Preplanned Studies

Effect of Earlier Vaccination and a Two-Dose Varicella Vaccine Schedule on Varicella Incidence — Beijing Municipality, 2007–2018

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Summary

What is already known about this topic?

The World Health Organization (WHO) varicella vaccines position paper states that countries where varicella is an important public health burden could consider introducing varicella vaccine (VarV) in the routine childhood immunization program (*1*). VarV has been available for many years in China but is not included in most routine immunization programs in China. As a result, substantial heterogeneity in vaccination coverage exists across regions.

What is added by this report?

In Beijing, adding a second dose of VarV for children and increasing coverage reduced the incidence of varicella. Lowering the age of the first dose of VarV to 12 months could further reduce varicella, especially among toddlers.

What are the implications for public health practice?

Governments should use economic analysis to consider inclusion of VarV into the routine children immunization program as a free vaccine and adopting a 2-dose schedule that starts at 12 months of age.

Varicella, also known as chickenpox, is a common childhood infectious disease caused by varicella-zoster virus (VZV). Varicella vaccine (VarV), with an estimated vaccine effectiveness of 94.0% (95% CI: 89.9%–98.9%) against VZV infection in a 2-dose pediatric schedule (*2*), has been available in China for many years. However, VarV has not been included in most routine immunization programs in China, including in Beijing Municipality. Considerable out-of-pocket costs are paid by parents, and coverage of VarV1 and VarV2 varies widely across the country from 20.8% to 97.8% (*3*–*5*). In October 2012, Beijing health authorities changed the VarV schedule of one dose given at 12 months or older to a 2-dose schedule with VarV1 at 18 months and VarV2 at 4 years. Since this change in the schedule, coverage levels in Beijing have been over 80.0% for VarV1 and 40.0% to 73.0% for VarV2 (*5*).

Varicella is not a nationally notifiable infectious disease in China, and therefore varicella epidemiology has not been well described in most areas of China. It is important for jurisdictions to monitor varicella incidence and VarV coverage to optimize use and impact of VarV. For example, a study that compared the annual incidence of varicella in Beijing Municipality and Ningbo City speculated that the optimal age of VarV1 administration to impact varicella epidemiology of children aged 12–24 months to be 12 months of age (*6*), but the study lacked VarV coverage data that potentially could support giving VarV at 12 months. In this study, we used 12 years of real world data to explore and quantify the impact of VarV1 and VarV2 on the incidence of varicella in Beijing.

Since 2007, clinicians in Beijing have been required to report varicella cases electronically within 24 hours to the National Notifiable Disease Reporting System (NNDRS). We systematically collated NNDRS varicella case information reported during 2007–2018 and determined overall and age-specific annual varicella incidence rates (per 100,000 population), defined as the annual number of cases divided by relevant age-appropriate population sizes obtained from the Beijing Municipal Bureau of Statistics. Data on children enrolled in Beijing's Childhood Immunization Information Management System (CIIMS) at the end of 2018 were used to assemble the 2006 to 2017 birth cohorts. VarV coverage was calculated by dividing the cumulative number of children who had received VarV in each birth cohort during each year by the total number of children in the corresponding birth cohort.

To visualize trends, we created heat maps of varicella incidence and VarV coverage by age group, geographical area, and year. Chi-squared and Cochran-

Armitage trend tests were used to evaluate trends across years. Linear regression was used to explore and quantify relationships between varicella incidence (dependent variable Y) and VarV coverage (independent variable X). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS/PASW, version 19.0, IBM, New York, USA) and R version 2.15.3 (https://www.r-project.org).

VarV1 coverage among children aged three years (the age of entering kindergarten) increased from 69.4% in 2007 to 86.0% in 2012 and stayed above 85.0% from 2012 through the end of the study period. After a 2-dose schedule was recommended in Beijing, VarV2 coverage among children aged 6 years (the age of entering primary school) increased consistently from 40.1% in 2013 to 74.5% in 2018. Varicella incidence at the age of 0–19 was approximately 300 cases per 100,000 population. In contrast with the previous 1-dose era, incidence decreased by 46.9% during 2012 to 2018 (P<0.001 for trend), varying by age group from 8.3% to 81.4%. Incidence among adults aged 20 years and older did not change (P>0.05 for trend) (Figure1).

When a single dose VarV was recommended for children aged ≥12 months, age-based coverage increased rapidly from 10.0% at 12 months to 50.0% at 14 months, then more gradually increased to 70.0% at 23 months. After the age for the first VarV dose was raised to 18 months, coverage was 10% at 18 months, increasing to 40.0% at 20 months, then further increasing to 70.0% at 22–23 months. At the same time, varicella incidence among children at 1 year of age increased 87.1%, from 366 cases per 100,000 population in 2012 to 684 cases per 100,000 population in 2018, with the most notable increase among children 13–20 months old (Figure 2).

