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Safety of 9-valent human papillomavirus vaccine administration among pregnant women: Adverse event reports in the Vaccine Adverse Event Reporting System (VAERS), 2014–2017

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ABSTRACT

Introduction: 9-valent human papillomavirus vaccine (9vHPV) was approved by the Food and Drug Administration (FDA) in December 2014. 9vHPV is not recommended during pregnancy, but some women of childbearing age may be inadvertently exposed. This study aims to evaluate reports submitted to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women exposed to 9vHPV.
Methods: We searched the 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. Disproportionate reporting of adverse events (AEs) was assessed using proportional reporting ratios (PRRs).
Results: A total of 82 pregnancy reports were identified. Sixty reports (73.2%) did not describe an AE and were submitted only to report the 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 non-pregnancy-specific AEs, injection site reaction (n = 3; 3.7%) was most common. No disproportionate reporting of any AE was found.
Discussion: No unexpected AEs were observed among these pregnancy reports.

1. Introduction

9-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 [1,2]. Previously, quadrivalent (4vHPV) and bivalent (2vHPV) vaccines had been licensed for use [3]. 9vHPV has been the only human papillomavirus vaccine distributed in the United States since late 2016 [4]. 9vHPV includes HPV types 31, 33, 45, 52, and 58, as well as those contained in the other two HPV vaccines [5]. It contains twice the concentration of the adjuvant amorphous aluminum hydroxyphosphate sulfate as 4vHPV [5,6]. Pre-licensure studies of 9vHPV showed that the most common local and systemic adverse events (AEs) were mild in nature and consisted in injection site pain and headache [5].

9vHPV is not recommended for use during pregnancy due to limited data on its safety in pregnancy [5,7,8]. However, some women of childbearing age might be inadvertently exposed during catchup vaccination [7,9,10]. Studies following 2vHPV and 4vHPV administration during pregnancy did not reveal concerning patterns of pregnancy-specific or infant/neonatal outcomes following vaccine administration [9–13]. Initial pre-licensure clinical study data did not indicate an overall increased risk of stillbirth or major birth defects when 9vHPV was inadvertently administered to pregnant women, compared to 4vHPV [5,14]. The proportion of spontaneous abortions was higher following 9vHPV than 4vHPV, but it was not higher than the expected background occurrence of spontaneous abortion in the general population [5,14]. The pre-licensure studies were limited by insufficient power to study less common conditions. This study aims to evaluate reports submitted to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women exposed to 9vHPV.

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2. Methods

2.1. Data source

The VAERS database 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) [15]. One of its main purposes is to identify possible vaccine safety signals, such as rare AEs that may be missed in pre-licensure clinical trials [15–17]. 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 [15,18–20]. Healthcare providers and others, such as parents of patients and patients themselves, are encouraged to voluntarily report any AE following vaccination [15]. AEs described in VAERS reports are often temporally associated with vaccination and may or may not include conditions caused by vaccination [15,21]. Not all reports describe AEs, and some may describe a vaccination error (e.g., vaccine administered to a patient of inappropriate age) [22]. 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) [23]. Severe events were defined as: AEs that resulted in death, life-threatening illness, hospitalization, prolongation of hospitalization, disability or permanent damage, or a congenital anomaly [18]. Although other medically important conditions (OMIC) are categorized as serious in the Code of Federal Regulations, they were not counted as serious in this study [18].

2.2. 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 strategies were used: (1) searched for any of the following MedDRA preferred terms: "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 the time of vaccination, and pre-existing illness variables, and (3) searched for reports for which the reporter had answered "yes" to the question "Is the report about vaccine(s) given to a pregnant woman?".

2.3. Report review

All VAERS reports were reviewed to extract information on pregnancy status at the time of vaccination, AEs, AE severity, vaccination errors, and date of last menstrual period or expected date of delivery. Our search yielded information on vaccination date, maternal age at the time of vaccination, vaccines administered concomitantly, and reporter type. Reports that indicated a woman was not pregnant at the time of vaccination or received 9vHPV more than a month prior to her last menstrual period were excluded. Reports of women experiencing AEs prior to receiving 9vHPV or that described AEs associated with administration of an HPV vaccine other than 9vHPV were also excluded.

AEs were characterized as primary maternal, secondary maternal, primary infant, or secondary infant. Primary AEs were the main diagnoses determined by the reviewer based on information in the VAERS report. 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. If a VAERS report described AEs in more than one person (i.e., mother and exposed infant), we treated each person as a separate report. Primary maternal AEs were further classified as pregnancy-specific or non-pregnancy-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) [24,25].

