Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Claudia Landazabal Date

Assessing the safety of nine-valent human papillomavirus vaccine administration among pregnant women: adverse event reports in the Vaccine Adverse Event Reporting System (VAERS),
2014-2017

By

Claudia Landazabal
MSPH

Epidemiology

_____

Dr. Saad B. Omer
Committee Chair

_____

Pedro L. Moro
Committee Member

Assessing the safety of nine-valent human papillomavirus vaccine administration among pregnant women: adverse event reports in the Vaccine Adverse Event Reporting System (VAERS), 2014-2017

By

Claudia Landazabal

B.A.
Washington University in St. Louis
2014

Thesis Committee Chair: Saad B. Omer, MBBS, MPH, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Epidemiology
2018

Introduction: There are over 79 million prevalent cases of human papillomavirus (HPV) in the United States (1). Chronic cases of HPV can cause cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers (2). Nine-valent human papillomavirus vaccine (9vHPV) can protect against the most prevalent disease types (3). Although the HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events (AEs) in the developing fetus, it is not recommended that pregnant women receive it (4, 5). However, some women of childbearing age might be inadvertently exposed during catchup vaccination (5-7). This study aims to assess the safety of 9vHPV administration during pregnancy.

Methods: We searched the Vaccine Adverse Event Reporting System (VAERS) database, a national post-licensure vaccine safety surveillance system, for reports of pregnant women vaccinated with 9vHPV in the United States between December 10, 2014 and December 31, 2017 (8). Reports and corresponding medical records (when available) were reviewed. AEs were characterized as primary maternal, secondary maternal, primary infant, or secondary infant. Primary maternal AEs were further classified as pregnancy-specific or nonpregnancy-specific. Vaccination errors were noted. Frequencies and percentages of AEs and vaccination errors were computed, and disproportionate reporting of AEs was assessed using proportional reporting ratios (PRRs) (9, 10).

Results: A total of 80 pregnancy reports were identified. Sixty reports (73.2%) did not describe an AE and were submitted due to vaccine exposure during pregnancy. The most frequently reported pregnancy-specific AE was spontaneous abortion (n = 3; 3.7%), followed by vaginal bleeding (n = 2; 2.4%). Among nonpregnancy-specific AEs, injection site reaction (n = 3; 3.7%) was most common. Just over one-fifth of reports described a vaccination error (n = 17; 21.3%). The PRR analyses comparing 9vHPV and 4vHPV vaccines, as well as 9vHPV and inactivated influenza vaccines, did not reveal disproportional reporting for any AE. Only codes for non-clinically important events exceeded the PRR threshold.

Discussion: No AE clusters or patterns of concern were observed among these pregnancy reports. CDC routinely monitors the safety of 9vHPV in the U.S. and will continue to monitor the safety of this vaccine in pregnancy (11).

Assessing the safety of nine-valent human papillomavirus vaccine administration among pregnant women: adverse event reports in the Vaccine Adverse Event Reporting System (VAERS), 2014-2017

By

Claudia Landazabal

B.A.
Washington University in St. Louis
2014

Thesis Committee Chair: Saad B. Omer, MBBS, MPH, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Epidemiology
2018

Acknowledgements

Very many thanks to my advisors, Dr. Saad B. Omer and Dr. Pedro L. Moro, for their mentorship and guidance throughout this process. Their feedback and suggestions were of great help in improving drafts, and their knowledge and experience was most valuable. Thanks also to Ms. Paige Lewis for her analytic assistance and Dr. Frank DeStefano, Dr. Maria Cano, and the other members of the Immunization Safety Office for their warm welcome and support.

Table of Contents

Background

Human papillomavirus (HPV) is estimated to account for over 70% of sexually transmitted infections in the United States (1). As such, it is the most common sexually transmitted infection, with over 79 million prevalent, and 14 million annual incident, cases (1). The average lifetime probability of acquiring HPV is over 80%, with estimated annual probability of acquiring a new infection peaking between the ages of 20 and 24 (25%) (1, 12).

Many cases of HPV are asymptomatic, and individuals that acquire the infection often spontaneously clear it without health consequences (13). However, chronic cases of HPV can cause poor health outcomes such as cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers, as well as genital warts (2). Cancer registry data from 2008 to 2012 indicated that the most common cancer occurring at an anatomic site associated with HPV (*i.e.,* HPV-associated cancer) among females was cervical carcinoma and among males was oropharyngeal squamous cell cancer (14). These data also suggested that, annually, nearly 39,000 cases of HPV-associated cancer are diagnosed, equating to an incidence rate of 11.7 per 100,000 people (14). Approximately 79% of these cases are estimated to be attributable to HPV infection (14).

There are over 150 HPV types, 13 of which can cause precancers or cancer (14, 15). The majority (80%) of cases of HPV-associated cancer caused by HPV are attributable to types 16 and 18 (14). HPV types 31, 33, 45, 52, and 58 account for an additional 12% of these cancers (14). An additional two common HPV types, 6 and 11, are non-oncogenic but cause 86% of genital warts cases and, rarely, cases of laryngeal papillomas (3, 16).

Fortunately, vaccines are available that can protect against the most prevalent oncogenic and non-oncogenic disease types (3). Nine-valent human papillomavirus vaccine (9vHPV) was approved by the Food and Drug Administration (FDA) in December 2014 and recommended by the Advisory Committee on Immunization Practices (ACIP) in February 2015 (17, 18). Previously, quadrivalent (4vHPV) and bivalent (2vHPV) forms of the vaccine had been licensed for use (3). 2vHPV prevents disease caused by HPV types 16 and 18; 4vHPV additionally offers protection against HPV types 6 and 11 (19, 20). 9vHPV includes HPV types 31, 33, 45, 52, and 58, as well as those contained in the other two HPV vaccines (21).

Infection with the HPV types against which these three vaccines offer protection is not uncommon in the population. A cross-sectional study analyzing National Health and Nutrition Examination Survey (NHANES) data collected on 4,943 individuals from the two years immediately prior to HPV vaccine introduction (2005 and 2006) suggested high levels of natural exposure (22). Average seroprevalence among individuals ages 14 to 59 for any (*i.e.*, oncogenic or non-oncogenic) of the nine HPV types included in 9vHPV was 40.5% for females and 19.4% for males (22). Seroprevalence for any of the seven oncogenic HPV types included in this vaccine was 30.0% and 11.9% among females and males, respectively (22). For 4vHPV, a separate study analyzing additional years of NHANES data (2003-2006) collected on 8,767 individuals found average seroprevalence for the four included HPV types to be 31.8% for women and 12.9% for men (23). Finally, for 2vHPV, the previously mentioned study that analyzed 9vHPV found average seroprevalence for HPV types 16 and 18 was 18.3% among females and 6.6% among males (22).

HPV vaccines exhibit excellent immunogenic profiles and are highly effective at preventing disease (24-27). With regard to immunogenicity, at least 99.5% of women not previously infected with HPV types covered by each of 9vHPV, 4vHPV, and 2vHPV undergo seroconversion to the included vaccine types within one month after administration of the third dose (24-26). With regard to vaccine effectiveness, several randomized, international, double-blind controlled trials have contributed to current knowledge (24-26, 28). One study of 14,215 women between the ages of 16 and 26 found that, among women administered 9vHPV who did not have serological and/or DNA evidence of infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58 at baseline or month 7 (representative of the beginning and end of the vaccination period), there was a 96.7% reduction in risk of high-grade cervical, vulvar, and vaginal disease associated with HPV types 31, 33, 45, 52, and 58, compared to 4vHPV (25). Similarly, there was a 96.3% reduction in risk of high-grade (grade 2 or 3) cervical epithelial neoplasia, adenocarcinoma in situ, and invasive cervical carcinoma (a substitute endpoint for cervical cancer) related to these five HPV types when comparing groups administered these two vaccines (25, 26).