Since 2013, VarV1 coverage has exceeded 80.0% in every Beijing county, but VarV2 coverage has varied widely (24.0%–71.6% in 2013 and 58.5%–89.3% in 2018). Linear regression showed that the incidence of varicella at 0–19 years of age (dependent variable Y) was negatively correlated with VarV2 coverage (independent variable X, with regression model, Y=456.32–3.07X; R^2=0.546; P<0.001). When VarV2 coverage increased to more than 80.0%, the model-predicted incidence at 0–19 years is 195 per 100,000 population, a 16.0% decrease compared with 2018 (with VarV2 coverage at 70.0%) and a 60.2% decrease compared with 2011 (single dose vaccination schedule; no second dose) (Figure 3).

In 2012–2018, the number of outbreaks in Beijing varied between 22 and 44 per year, 44.3% to 72.2% significant decreases compared with 79 outbreaks in 2007. The number of outbreak-related cases varied from 245 to 585 during 2012–2018, representing significant decreases of 38.9% to 74.4% compared to 958 outbreak cases in 2007.

DISCUSSION

Our analysis of 12 years of varicella surveillance data in Beijing showed that the incidence of varicella decreased significantly among people aged 0–19 years during 2007–2018 and that incidence was inversely associated with VarV2 coverage. Regression modeling showed that increasing VarV2 coverage to above 80.0% while maintaining VarV1 coverage ≥85.0% will lead to a further decrease in varicella incidence in Beijing. We found that when the recommended age for the first dose of VarV was raised from ≥12 months to 18months in Beijing in 2012, the incidence of varicella among children aged 12–20 months increased.

Based on World Health Organization (WHO) varicella vaccines position paper recommendations (*1*) and the observed benefits of VarV introduction in United States (*7*–*8*), it appears that a 2-dose VarV schedule should be introduced in China's routine immunization program in the future (*2*). Our study provides evidence to policymakers for improving varicella immunization strategies, including changing VarV reimbursement policies and vaccination scheduling.

The most commonly adopted VarV immunization schedules worldwide is administration of a first dose at 12–18 months and a second dose at 4–6 years of age (*9*). In Beijing, the age for the first dose (18 months) was slightly late, increasing the risk of varicella for children 12–17 months old due to lack of direct protection with VarV. About 90.0% of 18-month-old children were not able receive the first dose on time. There are two potential reasons for this delay. First, measles-mumps-rubella (MMR) vaccine, diphtheria-tetanus-acellular pertussis (DTaP) vaccine, and hepatitis A vaccine are administered during this age, which may make VarV a lower priority than these three Expanded Program on Immunization (EPI) vaccines. Second, healthcare workers do not strongly recommend that children receive non-EPI vaccines like VarV as soon as possible. To overcome these scheduling challenges and the increased incidence