Vaccination errors were noted when explicitly mentioned by the reporter or after review of the VAERS report. These errors were defined as: wrong drug administered (woman was administered 9vHPV when she should have been administered a different vaccine), drug administered to a patient of inappropriate age (woman was over the age of 26 when administered her first dose of 9vHPV), inappropriate schedule of drug administration (doses of 9vHPV did not follow the recommended 0, 1–2, and 6 month schedule or 0 and 6–12 month schedule, depending on the age of the woman), and extra dose administered (woman had already received three doses of HPV vaccine) [4,8,22].

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 [26]. This value was used to determine trimester of pregnancy, which was defined as: first (0–13 weeks), second (14–27 weeks), third (28+ weeks) [27].

2.4. Analysis

Frequencies and percentages of AEs and vaccination errors were calculated using SAS version 9.4 (SAS Institute Inc., Cary, NC). We assessed disproportionate reporting of AEs using proportional reporting ratios (PRRs) whereby the proportion of each MedDRA preferred term (e.g., spontaneous abortion) out of all MedDRA preferred terms after 9vHPV was compared to the proportion of the same MedDRA preferred term out of all MedDRA preferred terms after 4vHPV [28,29]. This method was chosen due to its relative simplicity and straightforward interpretation [28]. Reports that indicated vaccination with both HPV vaccines were excluded. 4vHPV is produced by the same manufacturer and uses the same adjuvant as 9vHPV, and these vaccines are similar 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 [3,5,6,9]. Given their similar composition and indications, 4vHPV was the natural comparison vaccine to use for 9vHPV [3,9].

For the 4vHPV vaccine comparison, we used VAERS reports identified from a previous study [9]. We ran two separate analyses, one of which included, and one of which excluded, manufacturer reports, as was done in the previous study [9]. 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 ≥ 3 reports in the 9vHPV group) [28]. Finally, we graphed trends of pregnancy reports following administration of 9vHPV and 4vHPV to assess how reporting changed over time.

VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research as stipulated in 45 CFR 46.102(d) [30]. Therefore, this investigation was not subject to institutional review board review or informed consent requirements.

3. Results

Our search strategy yielded 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) (Fig. 1). Thus, 80 pregnancy reports meeting inclusion criteria were identified and reviewed, two of which described both maternal and infant AEs, which were considered separately. Therefore, there were a total of 82 reports. The greatest number of reports was received in 2016 (Fig. 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 with known gestational age, 9vHPV was administered during the first trimester of pregnancy (n = 45; 75%) (Table 1). Median gestational age 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.

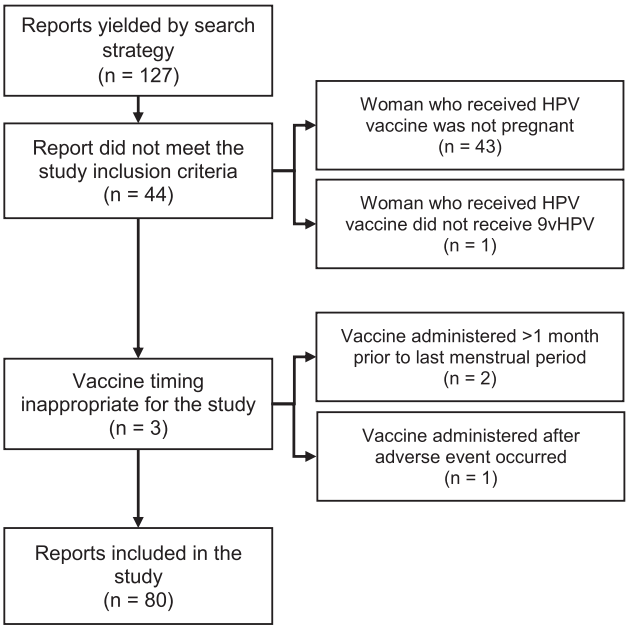

Fig. 1. Flow diagram of VAERS reports included and excluded in this study.