For 4vHPV, a separate study of 5,455 women between the ages of 16 and 24 found that, among women who did not have virologic evidence of infection with HPV types 6, 11, 16, or 18 at baseline through month 7, efficacy in preventing vulvar, vaginal, perineal, and perianal intraepithelial lesions or warts caused by HPV types included in the vaccine was 100%, compared to placebo (24). An additional study of 12,167 women between the ages of 15 to 26 found that, among women who did not have virologic evidence of infection with HPV type 16 or 18 at baseline or month 7, administration of

4vHPV led to a 98% reduction in risk of high-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, and invasive cervical carcinoma associated with HPV types 16 or 18, compared to placebo (28). Finally, for 2vHPV, a study of 16,162 women between the ages of 15 to 25 years found that, among women who did not have serologic and/or DNA evidence of infection with HPV type 16 or 18 at baseline or month 6, bivalent HPV vaccine led to a 92.9% reduction in risk of high-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, and invasive carcinoma associated with these HPV types, compared to hepatitis A vaccine (26).

HPV vaccination is recommended at age 11 or 12 for both males and females (4, 17, 29). In June 2006 (females) and October 2011 (males), ACIP recommended a three-dose immunization schedule, with the doses administered at 0, 2, and 6 months (4, 29). In October 2016, ACIP updated its recommendations for females and males age nine through 14 (30). Individuals beginning the vaccine series in this age range should now follow a two-dose schedule, with the doses administered between six and 12 months apart (30). The recommendation to follow a three-dose schedule still holds for those initiating the vaccine series upon or after turning 15, as well as for immunocompromised individuals (30). ACIP additionally recommends HPV vaccination for females between the ages of 13 and 26, and males between the ages of 13 and 21, not previously administered vaccine or who received insufficient doses (4, 17, 29). Although it is not recommended that pregnant women receive the HPV vaccine, some women of childbearing age might be inadvertently exposed during this catchup vaccination (5-7).

The three HPV vaccines are considered to have an acceptable safety record in the general population, with the most common adverse events (AEs) being mild in nature

(31). Pooled clinical trial data submitted to the FDA for vaccine approval suggested the most common local AE following 2vHPV, 4vHPV, and 9vHPV vaccination is injection site pain (19-21). For 2vHPV, 91.8% of females age 10-25 experienced injection site pain following vaccination, compared to 87.2% of subjects administered an adjuvant control, in studies with a combined total of over 23,500 subjects (19). Seven clinical trials of 4vHPV with a combined total of over 18,000 subjects showed slightly lower proportions; 83.9% of females age 9-26 experienced injection site pain following vaccination, compared to 75.4% of subjects administered an adjuvant control (20). Finally, in seven clinical trials of 9vHPV with a combined total of over 15,500 subjects, 89.3% and 89.9% of females age 9-15 and 16-26, respectively, experienced injection site pain following vaccination (21).

For systemic AEs, fatigue was most common following vaccination with 2vHPV and headache was most common following vaccination with 4vHPV and 9vHPV (19-21). For 2vHPV, 55.0% of females experienced fatigue within 7 days of vaccination, compared to 53.6% of subjects administered an adjuvant control (19). For 4vHPV, 28.2% of females age 9-26 experienced headache within one to 15 days after vaccination, compared to 28.4% of subjects administered an adjuvant control or saline placebo (20). Finally, for 9vHPV, 11.4% and 14.6% of females age 9-15 and 16-26, respectively, experienced headache within one to 15 days after vaccination with any dose of 9vHPV (21).

Serious AEs occurred in 6.4%, 0.8%, and 2.3% of subjects following administration of 2vHPV, 4vHPV, and 9vHPV respectively (19-21). Death following HPV vaccination was rare; only 0.05% of subjects administered 2vHPV and 0.1% of

subjects administered 4vHPV died (19, 20). The most common cause of death for both groups was motor vehicle accident (19, 20). For 9vHPV, fewer than 0.05% of subjects died, and no deaths were considered vaccine-related (21).

HPV vaccines are not recommended during pregnancy (5). Although the vaccine has not been causally associated with adverse outcomes of pregnancy or AEs in the developing fetus, data on vaccination during pregnancy are limited (4). Prior studies assessing AEs following 2vHPV and 4vHPV administration during pregnancy have not revealed any concerning patterns of pregnancy-specific or infant/neonatal outcomes following vaccine administration (6, 7, 32-36), with the exception of one study of 4vHPV (37).

To assess AEs following administration of 2vHPV in the general population, as well as specifically among pregnant women, Angelo *et al.* conducted a pooled analysis of data from 42 clinical studies in 40 countries (34). The results did not indicate a statistically significant difference in risk of spontaneous abortion among those administered 2vHPV from 60 days before pregnancy through the end of pregnancy and those administered a control (34). Percentages of birth defects, mean birth weight, and mean gestational age at time of delivery were found to be similar for newborns of women in both groups (34). In another study of 2vHPV, Baril *et al.* analyzed Clinical Practice Research Datalink General Practice Online Database medical records of 1,169 women between the ages of 15 and 25 living in the United Kingdom (35). Overall hazards of spontaneous abortion (according to the U.S. definition) did not differ statistically significantly between the unexposed group (those administered 2vHPV four to 18 months before pregnancy) and either exposed group (those administered 2vHPV from 30 days

before pregnancy through 45 days after pregnancy and those administered 2vHPV from 30 days before pregnancy through 90 days after pregnancy) (35). The odds of preterm birth, small size for gestational age, and birth defects among unexposed women were not found to differ statistically significantly from those in either exposed group (35). Finally, Panagiotou *et al.* analyzed data from a randomized control trial of 4,864 women (7,466 pregnancies) between the ages of 18 and 25 living in Costa Rica, as well as 2,836 unvaccinated women, to assess rates of spontaneous abortion following 2vHPV administration (36). Overall, no statistically significant differences in risk were observed between the unexposed groups (women vaccinated with Hepatitis A vaccine and unvaccinated women) and either exposed group (those administered 2vHPV from 89 days before conception through 89 days after conception and those administered 2vHPV at any time point relative to conception) (36).

Studies of 4vHPV have yielded similar findings. Goss *et al.* analyzed 1,752 prospective reports of 4vHPV exposure during pregnancy from the United States, Canada, and France submitted to the vaccine manufacturer (Merck and Co., Inc.) registry (7). This study did not find any concerning patterns of spontaneous abortions, fetal deaths, or birth defects following vaccine administration (7). Similarly, no unusual patterns of these, or other (*e.g.*, stillbirth, breech presentation), pregnancy-specific or infant/neonatal outcomes were observed by Moro *et al.* in a study that analyzed 147 non-manufacturer AE reports submitted to the Vaccine Adverse Event Reporting System (VAERS), a national post-licensure vaccine safety surveillance system (6, 38). Additionally, no concerning patterns of non-pregnancy specific outcomes (*e.g.* fever, nausea) were observed (6).

