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## 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  $\geq 1$  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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### 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

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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 ( $\geq 500$  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 sus-

pending 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  $\geq 1$  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

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