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Varicella Vaccine Effectiveness in Preventing Community Transmission in the 2-Dose Era

Dana Perella, MPH, Chengbin Wang, PhD^a, Rachel Civen, MD, MPH^b, Kendra Viner, PhD, MPH^c, Karen Kuguru, MPA^a, Irini Daskalaki, MD^c, D. Scott Schmid, PhD^a, Adriana S. Lopez, MHS^b, Hung Fu Tseng, PhD, MPH^d, E. Claire Newbern, PhD, MPH^a, Laurene Mascola, MD, MPH^c, and Stephanie R. Bialek, MD, MPH^b

^aPhiladelphia Department of Public Health, Philadelphia, Pennsylvania

^bCenters for Disease Control and Prevention, Atlanta, Georgia

^cLos Angeles County Department of Public Health, Los Angeles, California

^dSouthern California Permanente Medical Group, Kaiser Permanente, Pasadena, CA

Abstract

Objectives—We examined overall and incremental effectiveness of 2-dose varicella vaccination in preventing community transmission of varicella among children aged 4–18 years in two active surveillance sites. One-dose varicella vaccine effectiveness (VE) was examined in those aged 1–18 years.

Methods—From May 2009 through June 2011, varicella cases identified during active surveillance in Antelope Valley, CA and Philadelphia, PA were enrolled into a matched case-control study. Matched controls ± 2 years of the incident case's age were selected from immunization registries. A standardized questionnaire was administered to participants' parents, and varicella vaccination history was obtained from healthcare provider, immunization registry, or parent records. We used conditional logistic regression to estimate varicella VE against clinically-diagnosed and laboratory-confirmed varicella.

Results—One hundred twenty-five clinically-diagnosed varicella cases and 408 matched controls were enrolled. Twenty-nine cases were laboratory-confirmed. One-dose VE (1-dose vs. unvaccinated) was 75.6% [95% confidence interval (CI): 38.7–90.3%] in preventing any clinically-diagnosed varicella and 78.1% (95% CI: 12.7–94.5%) against moderate/severe, clinically-diagnosed disease (50 lesions). Among subjects aged 4 years, 2-dose VE (2-dose vs. unvaccinated) was 93.6% (95% CI: 75.6–98.3%) against any varicella and 97.9% (95% CI: 83.0–99.7%) against moderate/severe varicella. Incremental effectiveness (2-dose vs. 1-dose) was 87.5% against clinically-diagnosed varicella and 97.3% against laboratory-confirmed varicella.

Corresponding Author: Dana Perella, MPH, Acute Communicable Disease Program, Philadelphia Department of Public Health, 500 South Broad Street, 2nd Floor, Philadelphia, PA 19146, Phone: 215-685-6742, Fax: 215-238-6947, ; Email: dana.perella@phila.gov

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Compared with 1-dose breakthrough cases, 2-dose cases had shorter duration of rash ($P=0.01$) and were 80% less likely to develop vesicular rashes ($P=0.01$).

Conclusions—Two-dose varicella vaccination offered improved protection against varicella from community transmission among school-aged children compared with 1-dose vaccination.

Introduction

Between 1995 and 2005, the 1-dose varicella vaccination program in the United States (US) greatly reduced varicella incidence, hospitalizations, and deaths.¹⁻⁴ However, between 2001 and 2006, varicella outbreaks in school settings with high 1-dose vaccination coverage (>80% among students without varicella history) continued to be reported.⁵⁻¹¹ Clinical trial data had demonstrated that the immune response produced 6 weeks after 2-dose varicella vaccination was 12 times higher than levels following 1-dose vaccination, which translated into a 3-fold reduction in breakthrough varicella over a 10-year period.¹² Considering this, in 2006, the Advisory Committee on Immunization Practices recommended implementation of a routine two-dose varicella vaccination program for children aged 4 to 6 years.¹³

Declines in varicella incidence reported since 2006 along with varicella vaccine effectiveness estimates from a case-control study conducted as part of active surveillance of outbreaks in West Virginia indicate that the 2-dose regimen provides improved protection against varicella.¹⁴⁻¹⁸ However, limited field data exist on the performance of a 2-dose varicella vaccination program in preventing community transmission other than in outbreak settings that may underestimate the true vaccine effectiveness.^{18, 19} A community-based case-control study in Connecticut found 2-dose varicella vaccine effectiveness (VE) was 98.3% , but no 2-dose cases were identified in the study.²⁰ As this study demonstrates, obtaining precise 2-dose varicella VE estimates is challenging due to lower varicella incidence in the 2-dose era, particularly among recipients of both doses.

To further evaluate the 2-dose varicella VE, we conducted a matched case-control study to examine the overall and incremental VE of the 2-dose varicella vaccination regimen in preventing varicella among school-aged children (4 to 18 years) in two geographically and demographically diverse areas under active surveillance for varicella. Secondary study objectives were to estimate 1-dose VE among individuals aged 1 to 18 years during the 2-dose era and determine risk factors associated with breakthrough varicella among 2-dose recipients.

