Outbreak of varicella in a highly vaccinated preschool population

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SUMMARY

Background: Varicella vaccine is available for private purchase in Beijing, with single dose recommended for children aged ≥12 months before 2013. Despite the success achieved in reducing varicella incidence, varicella outbreaks continued to occur, including in schools and kindergartens among highly vaccinated children. We investigated a varicella outbreak in a preschool with high varicella vaccination coverage in Haidian district, Beijing.

Methods: Through questionnaires, data including children’s medical and vaccination history were collected from their parents. A case of varicella was defined as an acute, generalized, maculopapular-vesicular rash without other apparent cause in a child in the preschool from March 10 through March 29, 2010. Attack rates in vaccinated and unvaccinated children were calculated, and the analyses of vaccine effectiveness (VE) and risk factors for breakthrough disease (varicella occurring ≥42 days after vaccination) were conducted.

Results: A total of 12 cases occurred during the outbreak, and ten of them (83.3%) had breakthrough varicella. The index case with mild varicella occurred in a child who had been vaccinated four years previously. Questionnaires were returned for all of 150 children in the preschool. Of all the 150 children, 144 (96.0%) had no prior history of varicella disease. Among these children, 135(93.7%) had received single-dose varicella vaccine before the outbreak. VE was 84.5% [95% confidence interval (CI): 62.8%–93.5%] in preventing varicella of any severity, and VE was 92.2% (95% CI: 81.4%–96.8%) against moderate to severe varicella. Age at vaccination (<15 months vs. >15 months) and time since vaccination before the outbreak (<3 years vs. >3 years) were not associated with the increased risk of breakthrough varicella (p=0.124 and 1, respectively). All the varicella cases with vaccination history verified through immunization records had received varicella vaccine and measles-mumps-rubella vaccine >30 days apart.

Conclusions: Breakthrough infection with fever in vaccinated person may be as infectious as varicella in unvaccinated persons. High single-dose varicella vaccination coverage is effective in reducing varicella incidence, but not sufficient to prevent outbreak. To control varicella outbreak a second dose may deserve additional consideration.

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1. Introduction

Varicella is a highly contagious disease resulting from primary infection caused by varicella-zoster virus (VZV), with secondary attack rates of 60%-90% among susceptible household contacts.1,2 In the absence of a varicella vaccination program, most people become infected by mid-adulthood.3 A live attenuated varicella vaccine (Oka strain) was developed in 19744 and licenced for use in Beijing in 1997,5 and since then this vaccine has been shown to be highly effective in preventing varicella disease.6,7 Currently, varicella vaccine is available for private purchase but not included in national or provincial routine immunization programs in China. To control school-based varicella outbreaks, single-dose vaccination has been provided free of charge by the Beijing government since 2006 to unvaccinated children in schools and kindergartens in Beijing.6 Varicella vaccine is administrated immediately after an outbreak is identified, and this strategy in some settings has been demonstrated to be effective.5,10 Despite the success achieved in reducing varicella incidence, outbreaks continued to occur, including in schools and kindergartens among highly vaccinated populations.5,11

In March 2010, the Haidian Center for Disease Control and Prevention (CDC) was notified of a suspected varicella outbreak in
a preschool population with 1-dose varicella vaccination coverage >90% in Haidian district, Beijing. The Haidian CDC investigated the outbreak, and then conducted a retrospective cohort study aimed to (1) determine the coverage of varicella vaccination among children, (2) estimate the effectiveness of 1-dose varicella vaccine and (3) evaluate the potential risk factors for breakthrough disease.

2. Methods

2.1. Outbreak setting

The outbreak occurred in a private preschool in Haidian district, Beijing. During the outbreak, 150 children, mainly locals, were attending the preschool which was located in the ground floor of a residential building. There were six classrooms and a large room, where the children attending the preschool napped together, and with 15 staff members in the preschool. Approximately 90% of children were vaccinated.

2.2. Epidemiological investigation

Questionnaires were distributed to all of the children's parents in the preschool. Data about demographics, history of varicella disease, and vaccination status, including dates of vaccination, were collected. Varicella vaccination history was verified through immunization records or recalled by parents. Parents of varicella cases were contacted by telephone to collect information about the possible source and setting of exposure, clinical course of illness (e.g., date of rash onset, duration of rash, number of lesions, presence of fever, complications), and parental consent to collect blood specimens for testing. As a public health response to an outbreak, this investigation was determined not to be a human-subjects research.

