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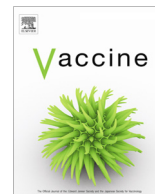
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# Varicella seroepidemiology in United States air force recruits: A retrospective cohort study comparing immunogenicity of varicella vaccination and natural infection



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## ABSTRACT

**Background/Objectives:** Infection with varicella zoster virus (VZV) produces lifelong immunity, but duration of post-vaccination immunity has not been established. The purpose of this study is to determine if a difference exists in the long-term seropositivity of anti-VZV antibodies in a cohort of young adults who were vaccinated against varicella as compared to a similar cohort with a history of chickenpox disease, and to determine which variables best predict waning seropositivity following varicella vaccination.

**Methods:** This retrospective cohort study captures immunization and serology data from approximately 10,000 recruits who entered basic military training between January 1, 2008, and December 31, 2015, and who have childhood immunization records in the Air Force Aeromedical Services Information Management System. Varicella vaccine immunogenicity was determined relative to the immunogenicity of chickenpox disease, as measured by multiplex flow immunoassay. Among vaccine recipients, waning seroimmunity was modeled and adjusted for several important covariates.

**Results:** Basic military trainees who received varicella vaccine in childhood were 24% less likely to be seropositive to VZV than trainees who were exempt from vaccine due to a history of chickenpox disease. There was no significant difference in seropositivity between male and female trainees. The odds of a vaccinated trainee being seropositive to VZV decreased by 8% with each year elapsed since vaccination. Seroprevalence declined below estimated herd immunity thresholds in vaccinated trainees born after 1994, and in the cohort as a whole for trainees born after 1995.

**Conclusion:** Despite prior vaccination, seroimmunity in a large cohort of young adults unexposed to wild-type VZV failed to meet the estimated threshold for herd immunity. If vaccination in accordance with the current US VZV vaccination schedule is inadequate to maintain herd immunity, young adults not previously exposed to wild-type VZV may be at increased risk for varicella outbreaks.

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## 1. Background

Varicella vaccine was first licensed in the United States in 1995, and the Advisory Committee on Immunization Practices (ACIP) published its initial recommendations in 1996, advising one vaccine dose to susceptible children under 12 years of age [1]. The incidence of varicella decreased by 90% over the next 10 years, from approximately 4 million yearly cases seen before the vaccine was available [2,3]. However, varicella outbreaks continued to occur in populations of highly-vaccinated schoolchildren, and ACIP recommended a second dose of varicella vaccine in 2006 [4]. By 2012, two-dose varicella vaccination coverage levels approached

the two-dose coverage levels of 82–94% seen for measles, mumps, and rubella (MMR), and wider adoption of two-dose varicella vaccination requirements for school entry have been instrumental in progression toward the Healthy People 2020 (HP2020) target of 95% of kindergarten children receiving two doses of varicella vaccine [5]. Despite this progress, estimated 2015 two-dose varicella vaccination coverage of 84.6% for adolescents aged 13–15 falls below the HP2020 target of 90% [6].

As the increased utilization of the varicella vaccine leads to reductions in circulating wild-type varicella-zoster virus (VZV), inadequately immunized children may acquire infection at an older age when they are at increased risk for severe infection [7]. This can be prevented by targeted vaccination of susceptible adolescents. ACIP criteria for evidence of immunity to varicella include documentation of age-appropriate vaccination, laboratory

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evidence of immunity, birth in the United States before 1980, or verification of a history of varicella disease (i.e., chickenpox) by a healthcare provider [4]. As verified by serologic surveys, confirmation of disease through either medical record review or patient/parent recall of disease has high sensitivity and positive predictive value in unvaccinated adolescents [8,9]. Seroconversion estimates following varicella vaccination are approximately 60–70% after one dose and 88% after two doses [9,10]. Despite a randomized controlled trial demonstrating one-dose vaccine efficacy of 94% and two-dose efficacy of 98% after 10 years [11], varicella outbreaks in immunized children with attack rates of 10–13% suggest varicella vaccine effectiveness of 82–85% among one-dose recipients and 86–88% among two-dose recipients [12–14]. In a nationwide retrospective study in Taiwan, annual breakthrough infections of chickenpox of up to 2% were seen among persons vaccinated against varicella [15]. Recent varicella outbreaks in the United States highlight the need for complete immunization against varicella [16], and more robust reporting data are needed to better monitor the outcomes of varicella vaccination programs [17].

