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Spontaneous reports of primary ovarian insufficiency after vaccination: A review of the vaccine adverse event reporting system (VAERS)

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ABSTRACT

Background: Since 2012, reports of primary ovarian insufficiency (POI) temporally associated with receipt of human papillomavirus (HPV) vaccine have been published leading to questions about a potential causal association. A Vaccine Safety Datalink study did not find an increased risk for POI after vaccination. We reviewed the Vaccine Adverse Event Reporting System (VAERS) to describe POI reports.
Methods: We searched VAERS, a U.S. passive surveillance system, for domestic POI reports received from 01/01/1990 to 12/31/2017 after any vaccination. The search used both Medical Dictionary for Regulatory Activity Preferred Terms and a text-based search for POI and its symptoms. All reports were reviewed, and the American College of Obstetricians and Gynecologists (ACOG) guidelines for POI diagnosis were applied. Data mining for disproportionate reporting was conducted.
Results: Six hundred fifty-two reports met the search criteria and clinical review identified 19 POI reports. Most reports (n = 16) were received between 2013 and 2017. The median age at vaccination was 14.5 years (range 10–25 years) and the median interval between first dose of vaccination and reporting the event to VAERS was 43 months (range 4–132 months; mean 59.6 months). Four reports met ACOG diagnostic criteria; one with an underlying cause (47XXX chromosomal abnormality) reported. Eleven reports documented menstrual irregularity $\geq$ 3 months; 5 had $\geq$ 1 laboratory test result used to diagnose POI. Eighteen of 19 reports described receipt of HPV vaccine with or without other vaccines. Other vaccines reported were meningococcal conjugate vaccine, hepatitis A, varicella and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis. Disproportionate reporting was found for three relevant coding terms after HPV vaccination.
Conclusions: POI is rarely reported to VAERS. Most reports contained limited diagnostic information and were submitted after published cases of POI following HPV vaccination. Results of our review do not suggest a safety concern.

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1. Introduction

Primary ovarian insufficiency (POI), also referred to as "premature ovarian failure", "premature ovarian insufficiency", or "premature menopause", is characterized by loss of ovarian function before the age of 40 years. It is estimated to occur in 0.01 % of women under 20 years, 0.1 % under 30 years, and 1 % of women under 40 years of age [1]. The clinical and laboratory features of POI are due to depletion or dysfunction of ovarian follicles and includes menstrual irregularity (e.g., amenorrhea, oligomenorrhea), delayed puberty, symptoms of estrogen deficiency (e.g., hot flushes and vaginal dryness), and elevated serum gonadotropins [2–5]. POI increases the risk for infertility, but natural pregnancy due to spontaneous ovarian activity may occur [6].

The etiology of POI is complex and pathogenesis includes a smaller pool of primordial follicles, increased follicular atresia, and altered maturation or recruitment of primordial follicles [7–8]. In many cases, the cause remains unknown after extensive medical evaluation [3,9–10]. Genetic defects (e.g. Turner syndrome, Fragile X-associated disorders, and autoimmune polyendocrine syndrome) and iatrogenic factors (e.g., chemotherapy, radiotherapy, and surgery) are known causes [4–5]. Autoimmunity is known to cause disease in hormone-producing glands such as Hashimoto's thyroiditis and Addison's Disease [11]. The exact

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pathogenesis of autoimmune diseases is poorly understood, but it is assumed to arise from complex interactions between genetic traits and non-hereditary factors (e.g. infections, drugs, chemicals, diet, and vaccines) [12]. Autoimmunity has been proposed as a potential etiology for POI because some cases have been associated with autoimmune endocrinopathies (e.g. hypothyroidism and hypoadrenalism), and antibodies to steroid-producing cells or ovaries have been detected in some patients with POI [10,13–14].

Reports of POI onset temporally associated with receipt of quadrivalent human papillomavirus (HPV) vaccine [(4vHPV) Gardasil, Merck)] have been published [15–17]. Since 2007, the Advisory Committee on Immunization Practices (ACIP) has recommended routine HPV vaccination for female adolescents in the United States (U.S.) to prevent HPV infection; a sexually transmitted infection that causes anogenital warts and several cancers [18]. In addition to HPV vaccination, ACIP recommendations for routine vaccination of adolescents includes Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) vaccine, seasonal influenza vaccine and quadrivalent Meningococcal Conjugate Vaccine [19]. In a large, nationally representative sample of U.S. adolescents, among vaccinated females about half received HPV vaccine concomitantly with other vaccines [20]. To our knowledge, except for 4vHPV, there are no published reports or studies of POI onset temporally associated with receipt of other vaccines.

