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## Varicella breakthrough infection and effectiveness of 2-dose varicella vaccine in China

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### ARTICLE INFO

#### Article history:

Received 30 August 2017

Received in revised form 18 April 2018

Accepted 4 May 2018

Available online xxxx

#### Keywords:

Varicella

Varicella vaccination

Vaccine effectiveness

Breakthrough varicella

### ABSTRACT

**Background:** 2-dose varicella vaccination has been available in Ningbo city, China since 2014 in the private sector. This study aimed to evaluate the breakthrough varicella infection rate, and to examine overall and incremental effectiveness of 2-dose varicella vaccination among Chinese children.

**Methods:** A retrospective investigation was done among native children born from 2008 to 2013 in active surveillance area in Ningbo, China. Between 2009 and 2016, demographic information and data on varicella vaccination were collected by Ningbo's Immunization Information System, and information of varicella infections were obtained from China Information System for Disease Control and Prevention. The logistic regression was conducted to estimate varicella vaccine effectiveness (VE).

**Result:** A total of 107,324 local children were enrolled in the cohort analysis and 95.11% of these children with no varicella disease history received at least 1-dose varicella vaccine from 2009 to 2016. The total breakthrough varicella infection rate (BVR) was 0.37% for all the vaccinated children and 0.04% for 2-dose vaccination. The annual BVR ranged from 0.01% to 0.49% for 1-dose of varicella vaccine and from 0.01% to 0.02% for 2-dose. The infection rates both in the unvaccinated children and the 1-dose children were decreasing after 2-dose vaccination implemented in 2014 (Unvaccinated:  $P < 0.001$  for trend; 1-dose:  $P = 0.003$  for trend). The VE against all varicella was 50.3% (95% CI: 39.8%–59.0%) for 1-dose ( $P < 0.001$ ) and 98.7% (95% CI: 98.1%–99.1%) for 2-dose ( $P < 0.001$ ), and the incremental VE was 97.4% (95% CI: 96.2%–98.2%) compared with 1-dose ( $P < 0.001$ ).

**Conclusion:** The 2-dose regimen provided excellent protection to prevent all varicella, and the universal 2-dose regimen of varicella vaccine should be recommended to prevent the varicella disease among children in China.

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### 1. Introduction

The live attenuated Oka strain varicella vaccine was developed in Japan in 1974 by Takahashi, and it was approved for use in Ningbo city, China in 1998. A 1-dose schedule was recommended for vaccination among healthy children at age  $\geq 12$  months since then if a child's parent is willing to pay for it in China. Since the use of 1-dose vaccine among children, significant declines were documented in the number of varicella cases, outbreaks, varicella-related hospitalizations and deaths [1,2]. However, due to both primary vaccine failure and waning vaccine-induced immunity, a lot of varicella breakthrough cases were reported by

hospital, and outbreaks of varicella still occurred in school and kindergartens with high 1-dose varicella vaccination coverage [3–5]. Therefore, a 2-dose varicella immunization strategy, which has also not been included in national routine immunization programs in China, was recommended to protect children from developing varicella and reduce outbreaks.

The 2-dose regimen is widely applied in the United States, Canada, Germany, and Japan [6,7]. And the overall varicella incidence rate was decreased after administration of 2-dose of varicella vaccine reported from epidemiology studies in USA and Spain [2,8,9]. Many outbreak investigations reported that the 2-dose regimen provided improved protection against varicella, except two studies which showed the vaccine effectiveness (VE) of 1 and 2 doses were similar [10,11]. In addition, two community-based case-control studies indicated that 2-dose varicella VEs were 93.6% and 98.3%, but no 2-dose cases were identified in one of the

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studies [12,13]. However, given the true VE may be underestimated in outbreak settings [14,15] and the lower varicella incidence in the 2-dose era [12,16], it is a challenge to estimate 2-dose breakthrough varicella infection rate (BVR) and VE.

From 2009, an active surveillance for varicella was conducted among population in Ningbo city, China. We conducted a community-based study in a surveillance area during 2009 and 2016 to evaluate BVRs of 1-dose and 2-dose varicella vaccine, and to assess overall and incremental vaccine effectiveness of 1-dose and 2-dose varicella vaccination in preventing varicella among native children born from 2008 to 2013.

## 2. Methods

### 2.1. Varicella surveillance

The varicella active surveillance project was conducted in Yuyao district, Yinzhou district and Ninghai county, through an agreement among Yuyao Centers for Disease Control and Prevention (CDC), Yinzhou CDC and Ninghai CDC. Yuyao district is located in the west of Ningbo and on the southern bank of the Yangtze River Delta. Yinzhou is one of the central districts of Ningbo city and covers an area of 1380 square kilometers. Ninghai county is situated on the south of Ningbo and covers about 1931 square kilometers. The populations of Yuyao, Yinzhou, and Ninghai county were 830000, 730000, and 580000, respectively.