Methods

Study Population and Setting

From May 2009 through June 2011, investigators from Antelope Valley (AV) and West Philadelphia Varicella Active Surveillance Project (VASP) conducted this matched case-control study in collaboration with the Centers for Disease Control and Prevention (CDC). Institutional review boards at all 3 participating institutions approved the study protocol. The target populations for case and control subject recruitment were residents aged 1 to 18 years from AV and Philadelphia. AV spans approximately 2,200 square miles of northern Los Angeles County and has a population of over 370,000 residents.²¹ Philadelphia is a large and

densely-populated metropolis with 1.5 million residents.²² During the study, the majority of AV residents <20 years of age were either Hispanic (51%) or non-Hispanic white (30%).²¹ Among those of same age in Philadelphia, 48% were non-Hispanic black, 28% were non-Hispanic white, and only 16% were Hispanic.²²

Case Recruitment

In AV and Philadelphia, varicella cases were identified prospectively using population-based active surveillance methods. Over 300 participating community-based sites (e.g., schools, healthcare provider offices, etc.) in each surveillance area reported suspected varicella cases or informed project staff that no cases occurred at their facility biweekly.^{15, 23} During the 2010-2011 academic year, active surveillance was expanded from West Philadelphia to include an additional 232 schools that were located in other areas of Philadelphia. Eligible case subjects in Philadelphia were also identified through citywide passive surveillance. All case reports were investigated using the standardized VASP questionnaire.^{15, 23}

Following investigation, a case subject was defined as an individual residing in AV or Philadelphia with no prior history of varicella and acute onset of a diffuse maculopapulovesicular rash or for previously vaccinated persons, modified maculopapular rash with few or no vesicles that a medical provider definitively diagnosed as varicella without any other apparent cause.^{15, 24} During May 2009 through July 2010, enrollment was limited to children aged 5 to 14 years with laboratory confirmation of varicella-zoster virus (VZV) by Polymerase Chain Reaction (PCR) testing. During August 2010 through June 2011, enrollment was expanded to include persons 1 to 18 years of age with laboratory and/or clinical diagnosis of varicella by a healthcare provider. Laboratory confirmation was expanded as well to include positive VZV-specific PCR, Direct Fluorescent Antibody (DFA) assay, or culture results.

Control Selection

Control subjects were selected from the Kaiser Permanente Southern California membership database and the Philadelphia Department of Public Health's Kids Immunization Database/Tracking System registry in AV and Philadelphia, respectively. Kaiser Permanente Southern California, an integrated health care system, provides comprehensive health services to 30% of AV residents aged 1 to 19 years; vaccine administration data for its members is stored in the Kaiser Immunization Tracking System and includes information on vaccine doses administered by providers inside and outside the Kaiser network or verified through school or provider records for vaccinations given prior to enrollment. Kaiser Permanente also was an active surveillance reporting site in AV. The Philadelphia Department of Public Health immunization registry has utilized health department birth records and vaccine administration reporting from healthcare providers to establish and maintain immunization records for all children aged 6 years in Philadelphia since 1995. The registry expanded to include children aged 18 years in 2007.

For each varicella case identified that met study inclusion criteria, we selected potential controls using incidence density sampling by extracting age-matched (± 2 years) records for all children from the pool of eligible controls aged 1 to 18 years who did not have a prior

varicella history documented in historic surveillance data or immunization registry.²⁵ A two-year age range for controls was chosen, since the routine 2-dose varicella vaccination recommendation spans ages 4 to 6 years.¹³ Moreover, since routine 1-dose coverage reached higher levels (>80%), protection from 1-dose varicella vaccination appears to remain consistent during the first few years after vaccination.¹³ Between 5 and 60 potential control subjects were randomly selected from the corresponding control pool for each incident case. In order to be able to analyze VE among the age groups for which the first and second doses of varicella vaccine are recommended, controls selected for cases aged 1 to 3 years had to be <4 years of age and controls selected for cases 4 years of age had to be 4 years of age. Study staff sent a study invitation letter and contacted parents or guardians of eligible control subjects via telephone. The first 3 eligible respondents who consented to participate comprised the controls for each incident case. Recruited controls were eligible to be controls for subsequent incident cases, and if s/he developed varicella at a later time point, were eligible for the study as a case subject.

Data Collection

Study staff obtained verbal consent and collected data from a parent or guardian of each subject by telephone using a standard questionnaire. Given limited study resources, we did not recruit cases and controls with non-English-speaking parents or guardians who could not provide consent due to the language barrier. The questionnaires captured information on demographics, varicella vaccination history, recent VZV exposures, underlying medical conditions, and use of immune suppressing medications. The case questionnaire, which has been described previously, included additional disease-specific questions and standardized prompts to obtain number of lesions.²³ VASP staff scheduled home visits to collect lesion specimens from eligible cases reported before their rashes had resolved. The CDC National VZV Laboratory performed PCR testing^{26, 27} on lesion specimens collected from suspected varicella cases. For a few cases, VZV-specific testing was conducted by hospital or commercial reference laboratories. Participating families received a \$10–\$20 gift card after completion of study-related activities, and AV healthcare providers were offered a \$20 gift card for every case reported with lesion specimens collected.