2.3. Case definitions

A case of varicella was defined as an acute, generalized, maculopapulovesicular rash without other apparent cause in a child in the preschool from March 10 to March 29, 2010. A varicella outbreak was defined as ≥5 cases of varicella occurring in a kindergarten or school within one week. Varicella disease was categorized as mild (<50 lesions), moderate (50-500 lesions), and severe (>500 lesions or presence of complications or hospitalization). Breakthrough disease was defined as varicella occurring >42 days after vaccination.12

2.4. Vaccine effectiveness (VE)

The attack rates in unvaccinated children (ARU) and vaccinated children (ARV) were calculated. Then VE was calculated as VE=(ARU- ARV)/ARU × 100%.11 Confidence interval (CI) for the VE was calculated as described previously.12 A case of varicella with mild disease was considered as a “noncase” patient when VE was calculated against moderate to severe varicella. Children with prior history of varicella before the outbreak, vaccinated less than 42 days before disease onset, vaccinated during the outbreak, and vaccination history not verified through immunization records, were excluded from VE analysis.

2.5. Risk factors for breakthrough varicella

We evaluated potential risk factors for breakthrough disease among vaccinated children without prior history of varicella, including age at the start of the outbreak, gender, years since vaccination calculated from the start of the outbreak, and age at vaccination. For children with history of varicella vaccination verified through immunization records, we determined whether the varicella vaccine and measles-mumps-rubella (MMR) vaccine had been administered within 30 days.

2.6. Laboratory investigations

Blood specimens of three varicella cases were collected and tested for VZV IgM antibodies using a commercial enzyme linked immunosorbent assay (ELISA, Virion/Serion, Würzburg, Germany), with whole extracted VZV proteins as a source of antigen.13 Testing was performed according to the manufacturer's instructions at the Haidian CDC net laboratory.

2.7. Statistical analysis

Data were entered into EpiData software (EpiData Association, Odense, Denmark). Pearson's chi-squared test and Fisher's exact test for categorical covariates were used to compare proportions, and the Wilcoxon rank-sum test was used to compare medians. All statistical analyses were performed with SPSS software (version 13.0; SPSS, Inc., Chicago, IL). 2-sided P values were reported with a significance level of P<0.05.

3. Results

3.1. Study population characteristics

During the outbreak, a total of 150 children in six classrooms were enrolled in the preschool. No staff developed varicella and all analyses were restricted to children. Questionnaires were completed and returned for all 150 children. Of all the 150 children, six (4.0%) with prior history of varicella disease were excluded for analysis (Figure 1). Among the 144 children without history of varicella disease, 135 (93.7%) had received vaccines before the outbreak and nine (6.3%) were unvaccinated. Four of the unvaccinated children vaccinated during the outbreak were excluded from further analysis; and none of them developed varicella. The remaining 140 children without prior varicella history ranged in age from 5.40 to 6.96 years (median: 5.92 years); 67 (47.9%) were females. Of the 135 vaccinated children, 129 (95.5%) were verified through immunization records, and six (4.5%, containing two cases of varicella), which were excluded for VE and risk factors analysis, were recalled by parents. Among single-dose vaccine recipients, the average age at vaccination was 18 months (median: 15 months; range: 12 to 60 months) and the average time since vaccination before the outbreak was 51 months (median: 54; range: 11 to 65 months).

3.2. Investigation of the index case

The index patient was a vaccinated, 5.5-year-old boy (born on July 6, 2004) who had an onset of rash on March 10, 2010, approximately 4.5 years after vaccination (July 13, 2005). He attended the preschool on the two days before the onset of rash and briefly on the morning on which his rash erupted, before he was taken home and diagnosed clinically. He was mildly ill, with a generalized rash consisting of <50 lesions and a fever of 38.1 °C, and had no complications. On the two days the child napped with other children in the large room as usual. His only known exposure to VZV recalled by his parents was contact with a varicella case in the waiting area of the hospital about on February 25, 2010 (2 weeks before the onset of rash in the index patient). He was not tested for VZV IgM, as there was no parental consent for blood collection.
3.3. Outbreak

The outbreak lasted from March 10 through March 29, 2010 (Figure 2). Overall 12 cases of varicella were distributed in all six classes and no cases occurred in children with prior history of varicella disease. The median age of children with varicella was 5.83 years (range: 5.44 to 6.13 years). Five (41.7%) of these children were girls. Ten (83.3%) occurred in vaccinated children and two (16.7%) in unvaccinated children. Overall, nine cases (75.0%) of varicella were mild, and three (25.0%) were moderate, and none was severe.