Table 1
US VAERS[a] reports in pregnant women following 9vHPV administration, 2014–2017 (n = 80).[b]

Characteristic		
Maternal age in years, median (range)[c]	21.5	(12–38)
Gestational age at time of vaccination in weeks, median (range)[d]	6.1	(0–37.1)
Trimester of pregnancy at time of vaccination (n = 60)[e]		
First (0–13 weeks), n (%)	45	(75.0)
Second (14–27 weeks), n (%)	7	(11.7)
Third (28+ weeks), n (%)	8	(13.3)
Reports of 9vHPV given with other vaccines, n (%)[f]	20	(25.0)
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] No serious reports were submitted.
[c] Maternal age was missing for 18 reports.
[d] Gestational age at time of vaccination was either not reported or unknown for 25 reports.
[e] Trimester of pregnancy at time of vaccination was either not reported or unknown for 20 reports.
[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.

Sixty reports (73.2%) did not describe an AE and were submitted due to vaccine exposure during pregnancy (Table 2). The most frequently reported pregnancy-specific AE was spontaneous abortion (n = 3; 3.7%), followed by vaginal bleeding (n = 2; 2.4%) (Table 2). Among non-pregnancy-specific AEs, injection site reaction (n = 3; 3.7%) was most common (Table 2). Two infant AEs were reported (Table 2). However, it is important to note that not all reports included follow-up through delivery; therefore, the total number of live births was not known. Only 25 reports provided information on the final outcome of the pregnancy (e.g., spontaneous abortion, elective abortion, live birth).

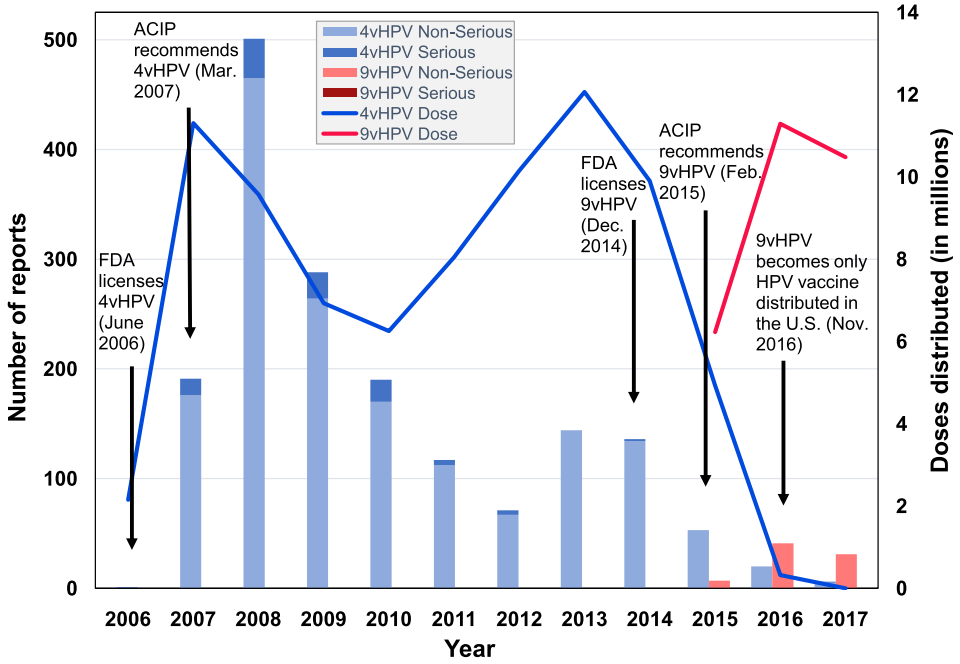

Fig. 2. Number of 9vHPV and 4vHPV pregnancy adverse event reports, both serious and non-serious, received in VAERS and doses of vaccine distributed, 2006–2017 [42].

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
Nausea/vomiting	1	1.2
Placenta previa	1	1.2
Polyhydramnios	1	1.2
Shoulder dystocia	1	1.2
Total	*10*	*12.2*
Non-pregnancy-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
Total	*2*	*2.4*
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.

Just over one-fifth of reports described a vaccination error (n = 17; 20.7%): five reports (29.4%) each indicated incorrect vaccine administration, vaccine administration to a patient of inappropriate age, and inappropriate schedule of vaccine administration, and two reports (11.8%) indicated an extra dose of vaccine administered. Among reports for which an incorrect vaccine was administered, four indicated that the woman should have received Tdap and one indicated the woman should have received influenza vaccine. Among reports for which the sole vaccination error was vaccine administration to a patient of inappropriate age, two indicated 9vHPV was administered to a woman age 27–30 years, two indicated a woman age 31–35 years, and one indicated a woman age 36–40 years. Among reports for which an extra dose of vaccine was administered, one indicated the woman had previously received three doses of 4vHPV and one indicated the woman had previously received three doses of 9vHPV. Of the 17 vaccination errors, 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).