Although published reports of POI associated with 4vHPV have been widely publicized and have raised concerns about the potential impact of HPV vaccination on female fertility [21–24], a population-based study by Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink study (VSD) did not find a statistically significant increased risk of POI after receipt of HPV or other adolescent vaccines [25]. To further evaluate reports of POI after vaccination, we conducted a clinical review of POI reports following vaccination in the Vaccine Adverse Event Reporting System.

2. Material and methods

2.1. Vaccine Adverse Event Reporting System (VAERS)

Established in 1990 and co-administered by CDC and the U.S. Food and Drug Administration (FDA), VAERS is a spontaneous reporting system for adverse events (AE) following vaccination. It serves as the national early warning system for detecting possible safety problems with U.S. licensed vaccines [26]. VAERS is not designed to evaluate a causal relationship between an AE and a vaccine but can detect possible vaccine safety problems that require further investigation using more robust systems and study designs.

VAERS accepts reports from anyone including healthcare providers, vaccine recipients, vaccine manufacturers and the general public. VAERS collects demographic information, medical history, type of vaccines administered, and a description of the AE experienced. Following receipt of a report, certified personnel code the signs, symptoms, past medical history, investigations, diagnoses and medical procedures using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology. The information in each report and the assigned MedDRA preferred terms (one or more) are entered into the database. In addition, each report is categorized as non-serious or serious using the FDA regulatory definition [27]. A report is coded as serious if an AE resulted in one or more of the following: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, birth defect, or permanent disability. Medical records are routinely requested and reviewed by physicians for serious events and pre-specified medically important conditions, such as anaphylaxis after influenza vaccines.

We searched VAERS from January 1, 1990 through December 31, 2017 (archived data from April 30, 2018) to identify U.S. reports of POI. An automated search using methods previously published [28–30] was conducted without restriction on age or vaccine type. The following MedDRA preferred terms (PT) were used: "Premature Menopause", "Ovarian Disorder", "Ovarian Failure", "Amenorrhea", "Infertility", "Infertility Female", "Blood Follicle Stimulating Hormone Increased", "Oestradiol Decreased", and "Estradiol Decreased". To ensure a more thorough search, a text-based search using the terms "Ovarian", "Amenorrhea" and "Premature Menopause" was also conducted. Duplicate reports were identified, and a final list of unique reports was created for further evaluation.

2.2. Clinical review of reports

Each report (including any available medical records) was manually reviewed by CDC physicians. Reports of cases of individuals with age at vaccination < 10 years or ≥ 35 years, and hearsay reports (i.e., case was heard indirectly by the reporter through the Internet or from an individual who is not involved with the care of the patient) were excluded. POI cases were identified through review of included reports and accompanying medical records if available. Fifty randomly selected reports were also reviewed to ensure consistency in the review process.

There is no consensus diagnostic criteria or case definition for POI. However, a commonly used diagnostic guideline proposed by the American College of Obstetricians and Gynecologists (ACOG) is follicle-stimulating hormone (FSH) levels in the post-menopausal range and low estradiol level on two separate occasions (minimum 1-month interval), associated with menstrual irregularities for ≥ 3 consecutive months [2].

The ACOG guidelines [2] was used as a guide to further characterize the POI cases as follows:

(1) Confirmed POI: All of the following were present:
- Menstrual irregularities for ≥ 3 consecutive months
- Follicle-stimulating hormone (FSH) in the post-menopausal range on ≥ 2 separate occasions ≥ 1-month apart
- Low estradiol level on ≥ 2 separate occasions ≥ 1 month apart

(2) Possible POI:
a. One of the following was present
- Menstrual irregularity for ≥ 3 consecutive months and one test result showing FSH level in postmenopausal range

OR
- Menstrual irregularity for ≥ 3 consecutive months and one test result showing low estradiol level

b. Report of POI diagnosed by a healthcare provider but without clinical information to assess duration of menstrual irregularity, or laboratory information to determine if elevated FSH or low estradiol was present.