In a study by Scheller *et al.*, data from the Danish Childhood Vaccine Database, Danish National Prescription Registry, and other Danish health and demographic registries were linked in part to determine HPV vaccination status for all women who were pregnant in Denmark during the study period (32). Vaccinated pregnant women and unvaccinated pregnant women were matched, allowing for the calculation of hazard and prevalence odds ratios (32). The study did not find a statistically significant difference in risk of spontaneous abortion, preterm birth, major birth defects, small size for gestational age, or low birth weight between women who did and did not receive 4vHPV during pregnancy (32). Finally, Lipkind *et al.* used Vaccine Safety Datalink data to compare outcomes of women who received 4vHPV during pregnancy or during the periconceptional period to those who received at least one dose of 4vHPV four to 18 months prior to becoming pregnant but not while pregnant or in the periconceptional period (33). The study found that the risks of preterm birth, major birth defects, small size for gestational age, and adverse maternal obstetric outcomes did not differ statistically significantly between groups (33). To our knowledge, only one study has found a noticeable difference in percentages of spontaneous abortions between African American women administered 2vHPV and a placebo (20.0% vs. 6.4%) (37). However, it is possible that differences in baseline characteristics between the two groups may have contributed to this finding (37).

Overall, these multiple studies of 2vHPV and 4vHPV have yielded consistent findings that are informative for healthcare providers and pregnant women alike. However, 9vHPV should be evaluated separately. Nine-valent HPV vaccine has been the only HPV vaccine distributed in the United States since late 2016 (30). Additionally,

while vaccination with both 2vHPV and 4vHPV has been shown to induce inflammatory nodules in mice, histological, injection site cytokine, and serum cytokine patterns have diverged for these two vaccines, potentially due in part to adjuvant differences (39, 40). 9vHPV, which has a different adjuvant quantity/formulation than either of the other two vaccines, may elicit unique inflammatory responses (3).

To our knowledge, no studies have addressed inflammatory response in pregnant women following HPV vaccination. However, results from a descriptive study of 46 pregnant women receiving trivalent influenza virus vaccine illustrate the potential for vaccination to elicit inflammatory responses in this group (41). The authors reported statistically significant increases in C-reactive protein (CRP) one and two days after vaccination, as well as a marginally significant increase in TNF-α two days after vaccination (41). Observed associations between pregnancy and decreased inflammatory responses in human and animal models have been interpreted as illustrating a possible mechanism by which the maternal immune system may avoid rejecting a fetus (41-47). Inflammation, therefore, could be positively correlated with risk of AEs among pregnant women (41, 48-51).

Initial pre-licensure clinical study data did not indicate an increased risk of spontaneous abortion or major birth defect when 9vHPV was inadvertently administered to pregnant women (21). However, these data were limited by insufficient power to study less common pregnancy-specific conditions. This study aims to assess the frequency of these and other adverse outcomes within a larger patient population to gauge the safety of 9vHPV administration during pregnancy.

Assessing the safety of nine-valent human papillomavirus vaccine administration among pregnant women: adverse event reports in the Vaccine Adverse Event Reporting System (VAERS), 2014-2017

Claudia S. Landazabal[1], Pedro L. Moro[2], Paige Lewis[2], Saad B. Omer[1, 3, 4]

[1] Emory University Rollins School of Public Health, Department of Epidemiology

[2] Centers for Disease Control and Prevention, National Center for Zoonotic and Emerging Infectious Diseases, Division of Healthcare Quality Promotion, Immunization Safety Office

[3] Emory University Rollins School of Public Health, Hubert Department of Global Health

[4] Emory Vaccine Center

Introduction: There are over 79 million prevalent cases of human papillomavirus (HPV) in the United States (1). Chronic cases of HPV can cause cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers (2). Nine-valent human papillomavirus vaccine (9vHPV) can protect against the most prevalent disease types (3). Although the HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events (AEs) in the developing fetus, it is not recommended that pregnant women receive it (4, 5). However, some women of childbearing age might be inadvertently exposed during catchup vaccination (5-7). This study aims to assess the safety of 9vHPV administration during pregnancy.

Methods: We searched the Vaccine Adverse Event Reporting System (VAERS) database, a national post-licensure vaccine safety surveillance system, for reports of

pregnant women vaccinated with 9vHPV in the United States between December 10, 2014 and December 31, 2017 (8). Reports and corresponding medical records (when available) were reviewed. AEs were characterized as primary maternal, secondary maternal, primary infant, or secondary infant. Primary maternal AEs were further classified as pregnancy-specific or nonpregnancy-specific. Vaccination errors were noted. Frequencies and percentages of AEs and vaccination errors were computed, and disproportionate reporting of AEs was assessed using proportional reporting ratios (PRRs) (9, 10).

Results: A total of 80 pregnancy reports were identified. Sixty reports (73.2%) did not describe an AE and were submitted due to vaccine exposure during pregnancy. The most frequently reported pregnancy-specific AE was spontaneous abortion (n = 3; 3.7%), followed by vaginal bleeding (n = 2; 2.4%). Among nonpregnancy-specific AEs, injection site reaction (n = 3; 3.7%) was most common. Just over one-fifth of reports described a vaccination error (n = 17; 21.3%). The PRR analyses comparing 9vHPV and 4vHPV vaccines, as well as 9vHPV and inactivated influenza vaccines, did not reveal disproportional reporting for any AE. Only codes for non-clinically important events exceeded the PRR threshold.

Discussion: No AE clusters or patterns of concern were observed among these pregnancy reports. CDC routinely monitors the safety of 9vHPV in the U.S. and will continue to monitor the safety of this vaccine in pregnancy (11).

Introduction

Human papillomavirus (HPV) is estimated to account for over 70% of sexually transmitted infections in the United States (1). As such, it is the most common sexually transmitted infection, with over 79 million prevalent, and 14 million annual incident, cases (1). The average lifetime probability of acquiring HPV is over 80% (12).

Many cases of HPV are asymptomatic, and individuals that acquire the infection often spontaneously clear it without health consequences (13). However, chronic cases of HPV can cause poor health outcomes such as cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers (2). Eighty percent of cases of HPV-associated cancer caused by HPV are attributable to types 16 and 18 (14). HPV types 31, 33, 45, 52, and 58 account for an additional 12% of these cancers (14). An additional two common HPV types, 6 and 11, are non-oncogenic but cause 86% of genital warts cases and, rarely, cases of laryngeal papillomas (3, 16).

Fortunately, vaccines are available that can protect against the most prevalent oncogenic and non-oncogenic disease types (3). Nine-valent human papillomavirus vaccine (9vHPV) was approved by the Food and Drug Administration (FDA) in December 2014 and recommended by the Advisory Committee on Immunization Practices (ACIP) in February 2015 (17, 18). It includes HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (21). Previously, quadrivalent (4vHPV) and bivalent (2vHPV) forms of the vaccine had been licensed for use (3).

The three HPV vaccines are considered to have an acceptable safety record in the general population, with the most common adverse events (AEs) being mild in nature (31). Pooled clinical trial data submitted to the FDA for vaccine approval suggested the

most common local AE following 2vHPV, 4vHPV, and 9vHPV vaccination is injection site pain (19-21). Fatigue is the most common systemic AE following vaccination with 2vHPV, and headache is the most common systemic AE following vaccination with 4vHPV and 9vHPV (19-21).