For case and control subjects, varicella vaccination administration dates were collected from the registries used for control selection, parental records, and the subject's healthcare provider. Study staff made efforts to validate vaccination information for all subjects with the immunization registry or healthcare provider records. If a discrepancy existed between these two sources, the source with the most complete information (i.e., highest number of doses) was used. We considered 1-dose varicella vaccination to be valid when given 4 days before a child's first birthday or later. Second-dose varicella vaccination was considered valid when administered 4 weeks after the first dose. The last dose also needed to be given >42 days before rash onset for cases (breakthrough varicella) or the matched incident case's onset for controls. Those given doses within 42 days were excluded.

Data analysis

For our main analysis, we combined data from both sites, since varicella vaccine coverage and risk for breakthrough varicella have not differed among socio-demographic

subgroups,^{13, 28} and the direction of estimates from each site were similar. We used two case definitions for varicella: clinically-diagnosed and laboratory-confirmed. Varicella severity was categorized based on the number of lesions reported as mild (<50 lesions), moderate (50–500 lesions) or severe (>500 lesions). The following VE estimates were calculated to examine protection against any varicella or moderate/severe disease alone (> 50 lesions): incremental 2-dose VE (2 doses vs. 1 dose), overall 2-dose VE (2 doses vs. unvaccinated), and overall 1-dose VE (1 dose vs. unvaccinated). All VE estimates were calculated using Greenwood and Yule's formula: $1 - \text{relative risk (RR)}$.¹⁹ In our study, RR refers to the risk of developing varicella among the subgroup with the higher number of varicella vaccine doses compared with the subgroup with fewer or no doses and was estimated with an odds ratio (OR) from conditional logistic regression to account for the matching variable (age). We were able to adjust for other potential confounders when examining VE against clinically-diagnosed disease using the combined site data. Changes in VE by time since vaccination (rash onset date minus the date of most recent varicella vaccination) were calculated using previously described methods.²⁵ The distribution of categorical or continuous variables between cases and controls were examined with Mantel-Haenszel chi-square test, Fisher's exact test, Mann-Whitney U test, or Kruskal-Wallis test where appropriate. All analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC).

Results

Case and Control Subject Characteristics

A total of 125 clinically-diagnosed varicella cases and 408 matched controls were enrolled. Of the 44 (35.2%) cases that had lesion specimens tested for VZV, 29 were laboratory-confirmed cases (all PCR positive), 11 were PCR negative (median lesion collection day: 5 [range: 2–21]), 2 had inadequate specimens, and 2 were culture negative. The median age of clinically-diagnosed cases was 2.1 years among those aged <4 years and 9.5 years among those aged ≥ 4 years (Table 1). For each case, 2 to 7 matched controls (median=3) were recruited after approaching a median of 5 (range: 5–15) and 29 (range: 5–60) eligible individuals in AV and Philadelphia, respectively. The distribution of demographic characteristics did not differ significantly between clinically-diagnosed case and control subjects, except daycare attendance among those aged ≥ 4 years ($P=0.03$). Most controls aged ≥ 4 years from AV and Philadelphia had received at least one dose of varicella vaccine (98.8% vs. 95.5%, $P=0.05$), and the majority in each site had received 2-doses (78.5% vs. 83.6%, $P=0.31$). While the proportion of vaccinated cases aged ≥ 4 years from each site was similar (91%–92%), the proportion of cases aged ≥ 4 years who were 2-dose recipients was slightly lower in AV than Philadelphia (41.1% vs. 59.5%, $P=0.08$).

Among clinically-diagnosed cases ≥ 4 years of age, rash severity and characteristics differed significantly by vaccination status with the majority of breakthrough cases reporting mild and mostly maculopapular rashes while most unvaccinated cases had 50–500 lesions that were mostly vesicular (Table 2). There was no severe varicella among 2-dose cases. Only two cases had >500 lesions; both were otherwise healthy adolescents, of whom, one was a 1-dose recipient and the other unvaccinated. None of the cases were hospitalized due to varicella or developed complications of varicella. Among breakthrough cases aged ≥ 4 years,

2-dose cases were more likely to have rashes that resolved in <1 week ($P=0.01$) and were less likely to have vesicular rashes ($P=0.01$) than 1-dose cases. Presence and duration of fever did not differ significantly between breakthrough and unvaccinated cases.

Varicella Vaccine Effectiveness

Among all unvaccinated and 1-dose participants, the effectiveness of 1-dose of varicella vaccine compared with no vaccine was 75.6% [95% confidence interval (CI): 38.7–90.3%] against all clinically-diagnosed varicella and 78.1% (95% CI: 12.7–94.5%) against moderate/severe disease (Table 3). The effectiveness of 2 doses of varicella vaccine compared to no vaccine among subjects aged 4 years was 93.6% (95% CI: 75.6–98.3%) against all clinically-diagnosed varicella and 97.9% (95% CI: 83.0–99.7%) against moderate/severe varicella. The incremental effectiveness of 2-dose varicella vaccination compared with 1-dose among participants 4 years of age was 87.5% (95% CI: 74.9–93.7%) in preventing any clinically-diagnosed varicella and 94.1% (95% CI: 72.4–98.8%) in preventing moderate/severe clinically-diagnosed disease.

