



Published in final edited form as:

*Vaccine*. 2017 August 03; 35(34): 4368–4373. doi:10.1016/j.vaccine.2017.06.065.

## Varicella outbreak in a highly-vaccinated school population in Beijing, China during the voluntary two-dose era

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### Abstract

**Background**—Two-dose varicella vaccination has been available in Beijing since 2012 in the private sector. We investigated a varicella outbreak in a highly vaccinated elementary school population.

**Methods**—A cohort study was carried out and a varicella case was defined as an acute onset of generalized maculopapulovesicular rash without other apparent cause in a student attending the school from March 29 through May 17, 2015. Breakthrough varicella was defined as varicella >42 days after the last vaccine dose among both 1- or 2-dose varicella vaccine recipients. Vaccination information was collected from immunization records; information on prior varicella and clinical presentations was collected by surveying students' parents.

**Results**—Of the 1056 students in the school, 1027 (97.3%) reported no history of varicella. Prior to the outbreak, 98.6% of students had received 1 dose of varicella vaccine, and most (63.2%) students received two doses. Twenty varicella cases were identified for an overall attack rate of 2.0%. Half of the cases occurred in the classroom of the index case-patient, a two-dose recipient who was not isolated after symptom onset. Breakthrough varicella accounted for 95% of cases (19/20) with attack rates of 14.3% (1/7), 1.6% (6/362) and 2.0% (13/649) among unvaccinated, one-dose, and two-dose students, respectively. Most case-patients (18/20, 90%) had <50 lesions. No difference in clinical presentations was found between one-dose and two-dose recipients with breakthrough varicella.

**Conclusion**—Moderate two-dose varicella vaccine coverage was insufficient to prevent a varicella outbreak. Two-dose recipients with breakthrough varicella are contagious. High two-dose varicella vaccine coverage and timely isolation of cases may be needed for varicella outbreak prevention in the two-dose era.

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### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

### Conflict of interest

None

## Keywords

Varicella; Outbreak; Breakthrough; Vaccine; Chickenpox

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## 1. Introduction

Varicella (chickenpox) is a highly contagious disease caused by infection with varicella zoster virus (VZV), and is characterized by a generalized pruritic vesicular rash. Although varicella is usually self-limiting and resolves within a week, severe complications (including death) can occur [1]. In the absence of vaccination, varicella is a universal infection acquired mainly in childhood. Varicella vaccines based on the live attenuated VZV (Oka strain) are now widely available throughout the world and represent the most effective measure for prevention and control of varicella [2,3].

In China, varicella vaccine was first licensed in 1998 for use as a single dose in the private sector for children aged at least 12 months of age. Uptake of the vaccine varies substantially among children in different geographic regions, ranging from low coverage in resource-limited areas to high coverage in large cities, such as Beijing, the site of current study [4–7]. Single-dose vaccination has been provided free of charge by the Beijing government since 2006 to unvaccinated students during outbreaks in school settings. However, varicella outbreaks still occur in school populations with high levels of one-dose coverage [5]. Since November 2012, a routine second dose of varicella vaccine has been offered in the private sector in Beijing to augment outbreak control; the municipality continues to offer free-of-charge single-dose vaccinations for unvaccinated students during outbreaks in school settings. In Beijing the school system is predominantly public and consists of elementary schools (up to grade 6), middle schools (grades 7 through 9) and high schools (grades 10 through 12).

On April 13, 2015, the Beijing Center for Disease Control and Prevention (CDC) was notified of a varicella outbreak in an elementary school. Because almost all students in the school had received either one or two doses of varicella vaccine before the outbreak, most cases were among vaccinated students and the majority were two-dose recipients. Beijing CDC and Xicheng District CDC investigated this outbreak to describe the outbreak; characterize clinical manifestations, particularly among two-dose recipients; assess vaccine effectiveness (VE); and examine risk factors associated with vaccinated cases and viral spread. This article summarizes findings from this investigation and discusses the implications for varicella outbreak control and vaccination policy in Beijing, China.

## 2. Methods

### 2.1. Outbreak setting

The outbreak occurred in a public elementary school for Grades 3 through 6 (“School A”) in Beijing. During the outbreak, 1056 students attended School A. The two five-story school buildings (north and south) included 28 classrooms—8 each for third and fourth grades, and 6 each for fifth and sixth grades—with 1–6 classrooms on each floor. All sixth-grade classes

were located in the North building, while all other classes were located in the South building. Mixing of students occurred in the classrooms, hallways, play areas, school buses, and at afterschool activities.