Although the HPV vaccine has not been causally associated with adverse outcomes of pregnancy or AEs in the developing fetus, it is not recommended that pregnant women receive the HPV vaccine (4, 5). However, some women of childbearing age might be inadvertently exposed during catchup vaccination (5-7). Prior studies assessing AEs following 2vHPV and 4vHPV administration during pregnancy have not revealed concerning patterns of pregnancy-specific or infant/neonatal outcomes following vaccine administration (6, 7, 32, 33). However, 9vHPV should be evaluated separately. Nine-valent HPV vaccine has been the only HPV vaccine distributed in the United States since late 2016 (30). Additionally, while vaccination with both 2vHPV and 4vHPV has been shown to induce inflammatory nodules in mice, histological, injection site cytokine, and serum cytokine patterns have diverged for these two vaccines, potentially due in part to adjuvant differences (39, 40). 9vHPV, which has a different adjuvant quantity/formulation than either of the other two vaccines, may elicit unique inflammatory responses (3).

Initial pre-licensure clinical study data did not indicate an increased risk of spontaneous abortion or major birth defect when 9vHPV was inadvertently administered to pregnant women (21). However, these data were limited by insufficient power to study less common pregnancy-specific conditions. This study aims to assess the

frequency of these and other adverse outcomes within a larger patient population to gauge the safety of 9vHPV administration during pregnancy.

Methods

Data source

The Vaccine Adverse Event Reporting System (VAERS) is a national post-licensure vaccine safety surveillance system jointly operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) (8). One of its main purposes is to identify possible vaccine safety signals, such as those that may be missed in pre-licensure clinical trials given an AE's rare nature (8, 52, 53). Manufacturers are required to report all post-vaccination AEs of which they become aware, while healthcare providers are required to report those AEs from the vaccine injury table and are encouraged to report any AE they believe may be causally associated with the vaccine (8, 54, 55). Others, such as parents of patients and patients themselves, are encouraged to report voluntarily (8). AEs described in VAERS reports are often temporarily associated with vaccination and may or may not include conditions caused by vaccination (8, 56). VAERS is not designed to assess for causality between an AE and a vaccine, and only rarely can the AE be assessed in VAERS (8, 56). Additionally, not all reports describe AEs, and some may describe a vaccination error (*e.g.*, vaccine administered to patient of inappropriate age). The signs, symptoms, and vaccination errors described in each report are coded with one or more terms using a clinically validated international medical terminology dictionary known as the Medical Dictionary for Regulatory Activities (MedDRA) (57). Report severity is determined on the basis of

criteria established by the Code of Federal Regulations (55). AEs that result in death, hospitalization, prolongation of hospitalization, life-threatening illness, or disability or permanent damage are categorized as serious (55).

Report search

We searched the VAERS database for reports of pregnant women vaccinated with 9vHPV in the United States between December 10, 2014 and December 31, 2017 (received by January 12, 2018). The following search strategies were used: (1) looked for MedDRA preferred terms containing any of the following: "drug exposure during pregnancy," "exposure during pregnancy," and "maternal exposure during pregnancy," (2) performed a text string search for the term "preg" within the symptom description, illness at time of vaccination, and pre-existing illness variables, and (3) looked for reports for which the reporter had answered "yes" to the question "Is the report about vaccine(s) given to a pregnant woman?" (6).

Report review

All reports and corresponding medical records (when available) were reviewed to extract information on pregnancy status at time of vaccination, AEs, AE severity, vaccination errors, and date of last menstrual period or expected date of delivery (6). Our search strategy yielded information on vaccination date, maternal age at time of vaccination, vaccines administered concomitantly, and reporter type. Reports that indicated a patient was not pregnant at the time of vaccination or received 9vHPV more than a month prior to becoming pregnant were excluded (6).

AEs were characterized as primary maternal, secondary maternal, primary infant, or secondary infant AEs. Primary AEs were the main diagnoses determined by the reviewer based on information in the VAERS report and/or medical records (when available). If multiple maternal and/or infant AEs were reported for the same person, the one with the greatest clinical significance was selected as primary and the others were listed as secondary (6). Reports of women receiving 9vHPV after experiencing AEs or that described AEs associated with administration of an HPV vaccine other than 9vHPV were excluded. Primary maternal AEs were further classified as pregnancy-specific or nonpregnancy-specific. Pregnancy-specific AEs of interest included spontaneous abortion (fetal demise < 20 weeks gestation), stillbirth (fetal demise ≥ 20 weeks gestation), and preterm delivery (live birth ≤ 37 weeks gestation) (58, 59). No specific assessment was made to investigate causality between reported AEs and 9vHPV (6).

Vaccination errors were noted when explicitly mentioned by the reporter or after review of the VAERS report. These errors were defined as follows: wrong drug administered (patient was administered 9vHPV when she should have been administered a different vaccine), drug administered to a patient of inappropriate age (patient was over the age of 26 when administered her first dose of HPV vaccine), inappropriate schedule of drug administration (doses of HPV vaccine did not follow the recommended 0, 2, and 6 month schedule or 0 and 6-12 month schedule, depending on the age of the patient), and extra dose administered (patient had already received three doses of HPV vaccine) (4, 30, 60).

Gestational age at the time of vaccination was calculated based on the date of a woman’s last menstrual period, expected date of delivery, or gestational age noted by the

reporter if neither of the other dates were given (61). This value was used to determine trimester of pregnancy, which was defined as follows: first (0-13 weeks), second (14-27 weeks), third (28+ weeks) (62).

Report analysis

Frequencies and percentages of AEs and vaccination errors were computed using SAS version 9.4 (SAS Institute Inc., Cary, NC). We assessed disproportionate reporting of AEs using proportional reporting ratios (PRRs), with the goal of determining whether any safety signals existed for 9vHPV (9, 10). This method compared proportions of MedDRA terms after 9vHPV administration during pregnancy to proportions of the same MedDRA terms after both 4vHPV and inactivated influenza vaccine administration during pregnancy (9). For the comparison between 9vHPV and 4vHPV, reports that indicated vaccination with both HPV vaccines were excluded. For the comparison between 9vHPV and influenza vaccine, reports of 9vHPV vaccination were excluded from the numerator if influenza vaccine was co-administered. Similarly, reports of influenza vaccination were excluded from the denominator if 9vHPV or 4vHPV was co-administered. 4vHPV is the precursor of 9vHPV and, because of their similar indications and composition, it was the natural comparison vaccine to use for 9vHPV (3). Influenza vaccines are recommended to be administered at any time during pregnancy, and their safety profile in pregnancy is better known than for most other vaccines (63, 64). However, the characteristics of pregnant women receiving influenza vaccines are different from those of pregnant women receiving 9vHPV since the indication and circumstances in which exposure occurs differ for these vaccines (3, 6, 63).

For both vaccine comparisons, we used VAERS reports identified for previous studies (6, 65, 66). For the 4vHPV comparison, we ran two separate analyses, one of which included, and one of which excluded, manufacturer reports, for the sake of comparability with a similar previous study (6). For the inactivated influenza vaccine comparison, reports for which live vaccines were administered concomitantly with influenza vaccines were excluded as these are contraindicated during pregnancy (67). MedDRA terms with disproportionately higher reporting after 9vHPV compared to 4vHPV were assessed using the criteria of Evans *et al.* (PRR ≥ 2, Yates $\chi^2 \geq 4$, and at least 3 reports in the 9vHPV group) (9). VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research as stipulated in 45 CFR 46.102(d) (6, 68). Therefore, this investigation was not subject to institutional review board review or informed consent requirements (6).

