Global Varicella Vaccine Effectiveness: A Meta-analysis

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abstract

CONTEXT: Several varicella vaccines are available worldwide. Countries with a varicella vaccination program use 1- or 2-dose schedules.

OBJECTIVE: We examined postlicensure estimates of varicella vaccine effectiveness (VE) among healthy children.


STUDY SELECTION: Publications that reported original data on dose-specific varicella VE among immunocompetent children.

DATA EXTRACTION: We used random effects meta-analysis models to obtain pooled one dose VE estimates by disease severity (all varicella and moderate/severe varicella). Within each severity category, we assessed pooled VE by vaccine and by study design. We used descriptive statistics to summarize 1-dose VE against severe disease. For 2-dose VE, we calculated pooled estimates against all varicella and by study design.

RESULTS: The pooled 1-dose VE was 81% (95% confidence interval [CI]: 78%–84%) against all varicella and 98% (95% CI: 97%–99%) against moderate/severe varicella with no significant association between VE and vaccine type or study design (P > .1). For 1 dose, median VE for prevention of severe disease was 100% (mean = 99.4%). The pooled 2-dose VE against all varicella was 92% (95% CI: 88%–95%), with similar estimates by study design.

LIMITATIONS: VE was assessed primarily during outbreak investigations and using clinically diagnosed varicella.

CONCLUSIONS: One dose of varicella vaccine was moderately effective in preventing all varicella and highly effective in preventing moderate/severe varicella, with no differences by vaccine. The second dose adds improved protection against all varicella.

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Dr Marin conceptualized and designed the study, reviewed the articles and collected the data, supervised the analysis, interpreted the data, drafted the initial manuscript, and revised the manuscript; Dr Marti conceptualized the study, reviewed part of the articles, interpreted the data, and reviewed and revised the manuscript; Ms Kambhampati carried out the meta-analyses, interpreted the data, and reviewed the manuscript; Dr Jeram conducted an initial literature review, reviewed part of the articles and collected the data, and reviewed the manuscript; Dr Seward conceptualized and designed the study, reviewed part of the articles, critically reviewed the manuscript, and interpreted the data; and all authors approved the final manuscript as submitted.

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A varicella vaccine, based on the attenuated live varicella zoster virus (VZV) Oka strain, was developed by Dr. Takahashi in Japan in the mid-1970s. Two decades later, the United States became the first country to implement a routine childhood varicella vaccination program after the vaccine was licensed in 1995. Varicella vaccines are now licensed and available throughout the world; however, they are recommended for routine use only in a small number of primarily industrialized countries. Where coverage rates are high, vaccination has resulted in important declines in varicella-related incidence, morbidity, and mortality.

Worldwide, there are several formulations of varicella vaccines; all contain live attenuated VZV, and all, except the vaccine licensed in South Korea, are based on the Oka strain of VZV isolated in Japan. Currently, varicella vaccines are licensed as a monovalent or a combination measles, mumps, rubella, varicella vaccine (MMRV). Monovalent vaccine is produced in the United States (VARIVAX; Merck & Co., Inc.), Belgium (Varilrix; GlaxoSmithKline), Japan (OKAVAX; Biken, distributed by Sanofi Pasteur), China (4 manufacturers: Shanghai Institute of Biologic Products, Changchun Keygen Biological Products Co, Ltd, Changchun BCHT Biotechnology Co [Baike], Changchun Changsheng Life Sciences Ltd), and Korea (Sudvax). MMRV is produced in the United States (ProQuad; Merck) and Belgium (Priorix-Tetra; GlaxoSmithKline).

Vaccine safety and efficacy were assessed in double-blind, placebo-controlled, 1-dose studies for 3 of the monovalent vaccines. MMV vaccines were licensed on the basis of noninferior immunogenicity of the antigenic components compared with simultaneous administration of MMR and varicella vaccines; an efficacy study for 2 doses of MMRV vaccine was performed after licensure. Efficacy studies conducted used vaccines with varying concentrations of the Oka strain, making comparisons across studies and inference of results to licensed vaccine formulations difficult; moreover, vaccine performance may be different under conditions of real-world use (vaccine effectiveness [VE]). Therefore, postlicensure evaluations of VE are important to inform public health programs and policies. We conducted a systematic literature review and descriptive and meta-analysis to assess the effectiveness of varicella vaccine among immunocompetent children to prevent (1) varicella of any severity (1 and 2 vaccine doses), (2) combined moderate and severe varicella (1 dose), and (3) severe varicella (one dose).