## 2.2. Case definition, data and specimen collection

A case of varicella was defined as acute onset of generalized maculopapulovesicular rash without other apparent cause [8] that occurred between March 29 and May 17, 2015 in a student attending School A. Varicella among vaccinated students (breakthrough varicella) was defined as a varicella-like rash that developed >42 days after the latest vaccination before outbreak among both 1- or 2-dose varicella vaccine recipients [8]. We used reports from the school nurses and the infectious disease surveillance system of Beijing CDC to identify cases. Varicella became a notifiable disease in Beijing in late 2006. Parents of all students attending School A received and returned a questionnaire to provide information on history of prior varicella; for students with disease during the outbreak, information on disease severity, complications, and potential sources of exposure was collected by phone interview with the parents. Rash severity was categorized as mild (<50 lesions), moderate (50–499 lesions), or severe (≥500 lesions). The vaccination status of each student prior to the outbreak was obtained from immunization records. Lesion or scab specimens for laboratory confirmation were collected from case-patients after consent from the parents/guardians; detection of VZV DNA was performed with real-time polymerase chain reaction targeting the highly conserved ORF62 region according to manufacturer's instructions (Uninovo, Jiangsu Province, China).

## 2.3. Outbreak control measures

Students with varicella were excluded from school until lesions crusted or no new lesions appeared (if their rash was solely maculopapular with no vesicles) once the outbreak was reported to Beijing CDC. From April 17 to 22, 2016, single-dose varicella vaccination was provided free of charge to unvaccinated students without a history of varicella. Afterschool activities were suspended and the classrooms, indoor play area, and school buses were disinfected after the outbreak was detected.

## 2.4. Statistical analyses

Sociodemographic factors and vaccination status of cases vs. non-cases were compared and tested with Pearson's chi-squared test, Fisher's exact test, or Student's *t*-test, as appropriate. Vaccination coverage at the start of the outbreak was calculated as the proportion of vaccinated students among those without a history of varicella [9]. Those with prior history of varicella were excluded because they had developed immunity against varicella following natural infection and were not eligible for vaccination. Varicella VE was calculated using the equation:  $(1 - \text{attack rate among students who received 1- or 2-doses of vaccine} / \text{attack rate among unvaccinated students without a history of varicella}) \times 100\%$ . Because few students were unvaccinated and only one unvaccinated student was infected, we used historical attack rates among unvaccinated children in a child care center in the United States (US) [10] to calculate 1- and 2- dose VE, respectively. We evaluated potential risk factors for breakthrough disease among two-dose varicella vaccine recipients; specifically, age at receipt of second-dose vaccine, time since the latest vaccination before outbreak, and

interval between first- and second-dose vaccination. Severity of breakthrough varicella between one- and two-dose recipients was compared using rash severity, rash duration, fever, and duration of isolation. All data were analyzed by using SAS V9.3 (SAS Institute, Cary, NC).

### 3. Results

#### 3.1. Study population

Among the 1056 students in School A, the 29 who had a history of varicella prior to the outbreak were excluded from analysis (Fig. 1). No staff or faculty developed varicella during the outbreak; all analyses were thus restricted to students. Among the 1027 students with no varicella history before the outbreak, 14 (1.3%) were unvaccinated, 364 (35.4%) had received one dose of vaccine, and 649 (63.2%) had received two doses of vaccine, totaling 98.6% schoolwide vaccination coverage with 1 dose before the outbreak. There was no difference across grades in overall vaccination coverage ( $P = 0.80$ ), but two-dose vaccination coverage was higher in the lower grades (69.9%, 63.6%, 62.2%, and 53.4% for grades 3, 4, 5, and 6, respectively;  $P < 0.001$  for trend). During the outbreak, seven unvaccinated students and two one-dose recipients received an additional dose of vaccine and were excluded from further analysis.

The average age of the 1018 students included in the study was 10.4 years (standard deviation [SD] = 10.3) and 49.6% were male. Among one-dose vaccine recipients ( $n = 362$ ), the average age at vaccination was 27.3 months (SD = 24.4) and the average time since vaccination (prior to the outbreak) was 8.3 years (SD = 2.3). Among two-dose vaccine recipients ( $n = 649$ ), the average ages at the first and second dose were 19.3 months (SD = 8.4) and 8.3 years (SD = 1.2), respectively, and the average time since last vaccination before the outbreak was 1.9 years (SD = 0.1), with an average 6.7-year interval (SD = 1.3) between the first and second vaccine doses.