An FDA physician who is board-certified in gynecology conducted an independent review of all POI cases identified by CDC physicians to adjudicate if each POI case was a "Confirmed POI", "Possible POI" or "Not POI case" using the guidelines above. Discrepant conclusions were discussed and resolved by both CDC and FDA physicians.

2.3. Data mining

We used the Multi-Item Gamma Poisson Shrinker algorithm in the Oracle Empirica Signal system to conduct empirical Bayes data mining among reports with female or unknown sex to assess disproportionality in AE reporting among all vaccines in the VAERS database [31–33]. The analyses (data lock point, July 9, 2020) were adjusted for sex and calendar year in which the report was received. The main statistical scores computed were the empirical Bayes Geometric Mean (EBGM) and the 90 % confidence interval (EB05, EB95). An elevated data mining statistic should be interpreted as a potential signal for further evaluation [32]. The EBGM does not reflect the magnitude of association between the vaccine of interest and an AE but provides an estimate of the relative reporting of an event for the vaccine of interest relative to all other vaccines and events in the VAERS database. An EB05 of ≥ 2.0 is commonly used as a criterion for considering an AE a potential signal because such a value suggests a high probability of the vaccine-event pair occurring at least twice as often as expected under the assumption that vaccine-events are randomly paired [32].

3. Ethics

Because VAERS is a routine surveillance program designed to improve an immunization program, it does not meet the definition of research; therefore, this work was not subject to Institutional Review Board evaluation and informed consent requirements.

4. Results

4.1. Clinical review

From January 1, 1990, through December 31, 2017, VAERS received a total of 571,178 U.S. reports. Our search criteria identified 652 unique reports of menstrual irregularity (including amenorrhea) or infertility. After excluding 154 reports [hearsay reports (n = 44) and reports with age of vaccination < 10 years or ≥ 35 years (n = 110)], 498 reports were retained for clinical review (Fig. 1). Most reports [452 (90.8 %)] were received between January 1, 2007 and December 31, 2017 and the most common vaccines reported were HPV vaccine [n = 385 (77.3 %)], influenza vaccine [n = 43 (8.6 %)], tetanus toxoid-containing vaccines [n = 42 (8.4 %)], meningococcal conjugate vaccine [n = 36 (7.2 %)], and varicella vaccine [n = 30 (6 %)].

Only 277 (55.6 %) reports and available medical records contained sufficient information to aid the determination of an underlying etiology for the menstrual irregularity (including amenorrhea) or infertility. Nineteen cases of POI were identified. Table 1 shows the characteristics of POI reports compared with non-POI reports and a clinical summary of POI cases is shown in Table 2. Most POI cases [n = 16 (84.2 %)] were reported to VAERS between 2013 and 2017. In the 13 reports with information

Table 1
Descriptive characteristics of POI and Non-POI reports following vaccination in the Vaccine Adverse Event Reporting System (VAERS) January 1, 1990- December 31, 2017.

Characteristics	POI cases n=19	Non-POI cases n=258
Reports obtained from PT search only	3 (15.8%)	19 (7.4%)
Year of vaccination (range)	2006 – 2016	1990 – 2017
1990 to 1999	0 (0%)	10 (3.9%)
2000 to 2009	7 (36.8%)	126 (48.8%)
2010 to 2017	6 (31.6%)	90 (34.9%)
Missing date	6 (31.6%)	32 (12.4%)
Year report received VAERS (range)	2007 – 2017	1990 – 2017
1990 to 1999	0 (0%)	8 (3.1%)
2000 to 2009	3 (15.8%)	111 (43%)
2010 to 2017	16 (84.2%)	139 (53.9%)
Median age at vaccination (range), years	14.5 (10 – 25)	18 (11 -34)
Missing age (n [%)])	3 (15.8%)	22 (8.5%)
Serious report[a]	8 (42.1%)	110 (42.6%)
Only one vaccine type listed in report	16 (84.2%)	208 (80.6%)
Type of reporter		
Manufacturer	9 (47.4%)	133 (51.6)
Patient/Parent	8 (42.1%)	62 (24%)
Healthcare Provider	2 (10.5%)	29 (11.2%)
Other	0 (0%)	36 (14%)

[a] Defined as a report of any of the following: death, life-threatening illness, hospitalization, prolongation of hospitalization, birth defect, or permanent disability.

