries (Danis et al., 2010; Yue et al., 2017; Zhu et al., 2014). VarV is a privately funded vaccine, and students from migrant families of low socio-economic status are less likely to receive VarV before or after moving to Shanghai, which may increase the risk of varicella infection. Fourthly, since 2010, the Shanghai government has implemented a disease absenteeism system in schools, and the new system was able to detect some cases that were not reported in NIDRS. Implementation of this system has led to increases in estimates of outbreak-based varicella incidence and outbreak numbers in schools. During the routine two-dose VarV era in the USA, outbreaks in kindergartens still accounted for 18% of school varicella outbreaks from 2015 to 2017 (Lopez et al., 2017). Therefore, although the proportion of varicella cases occurring in kindergartens was less than 8%, the increasing trend in varicella incidence among kindergarten students should inform the government that additional efforts are required in kindergartens to reduce the number of outbreaks.

This study found that the proportion of BV cases among all outbreak-related cases was 56.5%, higher than the results of a population-based survey (22%) (Chaves et al., 2008), but within the range of several outbreak-based studies (42–76%) (Leung et al., 2015; Zhang et al., 2014b; Zhu et al., 2017). It was also found that the proportion of BV cases showed an increasing trend from 30.4% in 2008 to 85.7% in 2017. During the routine single-dose VarV era in the USA, the proportion of vaccinated cases also increased from 3.5% of all cases in 1997 to 24% in 2000 and to 72% in 2005 (Chaves et al., 2008). This increase in the proportion of BV cases during school outbreaks was mainly due to the steady increase in VarV coverage, which is consistent with the results of Civen et al. (2008). It was also found that single-dose VarV coverage among schoolchildren born in 1996 and 2008 increased from 61.1% to 95.3% in Shanghai. As with the results of two previous studies (Chaves et al., 2008; Lu et al., 2013), we also observed a higher proportion of BV cases among younger students. In addition, as the number of BV cases increases, the risk of vaccinated students being exposed to contagious BV cases increases due to difficulties in early diagnosis and isolation of mild or atypical BV cases. This represents a risk factor for BV infection (Lim et al., 1998; Zhang et al., 2012).

In response to cases of BV, a two-dose VarV schedule has been implemented in several higher socio-economic status countries and regions since 2006 (Marin et al., 2007; Wutzler et al., 2017). The incidence of BV cases during outbreaks in daycare centers decreased significantly from 19% in regions with a single-dose VarV schedule to 3% in regions with a two-dose VarV schedule during outbreaks (Spackova et al., 2010). As geometric mean antibody concentrations increase roughly 10-fold following administration of the second dose of VarV in children, boosting may help students who have failed to respond to the priming immunization to mount a protective immune response (Bonanni et al., 2013). However, not all two-dose VarV recipients achieve antibody titers of $\geq$5 gpELISA units/ml, and seropositivity rates remained between 93% and 98% over the 1–9 years following two-dose vaccination (Kuter et al., 2004). The results of a meta-analysis also showed that VE against all varicella increased significantly from 81% in the single-dose VarV era to 92% in the two-dose VarV era (Marin et al., 2016). In addition, monitoring data showed that the numbers, size, and duration of varicella outbreaks in the USA have decreased significantly since the implementation of a routine two-dose VarV program (Leung et al., 2015). Fortunately, a voluntary two-dose VarV schedule has been recommended in Shanghai, China, since November of 2017 (Shanghai Municipal Health and Family Planning Commission, 2017) and was included in the immunization program of Shanghai in August 2018 (Figure 1). The schedule includes a first dose at 12 months followed by a second dose at 4 years.

In this study, it was found that although the number of school varicella outbreaks in Shanghai increased from 2006 to 2017, there was no significant change in outbreak-related varicella incidence. We believe that the implementation of VarV as a PEP strategy in Shanghai has played a critical role in controlling varicella outbreaks in schools. It was found that conducting PEP campaigns during school outbreaks could reduce the attack rate of varicella among schoolchildren. Several studies have shown that the VE of VarV as PEP during school outbreaks is significant (47.0–85.3%) (Cao et al., 2018; Ma et al., 2009; Wu et al., 2019; Wu et al., 2018). In addition, the incidence of varicella fell by 30.2% after the implementation of VarV as PEP in Guangzhou, China, in 2012 (Li, 2013). Therefore, the administration of VarV as PEP is an appropriate intervention for varicella outbreak control in countries where a two-dose VarV schedule has not yet been adopted.

This study has several strengths. Firstly, the number of participants was large in both cross-sectional studies, and their vaccination history was confirmed by school nurses. Secondly, 12 years of surveillance data were used to analyze incidence trends among schoolchildren. This study also has some limitations. Firstly, because we included only outbreak-related cases to calculate incidence, it is possible that we underestimated varicella incidence in schoolchildren. Secondly, as the proportion of BV cases increased dramatically over the time period studied, it is possible that we failed to detect or misdiagnosed some individuals due to the mild or atypical symptoms of BV, which would underestimate varicella incidence in schoolchildren. However, students with rashes caused by other conditions may also be erroneously diagnosed with varicella in the absence of laboratory confirmation during school outbreaks. Thirdly, the results of this study may not be generalizable to other areas with different demographic and epidemiological characteristics, as well as different VarV coverage rates.

In conclusion, although single-dose VarV coverage among schoolchildren was maintained at a high level during the voluntary single-dose VarV era in Shanghai, varicella outbreaks occurred frequently in kindergartens and schools. BV cases were common during outbreaks, and the proportion of BV cases among all outbreak-related cases showed an increasing trend over time in Shanghai. The administration of VarV as PEP is an appropriate intervention for varicella outbreak control before implementing a two-dose VarV schedule. In the future, long-term follow-up studies will be needed to assess whether the newly implemented two-dose VarV schedule is effective in reducing varicella incidence and in controlling the size of school outbreaks in Shanghai, China.

Author contributions

Qiang-song Wu, Xian Wang, and Yi Hu: study design and writing; Jing-yi Liu, Yuan-fang Chen, and Qi Zhou: questionnaire investigation; Yan Wang, Ji-da Sha, and Ze-liang Xuan: data collection; Qiang-song Wu, Lin-wei Zhang, and Lu Yan: data analysis. All of the authors have read and approved the final manuscript.

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Ethical approval

The use of outbreak-related data was approved by the Ethics Review Board of Xuhui District Center for Disease Control and Prevention. Informed consent was distributed to the students' parents to obtain their varicella history and vaccination status in this study.

Conflict of interest

No potential conflict of interest is reported by the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.09.009.

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