#### 3.2. Outbreak

The outbreak lasted approximately 1.5 months, from March 29 through May 17, 2015. Among the 1018 students included in the study, a total of 20 cases were identified for an overall attack rate of 2.0%. Laboratory testing was performed for seven cases; all were among one-dose recipients and confirmed as VZV by PCR. The index case-patient had received two doses of varicella vaccine, was in the sixth grade, developed fever on March 28 and moderate rash on March 29, and attended class without any isolation. Half of the cases occurred in the classroom of the index case-patient, of which 8 cases occurred within one incubation period (range 14–17 days) following rash onset of the index case-patient with school being the only known exposure per parental recall. All case-patients, excluding the index case-patient, were isolated with a median of 14 days (range: 6–21 days) after rash onset. There was no difference in attack rates between one- and two-dose vaccine recipients (1.6% vs. 2.0%,  $P = 0.70$ ), but the attack rate among vaccinated students was lower than the attack rate among unvaccinated students (14.3%,  $P = 0.02$ ) (Fig. 1). Using historical attack rates for varicella (88%) among unvaccinated children in a children care center [10], we calculated 1-dose varicella VE of 98.1% (95% confidence interval [CI]: 96.6–99.6%) and 2-

dose VE of 97.7% (95% CI: 96.5–98.9%) for preventing any varicella. As no severe varicella was identified in this outbreak, the VE against severe disease was 100% for both 1- and 2- dose recipients.

The outbreak was restricted to 7 out of the 28 classes in School A: two classrooms in each of the fourth, fifth, and sixth grades, and one in the third grade. The overall attack rate in these 7 classes was 9%, though the rate varied among unvaccinated (50%, 1/2), one-dose (7.2%, 6/83), and two-dose students (8.4%, 13/155). The highest attack rate (29.4%) occurred in the index case-patient's classroom; all other classrooms had attack rates lower than 10% (range: 2.6–7.3%), with 1–3 cases per class. Only one peak of cases ( $n = 13$ ) was observed in this outbreak, from April 12–16 (Fig. 2), and there was no difference in the vaccination coverage among students from the class of the index case and from other classes ( $P = 0.72$ ).

### 3.3. Disease characteristics

Most case-patients had mild rash (18; 90%) and were vaccinated (19; 95%) and 5 (25%) had fever. There were no case-patients with severe rash. Only two case-patients had moderate rash. One was unvaccinated and the other was a two-dose vaccine recipient (the index case-patient). No case-patients developed complications or were hospitalized. School exposure was the only source of infection for all case-patients, except two with unknown exposure history, including the index case-patient. The average age was 11.3 years ( $SD = 1.4$ ) among case-patients and most were students in the sixth grade (11; 55%) (Table 1). Cases and non-cases did not differ by vaccination status ( $P = 0.13$ ), sex ( $P = 0.63$ ), age at the second dose of vaccination ( $P = 0.33$ ), or time since the last vaccine dose ( $P = 0.84$ ), but cases were more likely than non-cases to be in sixth grade (55% vs. 19.4%,  $P = 0.005$ ) (Table 1).

### 3.4. Disease severity and risk factors for two-dose breakthrough varicella

There were no differences between one- and two-dose recipients with breakthrough varicella in rash severity ( $P = 1.0$ ), fever ( $P = 1.0$ ), duration of rash ( $P = 1.0$ ), or duration of isolation ( $P = 1.0$ ) (Table 2). In two-dose vaccine recipients, age at the second dose (<8 vs. ≥8 years) and interval between first and second (<5 vs. ≥5 years) doses were not associated with breakthrough varicella ( $P = 0.33$  and 1.0, respectively) (Table 1).

## 4. Discussion

We investigated a varicella outbreak in a Beijing elementary school where vaccine coverage with 1 dose before the outbreak was nearly 100%, and where 2/3 of vaccinated students had received two doses of varicella vaccine. We found that disease was introduced by a two-dose breakthrough case in a student and occurred almost exclusively among vaccinated students exposed at school. The majority of cases were among two-dose recipients, and half occurred in the class of the index case-patient who was not isolated after symptom onset. This study is the first report on a varicella outbreak initiated by a two-dose vaccine recipient with breakthrough varicella, indicating two-dose breakthrough varicella is still contagious. The findings further confirmed that children vaccinated with two doses of varicella vaccine may contract varicella, and moderate two-dose varicella vaccination coverage may not provide sufficiently high population immunity to prevent outbreaks [11]. This study also

confirms previous reports that one- and two-dose varicella vaccination is highly effective at mitigating the severity of breakthrough disease and reducing attack rates [12–14].