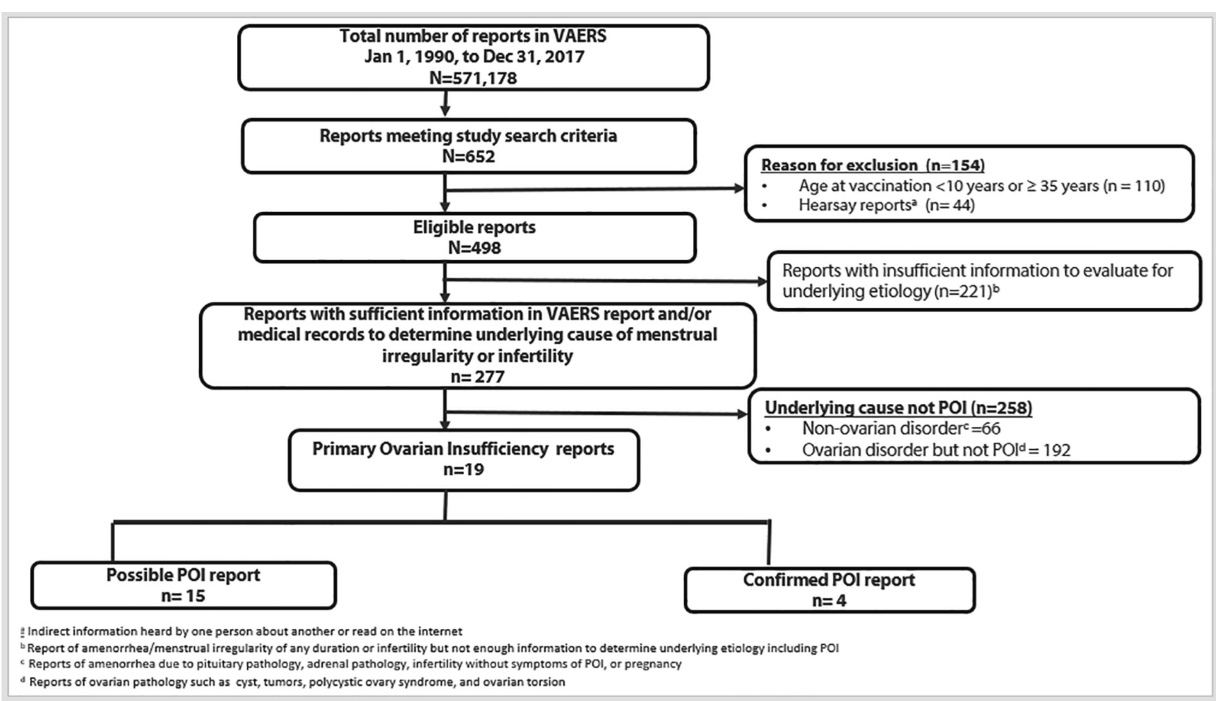

Fig. 1. Search strategy and review process to identify reports of primary ovarian insufficiency in the Vaccine Adverse Event Reporting System (VAERS), January 1, 1990 – December 31, 2017.

Table 2
Clinical summary of POI cases in the Vaccine Adverse Event Reporting System (VAERS) January 1, 1990- December 31, 2017.