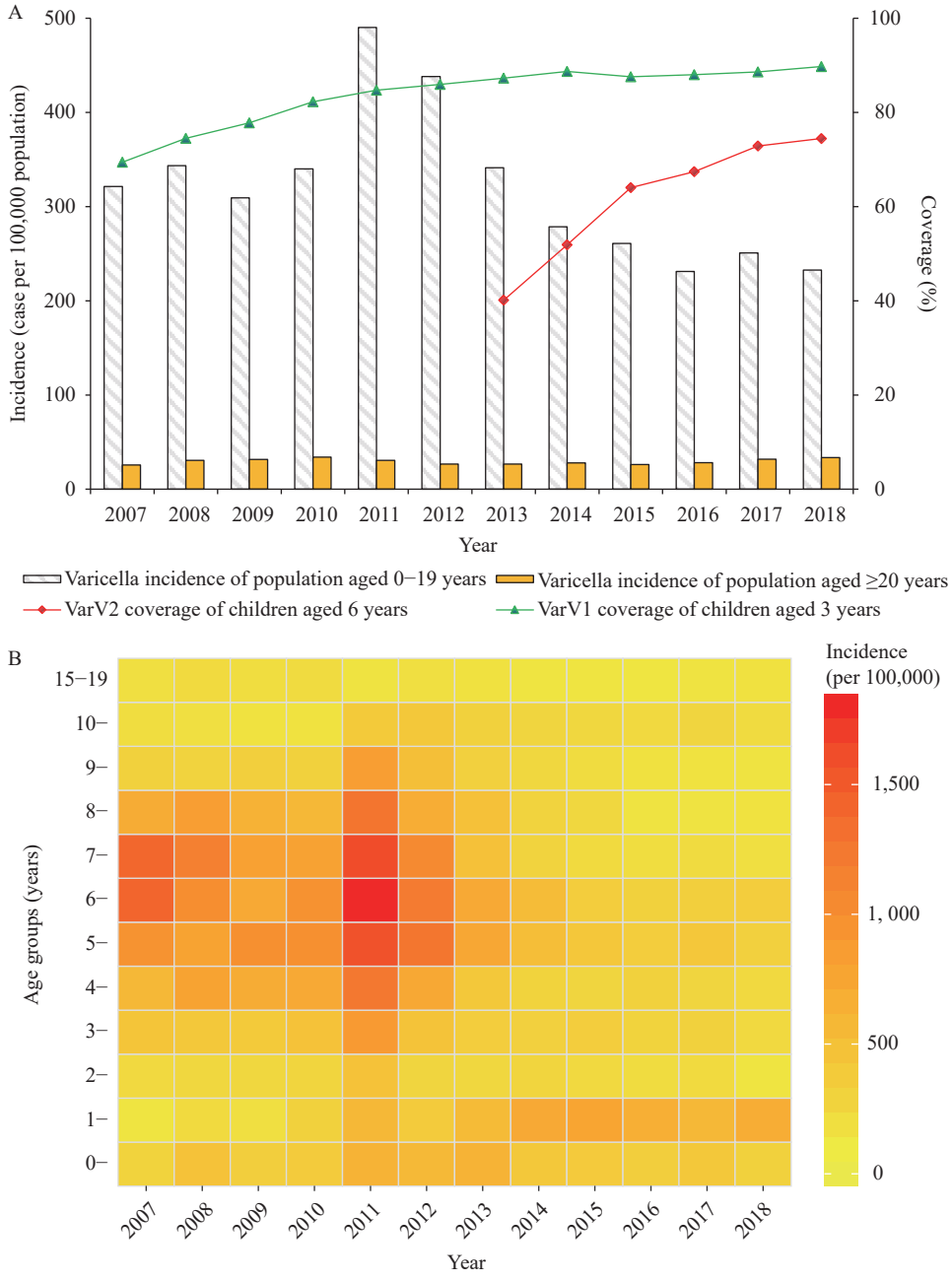

FIGURE 1. Varicella incidence (cases per 100,000 population, by year and by age group) and varicella vaccine (VarV) coverage (%) changes before and after the two-dose schedule recommendation in Beijing, 2007–2018. (A) Varicella incidence among people aged 0–19 years and ≥20 years, with superimposed varicella vaccine coverage of the first dose (VarV1) and second dose (VarV2) in Beijing, 2007–2018. (B) Heat map of varicella incidence in people aged 0–19 years during 2007–2018 in Beijing by age group.

among toddlers with an 18-month first dose, we suggest that the recommended age of the first dose should be set to 12 months.

Our study has some limitations that should be considered. First, our data were obtained from a passive surveillance system, which may be influenced by diagnostic technology, underreporting, and incomplete reporting. However, these real-world data encompass a twelve-year period with consistent reporting policies, and we believe this long and consistent reporting period can partially overcome this concern. Second, it was difficult to determine VarV coverage by month at each year of age. We therefore could not evaluate correlation between coverage and incidence among children aged 12–23 months.