As varicella vaccine is well-accepted and one-dose coverage was high in school settings in Beijing [4], Beijing initiated a two-dose varicella vaccination schedule in 2012 to further reduce outbreaks in school settings with high one-dose vaccination coverage [5]. Compared with a previously reported varicella outbreak in a Beijing elementary school of similar size and 1 dose vaccination coverage (98%), but with very low two-dose coverage (0.2%) [5], the current outbreak—which occurred in a school with moderate two-dose varicella vaccination coverage—had a substantially shorter duration (27 vs. 121 days), as well as smaller size (20 vs. 87 cases) and lower attack rates (2.0% vs. 9.4%) [5]. Moreover, the current outbreak also had substantially lower attack rate and shorter duration than an outbreak in a similarly highly vaccinated elementary school (97%) but lower 2-dose coverage (39%) in the US which lasted 108 days with 9.5% attack rate [11]. These findings suggest that even moderate two-dose vaccine coverage is effective in controlling varicella outbreaks, but it is still not high enough to prevent varicella transmission and outbreaks. Further efforts to increase and maintain two-dose vaccine coverage rates as high as 80% or above, as the World Health Organization recommends [15], might help prevent occurrence of outbreaks or further reduce duration and size if they occur.

Clinical trial and several observational studies found increased varicella VE of 2-dose than 1-dose vaccination [12–14,16]. Our outbreak investigation and another one in the similar school setting in US [11] found no difference in 1- and 2-dose varicella VE. The differential exposure to VZV in these two outbreaks, which was indicated in the low attack rates and substantial variation between classes, might lead to biased estimates on varicella VE, as equal exposure to disease is important but may not be achievable for VE assessment in outbreak investigations [17]. The findings of reduced outbreak size and duration in the current outbreak compared with outbreaks in similar school populations with high 1-dose coverage but almost no 2-dose vaccinees or low 2 dose coverage [5,11] were consistent with the changes in varicella outbreak characteristics before and after introduction of the 2-dose universal recommendation in the US [18], and the trend for smaller size of outbreaks with a greater proportion of 2-dose vaccine recipients [19]. Additionally, in the US a substantial decline of varicella disease burden had been observed after 2-dose varicella vaccination program introduction [20]. Taken together, these findings support that two doses of varicella vaccination offer increased protection than 1-dose vaccination and further increases in 2-dose vaccination coverage may confer more preventive effect. Future analyses of surveillance data on reported varicella in Beijing before and after the two-dose recommendation will document whether similar changes occur in Beijing.

It is well documented that one-dose breakthrough varicella is contagious; even persons who present with only maculopapular rash may transmit infection to susceptible individuals [21], and can cause outbreaks in school and daycare settings [5,9,22–25]. However, outbreaks started by a two-dose breakthrough varicella have not been previously documented. Consistent with recent reports [12,13], the clinical presentation of two-dose breakthrough varicella in the current outbreak was generally mild, similar to one-dose breakthrough

varicella [14]. This outbreak investigation reveals that breakthrough varicella in two-dose recipients are still contagious.

Isolation of students with varicella had been recommended to prevent transmission in school settings [25]. Our outbreak investigation suggested that the lack of isolation of the index case-patient may have been the main factor contributing to this outbreak, as half of the cases occurred in the classroom of the index case-patient. This further emphasizes the importance for timely isolation in preventing outbreaks in two-dose era, even though cases of breakthrough varicella are likely less contagious than unvaccinated cases [21]. Moreover, this also serves as a reminder not to rely solely on two-dose vaccination to prevent and control varicella outbreaks; traditional measures for outbreak control are still important in two-dose era. However, it may be more challenging to carry out isolation of breakthrough cases in the two-dose vaccine era: they tend to have milder disease than unvaccinated varicella which may not be immediately diagnosed [12,14], and parents may be less motivated to keep their children from school for a perceived minor illness, particularly when doing so may cause economic or logistic hardship. The occurrence of this outbreak further indicates the necessity of enforcing isolation in school settings and improving education of parents to gain cooperation.

Our study has several limitations. The majority of cases were clinically diagnosed with only few being confirmed by laboratory testing. The numbers of unvaccinated students and cases were very small and we used historical attack rate among unvaccinated to calculate VE. On the other hand, we had very high students' participation and vaccination information was collected from immunization records, therefore, limiting potential biases.