Infection with VZV produces lifelong immunity to chickenpox through T-cell proliferative responses and B-cell induction of anti-VZV antibodies, whereas vaccination may induce less robust levels of neutralizing antibodies [4,18]. The true duration of immunity after vaccination has not been established, and published studies describing long-term seroprevalence of anti-VZV antibodies among vaccinated persons are limited by small sample sizes [9]. While several studies have characterized seroprevalence of anti-VZV antibodies among various populations, there are no large studies characterizing long-term seroprevalence in a cohort with documented vaccine receipt compared to a cohort with documented history of chickenpox. In the context of evolving ACIP recommendations for varicella vaccination, this study analyzes a population of young adults entering military service, comparing those who acquired wild-type VZV infection in childhood to those who received varicella vaccination in childhood. With estimated varicella vaccine effectiveness and immunogenicity potentially lower than that needed to maintain herd immunity [19,20], young adult subpopulations unexposed to wild-type VZV may be at increased risk for varicella outbreaks. Negative outcomes due to chickenpox in young adults are estimated to be 2.2 times worse than expected in the pre-vaccine era [21] and the risk of death is 25 times greater compared to children aged 1–4 years [22]. Even in the absence of serologic evidence of immunity, vaccination typically attenuates such negative outcomes [4].

The purpose of this study is to measure the long-term seroprevalence of anti-VZV antibodies in a cohort of young adults who were vaccinated against varicella in comparison to those with a childhood history of chickenpox, and to determine risk factors for waning seropositivity post-vaccination. The results of this study may help characterize the effectiveness of current varicella vaccination policy and may assist in the identification of non-immune subpopulations that may be at increased risk for varicella outbreaks.

## 2. Methods

### 2.1. Overview

A retrospective cohort study was conducted to compare the long-term seroprevalence of anti-VZV antibodies in a cohort with documented varicella vaccination to that of a cohort with a history of chickenpox disease. Subgroup analyses were performed to determine if sex, histo-blood group antigen (HBGA) expression, or birth cohort modified the effect of this statistical relationship.

For the cohort of individuals who received varicella vaccination without a history of chickenpox disease, waning seroimmunity was modeled based on the time elapsed since the last vaccine dose and other covariates which may play roles in vaccine immunogenicity. This model was used to estimate the duration of protective immunity conferred by the varicella vaccine using estimated thresholds required to maintain herd immunity.

### 2.2. Study population and data source

Data for this study were supplied by the Health Care Informatics Division of the Air Force Medical Support Agency. Data were derived from recruits who entered US Air Force basic military training between January 1, 2008, and December 31, 2015, and who had documented childhood immunization records in the US Air Force's Aeromedical Services Information Management System (ASIMS). ASIMS is the electronic repository for immunization data for Military Health System beneficiaries receiving immunizations at US Air Force military treatment facilities since 1997. Individuals were excluded from analysis if vaccination status or vaccine exemption status could not be ascertained, such as for those who neither reported an exemption nor received a varicella vaccination as recorded in ASIMS. Qualitative titer results, vaccination history, and selected demographic and clinical data were obtained from ASIMS. Identifiable information was removed from the datasets prior to being released to the investigators. This study protocol was reviewed and approved by the Office of Research at the Uniformed Services University.

### 2.3. Primary exposure

The primary exposure variables were either medical exemption to the varicella vaccine due to a reported history of chickenpox disease or receipt of at least one varicella vaccine dose in the absence of a medical exemption. Subjects with both reported history of chickenpox disease and vaccine administration were classified as having a history of disease, resulting in disease and vaccine-only cohorts.

### 2.4. Primary outcome

The primary outcome of interest was the documented presence or absence of detectable anti-VZV antibodies, as measured within three days of starting basic military training. Serum specimens for all subjects were processed with the BioRad BioPlex 2200 MMRV IgG multiplex flow immunoassay, which has a sensitivity of 92.2% and specificity of 100% for the varicella component when compared to traditional testing via enzyme immunoassay [23], and overall agreement of 96% when compared to anticomplement immunofluorescence tests [24]. Subjects with negative titers received two varicella vaccine doses in accordance with standard immunization practices. Outcomes were extrapolated from ASIMS by either the presence of a vaccine exemption due to a positive titer for a seropositive subject or the subsequent administration of two varicella vaccine doses for a seronegative subject. Subjects for whom the outcome could not be ascertained were censored from analysis.

