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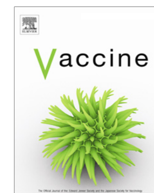

Final analysis of a study assessing genital human papillomavirus genoprevalence in young Australian women, following eight years of a national vaccination program

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A B S T R A C T

Objectives: The VACCINE [Vaccine Against Cervical Cancer Impact and Effectiveness] study evaluated the prevalence of quadrivalent vaccine-targeted human papillomavirus (HPV) genotypes (HPV 6, 11, 16, 18) amongst young women of vaccine-eligible age.
Methods: Between October 2011 – June 2015, women aged 18–25 years from Victoria, Australia, were recruited through targeted advertising on the social networking website Facebook. Participants completed an online questionnaire and provided a self-collected vaginal swab for HPV DNA detection and genotyping (Linear Array HPV genotyping assay). Self-reported HPV vaccination details were verified with the National HPV Vaccination Program Register (NHVPR).
Results: Of 1223 who agreed to participate, 916 (74.9%) completed the survey and, for 1007 (82.3%) sexually-active participants, 744 (73.9%) returned the self-collected swab, of which 737 contained detectable DNA. 184/737 (25.0%) were positive for HPV. Vaccine-targeted HPV genotypes were detected in only 13 (1.7%) women: 11 HPV 16 (six vaccinated after sexual debut, five unvaccinated) and two HPV 6. Prevalence of any of HPV 31/33/45 collectively was 2.9%, varying significantly by vaccination status (fully 2.0%, unvaccinated 6.8%; $p = 0.01$). Vaccination rates among the sexually-active cohort were high, with 65.6%, 71.6% and 74.2% of participants having received three, at least two or at least one dose of vaccine, respectively. Of women self-reporting HPV vaccination, the NHVPR confirmed one or more doses were received in 90%. Strong associations were observed between vaccination status, age, language spoken at home and country of birth, as well as between HPV detection and the number of male sexual partners.
Conclusion: Surveillance five to eight years' post-initiation of a national HPV vaccination program demonstrated a consistent and very low prevalence of vaccine-related HPV genotypes and some evidence of cross protection against related types amongst vaccine-eligible women from Victoria, Australia.
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1. Introduction

Phase 3 clinical trials of the first generation prophylactic human papillomavirus (HPV) vaccines showed excellent efficacy against HPV vaccine-type related infections and vaccine type-related disease end points, high immunogenicity with antibody levels much greater than that achieved from natural infection, and a reassuring safety profile [1–4]. However, real world vaccine impact and effectiveness outcomes are influenced by various parameters such as: the age of the target population; whether there is a catch-up period and, if so, the breadth of age and length of time it encompasses; the vaccine delivery infrastructure and acceptance of the program by the community, resulting in population based coverage [5]. Whilst coverage estimation and safety monitoring are

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essential for every vaccination program, WHO recommends that comprehensive surveillance for HPV vaccine impact and effectiveness is not essential in all settings [6]. This is because of the relative complexity and expense of such surveillance. Fortunately Australia, as some other early adopter, high-income countries, has developed a surveillance strategy which is being used to evaluate HPV vaccine impact [5,7].

In 2007, Australia became the first country to implement a government-funded, school-based program for young girls, with a catch-up program to 26 years of age to the end of 2009. The program, as of 2017, is still utilising the quadrivalent HPV vaccine (4vHPV targeting HPV 6/11/16/18 genotypes) as a 3 dose regimen [8]. In 2013, this program was extended to incorporate a gender-neutral approach, offering free 4vHPV vaccine in the same school-based delivery model to young boys, including a catch-up period to 15 years of age to the end of 2014. Through the national immunisation program, vaccination coverage of females has been high, not only in the school-based program with national dose 1/2/3 coverage by age 15 years currently 86/83/78%, respectively [9], but also in the catch-up program with over half of all young women aged 12–26 years in Australia fully-vaccinated [10]. Coverage rates in males to date are high, albeit slightly lower than those in girls [9].

Prior to vaccine implementation, during 2005–2007, an Australia-wide HPV genoprevalence survey was conducted on Aboriginal and Torres Strait Islander (respectfully referred to hereafter as Indigenous) and non-Indigenous women across geographical areas attending family planning clinics and having a Pap test. This survey described baseline HPV6/11/16/18 carriage rates of 35%, 18%, 6% and 2.3% in women aged 15–20, 21–30, 31–40 and 41–60 years of age, respectively [11,12]. At four to six years after the introduction of the 4vHPV vaccine program, we reported a substantial and sustained reduction of 86% in vaccine-targeted HPV infections (as measured by HPV DNA) in women aged below 25 years attending the same family planning clinics as compared to the pre-vaccine era [13,14]. Moreover, compared with the pre-vaccine implementation sample, adjusted prevalence ratios for vaccine-targeted HPV genotypes were 0.07 (95% CI: 0.04–0.14; $p < 0.001$) in fully-vaccinated women and 0.65 (95% CI: 0.43–0.96; $p = 0.03$) in unvaccinated women, which suggests herd protection, with an adjusted vaccine effectiveness of 86% for these genotypes for fully-vaccinated women compared with unvaccinated women (95% CI: 71–93; $p < 0.0001$) [14].