Results

Our search strategy yielded a total of 127 reports of pregnant women vaccinated with 9vHPV in the United States between December 10, 2014 and December 31, 2017. Forty-seven reports were excluded because either the report did not meet study criteria (n = 44) or because the vaccine timing was inappropriate for the study (n = 3) (Figure 1). Therefore, a total of 80 true pregnancy reports were identified and reviewed, two of which described both maternal and infant AEs, which were considered separately. The greatest number of reports were received in 2016 (Figure 2). Nearly all reports were submitted by the vaccine manufacturer (n = 62; 77.5%) or healthcare provider (n = 16;

20.0%) (Table 1). In three-fourths of the reports, 9vHPV was administered during the first trimester of pregnancy (n = 45; 75%) (Table 1). Median age of gestation was 6.1 weeks and median maternal age at the time of vaccination was 21.5 years (Table 1). Additional demographic and report characteristics are described in Table 1.

Sixty reports (73.2%) did not describe an AE and were submitted due to vaccine exposure during pregnancy (Table 2). No maternal or infant deaths were reported. The most frequently reported pregnancy-specific AE was spontaneous abortion (n = 3; 3.7%), followed by vaginal bleeding (n = 2; 2.4%) (Table 1). Among nonpregnancy-specific AEs, injection site reaction (n = 3; 3.7%) was most common (Table 2). Three infant AEs were reported (Table 2).

Just over one-fifth of reports described a vaccination error (n = 17; 21.3%). Of these, only six reported an AE, which included: injection site reaction (n = 2), spontaneous abortion (n = 1), polyhydramnios (n = 1), proteinuria (n = 1), and an unspecified AE (n = 1). Five reports (29.4%) each indicated incorrect vaccine administration, vaccine administration to a patient of inappropriate age, and inappropriate schedule of vaccine administration (Table 3). Among reports for which the wrong vaccine was administered, four (23.5%) indicated that the patient should have received Tdap and one (5.9%) indicated the patient should have received influenza vaccine. Two of these reports (11.8%) additionally indicated that 9vHPV was administered to a woman greater than age 30. Among reports for which the sole vaccination error was vaccine administration to a patient of inappropriate age, two (11.8%) indicated 9vHPV was administered to a patient age 27-30, two (11.8%) indicated a patient age 31-35, and one (5.9%) indicated a patient age 36-40. Among reports for which an extra dose of vaccine

was administered, one (5.9%) indicated the patient had previously received three doses of 4vHPV and one (5.9%) indicated the patient had previously received three doses of 9vHPV.

The PRR analyses comparing 9vHPV and 4vHPV vaccines, as well as 9vHPV and inactivated influenza vaccines, did not reveal disproportional reporting for any AE. Only MedDRA codes for non-clinically important events exceeded the PRR threshold (e.g. “exposure during pregnancy,” “no adverse event,” “pregnancy test urine positive”) (Table 4).

Discussion

During the period of this review, VAERS received 2,068 reports of females who were administered 9vHPV, of which 4% were pregnant. No AE clusters or patterns of concern were observed among these pregnancy reports. Nearly three-fourths of reports did not describe an AE and were likely submitted because 9vHPV is not recommended in pregnant women (5). Most 9vHPV pregnancy reports were received during 2016 and 2017, and, when considered alongside 4vHPV reporting trends, illustrate a Weber-like effect, likely due to past media attention surrounding 4vHPV (Figure 2) (69, 70). The Weber effect is an epidemiologic phenomenon whereby reporting rates peak in the second year following the marketing of a new product (or product perceived to be new) and then decline, despite constant prescribing rates (69). Similar phenomena have been observed with other vaccines (65).

Among reports describing an AE, the pregnancy-specific conditions most frequently reported were spontaneous abortion and vaginal bleeding, both of which are

relatively common during pregnancy generally. Estimates suggest that between 10% and 20% of pregnancies result in spontaneous abortion and approximately 12% of pregnant women experience vaginal bleeding (71-73). A previous review of 4vHPV pregnancy reports in VAERS also found that spontaneous abortion was the most commonly reported pregnancy-specific AE (6). Additionally, data from the Merck pregnancy registry for 4vHPV indicated that rates of spontaneous abortion were not higher than background rates in the general pregnant population (7).

Among nonpregnancy-specific AEs, the most commonly reported condition was injection site reaction, which is a known side effect of 9vHPV (21). All other reported AEs were diverse in nature and only affected a single mother or infant. While vaccination errors were not uncommon, only about a third of reports indicating a vaccination error also described an AE, the most common of which was of minimal concern (injection site reaction).

The proportional reporting ratio analyses did not yield any clinically important safety signals. 4vHPV was chosen for comparison to 9vHPV given the vaccine similarities in terms of recommended vaccination ages, recommendation that pregnant women do not receive the vaccine, and likelihood that most inadvertent vaccination would occur during the first trimester, when women may be unaware of their pregnancy status (3, 6). Influenza vaccine does not represent an ideal comparison group given that, unlike 9vHPV, it is recommended for all individuals 6 months of age and older, as well as at any time during pregnancy, and therefore is likely to be administered in roughly equal proportions across all three trimesters (3, 63). However, it was included as a comparison vaccine in the PRR analysis given its reassuring safety record (74).

Disproportionate reporting was only observed for non-clinically important MedDRA codes, but it is important to note that MedDRA preferred terms (PTs) may change over time and certain PTs may not have been in use during all vaccination time periods (Paige Lewis, CDC, "Personal Communication," 2018). Awareness of this change is important in interpreting observed reporting patterns. For example, the PT "exposure during pregnancy" was more frequently reported after 9vHPV than 4vHPV; however, this finding may be explained by the fact that this PT did not exist from 2006-2012 (Paige Lewis, CDC, "Personal Communication," 2018).

The results of this study are in line with those of initial pre-licensure 9vHPV clinical study data, which did not indicate increased risks of spontaneous abortion or major birth defect when the vaccine was inadvertently administered to pregnant women (21). They are also in line with prior studies assessing AEs following 4vHPV administration during pregnancy that have not revealed any concerning patterns of pregnancy-specific or infant/neonatal outcomes following vaccine administration (6, 7, 32, 33). An analysis of prospective reports of vaccine exposure during pregnancy from the United States, Canada, and France submitted to the vaccine manufacturer (Merck and Co., Inc.) registry did not find any concerning patterns of spontaneous abortions, fetal deaths, or birth defects following vaccine administration (7). An analysis of data from the Danish Childhood Vaccine Database, Danish National Prescription Registry, and other Danish health and demographic registries did not indicate a statistically significant difference in risk of spontaneous abortion, preterm birth, major birth defects, small size for gestational age, or low birth weight between women who did and did not receive 4vHPV during pregnancy (32). Finally, a Vaccine Safety Datalink study comparing

outcomes of women who received 4vHPV during pregnancy or during the periconceptional period to those who received at least one dose of 4vHPV four to 18 months prior to becoming pregnant but not while pregnant or in the periconceptional period found that the risks of preterm birth, major birth defects, small size for gestational age, and adverse maternal obstetric outcomes did not differ statistically significantly between groups (33). To our knowledge, only one study has found substantial differences in percentages of spontaneous abortions between African American women administered 4vHPV and a placebo (20.0% vs. 6.4%) (37). However, it is possible that differences in baseline characteristics between the two groups may have contributed to this finding (37). Overall, studies of 4vHPV have failed to demonstrate higher risks of AEs following vaccination during pregnancy, and the current study replicates this finding with 9vHPV.