### 2.5. Potential confounders and effect modifiers

Previous studies have reported higher post-vaccination seroprevalence of anti-measles, mumps, rubella, and influenza antibodies among women compared to men [25,26], suggesting sex may modify the effect of seropositivity following vaccine administration. Additionally, HBGA expression has been hypothesized to play a role in viral and vaccine immunogenicity [27,28]. Age may

also confound the relationship between exposure status and serologic immunity in the setting of variable vaccine availability, evolving vaccination recommendations, and decreasing exposure to wild-type VZV since the introduction of the varicella vaccine. Therefore, data on subjects' sex, HBGA expression, and year of birth were included in the analysis. Furthermore, data on the number of varicella vaccines received and the time elapsed between last varicella vaccine dose and serologic outcome determination were included in the model of waning immunity following varicella vaccine administration.

## 2.6. Statistical analysis

Descriptive epidemiological information was determined by stratification of the two exposure types. Continuous variables were analyzed using unpaired two sample Student's *t*-tests, and categorical variables were analyzed using Pearson's chi-square tests.

Risk ratios were computed to compare the long-term seroprevalence following vaccine administration to that of natural infection, and chi-square tests or Fischer exact tests with 5% two-sided significance levels were used to determine statistical significance, as appropriate for the covariate pattern. Effect modification was evaluated through stratification by sex, HBGA expression, and birth cohort. The Cochran-Mantel-Haenszel test was used to evaluate the presence of effect modification, and stratified results were presented where there was heterogeneity of risk ratios across strata.

For those in the vaccine exposure group, logistic regression was used to evaluate long-term seroprevalence based on the time elapsed since the last varicella vaccine dose. The dependent variable for the logistic regression model was varicella seropositivity. Independent variables included time elapsed since last vaccination dose, year of birth, sex, HBGA expression, and number of varicella vaccines received. Where the linearity assumption was reasonably met, covariates were modeled as continuous variables. Multiplex flow immunoassay-adjusted herd immunity thresholds were derived using the methods described by Plans [29] for determining enzyme immunoassay-based herd immunity thresholds, using the following equation:

$$p_c = I_c S_e + [(1 - I_c)(1 - S_p)]$$

For this equation,  $p_c$  is the critical prevalence for herd immunity,  $I_c$  is the accepted herd immunity threshold,  $S_e$  is the sensitivity of the test, and  $S_p$  is the specificity of the test. A varicella transmissibility factor of 7.32 was used to compute the accepted

herd immunity threshold [30]. Duration of protective immunity following vaccine administration was estimated by comparing model-predicted values to these threshold estimates.

For all statistical tests used, two-tailed statistical significance was evaluated using an alpha of 0.05. Statistical analyses were performed using STATA/IC v13.1 for Windows.

## 3. Results

### 3.1. Descriptive epidemiology

Of the 15,210 recruits with a childhood immunization record in ASIMS, varicella exposure status was ascertained for 10,174 recruits (Table 1). A slight majority (52.3%) of included recruits had a documented history of chickenpox, with the remainder having received at least one varicella vaccination in childhood. The mean year of birth was significantly different between these two exposure groups ( $p < 0.0001$ ), with vaccine recipients born a mean difference of three years after those with a history of chickenpox. The chickenpox and vaccine exposure groups were similar with respect to sex and HBGA expression ( $p = 0.144$  and  $p = 0.781$ , respectively), but they were significantly different when stratified by year of birth ( $p < 0.001$ ). Sensitivity analysis was performed to evaluate the effects of including subjects who had both history of chickenpox and received vaccine ( $n = 352$ , 90.9% seropositive), and all resulting descriptive statistics and measures of effect were similar when these recruits were included in the chickenpox exposure group.