Case Number	Age/Year vaccinated[a]	Vaccine(s) reported	Age POI diagnosed (years)	FSH/Estradiol levels	Additional information
Confirmed POI Cases[b]					
1	13 yr/2008	4vHPV	Unknown	FSH 27.86 µIU/ml and 96.5 µIU/ml Estradiol [34 pg/ml and 23 pg/ml]	• Year reported to VAERS: 2009. Menarche at 11 years. Amenorrhea onset after last dose of 4vHPV; approximately 8 months prior to evaluation by gynecologist. Diagnosed with premature menopause. Pelvic ultrasound and karyotype reported as normal.
2	23 yr/2010	4vHPV	23	FSH 78.2 mU/mL and 14.4 mU/mL Estradiol 59 pg/ml and140pg/ml	• Year reported to VAERS: 2013 Menarche 14 years. Stated oral contraceptive same day as vaccination. Onset of amenorrhea after vaccination. Evaluated by gynecologist within 2 months after vaccination for hot flushes for ~ 2 weeks, vaginal dryness, 3Ib weight loss and fatigue. Diagnosed with premature ovarian failure.
3	25 yr/2006	4vHPV	29	FSH 101.5mIU/ml and 92.35 U/L Estradiol = 8.5	• Year reported to VAERS: 2014 Menarche at age 13. Oral contraceptives (OCP) initiated at age 14 years for irregular periods. ~ 3 years after vaccination, discontinued OCP to conceive a child and was unsuccessful. Evaluated for infertility and diagnosed with premature ovarian failure. Normal female karyotype and pelvic ultrasound.
4	21 yr/2007	4vHPV	30	FSH 78.3mIU/ml and 59.7mIU/ml Estradiol = 28.3 pg/ml and 100 pg/ml	• Year reported to VAERS: 2017 History of irregular periods since menarche treated with oral contraceptive pills (OCP). Vaccinated with 3 doses of Gardasil between 2007 and 2008. Amenorrhea, hot flushes and hair thinning noticed after discontinuing OCP. Gynecologist diagnosed premature ovarian failure. Chromosomal analysis 46 XX and negative for Fragile X syndrome. Pelvic sonogram showed heterogeneous uterus without discrete fibroid and relatively small ovaries.
Possible POI Cases					
5	18 yr/2007	4vHPV	18	Not provided	• Year reported to VAERS: 2007 Amenorrhea of 2 months duration that began concurrent with receipt of vaccine dose #1. However, report also provides a date for onset date of amenorrhea that is 5 days after receipt of dose #2. Diagnosed with premature ovarian failure and Hashimoto's thyroiditis.
6	17 yr/2007	4vHPV, MenACWY-D, and Hepatitis A	~22	Not provided	• Year reported to VAERS: 2011 In 2009, reported severe pneumonia sinusitis, ear infection, diarrhea, vomiting, flu-like illness, chronic fatigue and alopecia. Report updated in 2011 with pyruvate kinase deficiency and a recent diagnosis of being post-menopausal. Onset of menstrual change 10 months after 1st vaccination in 2007.
7	Unknown	4vHPV	Unknown	Not provided	• Year reported to VAERS: 2013 14-year-old female patient diagnosed with premature menopause. No other clinical information including laboratory test result provided.
8	Unknown	4vHPV	Unknown	Not provided	• Year reported to VAERS: 2014 Report made by a registered nurse about a female patient who was diagnosed with premature ovarian failure by a physician in the facility. No other clinical information including laboratory test result was provided.
9	15 yr/2013	4vHPV and Influenza vaccine	16	Not provided	• Year reported to VAERS: 2014 Regular periods for 3 years prior to vaccination. At an unknown interval after 1st dose of vaccine, noticed very light period. Onset of amenorrhea at an unspecified date. Evaluated by reproductive endocrinologist and was found to have low ovarian reserve and anti-mullerian hormone level. Diagnosed with ovarian insufficiency and Raynaud's disease. No other clinical information including laboratory
10	11 yr/2011	4vHPV	15	Not provided	• Year reported to VAERS: 2014 Left oophorectomy due to ovarian torsion one-month prior to vaccination. Onset of abnormal menstrual periods after oophorectomy attributed to oral contraceptives pills given to regulate menstrual period. First dose of 4vHPV given approximately one month after oophorectomy. Evaluated by a biomedical physician 3 years after vaccination and diagnosed with ovarian failure
11	Unknown	4vHPV	Unknown	Not provided	• Year reported to VAERS: 2015 Vaccine administrator reported a patient was diagnosed with primary ovarian insufficiency. No other clinical information including laboratory test result provided.
12	12yrs/2010	Tdap (Boostrix®) and Varicella vaccine	18	FSH 53.9mIU/ml Estradiol 113 pg/ml	• Year reported to VAERS: 2016 Menarche at age 14 years. Presented 6 years after vaccination with irregular period and hot flushes of unknown duration; amenorrhea for 2 months. Diagnosed with premature ovarian failure by pediatric endocrinologist and reproductive endocrine gynecologist. Provider noted report was done because Boostrix® contains polysorbate 80; an ingredient also found in 4vHPV. Karyotype 47XXX.
13	Unknown/ 2008	4vHPV	Unknown	Not provided	• Year reported to VAERS: 2016 Report made by a physician assistant about a patient who was diagnosed with myasthenia gravis and premature ovarian failure. No other clinical information including laboratory test result was provided.