3.4. Outbreak control measures

Children with varicella were excluded from preschool until lesions crusted over. On March 27, 2010, varicella vaccinations were provided to four of the nine unvaccinated children. And the classrooms, nap room, indoor play area, and washing room were disinfected when the outbreak was detected. Publicity on prevention and control of varicella was implemented among the children's parents and the staffs in the preschool.

3.5. Laboratory analysis

Three varicella cases were confirmed by serological testing with VZV IgM positive, and two of them were vaccinated and the remaining one was unvaccinated. The remainders were epidemiologically linked.

3.6. VE and risk factors for breakthrough disease

The attack rates of varicella among unvaccinated and vaccinated children were 40.0% (two of five) and 6.2% (eight of 129), respectively. The attack rates of moderate to severe varicella

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Figure 1. Vaccination and varicella cases status, a varicella outbreak in a preschool in Haidian district, Beijing (n=150).

Figure 2. Number of children with varicella in the outbreak, by date of rash onset and vaccination in the preschool in Haidian district, Beijing (n=12).
among unvaccinated and vaccinated children were 20.0% (one of five) and 1.6% (two of 129). VE was 84.5% (95%CI: 62.8%–93.5%) in preventing varicella of any severity and 92.2% (95%CI: 81.4%–96.8%) against moderate to severe varicella. In single-dose recipients, age at vaccination (<15 months vs. ≥15 months) and time since vaccination before the outbreak (<3 years vs. ≥3 years) were not associated with the increased risk of breakthrough varicella (P=0.124 and 1, respectively, Table 1). All the vaccinated cases with vaccination verified through immunization records had received the varicella vaccine and the MMR vaccine >30 days apart.

4. Discussion

As previously described, compared with natural varicella, breakthrough disease is most commonly a milder, modified infection.16–19 Children with breakthrough varicella can still transmit the virus, although transmission is less frequent than from unvaccinated children with varicella. Therefore, its public health significance depends not only on its severity, but also on its potential for transmission. In school settings transmission between vaccinated children and adolescents raises the potential for sustained varicella transmission, even when vaccine coverage is high.17,18 In this outbreak, the index case with breakthrough varicella disseminated VZV among all six classes in the preschool, indicating that breakthrough disease with fever may be as infectious as varicella in unvaccinated persons. As the rashes in the index case were atypical maculopapulae rather than vesicula, the VZV was probably spread by airborne droplets from respiratory secretions. In a previous study of varicella transmission in households,20 persons with breakthrough disease were half as contagious as unvaccinated persons with varicella. Due to the intensity and duration of exposure, the transmission of breakthrough varicella to susceptible persons may vary in clustered facilities from households. Hence, further studies are needed to acquire transmission of breakthrough disease in schools and kindergartens population.

Previous investigations found vaccination at <15 months of age21,22 as a risk factor for breakthrough varicella. On the contrary, it was not associated with increased risk of breakthrough disease in our study. Previous retrospective outbreak-based studies11,23–25 indicated that children vaccinated three (or five) years and more before exposure were at increased risk for breakthrough infection during the outbreaks, suggesting a waning of immunity. Conversely, if waning immunity were a major risk factor, the VE would be expected to decline steadily with time, but the Vazquez et al.’s study found VE to be stable during the second through eighth years after vaccination.19 And in another study conducted from 1995 through 2009 in the United States,26 Roger Baxter et al. confirmed that 1-dose varicella vaccine provided excellent protection against moderate to severe disease, with no waning noted over a 14-year period. In our study, time since vaccination (three years and more before the outbreak) was not associated with an increased risk of breakthrough varicella, either. In this outbreak, no vaccinated cases had received MMR vaccine and varicella vaccine <30 days apart.