### 3.2. Relative immunogenicity

Overall, 72.4% of vaccine recipients had a positive titer to VZV, compared to 95.4% of those with a history of chickenpox disease (Table 2). Among the vaccinated cohort, 46% had received only one vaccine dose, and seroprevalence was similar regardless of number of vaccine doses received ( $p = 0.0710$ ). Varicella seropositivity was significantly lower in vaccine recipients compared to those with a history of chickenpox (RR = 0.76 [95% CI: 0.75–0.77]). These findings were homogeneous when stratified by sex and HBGA expression ( $p = 0.2483$  and  $p = 0.1774$ , respectively). However, there was significant heterogeneity of relative immunogenicity when stratified by birth cohort ( $p < 0.0001$ ), with varicella vaccination being least immunogenic compared to chickenpox for the birth cohort born after 1995 (RR = 0.69 [95% CI: 0.62–0.77]). Because of this heterogeneity, results from this study should be

**Table 1**  
Comparison of demographic and clinical characteristics by exposure group.

	Chickenpox	Vaccine	Total	p-value <sup>a</sup>
Number of subjects	5323 (52.3%)	4851 (47.6%)	10,174	
Year of birth, Mean (SD)	1990 (2.9)	1993 (2.8)	1991 (3.4)	<0.001
Sex, n (%)				
Male	4009 (75.3)	3593 (74.1)	7602 (74.7)	
Female	1313 (24.7)	1258 (25.9)	2571 (25.3)	0.144
Histo-blood group antigen, n (%)				
A	1742 (37.0)	1657 (36.9)	3399 (36.9)	
B	583 (12.4)	535 (11.9)	1118 (12.2)	
AB	168 (3.6)	174 (3.9)	342 (3.7)	
O	2210 (47.0)	2127 (47.3)	4337 (47.2)	0.781
Year of birth, n (%)				
<1986	165 (3.1)	45 (1.0)	211 (2.1)	
1986–1990	2580 (48.5)	823 (17.0)	3403 (33.5)	
1991–1995	2462 (46.2)	3085 (63.6)	5547 (54.5)	
1996+	116 (2.2)	893 (18.4)	1009 (9.9)	<0.001

<sup>a</sup> Two-sample *t*-test for year of birth; chi-square test for sex, histo-blood group antigen, and year of birth strata.

**Table 2**  
Relative immunogenicity of the varicella vaccine compared to chickenpox, for the overall cohort and stratified by immunogenic variable.

	Number of subjects	(+) Titers to VZV	Risk ratio [95% CI]	p-value <sup>a</sup>
<i>Overall</i>				
Vaccine only (pooled)	4802	72.4%	0.76 [0.75–0.77]	<0.0001
1 dose	2299	71.2%	0.75 [0.73–0.77]	<0.0001
2+ doses	2505	73.5%	0.77 [0.75–0.79]	<0.0001
Chickenpox	5253	95.4%	1.0 [reference]	–
Total	10,055	84.4%	–	–
<i>Subgroup analysis</i>				
<i>Sex</i>				
Male	7521	84.1%	0.75 [0.74–0.77]	
Female	2533	85.3%	0.77 [0.75–0.80]	0.2483
<i>Histo-blood group antigen</i>				
A	3383	82.8%	0.76 [0.73–0.78]	
B	1112	84.3%	0.76 [0.72–0.81]	
AB	340	79.4%	0.67 [0.59–0.75]	
O	4321	83.9%	0.74 [0.72–0.77]	0.1774
<i>Year of birth</i>				
<1986	492	94.9%	0.84 [0.72–0.98]	
1986–1990	5687	94.1%	0.91 [0.89–0.93]	
1991–1995	7614	82.3%	0.78 [0.76–0.80]	
1996+	1236	57.6%	0.69 [0.62–0.77]	<0.0001

<sup>a</sup> Chi-square test for overall cohort, Mantel-Haenszel test for homogeneity when stratified by subgroup.

interpreted by birth cohort rather than using the aforementioned pooled estimate of relative immunogenicity.

The relative immunogenicity conferred by both varicella vaccine and chickenpox disease declines with successive birth year, although the decline is more precipitous with the vaccine only cohort (Fig. 1). Varicella seroprevalence remains at or above levels estimated to provide herd immunity among those with a history of chickenpox disease, regardless of birth year, while seroprevalence fails to achieve herd immunity thresholds for vaccine recipients born after 1993.