METHODS

Identification of Studies

The complete search strategy is described in the Supplemental Information (Supplemental Table 1). In brief, we searched for reports published between 1995 (year the varicella vaccine was first recommended for routine vaccination) and December 15, 2014, in the following databases: Medline, Embase, Cochrane libraries, and CINAHL. We used search terms including “varicella,” “chickenpox,” “vaccine,” “vaccination,” “effectiveness,” “effective,” and “performance” to identify reports that presented data on varicella vaccine effectiveness. We did not restrict our search by language.

Study Selection and Data Collection

Each article title and abstract was reviewed by 2 authors, and relevant publications were selected for full-text review. The criteria for assessment of eligibility for meta-analysis included the following: (1) original report on dose-specific varicella VE and (2) the population studied was immunocompetent children. Clinical trials and studies that reported VE for postexposure prophylaxis were excluded. For each study included in the analysis, we abstracted information on study setting, study design including case definition and classification of disease severity, vaccine studied, number of vaccine doses, number of study participants age ≥12 months, and VE with confidence intervals.

Analysis

We used random effects meta-analysis models to obtain pooled 1-dose VE estimates and 95% confidence intervals (CIs) for monovalent vaccines by disease severity (against varicella of any severity [all varicella] and against combined moderate and severe varicella). Within each of the 2 categories of disease severity we assessed pooled VE by vaccine and by study design. For studies in countries where >1 varicella vaccine is licensed, if publications did not specify the vaccine studied, we classified VE estimates as for “mixed/multiple vaccines.” For 2-dose VE, because most studies included multiple vaccines, we calculated pooled estimates and 95% CIs overall against varicella of any severity and stratified by study design. To be included in the analysis, a publication had to report VE and a measure of its variance (CI) or the raw numbers to allow us to calculate CI. When CI or raw numbers were not reported, we contacted the authors to obtain 1 of them. For 1 study that reported VE and CIs for 4 birth cohorts and an overall VE without CI, we pooled estimates from the 4 birth cohorts to calculate CI for the overall VE. When publications reported crude and adjusted VE, we included the adjusted estimates. VE was calculated as 1 – relative risk (RR) or 1 – odds ratio (OR), depending on the study design. To calculate the pooled VE estimates, we
first obtained the RR / OR for each study using the formula $RR / OR = (1 – VE) * 100$. We then calculated the pooled OR, and transformed the pooled OR into a pooled VE estimate $(VE = 1 – OR) * 100$. We assessed residual heterogeneity by calculating the $I^2$ statistic. Publication bias was assessed by using Egger’s regression test. We conducted mixed-effects meta-regression analyses by using restricted maximum likelihood estimation, among the studies that reported VE on all varicella and combined moderate and severe varicella, to investigate potential sources of heterogeneity and identify any differences by vaccine or study design. All analyses were conducted by using the metafor package in R.\textsuperscript{24,25}

For the analysis of combined moderate and severe varicella or severe only we used the definitions and classification from each study and excluded studies that did not provide these classifications. In most studies, severity of disease was defined by the number of skin lesions and incidence of complications or hospitalization as mild, <50 lesions; moderate, 50 to 500 lesions; and severe, ≥500 lesions or a serious complication or hospitalization; the combined moderate and severe category includes cases in the last 2 categories. Several studies used a different number of lesions to define severe disease, or assessed severity based on a disease-severity score modified from the clinical trials, a combination of criteria that included number of days with fever, number of lesions, number of days the patient needed rest and presence of complications, hospitalization only, or parental assessment of severity (Supplemental Information). VE estimates against moderate varicella only\textsuperscript{26,27} were included in the analysis of VE against combined moderate and severe varicella. One study that also reported VE against moderate disease alone provided data in the publication that allowed us to calculate VE against combined moderate and severe varicella; we used VE against combined moderate and severe varicella for this study.\textsuperscript{20}

We used descriptive statistics to present the findings on 1-dose VE against severe disease alone because none of the publications reported CIs for VE against severe disease, mainly due to the absence of severe cases among vaccinated patients. Additionally, publications that reported no cases of severe disease were assigned a VE of 100% against severe disease for our analysis. One study reported VE against varicella-related hospitalizations\textsuperscript{23}; this estimate was included in the summary of findings for severe disease.

**RESULTS**

We screened 872 nonduplicate articles for eligibility and identified 105 potentially relevant studies for further review. After excluding 63 studies, 42 original studies met our inclusion criteria for meta-analysis (Fig 1; references listed in Supplemental Table 2 of the Online Supplemental Information). These studies originated from the United States (23), China (4), Germany (3), Israel (3), Italy (2), Spain (2), Taiwan (2), Australia (1), Turkey (1), and Uruguay (1).

