



# Strong Additional Effect of a Second Varicella Vaccine Dose in Children in Germany, 2009-2014

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**Objectives** Vaccine effectiveness (VE) of 1 and 2 varicella vaccine doses in children aged 1-4 years in Germany was evaluated to determine the additional effect of a second dose recommended at least 4 weeks after the first dose and before the second birthday.

**Study design** To estimate the VE, the proportion of cases vaccinated was compared with the proportion of the population vaccinated using nationwide sentinel surveillance data from 2009-2014 and health insurance claims data covering the period January 2009-March 2014, respectively. A general linear model was used to estimate the OR of vaccination in the cases and the population and the corresponding CIs to observe the stability of the VE estimates over time, and to assess the incremental effectiveness of a second dose.

**Results** The overall VE after 1 dose was 86.6% (95% CI: 85.2-87.9), ranging between 94.6% (95% CI: 87.9-97.6) in the first quarter of 2011 and 50.3% (95% CI: 7.3-73.4) in the third quarter of 2013. The overall VE after 2 doses was 97.3% (95% CI: 97.0-97.6), ranging between 99.5% (95% CI: 97.8-99.9) in the second quarter of 2009 and 91.3% (95% CI: 85.7-94.8) in the third quarter of 2013. The incremental VE of 2 doses was 84.6% (95% CI: 81.7-86.9).

**Conclusions** The substantially higher VE of 2 varicella vaccine doses compared with 1 dose in young children and the strong additional effect of the second dose support the public health relevance of a 2-dose schedule and the success of the early second vaccine dose. (*J Pediatr* 2016;173:202-6).

To reduce the burden of disease due to varicella, varicella vaccination was recommended in a 1-dose schedule in Germany in 2004 for all children aged 11-14 months.<sup>1</sup> In 2009, a second vaccine dose was recommended for all children aged 15-23 months, with at least 4 weeks between the doses.<sup>2</sup> Individual catch-up of missing vaccine doses is recommended before the 18th birthday. By 2013, varicella vaccination coverage had increased, with 82.7% of children aged 4-7 years having received 1 dose and 76.8% having had 2 doses.<sup>3</sup> After varicella vaccination was implemented, national and regional surveillance data showed a reduction in the number of varicella cases<sup>4-6</sup> and varicella-associated complications and hospitalizations.<sup>7,8</sup> An additional impact of the second vaccine dose has been described previously,<sup>9</sup> but the vaccine effectiveness (VE) with the 2-dose schedule has not been investigated at the population level in Germany.

In the US, varicella vaccination for all children started in 1996, and a second vaccine dose was recommended in 2006 in response to varicella outbreaks in schools and childcare centers in which children vaccinated once contracted varicella infections.<sup>10</sup> Prior to the new recommendation, clinical studies reported that the percentage of vaccinees with serum protective antibody levels as well as the geometric mean titers were substantially higher after 2 varicella vaccine doses compared with 1 dose.<sup>11,12</sup> The second vaccine dose proved to be successful in outbreak control.<sup>13</sup> Following the introduction of the 2-dose schedule, a further decrease in the incidence of varicella was observed in the US.<sup>14</sup>

The vaccination schedule in Germany differs from that in the US, where the second dose is administered at an older age (4-6 years). In the US, the second dose was implemented 10 years after starting the varicella immunization program, while this interval was only 5 years in Germany. Therefore, the results from the US may not be directly transferrable to varicella epidemiology in Germany. Furthermore, Germany is surrounded by countries that have not implemented routine childhood varicella immunization, and virus circulation may be ongoing, despite a substantial decrease in the incidence of varicella in Germany.

The aim of the present study was to generate reliable estimates of VE of the 2-dose varicella vaccination strategy implemented in Germany and to determine the additional effect of the second varicella vaccine dose in children aged 1-4 years in Germany.

## Methods

### Statistical Analyses of the VE

The VE was estimated according to the screening method by calculating the OR as below, where PCV denotes the proportion of cases vaccinated and PPV denotes the proportion of the population vaccinated.<sup>15</sup>

ASHIP	Associations of Statutory Health Insurance Physician
VE	Vaccine effectiveness

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$$VE = 1 - \frac{PCV}{1 - PCV} \times \frac{1 - PPV}{PPV} = 1 - OR$$

The OR was then fitted in a generalized linear model with a binomial error structure.<sup>16</sup> The generalized linear model was used to estimate the VE and the corresponding 95% CIs for 1 and 2 doses over the entire period and stratified by the year and quarter to observe the variability in the estimates over time. Another model for the OR was also fitted with factors denoting the time (the year and quarter) and vaccine dose to detect the possible effect of time and the incremental effectiveness of 2 vaccine doses compared with 1. Model selection was done using the Bayesian information criterion.<sup>16</sup> All analyses were performed using StataSE 14 (StataCorp, College Station, Texas).