VE estimates were higher but not significantly in AV than Philadelphia. Among subjects aged 4 years from AV, 2-dose VE and incremental VE against any clinically-diagnosed varicella were 98.4% and 92.4%, respectively. In Philadelphia, 2-dose VE and incremental VE among subjects 4 years old were 92.7% and 79.8%, respectively. Two-dose VE estimates did not differ significantly between sites ($P=0.20$); however, the small number of unvaccinated cases (5) and controls (6) may have led to unstable VE estimates by site.

Among the 26 laboratory-confirmed cases aged 4 years and their matched controls, 2-dose varicella VE was 95.9% (95% CI: 23.2–99.8%), and incremental VE was 97.3% (95% CI: 88.9–100%). Because data were sparse, we could not assess effectiveness of 1-dose of varicella vaccine against laboratory-confirmed varicella.

Risk Factors for Breakthrough Varicella among 2-dose Varicella Vaccine Recipients

Among 2-dose varicella vaccine recipients, there was no association between time since receiving dose 2 and breakthrough varicella ($P=0.17$, Table 4). However, those who received the second dose after 6 years of age were 60% less likely to have breakthrough varicella than those who had received the second dose at an earlier age ($P=0.009$). A longer time interval between receiving 1- and 2-dose varicella vaccine (>5 vs. 5 years) was associated with lower odds of developing breakthrough varicella (OR=0.5, $P=0.03$, Table 4). Subjects receiving dose 2 after 6 years of age were older than those receiving the second dose varicella vaccine earlier (12.7 vs. 7.0 years, $P<0.001$) as were subjects with a time interval between 1- and 2-dose varicella vaccine > 5 years compare with those having a shorter interval between doses (13.0 vs. 7.4 years, $P<0.001$).

Discussion

During the first 5 years following implementation of 2-dose varicella vaccination program, we found that two doses conferred significantly improved protection against varicella disease from community transmission among school-aged children compared with the 1-dose regimen. By 2010, AV and West Philadelphia reported >60% 2-dose varicella

vaccination coverage among 5-year old children, and 67% to 78% reductions in overall varicella incidence since 2006.¹⁵ Our study provides more direct evidence on the protective effect of a 2-dose regimen of varicella vaccine for children. Incremental effectiveness of the 2-dose varicella vaccination regimen among all subjects aged 4 years was 88%–97% against all forms of disease and also highly protective against moderate/severe varicella (94%). The reduction in community circulation of VZV as a result of high 2-dose coverage will also protect children who are immunocompromised and not eligible for varicella vaccination. Additional benefits of routine childhood varicella vaccination may include reduced risk of herpes zoster among vaccinated children.²⁹

In 2006, concerns about the effectiveness of the 2-dose regimen were raised following a varicella outbreak in an Arkansas elementary school with 97% 1-dose varicella vaccination coverage and 41% 2-dose coverage.³⁰ Consistent with our findings, incremental effectiveness estimates from all but one subsequent outbreak investigations and epidemiologic studies in the US have been much higher (>90% vs. 28% from Arkansas outbreak).^{18, 20, 31, 32} Incremental effectiveness estimates from school varicella outbreak surveillance in Indiana and West Virginia during 2009-2010 were 86% and 64%, respectively.^{18, 32} Among approximately 2,800 patients who were recruited into a prospective cohort study in 1995 at 2-years of age and received a second dose through catch-up vaccination, there were no cases of breakthrough varicella observed through 2009.³¹ Similarly, no 2-dose breakthrough varicella cases were identified in a community-based case-control study conducted by Shapiro et al. between 2006 and 2010.²⁰

Given the excellent protection provided by the 2-dose regimen in preventing moderate and severe disease, it is not surprising that the majority of 2-dose breakthrough cases (69%) had mild rashes with <50 lesions and none had severe varicella. These findings were consistent with 2-dose era active surveillance data and other epidemiologic studies.^{15, 18, 20, 31} No cases in our study were hospitalized or fatal. Likewise, further declines in varicella-related hospitalizations since implementation of the 2-dose varicella vaccination era have also been documented in the literature.^{15, 33} Although there was no difference in rash severity observed between 1- and 2-breakthrough cases, average illness duration for 2-dose breakthrough cases was slightly shorter than 1-dose cases and fewer 2-dose cases developed mostly vesicular rashes. The shorter duration of mild breakthrough illness among 2-dose recipients may add to the cost savings from use of this regimen and infectiousness may be lowered given the lower proportion of vesicular rashes among 2-dose breakthrough cases.