### 3.3. Multivariate modeling of waning immunity

Of the 4802 recruits who received the varicella vaccine in childhood, 4584 (95.4%) received the varicella vaccine in accordance with standard US practices and with at least three weeks lapsing between vaccine administration and titer measurement. These subjects were included in the logistic regression model of waning immunity following varicella vaccination. Among these vaccine recipients, seroprevalence fell below estimated levels required for herd immunity when more than four years had elapsed since the last varicella vaccine dose (Fig. 2).

The odds of a positive varicella titer decreased by 8% for each successive year that elapsed since administration of the last vaccine dose, after adjusting for year of birth, number of vaccines received, sex, and HBGA expression (adjusted OR = 0.92 [ $p < 0.001$ ]) (Table 3). The covariate-adjusted odds of a positive varicella titer decreased by 21% with each successive year of birth (adjusted OR = 0.79 [ $p < 0.001$ ]). Modeling the interaction between year of birth and time elapsed since last vaccine dose did not improve the predictive value of the model. Compared to vaccine recipients who only received one varicella vaccine dose, the unadjusted odds of a positive varicella titer increased when subjects received two (OR = 1.22 [ $p = 0.003$ ]) or three (OR = 2.92 [ $p = 0.005$ ]) vaccine doses, but this relationship did not remain statistically significant after covariate adjustment. Sex did not significantly affect varicella seropositivity in either the crude or adjusted models.

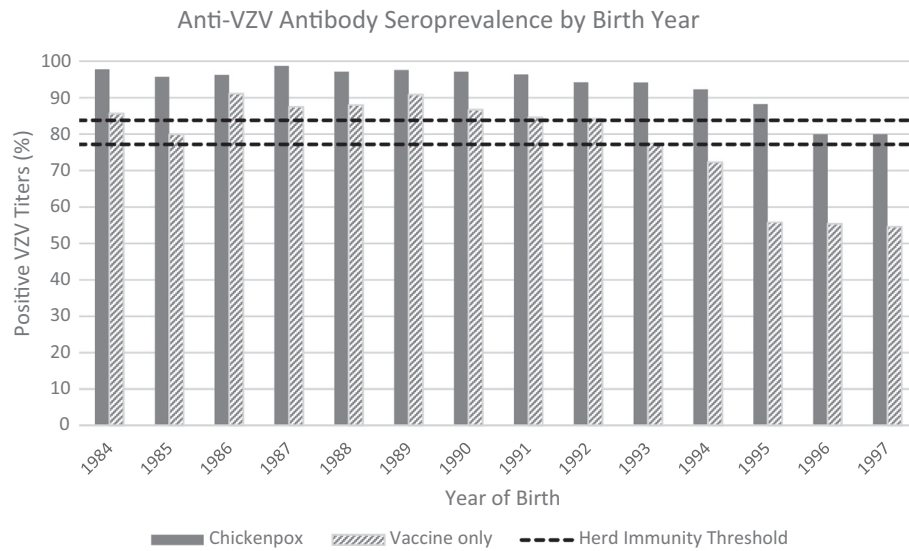
Among the vaccine recipients included in this model, an additional 284 subjects had unknown HBGA expression. Sensitivity analysis was performed to evaluate the effects of excluding

subjects with missing HBGA data, and resulting adjusted measures of effect for all variables included in the model were similar after excluding those with missing HBGA data. Subjects with type AB blood had 32% lower covariate-adjusted odds of a positive varicella titer compared to those with type A blood (adjusted OR = 0.68 [ $p = 0.033$ ]). There was no significant difference in the covariate-adjusted odds of a positive varicella titer for those with type B or type O blood compared to those with type A blood. There was no statistically significant interaction between HBGA expression and any of the other covariates included in this model.