We found a high effectiveness of the varicella vaccine during the outbreak. Efficacy of 1-dose varicella vaccine was high in clinical trials and the VE was confirmed in postlicensure studies to be 80% to 94% in preventing varicella and highly effective in preventing moderate to severe disease.26 The 84.5% VE that we noted was similar to the VE found by Vazquez et al. (85%) and Izurieta et al. (86%).27,28 The VE against combined moderate and severe varicella in our study (92.2%) was similar to the VE (86%-100%) based on varicella outbreak investigation reported in a review on varicella VE in the US vaccination program.29 These findings support the observation that the vaccine is highly effective but is not guaranteed to prevent varicella. Our study also indicated 93.7% vaccination coverage was not sufficient to prevent outbreak in the preschool population. Modeling predicts that varicella vaccination coverage will need to reach 97% to achieve the background immunity required to prevent outbreaks.30 But in previous studies7,31,32 even with 98.3-100% varicella vaccination coverage outbreaks still occurred. These outbreak investigations highlight challenge related to the control of varicella outbreaks with the single-dose varicella vaccination program and the need for further prevention of varicella including through 2-dose vaccination.

The findings from our study and other varicella outbreak investigations, and other scientific evidence were taken into account when, in November 2012, the Beijing CDC adapted technical guidelines33 and recommended that children ≥18 months of age should be administrated one dose of varicella vaccine and a second dose at 4 years of age. The guideline also

### Table 1

Univariate analysis of potential risk factors for breakthrough varicella *(n=129)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breakthrough varicella</th>
<th>Well</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=8), n(%)</td>
<td>(N=121), n(%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.68–6.13</td>
<td>5.40–6.72</td>
<td>0.891b</td>
</tr>
<tr>
<td>Range</td>
<td>5.90</td>
<td>5.92</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.90</td>
<td>5.94</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 3(4.4)</td>
<td>65(95.6)</td>
<td>0.475c</td>
</tr>
<tr>
<td></td>
<td>Female: 5(8.2)</td>
<td>56(91.8)</td>
<td></td>
</tr>
<tr>
<td>Age at vaccination</td>
<td>&lt;15 months: 7(9.9)</td>
<td>64(90.1)</td>
<td>0.124d</td>
</tr>
<tr>
<td></td>
<td>≥15 months: 1(1.7)</td>
<td>57(98.3)</td>
<td></td>
</tr>
<tr>
<td>Time since vaccination before outbreak</td>
<td>&lt;3 years: 0(0)</td>
<td>5(100.0)</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>&gt;3 years: 8(6.4)</td>
<td>116(93.6)</td>
<td></td>
</tr>
<tr>
<td>Time between varicella and MMR vaccination*</td>
<td>&lt;30 days: 0(0)</td>
<td>2(100.0)</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>≥30 days: 8(8.1)</td>
<td>91(91.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MMR: measles, mumps, and rubella.

a Six children whose vaccination history recalled by parents were excluded from analysis.
b Wilcoxon rank-sum test.
c Fisher’s exact test.
d Continuity correction for Pearson’s chi-squared test.
e 101 children’s immunization records of MMR vaccination were available.
recommended that a second catch-up dose of varicella vaccine be given to children and adolescents, who previously had received one dose. As no long-term data are available on the duration of immunity afforded by the second dose of vaccine in China, further study should be conducted to evaluate VE of the 2-dose policy. Two strengths distinguish this investigation. Excellent response rates contributed to completeness of case ascertainment and the verification to immunization records got the children’s vaccination history correctly, and both of these helped minimize the recall bias in estimation of VE.

Several limitations should be considered in interpreting our findings. First, the small number of unvaccinated children (n=5) and unvaccinated cases (n=2) makes it approximately impossible to get a reliable VE estimation using the attack rate in the unvaccinated children from this preschool, and limited our ability to explore the effects of the time since vaccination and the age at vaccination. Second, due to the population confined to the children in preschool, we could not acquire the association between breakthrough disease and five years and more since vaccination in this study. Furthermore, most cases were not laboratory confirmed, and any misdiagnosis of varicella could result in overestimated or underestimated VE. Rashes mistaken for breakthrough disease (such as insect bite or enteralviral infections) could have falsely lowered the estimate of VE, although these conditions occur infrequently in early spring. Subtle presentations of breakthrough disease that were not clinically recognized could have led to a false elevation of the estimate of VE.

5. Conclusions

Breakthrough infection with fever in vaccinated person may be as infectious as varicella in unvaccinated persons. As the level of varicella vaccination heightens and varicella morbidity declines, the transmissions to susceptible persons due to breakthrough varicella should be assessed. High single-dose varicella vaccination coverage is effective in reducing varicella incidence, but not sufficient to prevent outbreak. To control varicella outbreak, the need for a second dose of varicella vaccination may deserve additional consideration, although the effect of this policy will need to be evaluated in the future.

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