In our study and as reported by others,^{1, 18, 34} breakthrough varicella generally has a modified appearance with few or no vesicular lesions, making it challenging to diagnose clinically. PCR testing of lesion specimens to detect VZV is highly sensitive and specific.³⁵ However, as demonstrated during the investigation of a suspected varicella outbreak in a Texas School District in 2011, the utility of VZV-specific PCR testing can be limited when only macular lesions are present or lesion specimens are not collected early in the course of illness. In the absence of better laboratory tools, clinical and epidemiologic data will remain necessary to support the confirmation of varicella disease.³⁶ In the Texas outbreak, the incremental effectiveness of 2-dose varicella vaccination against any form of clinically-diagnosed varicella varied widely across the two involved schools (21% and 72%).³⁶ We

therefore chose to examine 2-dose varicella VE using 2 different case definitions for breakthrough varicella--one based on clinical and epidemiologic criteria and the other using laboratory confirmation alone. Both definitions produced similar estimates for 1-dose and 2-dose varicella VE when unvaccinated individuals were used as the comparison group. Although incremental effectiveness against laboratory-confirmed disease was slightly higher compared with the incremental effectiveness against clinically-diagnosed disease (97% vs. 88%), both estimates demonstrate that the 2-dose varicella vaccine regimen is highly effective in preventing varicella due to sporadic VZV circulation in the community.

Data on risk factors for 2-dose breakthrough varicella are limited. Similar to Thomas et al.,¹⁸ we did not find a significant association between time since 2-dose vaccination and the development of breakthrough varicella; however, in both studies, findings may have been impacted by the low number of varicella cases among 2-dose recipients. We were surprised that those who were older at time of 2-dose varicella vaccination or had >5 years between dose 1 and dose 2 had lower likelihood of breakthrough varicella. These findings may reflect a lower risk of VZV exposure or shorter exposure durations among older subjects in middle school and high school, since they are less likely to spend several hours with the same class of students throughout the school day.

Our findings are subject to the following limitations. Given high 1-dose varicella vaccine coverage among children 4 years of age and older¹⁵, very few unvaccinated subjects were identified, which resulted in wide confidence intervals for our estimates of varicella VE. Similarly, the small number of laboratory-confirmed 2-dose breakthrough varicella cases limited our ability to identify risk factors for or describe the characteristics of breakthrough disease in 2-dose vaccinees. Lastly, it should be noted that although we used the best available sources of case and control subjects for our study, ascertainment of mild varicella cases was likely incomplete. The data source used to identify controls in the Antelope Valley area only represented 30% of the source population, and the response rate among potential controls selected from the immunization registry was low in Philadelphia due to incomplete or outdated contact information. Despite these potential limitations, the distributions of demographic characteristics (i.e., sex, race, and ethnicity) among control subjects were similar to population estimates for residents under 18 years of age in each site. In AV, 2-dose varicella vaccination coverage was moderately high (84%) among kindergarten students during the 2009–2010 school year and 98%–99% among Kaiser members aged 5 to 6 years in 2010.¹⁵ The use of Kaiser members only as controls likely did not impact 2-dose varicella VE, but may have resulted in slightly higher incremental effectiveness estimates.

With improved protection provided by the 2-dose varicella vaccination compared with the 1-dose regimen as demonstrated in our study and others, it will be important to expand school immunization requirements to include 2-dose varicella vaccination. By 2012, 36 states had a 2-dose varicella vaccination elementary school entry requirement, and 2-dose varicella vaccine coverage among 7-year olds in 6 sentinel sites had reached moderate to high levels (79.9%–92.0%).³⁷ Catch-up varicella vaccination will be particularly important for 1-dose vaccinees at increased risk for exposure to persons with varicella or herpes zoster (i.e., international travelers, healthcare workers). Continued monitoring of 2-dose varicella VE is also warranted, in order to ensure protection is sustained over time.