To consider HPV genoprevalence for the general population in an Australian setting, and evaluate vaccine impact in women of vaccine-eligible age, we designed a novel approach utilising recruitment of young women 18–26 years of age through Facebook. This Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE) study used an online questionnaire, via a password protected website, and a self-collected vaginal sample which was sent through the post to the laboratory for HPV DNA detection and genotyping [15]. The use of social networking sites is a common way young people communicate and, as we previously reported in a young women's health study, this approach results in recruitment of participants largely representative of a general population of young women [16]. Currently in Australia, of young women 18–29 years of age, 99% have a Facebook account [17], with 75% accessing it daily. In an interim analysis at two years into the VACCINE study, and six years following commencement of the National HPV Vaccination program, we reported a prevalence of vaccine-related types of 1.6% among 431 young women [18]. Those positive were all HPV 16 detected, vaccinated women, all of whom had received their vaccine after their sexual debut [18]. We now report the final results of this study for women tested for HPV four to eight years after the HPV vaccine program began.

2. Methods

2.1. Participant recruitment

The study protocol was approved by the Royal Women's Hospital Human Research and Ethics Committees and was carried out according to the National Statement on Ethical Conduct in Research Involving Humans produced by the National Health and Medical Research Council of Australia. Inclusion criteria for participation in the VACCINE study were being female, aged 18–25 years, living in the State of Victoria, Australia, with provision of verbal and written informed consent. Recruitment was over the study period of October 2011 to June 2015, via Facebook advertisements and as previously described [15,18]. In brief, advertisements appeared randomly on Facebook profiles of users matching our inclusion criteria. Then prospective participants who clicked on an advertisement were directed to the secure VACCINE study website (www.VACCINE.org.au), where they were provided with an introduction to the study, and if they were interested, a link to the registration page. Expressions of interest were followed up with a telephone call by a VACCINE study coordinator. Following verbal consent, participants were emailed a link to an online questionnaire and a written (electronic) copy of the participant information and consent form. Questionnaire data collected included basic demographics, sexual activity and behaviour, knowledge, experience and attitudes to cervical cytology screening, HPV and HPV vaccination. In addition to self-reported HPV vaccination status, participants consented for researchers to verify their vaccination status through the National HPV Vaccination Program Register (NHVPR). Reporting to NHVPR is virtually complete through the School Program, but was voluntary for general practitioners delivering vaccination to young women during the catch-up program and remains under notified for missed school doses caught up in general practice [19].

Those participants who were sexually-active were asked to self-collect a dry vaginal swab, as per instructions. Briefly, participants were instructed not to collect a swab sample within 48 h of sexual contact. Participants were instructed to insert the tip of the swab (Regular nylon flocked specimen collection dry swab, 80 mm, cat. #552C; Copan Flock Technologies Srl, Brescia, Italy) into their vaginal opening in a manner similar to the way that they would insert a tampon. The instructions further stated that while holding the handle, the swab was to be inserted to approximately half the length of a finger and rotated gently several times, then removed slowly and placed back inside the original dry plastic tube and closed tightly. Participants were instructed to write their initials, date of birth and the date that the sample was taken on the outside of the tube. A ziplock sealed plastic bag, cardboard tube to protect against crushing and a reply-paid, self-addressed A5-sized padded envelope were provided for return post of the sample to the laboratory for processing. Return samples were delivered by routine postal service, logged and refrigerated upon receipt.

2.2. HPV DNA genoprevalence

All sample processing for HPV DNA detection and genotyping was performed at the Royal Women's Hospital Department of Microbiology and Infectious Diseases molecular microbiology laboratory. Samples were resuspended by agitation in 400 μL phosphate-buffered saline (PBS) within 72 h of receipt and stored in a −80 °C freezer until ready for DNA extraction using an automated MagNAPure 96 isolation and purification system (Roche Molecular Diagnostics, Pleasanton CA). A qPCR assay for a 260 bp fragment of the human beta-globin gene was performed using a LightCycler 480 (Roche Molecular Diagnostics) to assess whether

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