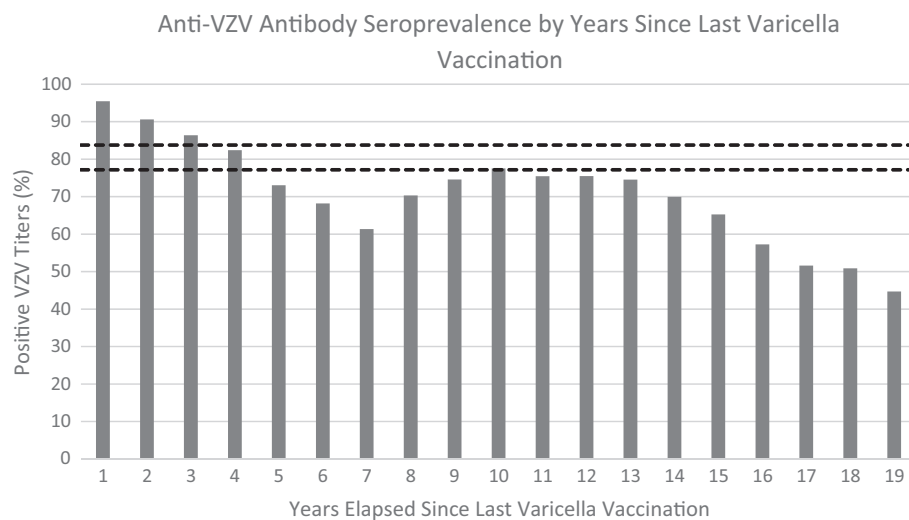
## 4. Discussion

This study demonstrates that the varicella vaccine produces shorter-lived seropositivity, as compared with natural infection, and the relative seropositivity decreases with later birth cohorts. With the declining incidence of chickenpox since the introduction of the varicella vaccine in the United States in 1995 [2,3], the decreasing seropositivity among younger birth cohorts may be due to reduced natural immunity boosting from exposure to wild-type VZV. Despite vaccination in accordance with ACIP recommendations, 15.6% of this study cohort were found to have no serologic evidence of varicella immunity. Although serostatus may underestimate true immunity among vaccinated individuals, the relationship found in this study between seropositivity and time elapsed since last varicella vaccination suggests that vaccinated populations previously unexposed to wild-type VZV may be at increased risk for varicella outbreaks. Clinical and public health personnel in these settings may benefit from access to VZV antibody assays that can reliably predict immunity secondary to chickenpox disease and varicella vaccination—assays which currently are not commercially available.

Among vaccine recipients with no history of chickenpox disease, year of birth and time elapsed since last vaccine dose are the most important predictors of varicella seropositivity. Since seroprevalence may fall below herd immunity thresholds four years after vaccination, additional varicella booster vaccinations may be required to maintain herd immunity in congregate settings, such as schools and military training sites, and for women of child-bearing age to minimize the risk of congenital varicella syndrome and neonatal transmission.



**Fig. 1.** Anti-VZV antibody seroprevalence by birth year. Dashed lines represent the estimated threshold to provide herd immunity, adjusted for the sensitivity and specificity of the multiplex flow immunoassay used to measure varicella titers.



**Fig. 2.** Anti-VZV antibody seroprevalence in vaccine recipients by years elapsed since last varicella vaccine dose, rounded to the nearest year. Dashed lines represent the estimated threshold needed to maintain herd immunity, adjusted for the sensitivity and specificity of the multiplex flow immunoassay used to measure varicella titers.

While sex has been previously reported to modify the effects of influenza vaccine immunogenicity [26], sex was not shown in this study to affect either the relative immunogenicity of the varicella vaccine or the duration of seropositivity following varicella vaccine administration. Histo-blood group antigens are thought to affect vaccine and viral immunogenicity, especially among enteric pathogens [27,28,31–33], and the relationship between HBGAs and immunogenicity to varicella vaccine has not been previously described. The significant association identified in this study may warrant further research.

**4.1. Strengths and limitations**

The most significant strengths of this study were the large cohort size permitting subgroup analyses and the database’s longitudinal nature with accurate serologic outcomes. Additionally, this study has good internal validity as the study cohort is composed of former military dependents, of similar socioeconomic status with assured access to reliable medical care. The only significant

difference between the vaccinated and disease exposure groups was their year of birth. As a condition of entry into military service, all members of this cohort are free of immunocompromising conditions at the time of serologic outcome determination. In addition, this large cohort of young adult military recruits is sufficiently diverse to be generalizable to other US populations.

This study also has several limitations. First, given the sensitivity of the immunoassay used to assess serostatus, some false negatives were likely. Outcome misclassification would be non-differential with respect to exposure status, however, thus biasing results toward the null. While herd immunity threshold estimates were adjusted for the test characteristics of the assay [29], further studies are needed to assess the longevity of anti-VZV antibodies post-vaccination using more sensitive measures of seroimmunity. Second, since dates of chickenpox disease were unknown, the dataset did not permit characterization of waning immunity following a history of disease. Third, although the study incorporated several important covariates, other variables that may influence vaccine immunogenicity (e.g., genetic factors [34,35]) were unavailable.