VAERS strengths lie in its flexibility and ability to quickly detect rare and/or previously unrecognized AEs (75). This national system can provide near real-time information on the safety of vaccines (38). However, it has a number of important limitations, which in this study included lack of complete data and accuracy of reports (8). For example, some individuals who submitted the VAERS form did not supply all information relevant to the study (*e.g.*, last menstrual period, which would have allowed for the calculation of gestational age at time of vaccination and trimester of pregnancy). VAERS does not collect information on the number of 9vHPV pregnant vaccinees; therefore, it is not possible to calculate rates of AEs among pregnant women receiving 9vHPV (38). Underreporting or overreporting can be problematic, the first due to the voluntary nature of report submission and the second due to media attention and/or the

severity of the AE; serious reports are thought to be reported more frequently than non-serious reports (8, 38). In our study, the relatively small number of spontaneous abortion reports submitted likely represents substantial underreporting of this event, given the relative frequency of this event during pregnancy (71, 72).

Conclusion

9vHPV is not recommended during pregnancy; however, because of the age group in which it is indicated, may be inadvertently administered to pregnant women (5). Therefore, monitoring the safety of the vaccine in this subpopulation is important. The findings of this study are reassuring as no clusters or concerning patterns of AEs were observed. CDC routinely monitors the safety of 9vHPV in the U.S. and will continue to monitor the safety of this vaccine in pregnancy (11).

References

1. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sexually transmitted diseases.* 2013;40(3):187-93.
2. Centers for Disease Control and Prevention. Genital HPV Infection - Fact Sheet. U.S. Department of Health and Human Services. https://www.cdc.gov/std/hpv/stdfact-hpv.htm. Accessed 2018.
3. Centers for Disease Control and Prevention. HPV Vaccine Information for Clinicians. U.S. Department of Health and Human Services. https://www.cdc.gov/hpv/hcp/need-to-know.pdf. Published December 20, 2016. Accessed 2018.
4. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2007;56(Rr-2):1-24.
5. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2014;63(Rr-05):1-30.
6. Moro PL, Zheteyeva Y, Lewis P, et al. Safety of quadrivalent human papillomavirus vaccine (Gardasil) in pregnancy: adverse events among non-manufacturer reports in the Vaccine Adverse Event Reporting System, 2006-2013. *Vaccine.* 2015;33(4):519-22.

7. Goss MA, Lievano F, Buchanan KM, et al. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. *Vaccine.* 2015;33(29):3422-8.

8. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *The Pediatric infectious disease journal.* 2004;23(4):287-94.

9. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and drug safety.* 2001;10(6):483-6.

10. Banks D, Woo EJ, Burwen DR, et al. Comparing data mining methods on the VAERS database. *Pharmacoepidemiology and drug safety.* 2005;14(9):601-9.

11. Centers for Disease Control and Prevention. Human Papillomavirus (HPV) Vaccine Safety. U.S. Department of Health and Human Services. https://www.cdc.gov/vaccinesafety/vaccines/hpv-vaccine.html. Accessed 2018.

12. Chesson HW, Dunne EF, Hariri S, et al. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sexually transmitted diseases.* 2014;41(11):660-4.

13. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2015;64(Rr-03):1-137.

14. Viens LJ, Henley SJ, Watson M, et al. Human Papillomavirus-Associated Cancers - United States, 2008-2012. *MMWR Morbidity and mortality weekly report.* 2016;65(26):661-6.

15. Bernard HU, Burk RD, Chen Z, et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology*. 2010;401(1):70-9.

16. Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. *The Journal of infectious diseases.* 2009;199(6):805-14.

17. Petrosky E, Bocchini JA, Jr., Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morbidity and mortality weekly report.* 2015;64(11):300-4.

18. Gruber MF. *December 10, 2014 Approval letter—GARDASIL 9*. Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2014.

19. GlaxoSmithKline. Highlights of Prescribing Information. CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM240436.pdf. Published 2009. Accessed 2018.

20. Merck Sharp & Dohme Corp. Highlights of Prescribing Information. GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. Merck & Co., Inc. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf. Published 2006. Accessed 2018.

21. Merck Sharp & Dohme Corp. Highlights of Prescribing Information. Gardasil®9 (Human Papillomavirus 9-valent Vaccine, Recombinant). Merck & Co., Inc. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf. Published 2014. Accessed 2018.

22. Liu G, Markowitz LE, Hariri S, et al. Seroprevalence of 9 Human Papillomavirus Types in the United States, 2005-2006. *The Journal of infectious diseases.* 2016;213(2):191-8.

23. Introcaso CE, Dunne EF, Hariri S, et al. Prevaccine era human papillomavirus types 6, 11, 16 and 18 seropositivity in the U.S.A., National Health and Nutrition Examination Surveys, 2003-2006. *Sexually transmitted infections.* 2014;90(6):505-8.

24. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *The New England journal of medicine.* 2007;356(19):1928-43.

25. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *The New England journal of medicine.* 2015;372(8):711-23.

26. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet (London, England).* 2009;374(9686):301-14.

27. Schiller JT, Castellsagué X, Garland SM. A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines. *Vaccine.* 2012;30(0 5):F123-38.

28. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *The New England journal of medicine.* 2007;356(19):1915-27.

29. Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morbidity and mortality weekly report.* 2011;60(50):1705-8.

30. Meites E, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination - Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morbidity and mortality weekly report.* 2016;65(49):1405-8.

31. Phillips A, Patel C, Pillsbury A, et al. Safety of Human Papillomavirus Vaccines: An Updated Review. *Drug safety.* 2018;41(4):329-46.

32. Scheller NM, Pasternak B, Molgaard-Nielsen D, et al. Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes. *The New England journal of medicine.* 2017;376(13):1223-33.

33. Lipkind HS, Vazquez-Benitez G, Nordin JD, et al. Maternal and Infant Outcomes After Human Papillomavirus Vaccination in the Periconceptional Period or During Pregnancy. *Obstetrics and gynecology.* 2017;130(3):599-608.

34. Angelo MG, David MP, Zima J, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. *Pharmacoepidemiology and drug safety.* 2014;23(5):466-79.

35. Baril L, Rosillon D, Willame C, et al. Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. *Vaccine.* 2015;33(48):6884-91.

36. Panagiotou OA, Befano BL, Gonzalez P, et al. Effect of bivalent human papillomavirus vaccination on pregnancy outcomes: long term observational follow-up in the Costa Rica HPV Vaccine Trial. *The BMJ.* 2015;351:h4358.

37. Clark LR, Myers ER, Huh W, et al. Clinical trial experience with prophylactic human papillomavirus 6/11/16/18 vaccine in young black women. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2013;52(3):322-9.

38. Shimabukuro TT, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine.* 2015;33(36):4398-405.

39. Kashiwagi Y, Maeda M, Kawashima H, et al. Inflammatory responses following intramuscular and subcutaneous immunization with aluminum-adjuvanted or non-adjuvanted vaccines. *Vaccine.* 2014;32(27):3393-401.