Our outbreak investigation demonstrated that two-dose breakthrough varicella can be contagious and moderate two-dose varicella vaccine coverage was insufficient to prevent a varicella outbreak. Therefore, increasing two-dose varicella vaccine coverage and enforcing timely isolation of varicella cases may be needed to further prevent and control varicella outbreaks in the two-dose varicella vaccination era. Universal 2-dose recommendation or free 2-dose vaccination during outbreak might be possible measures to further increase 2-dose varicella vaccination coverage in Beijing, China.

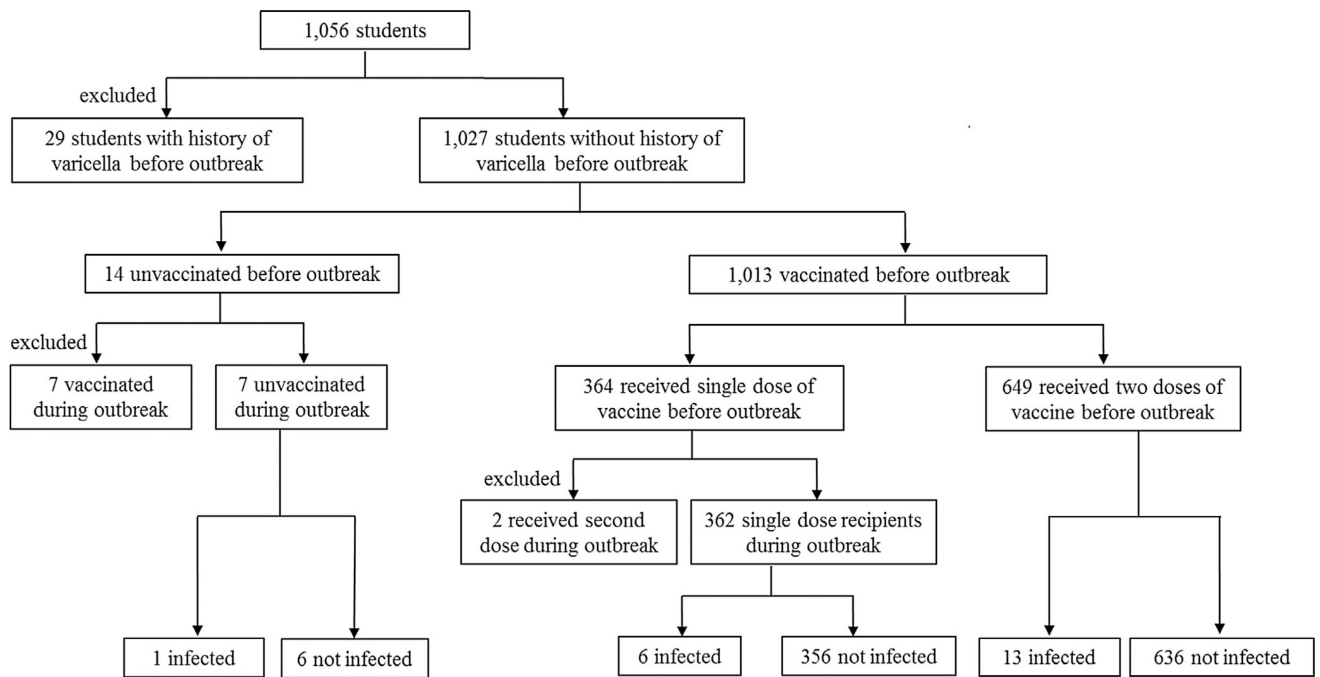
## Acknowledgments

We highly appreciate the help from the school nurses and the clinical practitioners in this outbreak investigation, the participation of the parents and students, and the thoughtful inputs from Dr. Kathleen Dooling and editorial service from Ms. Mary Ann Hall.