**Table 3**  
Multivariate logistic regression model characterizing waning immunity in varicella vaccine recipients.

	Positive VZV titer n = 3271	Negative VZV titer n = 1313	Crude OR [95% CI] <sup>a</sup>	Adjusted OR [95% CI] <sup>b</sup>
Years since last vaccine dose, mean (SD) <sup>c</sup>	7.9 (5.0)	10.0 (5.1)	0.92 [0.91–0.93] <sup>e</sup>	0.92 [0.90–0.93] <sup>e</sup>
Year of birth, mean (SD) <sup>d</sup>	1992 (2.6)	1994 (2.2)	0.77 [0.75–0.80] <sup>e</sup>	0.79 [0.77–0.82] <sup>e</sup>
<i>Number of varicella vaccines received, n (%)</i>				
1	1456 (44.5)	654 (49.8)	1.0 [reference]	1.0 [reference]
2	1763 (53.9)	651 (49.6)	1.22 [1.07–1.38] <sup>e</sup>	0.81 [0.65–1.01]
3	52 (1.6)	8 (0.6)	2.92 [1.38–6.18] <sup>e</sup>	1.86 [0.85–4.11]
<i>Sex, n (%)</i>				
Male	2397 (73.3)	997 (75.9)	1.0 [reference]	1.0 [reference]
Female	874 (26.7)	316 (24.1)	1.15 [0.99–1.33]	1.02 [0.86–1.19]
<i>Histo-blood group antigen, n (%)</i>				
A	1117 (37.1)	474 (36.9)	1.0 [reference]	1.0 [reference]
B	370 (12.3)	145 (11.3)	1.08 [0.87–1.35]	1.06 [0.85–1.34]
AB	106 (3.5)	62 (4.8)	0.73 [0.52–1.01]	0.68 [0.48–0.97] <sup>e</sup>
O	1421 (47.1)	605 (7.0)	1.0 [0.86–1.15]	0.99 [0.85–1.15]

<sup>a</sup> Unadjusted odds of having a positive anti-VZV titer.

<sup>b</sup> Covariate-adjusted odds of having a positive anti-VZV titer. Co-variables include years since last varicella vaccine dose, year of birth, number of varicella vaccines received, sex, and histo-blood group antigen expression. Subjects with missing histo-blood group antigen data (n = 284) were censored from analysis.

<sup>c</sup> Modeled as a continuous variable. Odds ratios represent the odds of a positive anti-VZV titer for each successive year that has elapsed since the last vaccine dose.

<sup>d</sup> Modeled as a continuous variable. Odds ratios represent the odds of a positive anti-VZV titer for a given birth year cohort compared to the birth cohort of the previous birth year.

<sup>e</sup> p < 0.05.

Fourth, this study relied on parental report for history of chickenpox disease; verification was infeasible. Finally, this study relied on measures of humoral immunity, which may less reliably predict disease risk than measures of cell-mediated immunity [36–38]. However, serologic evidence of immunity is the international standard by which vaccine immunogenicity is currently measured [37–41], and although seronegativity and disease susceptibility are not identical, loss of detectable antibody is associated with an increased risk of breakthrough disease [42].

## 5. Conclusion

This study was conducted in a large population of US adults who have accessible, accurate electronic childhood immunization records, and who had varicella titers drawn in early adulthood. Seroprevalence as measured by multiplex flow immunoassay in the cohort of study subjects born after implementation of the US varicella vaccination program in 1995 is below the threshold estimated to provide herd immunity. Additional studies which reliably measure long-term immune response to vaccination are needed. If vaccination in accordance with the current US VZV vaccination schedule is inadequate to maintain herd immunity, young adults not previously exposed to wild-type VZV may be at increased risk for varicella outbreaks.

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## Contributors

JRD designed the study, analyzed data, wrote and revised the manuscript. CTW, BJW, and AAC designed the study, wrote and revised the manuscript.

## Disclaimer

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## Conflicts of interest

None.

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