40. Garcon N, Morel S, Didierlaurent A, et al. Development of an AS04-adjuvanted HPV vaccine with the adjuvant system approach. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy.* 2011;25(4):217-26.

41. Christian LM, Iams JD, Porter K, et al. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. *Vaccine.* 2011;29(48):8982-7.

42. Fofie AE, Fewell JE, Moore SL. Pregnancy influences the plasma cytokine response to intraperitoneal administration of bacterial endotoxin in rats. *Experimental physiology.* 2005;90(1):95-101.

43. Aguilar-Valles A, Poole S, Mistry Y, et al. Attenuated fever in rats during late pregnancy is linked to suppressed interleukin-6 production after localized inflammation with turpentine. *The Journal of physiology.* 2007;583(Pt 1):391-403.

44. Ashdown H, Poole S, Boksa P, et al. Interleukin-1 receptor antagonist as a modulator of gender differences in the febrile response to lipopolysaccharide in rats. *American journal of physiology Regulatory, integrative and comparative physiology.* 2007;292(4):R1667-74.

45. Elenkov IJ, Wilder RL, Bakalov VK, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. *The Journal of clinical endocrinology and metabolism.* 2001;86(10):4933-8.

46. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clinical and experimental immunology.* 1996;106(1):127-33.

47. Makhseed M, Raghupathy R, Azizieh F, et al. Mitogen-induced cytokine responses of maternal peripheral blood lymphocytes indicate a differential Th-type bias in normal pregnancy and pregnancy failure. *American journal of reproductive immunology (New York, NY : 1989).* 1999;42(5):273-81.

48. Murtha AP, Sinclair T, Hauser ER, et al. Maternal serum cytokines in preterm premature rupture of membranes. *Obstetrics and gynecology.* 2007;109(1):121-7.

49. Borzychowski AM, Sargent IL, Redman CW. Inflammation and pre-eclampsia. *Seminars in fetal & neonatal medicine.* 2006;11(5):309-16.

50. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. *American journal of reproductive immunology (New York, NY : 1989).* 1998;40(2):102-11.

51. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. *American journal of obstetrics and gynecology.* 1999;180(2 Pt 1):499-506.

52. Ellenberg SS. Safety considerations for new vaccine development. *Pharmacoepidemiology and drug safety.* 2001;10(5):411-5.

53. Fritzell B. Detection of adverse events: what are the current sensitivity limits during clinical development? *Vaccine.* 2001;20 Suppl 1:S47-8.

54. Institute of Medicine (US) Committee on Review of Priorities in the National Vaccine Plan. *Priorities for the National Vaccine Plan*. Washington (DC): National Academies Press (US), 2010.

55. U.S. Food and Drug Administration. U.S. Code of Federal Regulations, 21 CFR 600.80. Silver Spring, MD: U.S. Department of Health and Human Services. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80. Accessed 2018.

56. Centers for Disease Control and Prevention. Understanding the Vaccine Adverse Event Reporting System (VAERS). U.S. Department of Health and Human

Services. https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-vaers-color-office.pdf. Accessed 2018.

57. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. MedDRA. http://www.ich.org/products/meddra.html. Accessed 2018.

58. Chapter 1 - Overview of Obstetrics. In: Cunningham F, Leveno K, Bloom S, et al., eds. *Williams Obstetrics*. 23 ed. New York, NY: McGraw-Hill Companies, Inc.; 2010.

59. Chapter 9 - Abortion. In: Cunningham F, Leveno K, Bloom S, et al., eds. *Williams Obstetrics*. 23 ed. New York, NY: McGraw-Hill Companies, Inc.; 2010.

60. Hibbs BF, Moro PL, Lewis P, et al. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000-2013. *Vaccine.* 2015;33(28):3171-8.

61. Medical College of Wisconsin. Pregnancy Date Calculator. https://www.mcw.edu/calculators/pregnancydate.htm. Accessed 2018.

62. Chapter 8 - Prenatal Care. In: Cunningham F, Leveno K, Bloom S, et al., eds. *Williams Obstetrics*. 23 ed. New York, NY: McGraw-Hill Companies, Inc.; 2010.

63. Centers for Disease Control and Prevention. Key Facts About Seasonal Flu Vaccine. U.S. Department of Health and Human Services. https://www.cdc.gov/flu/protect/keyfacts.htm. Accessed 2018.

64. Munoz FM. Safety of influenza vaccines in pregnant women. *American journal of obstetrics and gynecology.* 2012;207(3 Suppl):S33-7.

65. Moro PL, Broder K, Zheteyeva Y, et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System. *American journal of obstetrics and gynecology.* 2011;205(5):473.e1-9.

66. Moro PL, Broder K, Zheteyeva Y, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. *American journal of obstetrics and gynecology.* 2011;204(2):146.e1-7.

67. Kroger AT, Atkinson WL, Marcuse EK, et al. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2006;55(Rr-15):1-48.

68. Office for Human Research Protections (OHRP). U.S. Code of Federal Regulations, 45 CFR 46.102. U.S. Department of Health and Human Services. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.102. Accessed 2018.

69. Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy.* 2004;24(6):743-9.

70. Eberth JM, Kline KN, Moskowitz D, et al. The role of media and the Internet on vaccine adverse event reporting: a case study of HPV vaccination. *The Journal of*

adolescent health : official publication of the Society for Adolescent Medicine. 2014;54(3):289-95.

71. Goldhaber MK, Fireman BH. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. *Epidemiology (Cambridge, Mass).* 1991;2(1):33-9.

72. Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *American journal of epidemiology.* 1981;114(4):548-53.

73. Ananth CV, Savitz DA. Vaginal bleeding and adverse reproductive outcomes: a meta-analysis. *Paediatric and perinatal epidemiology.* 1994;8(1):62-78.

74. Global Advisory Committee on Vaccine Safety. Safety of Immunization during Pregnancy: a review of the evidence. World Health Organization. http://www.who.int/vaccine_safety/publications/safety_pregnancy_nov2014.pdf. Published 2014. Accessed 2018.

75. Singleton JA, Lloyd JC, Mootrey GT, et al. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. VAERS Working Group. *Vaccine.* 1999;17(22):2908-17.

76. Markowitz L. Update: Recommendations for HPV Vaccination. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/ed/ciinc/downloads/2016-10-26/recommendations-hpv-2-doses-2016.pdf. Accessed 2018.