### Data Collection on the Proportion of Vaccinated among All Varicella Cases

The proportion of cases vaccinated was estimated using data on outpatient varicella cases. The data were collected by sentinel surveillance from a countrywide convenience sample of about 900 medical practices. The sentinel participants provided data on the monthly aggregated number of varicella cases (including zero) by age groups (1-4 years, 5-9 years etc.) and the total number of vaccinated varicella cases. Additionally, each practice provided a single report on each vaccinated varicella patient seen in the practice. The report included information on demographic factors and vaccination. The procedure of the sentinel surveillance was approved by the Ethics Commission of the Charité, Berlin, Germany and was performed as described previously.<sup>4,9</sup> The merging of monthly reports and single reports per practice resulted in a database on the monthly observations of each practice. The data were cleaned in a stepwise manner by excluding or correcting observations where there were inconsistencies or constraints (Table I; available at [www.jpeds.com](http://www.jpeds.com)). Observations were deemed to be inconsistent if the aggregated monthly number of vaccinated cases did not equal the number of single case reports. Constraints were defined as cases in which the onset date was within 42 days after vaccination and as sentinel practices failing to report regularly. Regular reporting was defined as submitting at least 1 report every quarter during the time a practice was registered with the sentinel system. The remaining observations on the cases aged 1-4 years were summed up by quarter and year to the total number of varicella cases, as well as to the number of cases vaccinated once and twice. From the first quarter of 2009 to the fourth quarter of 2014, the quarterly proportion of cases vaccinated were determined separately for cases vaccinated once and twice.

The impact of variations in the data cleaning procedure was investigated in a sensitivity analysis. We tested different reporting frequencies of sentinel practices (every month, at least once per quarter, or at least once during participation) as well as inclusion or exclusion of vaccinated cases tested polymerase chain reaction-negative (laboratory testing was conducted only in about 20% of the vaccinated patients).

### Data Collection on the Proportion of Vaccinated in the Population

Data on the cross-sectional varicella vaccination coverage of the study group (aged 1-4 years) was derived from health insurance claims data, as described previously.<sup>17</sup> Briefly, physicians submit insurance refund claims for medical services, including vaccinations, provided to those with statutory health insurance (~85% of the total population in Germany) to the Associations of Statutory Health Insurance Physicians (ASHIPs). The ASHIPs extract anonymized (but still linkable) data and submit the data to the "ASHIP vaccination monitoring project" at the National Public Health Institute in Germany. ASHIP data on varicella vaccination were available for the first quarter of 2009 to the first quarter of 2014. The data were assembled by counting first and second vaccine doses by age and quarter using a retrospective cohort approach. Insured patients aged 1-4 years were included in the cohorts if they had a documented physician contact at the beginning and end of the follow-up within their respective age segment. The data were weighted by the number of live births within each ASHIP region to obtain countrywide varicella vaccination coverage estimates. Missing data for the last 3 quarters in 2014 were extrapolated from the first quarter of 2014. The proportion of the population vaccinated per quarter was calculated separately for 1 and 2 vaccine doses.

A sensitivity analysis of the available data was conducted to test the variation in varicella vaccination coverage in the fourth quarter of 2012 to the first quarter of 2014.

## Results

After the stepwise validation procedure, the total number of remaining monthly observations was 31 288, with 8153 reported varicella cases at age 1-4 years. Of those, 403 (4.9%) cases were vaccinated only once, and 285 (3.5%) were vaccinated twice (Table I). One-dose varicella vaccination coverage decreased from 45.2% in the first quarter of 2009 to 18.8% in the first quarter of 2014 among children aged 1-4 years (Table II; available at [www.jpeds.com](http://www.jpeds.com)). In the same period, 2-dose varicella vaccination coverage increased from 28.1% to 68.3% (Table III; available at [www.jpeds.com](http://www.jpeds.com)).

The overall estimate of VE after 1 dose of varicella vaccine was 86.6% (95% CI: 85.2-87.9). The yearly means of 1-dose VE varied between 92.0% (95% CI: 89.2-94.0) in 2010 and 76.1% (95% CI: 68.2-82.1) in 2014 (Table II). The quarterly estimation of 1-dose VE varied considerably, ranging between 94.6% (95% CI: 87.9-97.6) in the first quarter of 2011 and 50.3% (95% CI: 7.3-73.4) in the third quarter of 2013. Starting in 2010, the VE in the third quarter was always lower than that in the other quarters of the year (Table II).

The overall estimate of the VE after 2 varicella vaccine doses was 97.3% (95% CI: 97.0-97.6). The yearly estimates

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