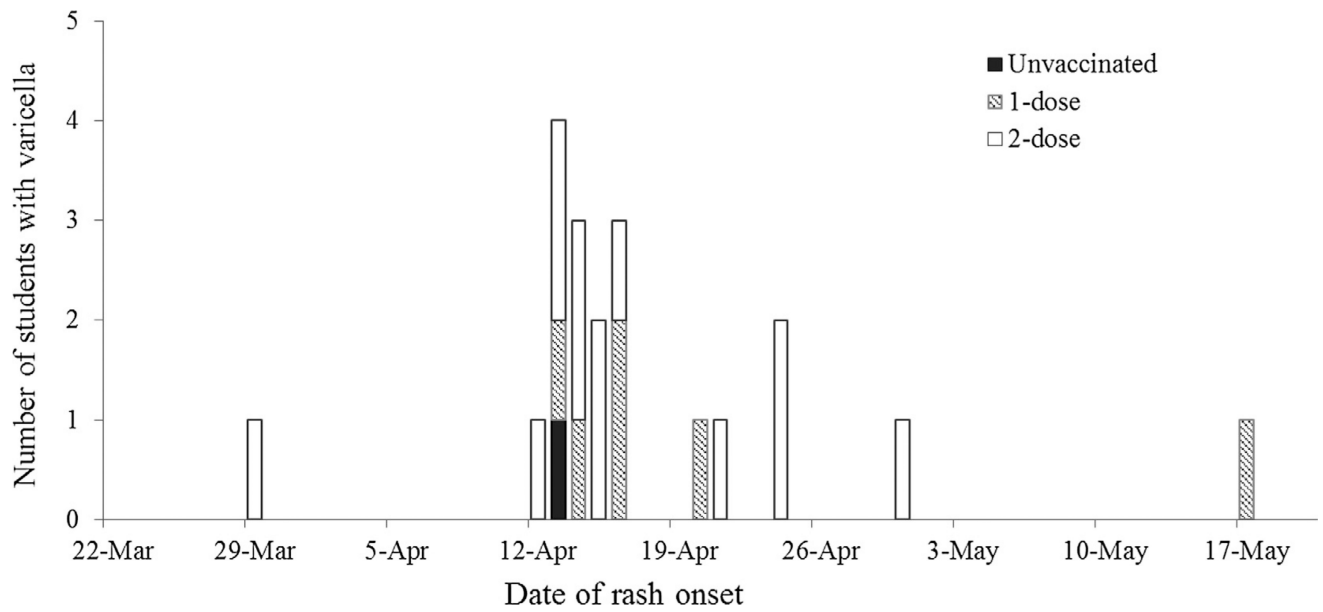
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**Fig. 1.** Varicella vaccination, disease history, and case status among students in a varicella outbreak in School A, Beijing, 2015.



**Fig. 2.**  
Varicella cases by date of rash onset and vaccination status (n = 20), School A, Beijing, March 29–May 17, 2015.

**Table 1**

Comparison of students with and without varicella during a varicella outbreak, School A, Beijing, 2015 (N = 1018).

Characteristic	Students with varicella (N = 20), n (%)	Students without varicella (N = 998), n (%)	P value
Sex: female	9 (45.0)	504 (50.5)	0.63
Age in years prior to outbreak: mean (SD)	11.3 (1.4)	10.3 (1.2)	<0.001
Vaccination status before outbreak			0.06
Unvaccinated	1 (5.0)	6 (0.6)	
1-dose	6 (30.0)	356 (35.7)	
2-dose	13 (65.0)	636 (63.7)	
Distribution of cases and non-cases across grades			0.005
3	3 (15.0)	314 (31.5)	
4	4 (20.0)	294 (29.5)	
5	2 (10.0)	196 (19.6)	
6	11 (55.0)	194 (19.4)	
Age at the second dose of varicella vaccination <sup>†</sup>			0.33
<8 years	4 (30.8)	282 (44.3)	
8 years	9 (69.2)	354 (55.7)	
Interval between 1- and 2-dose vaccination <sup>*</sup>			1.0
5 years	0 (0.0)	43 (6.8)	
>5 years	13 (100.0)	593 (93.2)	

<sup>\*</sup> 2-dose recipients only.

**Table 2**

Disease severity between 1- and 2-dose breakthrough varicella case-patients during a varicella outbreak, School A, Beijing, 2015.

Characteristics of breakthrough varicella	1-dose (N = 6), n (%)	2-dose (N = 13), n (%)	P value
Rash severity			1.0
Mild (<50 lesions)	6 (100.0)	12 (92.3)	
Moderate (50–499 lesions)	0 (0.0)	1 (7.7)	
Severe (≥ 500 lesions)	0 (0.0)	0 (0.0)	
Most lesions were vesicular from parental recall			0.32
Yes	1 (16.7)	0 (0.0)	
No	5 (83.3)	13 (100.0)	
Rash duration			1.0
<1 week	3 (50.0)	5 (38.5)	
≥ 1 week	3 (50.0)	8 (61.5)	
Fever			1.0
Yes	1 (16.7)	4 (30.8)	
No	5 (83.3)	9 (69.2)	
Duration of isolation			1.0
≤ 10 days	1 (16.7)	3 (25.0)	
>10 days	5 (83.3)	9 (75.0)	