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References

1. Chaves S, Zhang J, Civen R, et al. Varicella disease among vaccinated persons: clinical and epidemiologic characteristics, 1997-2005. *J Infect Dis.* 2008; 197(Suppl 2):S127–S131. [PubMed: 18419385]
2. Guris D, Jumaan A, Mascola L, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995-2005. *J Infect Dis.* 2008; 197(Suppl 2):S71–S75. [PubMed: 18419413]
3. Lopez A, Zhang J, Brown C, Bialek S. Varicella-related hospitalizations in the United States, 2000-2006: the 1-dose varicella vaccination era. *Pediatrics.* 2011; 127(2):238–245. [PubMed: 21199857]
4. Marin M, Zhang J, Seward J. Near elimination of varicella deaths in the US after implementation of the vaccination program. *Pediatrics.* 2011; 128 (2):214–220. [PubMed: 21788222]
5. Centers for Disease Control and Prevention (CDC). Outbreak of varicella among vaccinated children--Michigan, 2003. *MMWR Morb Mortal Wkly Rep.* 2004; 53(18):389–392. [PubMed: 15138400]
6. Centers for Disease Control and Prevention (CDC). Varicella outbreak among vaccinated children--Nebraska, 2004. *MMWR Morb Mortal Wkly Rep.* 2006; 55(27):749–752. [PubMed: 16837895]
7. Lopez A, Guris D, Zimmerman L, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose. *Pediatrics.* 2006; 117(6):e1070–1077. [PubMed: 16740809]
8. Nguyen M, Perella D, Watson B, Marin M, Renwick M, Spain CV. Incremental effectiveness of second dose varicella vaccination for outbreak control at an elementary school in Philadelphia, Pennsylvania, 2006. *Pediatr Infect Dis J.* 2010; 29(8):685–689. [PubMed: 20354463]
9. Parker AA, Reynolds MA, Leung J, et al. Challenges to implementing second-dose varicella vaccination during an outbreak in the absence of a routine 2-dose vaccination requirement — Maine, 2006. *J Infect Dis.* 2008; 197(Suppl 2):S101–S107. [PubMed: 18419381]
10. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics.* 2004; 113(3):455–459. [PubMed: 14993534]
11. Civen R, Lopez AS, Zhang J, et al. Varicella outbreak epidemiology in an active surveillance site, 1995-2005. *J Infect Dis.* 2008; 197(Suppl 2):S114–S119. [PubMed: 18419383]
12. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J.* 2004; 23(2):132–137. [PubMed: 14872179]
13. Marin M, Güris D, Chaves S, Schmid S, Seward J. Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2007; 56(RR-4):1–40. [PubMed: 17585291]
14. Centers for Disease Control and Prevention. Evolution of varicella surveillance--selected states, 2000-2010. *MMWR Morb Mortal Wkly Rep.* 2012; 61(32):609–612. [PubMed: 22895384]
15. Bialek S, Perella D, Zhang J, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. *Pediatrics.* 2013; 132(5):e1134–1140.

16. Daly E, Anderson L, Dreisig J, Dionne-Odom J. Decrease in varicella incidence after implementation of the 2-dose recommendation for varicella vaccine in New Hampshire. *Pediatr Infect Dis J*. 2013; 32(9):981–983. [PubMed: 23538516]
17. Kattan J, Sosa L, Bohnwagner H, Hadler J. Impact of 2-dose vaccination on varicella epidemiology: Connecticut--2005-2008. *J Infect Dis*. 2011; 203(4):509–512. [PubMed: 21199882]
18. Thomas C, Shwe T, Bixler D, et al. Two-dose varicella vaccine effectiveness and rash severity in outbreaks of varicella among public school students. *Pediatr Infect Dis J*. 2014; 33(11):1164–1168. [PubMed: 24911894]
19. Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. *Epidemiol Rev*. 1996; 18(2):99–117. [PubMed: 9021306]
20. Shapiro E, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011; 203(3):312–315. [PubMed: 21208922]
21. 2009 Population Estimates: Walter R. McDonald & Associates, Inc. (WRMA) for Urban Research, Los Angeles County ISD. 2010 Apr 26.
22. 2010 Population Estimates. Philadelphia, PA: Claritas Inc.; 2010.
23. Seward J, Watson B, Peterson C, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. *JAMA*. 2002; 287(5):606–611. [PubMed: 11829699]
24. Leung J, Harpaz R, Baughman A, et al. Evaluation of laboratory methods for diagnosis of varicella. *J Infect Dis*. 2010; 202 (10):1486–1491. [PubMed: 20929354]
25. Niccolai L, Ogden L, Muehlenbein C, Dziura J, Vázquez M, Shapiro E. Methodological issues in design and analysis of a matched case-control study of a vaccine's effectiveness. *J Clin Epidemiol*. 2007; 60(11):1127–1131. [PubMed: 17938054]
26. Loparev V, McCaustland K, Holloway B, Krause P, Takayama M, Schmid D. Rapid genotyping of varicella-zoster virus vaccine and wild-type strains with fluorophore-labeled hybridization probes. *J Clin Microbiol*. 2000; 38(12):4315–4319. [PubMed: 11101557]
27. Loparev VN, Argaw T, Krause PR, Takayana M, Schmid DS. Improved identification and differentiation of varicella-zoster virus (VZV) wild-type strains and an attenuated varicella vaccine strain using a VZV open reading frame 62-based PCR. *J Clin Microbiol*. 2000; 38(9):3156–3160. [PubMed: 10970349]
28. [Accessed Sept 30, 2014] Estimated vaccination coverage with 1+varicella among children 19-35 months of age by state and immunization action plan area. National Immunization Survey. <http://www.cdc.gov/vaccines/imz-managers/coverage/nis/child/index.html>
29. Weinmann S, Chun C, Schmid D, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. *J Infect Dis*. 2013; 208(11):1859–1868. [PubMed: 23922376]
30. Gould P, Leung J, Scott C, et al. An outbreak of varicella in elementary school children with two-dose varicella vaccine recipients--Arkansas, 2006. *Pediatr Infect Dis J*. 2009; 28(8):678–681. [PubMed: 19593254]
31. Baxter R, Ray P, Tran T, et al. Long-term effectiveness of varicella vaccine: a 14-year, prospective cohort study. *Pediatrics*. 2013; 131(5):e1389–1396. [PubMed: 23545380]
32. Hazen, D.; Baker, L. 45th National Immunization Conference. Washington, DC; 2011. Vaccine efficacy estimates during institutional-based outbreaks, Indiana 2010.
33. Baxter R, Tran T, Ray P, et al. Impact of vaccination on the epidemiology of varicella: 1995-2009. *Pediatrics*. 2014; 134(1):24–30. [PubMed: 24913796]
34. Watson B, Piercy S, Plotkin S, Starr S. Modified chickenpox in children immunized with the Oka/Merck varicella vaccine. *Pediatrics*. 1993; 91(1):17–22. [PubMed: 8416499]
35. Weinmann S, Chun C, Mullooly J, et al. Laboratory diagnosis and characteristics of breakthrough varicella in children. *J Infect Dis*. 2008; 197 (Suppl 2):S132–138. [PubMed: 18419386]
36. Mahamud A, Wiseman R, Grytdal S, et al. Challenges in confirming a varicella outbreak in the two-dose vaccine era. *Vaccine*. 2012; 30(48):6935–6939. [PubMed: 22884663]
37. Lopez A, Cardemil C, Pabst L, Cullen K, Leung J, Bialek S. Two-dose varicella vaccination coverage among children aged 7 years--six sentinel sites, United States, 2006-2012. *MMWR Morb Mortal Wkly Rep*. 2014; 63(8):174–177. [PubMed: 24572613]