(*continued on next page*)

Table 2 (*continued*)

Case Number	Age/Year vaccinated[a]	Vaccine(s) reported	Age POI diagnosed (years)	FSH/Estradiol levels	Additional information
14	10 yr/2007	4vHPV	16	Not provided	• Year reported to VAERS: 2016 Report made by a physician. In 2013 during a visit to an emergency department for unspecified symptoms, she was referred to a fertility institution for evaluation and was subsequently diagnosed with premature ovarian failure based on "high hormone levels". No other clinical information including laboratory test result was provided.
15	~14 yr/ 2014	4vHPV	~15	Not provided	• Year reported to VAERS: 2016 Report made by a physician about a 16-year old female on progesterone and estradiol patch to induce menses. On an unknown date in 2015, she experienced amenorrhea and was diagnosed with primary ovarian failure based on rising FSH and LH. No other clinical information including laboratory test result was provided.
16	12 yr/2007	4vHPV, MenACWY-D, and Hepatitis A	Unknown	Not provided	• Year reported to VAERS: 2016 Menarche between 11 and 12 years old. Normal puberty and menses before vaccination. After vaccination, had amenorrhea, cold intolerance and difficulty falling asleep of unknown duration. Evaluation by gynecologist for secondary amenorrhea and was diagnosed with premature ovarian failure, Hashimoto's disease, fibromyalgia, and chronic fatigue.
17	Unknown	9vHPV	18	Not provided	• Year reported to VAERS: 2017 On an unknown date, after receiving the vaccination with 9vHPV, the patient was diagnosed with premature ovarian failure. No other clinical information including laboratory test result was provided.
18	~18 yr/ 2006	4vHPV	?29	Not provided	• Year reported to VAERS: 2017 29-year-old on Mirena®. At an unknown date after completing all doses (reported as "recently"), she was diagnosed with ovarian insufficiency by a gynecologist. No other clinical information including laboratory test result was provided.
19	14–15 yr/ Unknown	9vHPV	16	Not provided	• Year reported to VAERS: 2017 Onset of menorrhea after last vaccine dose. At an unspecified interval, she was evaluated by a pediatric endocrinologist and diagnosed with ovarian failure.

4vHPV= Quadrivalent HPV vaccine 9vHPV= Nine valent HPV vaccine; Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed; FSH= Follicle-stimulating hormone.

[a] For multiple dose vaccines, used the year of administration of the first dose.

[b] Confirmed POI cases i.e. met all ACOG diagnostic criteria (1) Menstrual irregularities for ≥3 consecutive months (2) Follicle-stimulating hormone (FSH) in the post-menopausal range on ≥2 separate occasions ≥1-month apart and (3) Low estradiol level on ≥2 separate occasions ≥1 month apart.

on the date of first dose of vaccination, the median interval between the date of first dose of vaccination and the date the event was reported to VAERS was 43 months (range 4–132 months; mean = 59.6 months). Only 2 reports specified the time to onset of POI symptoms: Table 2 Case #2 (~2 months) and Case #6 (10 months)]. Eleven reports described menstrual irregularity ≥ 3 months, 5 reported ≥ 1 laboratory result consistent with a diagnosis of POI, and 4 met the study criteria for Confirmed POI (Table 2). An underlying cause for POI was reported in one case (Table 2 Case #12); 47XXX chromosomal abnormality. Eighteen cases reported receipt of HPV vaccine: three concurrently with other vaccines (meningococcal conjugate vaccine, hepatitis A vaccine, varicella vaccine, and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine).

4.2. Data mining

There were three vaccine–event pairs reported at least twice as often as expected among female or unknown sex with all three reported following HPV vaccination (Gardasil). We observed disproportionate reporting for the PTs Amenorrhea, Premature Menopause, and Infertility Female.