Since 2009, local health providers and physicians in the varicella surveillance areas have been required to report a varicella case electronically via China Information System for Disease Control and Prevention (CISDCP) within 24 h. The epidemiologic information was recorded for a clinically diagnosed varicella case: age, sex, current home address, household registration, symptoms onset date, diagnosis date, vaccine history. Additionally, public health doctors of the surveillance area were requested to find varicella case from hospitals, community health service center, schools and kindergartens every week. Once an unreported varicella case was found, the doctor immediately investigated the case and then supplementally reported the case electronically via CISDCP timely.

### 2.2. Vaccination

During 2008–2013, there were five varicella vaccines available for each year in Ningbo: Varilrix® (GlaxoSmithKline) and four domestic vaccines (Baiké, Changsheng, Keygen, and Shanghai). And only the four domestic varicella vaccines were used from 2008 to 2016. The five varicella vaccines have similar concentrations of Oka strain VZV: >1995 plaques forming unit/dose (0.5 mL) in Varilrix, and >2000 plaques forming unit/dose (0.5 mL) in the homemade vaccines. The five vaccines have the same temperature requirement (2–8 °C) for cold-chain storage and transportation.

Before 2014, 1-dose varicella vaccine was recommended for children aged  $\geq 12$  months in Ningbo, and from 2014, the 2-dose regimen was recommended for children by Zhejiang province CDC: the first dose to be provided at 12–18 months, ideally 15 months, and the second to be provided at 3–4 years old, ideally before kindergarten enrollment in order to provide proof of a complete course of vaccination prior to enrollment [17].

### 2.3. Study population and data collection

Ningbo's Immunization Information System (NBIIS) was developed in 2004 which was the one of earliest Immunization Information System in the Chinese mainland. NBIIS is a computerized information system maintaining demographic information and

immunization data for children living in Ningbo city, and all immunization clinics in Ningbo were enrolled in NBIIS since 2004. Through NBIIS, we selected consecutive 6-year birth cohorts as target population for study who must met following requirements: (1) a child was born between 2008 and 2013 and was a local resident in the surveillance area; (2) a child had received his or her vaccines (such as hepatitis B vaccine, diphtheria pertussis tetanus, measles vaccine, et al.) in the local immunization clinics before 12 months, which could keep a high retention rate of the birth cohort; (3) a child had no previous history of varicella disease prior to varicella vaccination. In addition, the demographic information and varicella vaccination status of the birth cohorts were continuously obtained from NBIIS from 2009 to 2016. All those born in the year 2008 were assigned to the 2008 birth cohort, and so on for the rest of the years.

Data of varicella with diseases onset from 2009 to 2016, were derived from CISDC and were added to the database of the selected birth cohorts. Varicella was diagnosed based on clinical manifestations with an acute maculopapulovesicular rash without other apparent cause [18]. This study was approved by the Ethics Committee of Ningbo Municipal CDC.

### 2.4. Definitions

Breakthrough varicella was defined as a case that developed >42 days after vaccination [19]. Breakthrough infection rate was defined as the proportion of breakthrough infection among children who had received varicella vaccinations.

### 2.5. Statistics

Difference in incidence of infection between the vaccinated and unvaccinated or in vaccine coverages among the different surveillance sites was analyzed using chi-square test or Fisher's test. The armitage trend test was used to assess the trend of incidence and BVR for each year from 2014 to 2016. The varicella VE was defined as  $(1 - \text{relative risk (RR)}) \times 100\%$ , where RRs were calculated using logistic regression. The unvaccinated subjects served as a reference group for 1-dose and 2-dose VE calculation. The 1-dose recipients served as a reference group for calculating incremental VE, defined as the additional protection conferred by 2-dose vaccination compared with 1-dose vaccination. All analyses were performed with SAS version 9.3 (SAS Inc., Cary, NC). 2-sided P values were reported with a significance level of  $P < 0.05$ .

## 3. Results

### 3.1. Study population and vaccine coverage

There were 111,493 newborns who met the requirements in NBIIS between 2008 and 2013. About 3.88% newborns moved out of Ningbo City whose vaccination records were interrupted in NBIIS, and their medical information also could not be found in CISDC from 2009 to 2016. Overall, a total of 107,324 newborns (96.12% of all the newborns) were enrolled in this cohort analysis. Among them, 102,078 children with no varicella disease history received  $\geq 1$ -dose varicella vaccine from 2009 to 2016, and its coverage rate was 95.11% (range 94.98–95.24%). 24,025 of the 102,078 children injected just 1-dose vaccine with 22.39% (range 22.14–22.63) vaccination rate. And 78,053 of the 102,078 children received 2-dose varicella vaccine from 2014 to 2016, whose immunization rate was 72.23% (range 72.46–72.99). Varicella coverage rates for the birth cohort 2008–2013 were shown in Table 1. The Immunization coverage rate of  $\geq 1$ -dose vaccination was 95.15% (53785/56527) for male, 95.07% (48293/50797) for female

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