Abbreviations

AV	Antelope Valley
CDC	Centers for Disease Control and Prevention
CI	Confidence Intervals
DFA	Direct Fluorescent Antibody
OR	Odds Ratio
PCR	Polymerase Chain Reaction
RR	Relative Risk
US	United States
VE	Vaccine Effectiveness
VASP	Varicella Active Surveillance Project
VZV	Varicella Zoster Virus

What's Known on This Subject

Declines in varicella incidence since 2006 and vaccine effectiveness estimates from outbreak investigations indicate that 2-dose varicella vaccination provides improved protection against varicella. Limited data exist on the performance of 2-dose varicella vaccination in preventing community transmission outside outbreak settings.

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What This Study Adds

Two-dose varicella vaccination improved protection against community transmission of varicella among school-aged children in two geographically and demographically diverse areas compared with 1-dose vaccination. Our study provides more direct evidence on the protective effect of a 2-dose varicella vaccine regimen.

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Table 1
Demographic and vaccination characteristics of clinically-diagnosed varicella case and control subjects from Philadelphia, Pennsylvania and Antelope Valley, California, 2009-2011^a

	Aged 1-3 years		Aged 4 years		p value
	Cases (n=32) n (%)	Controls (n=103) n (%)	Cases (n=93) n (%)	Controls (n=305) n (%)	
Median age	2.1 (1.0-3.9)	2.2 (1.1-3.9)	9.5 (4.0-18.9)	9.3 (4.1-18.9)	0.58
Surveillance site					0.48
Antelope Valley, CA	9 (28.1)	33 (32.0)	56 (60.2)	171 (56.1)	
Philadelphia, PA	23 (71.9)	70 (68.0)	37 (39.8)	134 (43.9)	
Vaccination status					<0.001
Unvaccinated	9 (28.1)	4 (3.9)	8 (8.6)	8 (2.6)	
1-dose	22 (68.8)	98 (95.1)	40 (43.0)	50 (16.4)	
2-dose	1 (3.1)	1 (1.0)	45 (48.4)	247 (81.0)	
Race					0.43
White	12 (37.5)	46 (44.7)	59 (63.4)	171 (56.1)	
African American	9 (28.1)	40 (38.8)	25 (26.9)	95 (31.1)	
Other	11 (34.4)	17 (16.5)	9 (9.7)	39 (12.8)	
Ethnicity					0.20
Hispanic	14 (45.2)	33 (32.0)	40 (43.0)	109 (35.7)	
Non-Hispanic	17 (54.8)	70 (68.0)	53 (57.0)	196 (64.3)	
Sex					0.87
Male	16 (50.0)	60 (58.3)	47 (50.5)	157 (51.5)	
Female	16 (50.0)	43 (41.7)	46 (49.5)	148 (48.5)	
Born in US					1.00
Yes	31 (100.0)	103 (100.0)	91 (97.8)	296 (97.0)	
No	0 (0.0)	0 (0.0)	2 (2.2)	9 (3.0)	
Immunosuppressing condition					1.00
Yes	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	
No	32 (100.0)	103 (100.0)	92 (100.0)	303 (99.3)	
Asthma					0.26
Yes	6 (18.8)	19 (18.6)	19 (20.4)	47 (15.5)	

	Aged 1–3 years			Aged 4 years		
	Cases (n= 32) n (%)	Controls (n=103) n (%)	p value	Cases (n=93) n (%)	Controls (n=305) n (%)	p value
Attend daycare						
No	26 (81.3)	83 (81.4)	0.62	74 (79.6)	257 (84.5)	0.03
Yes	13 (40.6)	47 (45.6)		6 (4.5)	47 (15.4)	
No	19 (59.4)	56 (54.4)		87 (93.5)	258 (84.6)	

^aMissing and unknown responses excluded. Valid percentages presented.