**One-Dose VE**

Almost two-thirds of studies of 1-dose varicella VE (64%, 27 of 42) were conducted during outbreak investigations and used a retrospective cohort study design; 2 additional studies used a retrospective cohort study design based on data from electronic databases (Supplemental Table 2). Other methods used included matched case-control study (24%, 10 of 42), prospective cohort study (1), household contact study (1), and time-series modeling (1) (Supplemental Table 2). The populations studied included children in different settings such as child-care centers, schools, community clinical practices, hospitals, outpatient setting, and households. Ages of participants varied, overall ranging from 12 months to 18 years, but VE was predominantly calculated among preschool and elementary school–age children (Supplemental Table 2). Most studies used as an outcome clinically diagnosed varicella with details on illness obtained from parents; 5 studies used laboratory confirmed varicella as their outcome (Supplemental Table 2).

The 42 publications reported for 1-dose monovalent vaccines 58 VE estimates for prevention of all varicella (Fig 2), 34 estimates for prevention of combined moderate and severe varicella (including 2 studies that provided estimates for moderate varicella alone; Fig 3), and 25 estimates for prevention of severe varicella. Only 1 study reported MMRV VE (1 and 2 doses).\textsuperscript{27}

The pooled 1-dose VE for prevention of all varicella was 81% (95% CI: 78%–84%, $I^2 = 88$%; Fig 2). Most postlicensure studies were reported from the United States and as a result, most VE estimates were for Varivax ($n = 26$; Fig 2 and Supplemental Table 2). Studies conducted in other countries assessed Varilrix, Okavax, and various other varicella vaccines. When stratified by vaccine, pooled 1-dose estimates were as follow: Varivax 82% (95% CI: 79%–85%, $I^2 = 62$%), Varilrix 77% (95% CI: 62%–85%, $I^2 = 92$%), other vaccines 86% (95% CI: 78%–91%, $I^2 = 39$%), or mixed/multiple vaccines 81% (95% CI: 76%–85%, $I^2 = 85$%; Fig 2). The only VE reported for 1 dose of MMRV/Priorix-Tetra was 55% (95% CI: 8%–79%). Pooled VE estimates were also similar by study design: 81% (95% CI: 76%–84%, $I^2 = 92$%) for cohort and 83% (95% CI: 78%–82%, $I^2 = 93$%) for case–control studies.
79%–86%, \( I^2 = 42\% \) for case-control studies (Supplemental Fig 5).

The pooled 1-dose VE for prevention of combined moderate and severe varicella was 98% (95% CI: 97%–99%, \( I^2 = 85\% \); Fig 3). The estimates by vaccine were similar to the overall pooled VE: Varivax 98% (95% CI: 95%–99%, \( I^2 = 86\% \)), Varilrix 98% (95% CI: 89%–100%, \( I^2 = 79\% \)), mixed/multiple vaccines 99% (95% CI: 95%–100%, \( I^2 = 86\% \); Fig 3).

When stratified by study design the pooled estimates were 98% (95% CI: 97%–99%, \( I^2 = 87\% \)) for cohort and 97% (95% CI: 93%–99%, \( I^2 = 69\% \)) for case-control studies (Supplemental Fig 6).

In the meta-regression analyses, no significant association was found between VE and vaccine type or study design (all \( P > .1 \); Supplemental Table 3).

Of the 25 estimates for VE for prevention of severe disease, for 24 VE was 100%; 1 study reported a VE of 85% (for prevention of varicella-related hospitalizations).23 The only VE for 1 dose MMRV/Priorix-Tetra for prevention of severe disease was 100%.

**Two-Dose VE**

There were 8 publications that reported 9 estimates for 2-dose VE, 8 for monovalent varicella vaccines and 1 for MMRV/Priorix-Tetra. The pooled 2-dose VE for monovalent vaccines was 92% (95% CI: 88%–95%, \( I^2 = 57\% \)) and by study design: 91% (95% CI: 84%–95%, \( I^2 = 74\% \)) for cohort and 95% (95% CI: 90%–97%, \( I^2 = 0\% \)) for case-control studies (Fig 4). The only VE reported for 2 doses of MMRV/Priorix-Tetra was 91% (95% CI: 65%–98%).

There was evidence of publication bias as indicated by Egger’s regression test in some subgroups analyzed but not in others (Supplemental Table 4).

**DISCUSSION**

This is the first study to systematically assess the effectiveness of varicella vaccines currently available worldwide. In our analyses that included children in 42 studies, within the first decade after vaccination, 1 dose of varicella vaccine was moderately effective at preventing all varicella (81%) and highly effective at preventing combined moderate and severe varicella (98%). Noteworthy is the consistency of the findings, with similar pooled estimates whether the analysis was stratified by individual vaccines or study design. Additionally, 2 doses of varicella vaccine were highly effective at preventing all varicella.