The PRR analyses comparing 9vHPV and 4vHPV vaccines did not reveal disproportionate reporting of any AE.

4. Discussion

During the period of this review, VAERS received 2068 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 (60 of 82) did not describe an AE and were likely submitted because 9vHPV is not recommended in pregnant women [7]. Most 9vHPV pregnancy reports were received during 2016 and 2017 and, when considered alongside 4vHPV reporting trends, illustrate a Weber-like effect (Fig. 2) [31]. 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 [31]. Similar trends have been observed with other vaccines [32].

Among reports describing an AE, the pregnancy-specific conditions most frequently reported were spontaneous abortion (3.7% of reports) and vaginal bleeding (2.4% of reports), 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 [33–35]. A previous review of 4vHPV pregnancy reports in VAERS also found that spontaneous abortion was the most commonly reported pregnancy-specific AE [9]. 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 [10]. A similar registry was set up for 9vHPV; however, currently there are no safety data available [5].

Among non-pregnancy-specific AEs, the most commonly reported condition was injection site reaction (3.7% of reports), which is a known side effect of 9vHPV [5]. A recent review of the VAERS database found that the proportion of reports describing injection site reactions following 9vHPV among non-pregnant women varied from 6.3% to 8.8%, depending on the type of local reaction [36].

All other reported AEs in this study 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 injection site reaction. The PRR analyses did not reveal any safety signals.

The results of this study are in line with those of initial pre-licensure 9vHPV clinical study data, which did not indicate overall increased risks of stillbirth or major birth defects when 9vHPV was inadvertently administered to pregnant women, compared to 4vHPV [5,14]. In a pre-licensure study, the risk of spontaneous abortion was higher among women administered 9vHPV compared to 4vHPV (17/85 or 20.0% vs. 8/87 or 9.2%) within 30 days of pregnancy initiation; however, the number of cases in each group was relatively small [14]. Additionally, since these women were not randomly assigned to either group but, rather, were inadvertently exposed to the vaccine, there may be unrecognized confounders or biases that may explain these differing rates. Finally, the rates following 9vHPV were comparable to background rates of this condition [5,14]. The findings for 9vHPV are 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 [9–13]. An analysis of prospective reports of vaccine exposure during pregnancy from the United States, Canada, and France submitted to the vaccine manufacturer (Merck & Co., Inc.) registry did not find any concerning patterns of spontaneous abortions, fetal deaths, or birth defects following 4vHPV administration [10]. 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 [11]. Finally, two Vaccine Safety Datalink studies assessing the safety of 4vHPV during pregnancy did not find cause for concern [12,13]. One study, which compared outcomes of women who received 4vHPV during pregnancy or during the periconceptional period to those who received at least one dose of 4vHPV 4–18 months prior to their last menstrual period 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 significantly between groups [12]. The other study, which compared outcomes of women who received 4vHPV during pregnancy to those who received at least one dose of 4vHPV 16–22 weeks before their last menstrual period but not while pregnant or in the peripregnancy period, found that the risk of spontaneous abortion

did not differ significantly between groups [13]. 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.

VAERS' strengths lie in its flexibility and ability to quickly detect rare or previously unrecognized AEs [38]. This national system can provide near real-time information on the safety of vaccines before any safety data become available in other surveillance systems in the United States [39]. VAERS may also complement safety data from other systems (e.g., Vaccine Safety Datalink) or provide preliminary data before epidemiological studies are implemented and conducted [40]. However, it has a number of limitations, which in this study included lack of complete data and accuracy of reports [15]. 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 the 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 [39]. Underreporting or overreporting can be problematic, the first due to the primarily 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 nonserious reports [15,39]. In our study, the relatively small number of spontaneous abortion reports submitted likely represents substantial underreporting of this event, given its relative frequency during pregnancy [33,34].

5. Conclusion

The findings of this study appear to be reassuring as no unexpected AEs were observed among pregnant women exposed to 9vHPV. 9vHPV is not recommended during pregnancy; however, because of the age group in which it is indicated, it may be inadvertently administered to pregnant women who are unaware they are pregnant [7]. Therefore, monitoring the safety of the vaccine in this subpopulation is important, including in active surveillance systems such as CDC's Vaccine Safety Datalink. CDC routinely monitors the safety of 9vHPV in the United States and will continue to monitor the safety of this vaccine in pregnancy [41].

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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