In conclusion, ensuring 12-month vaccination with

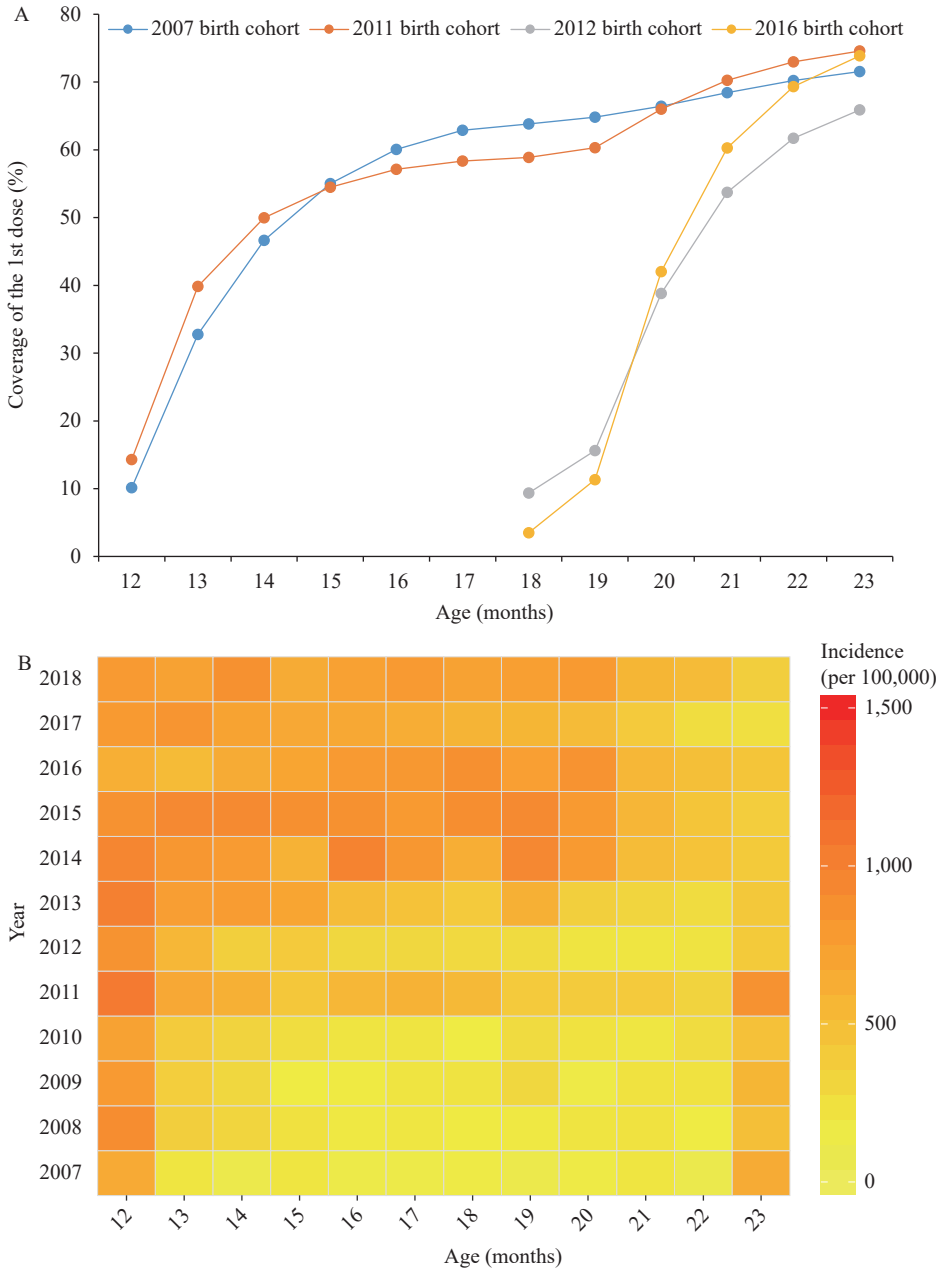

FIGURE 2. Varicella vaccine (VarV) coverage (%) and varicella incidence (cases per 100,000 population) changes in children aged 12–23 months during 2007–2018 in Beijing. (A) First dose VarV coverage among children aged 12–23 months in 2007 and 2011 birth cohorts (the age of the first dose of varicella vaccine was 12 months), and 2012 and 2016 birth cohorts (the first-dose was recommended at 18 months). (B) Heat map time series of varicella incidence per 100,000 population aged 12–23 months during 2007–2018 in Beijing by month of age.

VarV and maintaining two-dose coverage above 80.0% would be useful for varicella control. Including the varicella vaccine into EPI as a free vaccine could increase acceptance and coverage, but additional studies, especially cost-benefit studies, should be conducted to help make such a policy recommendation. Our study can provide evidence for areas with high burdens of varicella to improve disease control and prevention strategies.

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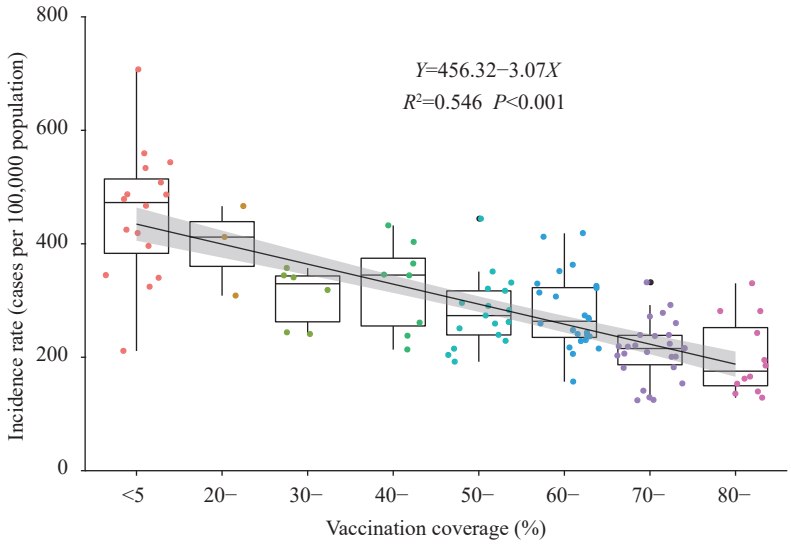

FIGURE 3. Boxplot with a scatter plot of varicella incidence of populations aged 0–19 years (cases per 100,000 population) by different varicella vaccine (VarV) coverage levels (%). The corresponding regression equation for the regression line shown is Y=α+βX (Y is varicella incidence, X is VarV coverage in children aged six years).

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