Most of the reported 1-dose VE estimates for prevention of all varicella were close to the pooled estimate; however, 1 estimate for MMRV was 55%, and 2 estimates were <50%, 1 each for Varivax and Varilrix, 44% and 20%, respectively.27–29 These estimates were all calculated during outbreak investigations.
that tend to underestimate the performance of vaccines; outbreaks that come to public health attention may be exceptions in which the vaccine failed and therefore may represent the lower range of vaccine effectiveness versus situations in which the vaccine worked well and prevented outbreaks and where no investigations are done.\textsuperscript{30} Although there are no definitive explanations for the low effectiveness, in outbreak investigations, there are confounders not able to be controlled for; the force of infection may be high in some outbreaks or the degree of exposure may be variable across study participants; additionally, such values could be identified by chance, especially during investigations conducted in settings where there is epidemiologic evidence of vaccine failure (outbreaks). This highlights that more than a few estimates are needed to accurately assess VE. A previous meta-analysis that included VE calculated during varicella outbreaks from 14 publications through 2004 reported a pooled 1-dose VE of 72.5\%.\textsuperscript{31}

Fewer studies assessed 2-dose VE in children. Overall, 2 doses of vaccine provided 10\% or better protection than 1 dose. However, 2 of the estimates, both from outbreak investigations, were <90\% and that may have lowered the pooled estimate to the lower 90s.\textsuperscript{32,33}

The pooled VE estimates we report for 1 dose are a compilation of VE at different points of time since vaccination, primarily within the first decade. Considering the age of participants in the studies and vaccine recommendations in each country, the median time since vaccination is likely lower than 10 years. Within this time frame, some studies described a higher risk for vaccine failure with time since vaccination (using a cutoff of 3, 4, or 5 years).\textsuperscript{22,26,28,34-36} but other studies did not find this association\textsuperscript{27,37-41}; in all these studies, conducted during outbreak investigations, the sample sizes were usually insufficient to assess the independent effect of time since vaccination as a risk factor. Four studies reported decline in VE with time since vaccination; however, the differences did not reach statistical significance.\textsuperscript{42-45} Vazquez et al used laboratory confirmed cases and described a decline in VE for Varivax between years 1 and 2 (from 97\% to 86\%) after vaccination but not subsequently (up to 7 years of follow-up, 84\%)\textsuperscript{46}; another study in the United States reported a significant decline in 1-dose VE from 94\% within 5 years after vaccination to 88\% for 5 to 9 years and 82\% for $\geq$10 years after vaccination.\textsuperscript{47} Additionally, Bayer et al in their meta-analysis of outbreak data, concluded waning immunity based on data from four studies which all showed a decrease in VE by time since vaccination (data available for an average of 4 to 6 years since

![FIGURE 2](random-effects-model-of-1-dose-varicella-ve-for-prevention-of-all-varicella-by-vaccine.png)
When interpreting the results of these studies, consideration should be given to the fact that they did not adjust for likelihood of exposure or force of infection which declined over time due to changing varicella epidemiology with the implementation of vaccination programs. This results in differential exposure by age group and can confound interpretation of waning effectiveness. One large study that controlled for likelihood of exposure and age examined 10 years of active surveillance data (1995–2004) from a sentinel population and reported an increase in incidence of varicella among vaccinated persons with time since vaccination after the first dose although the rate of breakthrough varicella was still very low. Only 1 study examined 2-dose VE by time since vaccination and found no difference in VE through 5 years since the second dose; there were too few subjects to confidently examine VE >5 years after the second dose.