Table 1. U.S. VAERS[a] Reports in Pregnant Women Following 9vHPV Administration, 2014-2017 (n = 80)

Characteristic	
Maternal age in years, median (range)[b]	21.5 (12-38)
Gestational age at time of vaccination in weeks, median (range)[c]	6.1 (0.0-37.1)
Trimester of pregnancy at time of vaccination (n = 60)[d]	
First (0-13 weeks), n (%)	45 (75.0)
Second (14-27 weeks), n (%)	7 (11.7)
Third (28+ weeks), n (%)	8 (13.3)
Serious reports, n (%)[e]	0 (0.0)
Reports of 9vHPV given with other vaccines, n (%)[f]	20 (25.0)
No. of reports of 9vHPV given with at least one live vaccine, n (%)	8 (10.0)
Type of reporter	
Manufacturer, n (%)	62 (77.5)
Healthcare provider, n (%)	16 (20.0)
Other, n (%)	2 (2.5)

[a] Vaccine Adverse Event Reporting System

[b] Maternal age was missing for 18 reports

[c] Gestational age at time of vaccination was either not reported or unknown for 25 reports

[d] Trimester of pregnancy at time of vaccination was either not reported or unknown for 20 reports

[e] Six reports were coded as serious; however, upon clinical review, it was determined that these described other medically important conditions that did not meet serious report criteria per the Code of Federal Regulations

[f] Most common vaccines given concomitantly with 9vHPV were meningitis (Menactra) in 8 (15.4%) reports, hepatitis A in 7 (13.5%) reports, measles, mumps, and rubella in 7 (13.5%) reports, varicella in 7 (13.5%) reports, and inactivated polio in 5 (9.6%) reports

Table 2. Primary Adverse Events in Pregnant Women and Infants Following Maternal 9vHPV Administration, VAERS[a] 2014-2017 (n = 80)[b]

Adverse Events	**n**	**%**
Pregnancy-specific outcomes		
Spontaneous abortion	3	3.7
Vaginal bleeding	2	2.4
Elective abortion	1	1.2
Placenta previa	1	1.2
Polyhydramnios	1	1.2
Nausea/vomiting	1	1.2
Total	*9*	*11.0*
Nonpregnancy-specific outcomes		
Injection site reaction	3	3.7
Malaise	1	1.2
Elevated BMI during pregnancy	1	1.2
Proteinuria	1	1.2
Urinary tract infection	1	1.2
Total	*7*	*8.5*
Infant/neonatal outcomes		
Excessive weight loss	1	1.2
Renal impairment and manifestations	1	1.2
Shoulder dystocia	1	1.2
Total	*3*	*3.7*
Unspecified adverse event	3	3.7
No adverse event	60	73.2

[a] Vaccine Adverse Event Reporting System

[b] Two reports included both maternal and infant adverse events

Table 3. 9vHPV Vaccination Errors in Pregnant Women, VAERS[a] 2014-2017 (n = 17)

Vaccination Error	**n**	**%**
Wrong vaccine administered[b]	5	29.4
Vaccine administered to patient of inappropriate age[c]	5	29.4
Inappropriate schedule of vaccine administration[d]	5	29.4
Extra dose administered	2	11.8

[a] Vaccine Adverse Event Reporting System

[b] Equivalent to MedDRA code "wrong drug administered"

[c] Equivalent to MedDRA code "drug administered to patient of inappropriate age"

[d] Equivalent to MedDRA code "inappropriate schedule of drug administration"

Table 4. Proportional Reporting Ratio (PRR) Analysis MedDRA[a] Code Signals for 9vHPV (2014-2017) vs. 4vHPV (2006-2012) and 9vHPV (2014-2017) vs. Influenza (2010-2016) Comparisons, VAERS[b]

MedDRA Code[c]	9vHPV n (%)	4vHPV n (%)	Ratio of Proportions (95% CI)
Exposure during pregnancy	75 (93.8)	4 (0.4)	217.27 (81.58 - 578.61)
No adverse event	24 (30.0)	7 (0.8)	39.73 (17.67 - 89.34)
Pregnancy test urine positive	13 (16.3)	8 (0.9)	18.83 (8.04 - 44.08)
Ultrasound antenatal screen	4 (5.0)	4 (0.4)	11.59 (2.95 - 45.46)
Wrong drug administered[d]	5 (6.3)	10 (1.1)	5.79 (2.03 - 16.54)
Human chorionic gonadotropin positive	4 (5.0)	0 (0.0)	N/A
Maternal exposure before pregnancy	3 (3.8)	0 (0.0)	N/A
	9vHPV n (%)	**Influenza n (%)**	**Ratio of Proportions (95% CI)**
Pregnancy test positive	14 (18.9)	8 (1.6)	12.01 (5.22 - 27.65)
Pregnancy test urine positive	12 (16.2)	9 (1.8)	9.15 (3.99 - 20.97)
No adverse event	22 (29.7)	59 (11.6)	2.56 (1.67 - 3.91)
Exposure during pregnancy	70 (94.6)	237 (46.7)	2.03 (1.82 - 2.26)

[a] Medical Dictionary for Regulatory Activities

[b] Vaccine Adverse Event Reporting System

[c] MedDRA preferred terms (PTs) may change over time and certain PTs may not have been in use during certain time periods

[d] "Drug" refers to vaccine

Figure 1. Flow Diagram of VAERS Reports Included and Excluded in this Study

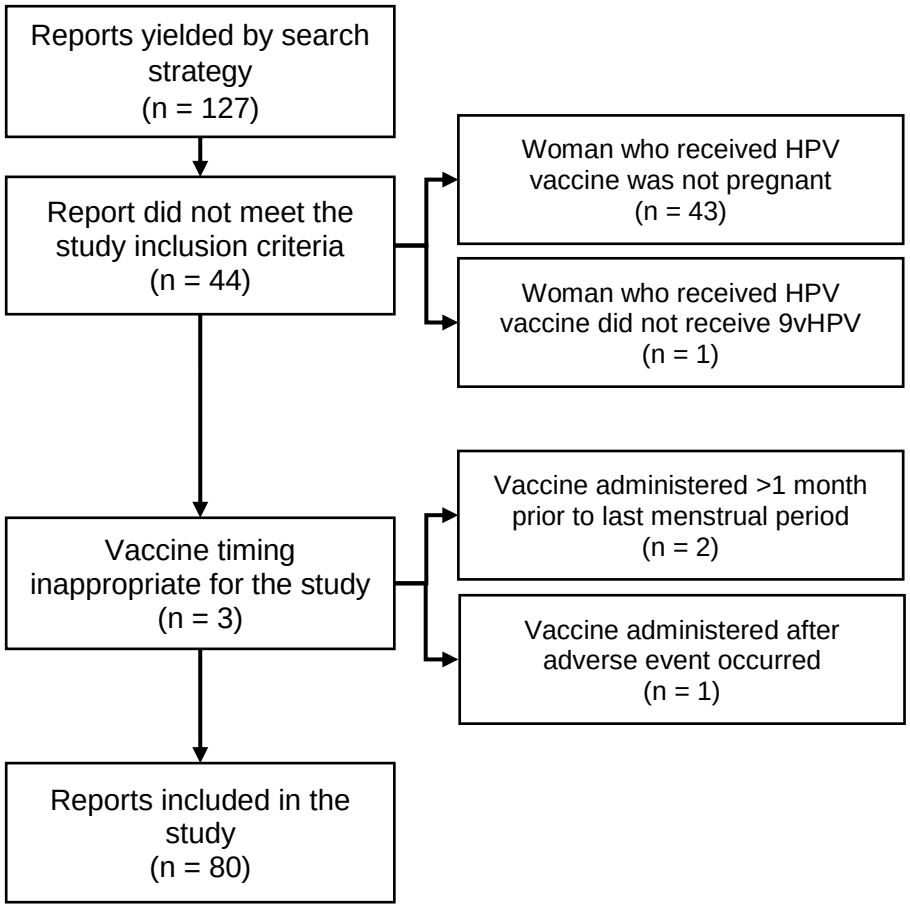

Figure 2. Number of 9vHPV and 4vHPV Serious and Non-Serious Reports received in VAERS, 2006-2017