Table 2

Varicella disease severity by vaccination status for clinically-diagnosed varicella case-subjects aged 4 years in Philadelphia, Pennsylvania and Antelope Valley, California, 2009-2011^a

	Varicella Vaccination status				Overall p value	2- vs. 1-dose p value
	Unvaccinated (n=8) n (%)	1-dose (n=40) n (%)	2-dose (n=45) n (%)			
Rash severity ^b					0.01	0.81
Mild (<50 lesions)	1 (12.5)	26 (65.0)	31 (68.9)			
Moderate/severe (50–500 lesions)	6 (75.0)	13 (32.5)	14 (31.1)			
Severe (>500 lesions)	1 (12.5)	1 (2.5)	0 (0.0)		0.36	0.11
Fever						
Yes	2 (25.0)	16 (41.0)	11 (24.4)			
No	6 (75.0)	23 (59.0)	34 (75.6)		<0.001	0.01
Most lesions are vesicular						
Yes	3 (60.0)	9 (23.1)	2 (4.5)			
No	2 (40.0)	30 (76.9)	42 (95.5)		0.86	0.57
Days of fever: median (IQR)	2 (0–3)	1.5 (1–2.5)	2 (1–2)		0.01	0.01
Rash duration						
<1 week (<7 days)	2 (25.0)	10 (25.6)	24 (53.3)			
1 week (7 days)	6 (75.0)	29 (74.4)	21 (46.7)		0.17	0.89
School missed						
1 school week (5 days)	2 (33.3)	3 (8.6)	3 (7.7)			
>1 school week (>5 days)	4 (66.7)	32 (91.4)	36 (92.3)			

IQR: interquartile range

^aMissing and unknown responses excluded. Valid percentages presented.

^bRash severity was defined as follows: 1) <50 or the total number of spots could be counted in 30 seconds; 2) 50–249 or you could place the child's hand between the spots without touching a spot; 3) 250–500 or you could NOT place a child's hand between the spots without touching a spot; or 4) >500 spots or the spots were so close you could hardly see normal skin.

Table 3
Varicella vaccine effectiveness against all varicella and moderate/severe varicella in Philadelphia, Pennsylvania and Antelope Valley, California, 2009-2011

	Unvaccinated and 1-dose Participants Regardless of Age				Participants 4 years ^a	
	Cases	Controls	VE (95% CI)	Cases	Controls	VE (95% CI)
VE against any clinically-diagnosed varicella	n=79	n=160		n=93	n=305	
Unvaccinated	17 (21.5)	12 (7.5)	Reference	8 (8.6)	8 (2.6)	Reference
1-dose	62 (78.5)	148 (92.5)	75.6 (38.7–90.3)	40 (43.0)	50 (16.4)	49.1 (0–85.7)
2-dose	--	--	--	45 (48.4)	247 (81.0)	93.6 (75.6–98.3)
Incremental VE (2-dose vs. 1-dose)	--	--	--			87.5 (74.9–93.7)
VE against Moderate/severe clinically-diagnosed varicella (50 lesions)	n=28	n=49		n=35	n=119	
Unvaccinated	10 (35.7)	6 (12.2)	Reference	7 (20.0)	5 (4.2)	
1-dose	18 (64.3)	43 (87.8)	78.1 (12.7–94.5)	14 (40.0)	20 (16.8)	64.2 (0–93.1)
2-dose	--	--	--	14 (40.0)	94 (79.0)	97.9 (83.0–99.7)
Incremental VE (2-dose vs. 1-dose)	--	--	--			94.1 (72.4–98.8)

VE: vaccine effectiveness

^a Adjusted for ethnicity given significant differences between cases and controls aged 4 years in Philadelphia. Although daycare attendance differed among cases and controls aged 4 years, only a small proportion of each group attended daycare (<16%) and adding this variable to the model produced VE estimates similar to those presented.

Table 4
Risk factors associated with breakthrough varicella among 2-dose varicella vaccinees aged 4 years

	Cases, n (%) (n=45)	Controls, n (%) (n=247)	OR (95% CI)	P values
Time since 2-dose varicella vaccination				
<1 years	6 (13.3)	46 (18.6)	Reference	
1-3 years	19 (42.2)	118 (47.8)	1.2 (0.5–3.3)	0.67
>3 years	20 (44.4)	83 (33.6)	1.8 (0.7–4.9)	0.22
Age at receiving 2-dose varicella vaccine				
6 years	33 (73.3)	128 (51.8)	Reference	
>6 years	12 (26.7)	119 (48.2)	0.4 (0.2–0.8)	0.009
Time interval between receiving 1- and 2- dose varicella vaccine				
5 years	34 (75.6)	144 (58.3)	Reference	
>5 years	11 (24.4)	103 (41.7)	0.5 (0.2–0.9)	0.03