The VE findings are supported by immunologic and epidemiologic data. Immunogenicity studies from the United States reported that primary vaccine failure occurs in 9% to 14% of children after 1 dose of vaccine. A small study found that 24% of infants lacked VZV antibody measured by fluorescent antibody to membrane antigen a median of 4 months after vaccination. The second dose of varicella vaccine in children produced an improved immunologic response as measured by the proportion of subjects with titers of ≥5 glycoprotein-based enzyme-linked immunosorbent assay, an approximate correlate of protection, (99.6% vs 86% 6 weeks after the second and first dose, respectively) and higher geometric mean titers. Countries that introduced varicella vaccination have experienced substantial reductions in varicella incidence, severe morbidity and mortality, and evidence of herd protection beyond the age groups targeted by vaccination. By the end of the decade of the 1-dose program in the United States, when vaccine coverage had reached ~90%, varicella incidence had declined 90% or more, hospitalization in children decreased ≥95%, and deaths had been nearly eliminated; effects of vaccination were documented within 5 years of the program in communities where vaccine coverage among young children had reached ~80%. In Germany, where a 1-dose national vaccination program was implemented in 2004, a decline of 55% in cases and 82% in varicella complications was observed from 2005 to 2009 using data from physician-based sentinel surveillance. In Canada, where the 1-dose varicella vaccination program was recommended in 1999, declines of 81% to 88% in the number of hospitalized varicella cases were reported between 2000 and 2008, with impact of the vaccination program being noted beginning 1 to 2 years after the start of the program.
vaccination coverage ranged from 74% to 91% in 2007–2008. The impact of a 1-dose vaccination program on varicella and its severe morbidity has also been described from Taiwan, Uruguay, Australia, and Italy. Protection against severe disease among those vaccinated appears to be maintained after 1 dose of vaccine. No increases in rate of complications, hospitalizations or deaths have been reported with time since vaccination in countries with a 1-dose program. The 1 study mentioned earlier that used a active surveillance data reported that among vaccinated persons, varicella was twice as likely to be moderate/severe in those who developed disease >5 years after vaccination compared with those who became ill <5 years after vaccination; moderate/severe varicella was defined as >50 skin lesions in this study.

Despite considerable success in controlling varicella and its severe complications with the 1-dose varicella vaccine program in the United States, cases and varicella outbreaks (although less in number, smaller in size, and of shorter duration) continued to occur in highly vaccinated school students. This, coupled with the evidence that 2 doses induce a higher immune response and higher effectiveness, resulted in adoption of a routine 2-dose policy for children in 2006. During the first 5 years after introduction of the 2-dose program, reported varicella incidence has declined further to the lowest level since the start of the vaccine program, with fewer outbreaks and additional declines in varicella-related hospitalizations. In Navarre region, Spain, where a 2-dose routine childhood program was introduced from the beginning and high coverage was achieved early in the program, a decline of 98.5% in incidence in children and 88% in hospitalizations were achieved within a period of only 5 years.

Our study has several limitations. The majority of studies assessed VE using clinically diagnosed varicella cases and the evaluations occurred during outbreak investigations that tend to underestimate the performance of vaccines. We did not perform a formal quality assessment of the studies included; all were published in peer-review publications however, we excluded 2 due to methodologic issues identified during the review. When stratified by vaccine, there was some evidence of heterogeneity in the 1-dose estimates, suggested by I² >75%. This finding may be due to variations in study design and size. There was also some evidence of publication bias in the estimates from the publications that reported on moderate-severe varicella, suggesting that higher ORs could have come from smaller studies, which could lead to some overestimation of our pooled estimates. Most studies are from high-income countries with few from middle-income and none from low-income countries.

Available data support similar performance of the various 1-dose monovalent varicella vaccines in preventing varicella. One-dose varicella vaccine is moderately effective (81%) for preventing all varicella and highly effective (98%) for preventing combined moderate and severe varicella. The second dose adds improved protection against all varicella (92%). The impact of varicella vaccination in decreasing morbidity and mortality due to varicella is well documented during the first 2 decades of program implementation. The duration of protection after 1 dose is not fully understood or studied, especially in settings of low varicella incidence however, live viral vaccines because they actively replicate in the body commonly provide durable immunity. It is unknown what role waning immunity after an initial response and primary immunologic failure rates play in the inability of 1 dose of vaccine to provide complete protection. The fact that varicella in vaccinated persons is usually highly modified suggests partial protection or inadequate induction of a totally protective immune response, not primary vaccine failure. To date, there is no evidence of increased severe outcomes (death or hospitalization rates) at population level with time since 1 dose of vaccine. Assessment of vaccine effectiveness in recipients who are >10 to 20 years after vaccinations with both 1 and 2 doses is needed. One dose is sufficient to reduce mortality and severe morbidity from varicella but not to prevent limited virus circulation and outbreaks. To further reduce the number of cases and outbreaks and transmission 2 doses are needed. Additionally, the widespread use of
varicella vaccine could reduce herpes zoster incidence among the vaccinated populations; several studies reported a lower risk for herpes zoster among varicella-vaccinated children and a decline in herpes zoster incidence among cohorts targeted for varicella vaccination.

**REFERENCES**


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**ABBREVIATIONS**

CI: confidence interval
MMRV: combination measles, mumps, rubella, varicella vaccine
OR: odds ratio
RR: relative risk
VE: vaccine effectiveness
VZV: varicella zoster virus


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