Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 9 November 2016
Received in revised form 9 March 2017
Accepted 15 March 2017
Available online xxxx

Keywords:
Varicella
Chickenpox
Vaccine
Immunogenicity
Outbreak
Herd immunity

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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http://dx.doi.org/10.1016/j.vaccine.2017.03.054
0264-410X/Published by Elsevier Ltd.

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 detectible 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

Please cite this article in press as: Duncan JR et al. Varicella seroepidemiology in United States air force recruits: A retrospective cohort study comparing immunogenicity of varicella vaccination and natural infection. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.03.054