5. Discussion

Menstrual irregularities (including amenorrhea) and female infertility were infrequently reported to VAERS. Among these reports, POI cases were rare. To ensure our search for POI reports was thorough, we used two different automated search methods and included a wide range of diagnosis code and symptoms that are associated with POI. In addition, we conducted a clinical review of all reports and found that only about half the reports included enough clinical information for the reviewers to determine the underlying etiology of the reported symptoms. Of the 19 POI diagnosis identified, only five included at least one laboratory test result required to diagnose POI.

POI, irrespective of its etiology, is a rare disease with insidious onset and variable clinical presentation [4,34]. These characteristics often result in the inability to properly define its onset, delay in clinical evaluation, and delay in making a diagnosis [35]. Delay in diagnosis is especially likely to occur during the adolescent period when menstrual irregularities frequently occur [36,37]. VAERS reports may contain incomplete information. In our study, only 2 reports had information about the onset of symptoms and one of these (Case 2) contained conflicting information regarding the precise sequence of events.

To our knowledge, there are six published case reports of POI onset after vaccination and all were reported in adolescents and young adults after receipt of 4vHPV [15–17]. There have also been two cases reported after 4vHPV in the media [22,23] but it is unclear if these overlap with those published in medical journals. The wide media publicity given to these cases may have influenced reporting of POI-related symptoms to VAERS. Although a large proportion of adolescents receive other vaccines on the same day as HPV vaccine,[20] most of the POI reports identified in our search listed only receipt of HPV vaccine. Similar to the study by Gong et al,[38] data mining in our study observed disproportionate reporting of POI related PTs in VAERS compared to other vaccines. However, compared to Gong et al,[38] our study included clinical review of VAERS report and medical records if available. Although majority of reports identified in our study noted receipt of HPV vaccine (with or without other vaccines), clinical review determined that the AEs contained in most reports were either pregnancy- related (such as amenorrhea due to pregnancy), hearsay reports, or also noted the presence of other conditions that cause symptoms similar to POI such as pituitary pathology and polycystic ovary syndrome.

VAERS, a spontaneous national system, can be used to generate hypotheses regarding adverse events following vaccination that require further evaluation using more robust research methods [39]. Despite disproportionate reporting of POI related terms in VAERS, our clinical review showed most of these reports are not POI cases. Several limitations of empirical Bayes data mining also need to be considered. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they indicate statistical associations that may serve as a signal for further investigation. Data mining cannot differentiate between an emerging association and an existing association. Additionally, EBGM is a disproportionality statistic, so it is dependent on the number of cases/reports with the vaccine, event, vaccine-event combination and the number of reports in the database. Consequently, changes relative to any of these can affect EBGM. In addition, a study by Naleway et al[25] conducted in VSD using a more robust research method, did not find a statistically significant elevated risk of POI after receipt of routine adolescent vaccines including HPV vaccines [age-adjusted hazard ratio was 0.30 (95 % CI: 0.07–1.36) after HPV vaccination, 0.88 (95 % CI: 0.37–2.10) after Tdap, 1.42 (95 % CI: 0.59–3.41) after inactivated influenza vaccination, and 0.94 (95 % CI: 0.27–3.23) after MenACWY vaccination].

As previously described, VAERS is subject to many limitations [26]. Because VAERS relies on voluntary reporting, underreporting and stimulating reporting can occur. In addition, reports can only be made after the adverse events occur and are recognized to be possibly related to receipt of a vaccine. For POI, there may be significant underreporting due to the insidious onset, the prolonged length of time between onset and diagnosis, and the recognition of possible association with vaccination. However, there may also be stimulating reporting of menstrual irregularities after receipt of a specific vaccine based on widespread publicity. The variability in clinical presentation posed an additional challenge in identifying POI reports in VAERS. To overcome this limitation, we used a broad range of search terms, but this also resulted in pulling many reports unrelated to POI including pregnancy, ovarian pathology, and polycystic ovary syndrome. Lastly, it is not possible to calculate the incidence or prevalence of POI using VAERS because the system does not collect the number of vaccine doses administered.

6. Conclusion

Our clinical review of VAERS found very few reports of POI after vaccination, and most contained limited diagnostic information. Most reports were submitted after media publicity of POI onset after HPV vaccination. Results of our review do not suggest a safety concern.

7. 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 or Food and Drug Administration.

Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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