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Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009–2015

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ABSTRACT

Background: The Food and Drug Administration (FDA) approved quadrivalent human papillomavirus vaccine (4vHPV) for use in females and males aged 9–26 years, since 2006 and 2009 respectively. We characterized reports to the Vaccine Adverse Event Reporting System (VAERS), a US spontaneous reporting system, in females and males who received 4vHPV vaccination.

Methods: We searched VAERS for US reports of adverse events (AEs) following 4vHPV from January 2009 through December 2015. Signs and symptoms were coded using Medical Dictionary for Regulatory Activities (MedDRA). We calculated reporting rates and conducted empirical Bayesian data mining to identify disproportional reports. Clinicians reviewed available information, including medical records, and reports of selected pre-specified conditions.

Findings: VAERS received 19,760 reports following 4vHPV; 60.2% in females, 17.2% in males, and in 22.6% sex was missing. Overall, 94.2% of reports were non-serious; dizziness, syncope and injection site reactions were commonly reported in both males and females. Headache, fatigue and nausea were commonly reported serious AEs. More than 60 million 4vHPV doses were distributed during the study period. Crude AE reporting rates were 327 reports per million 4vHPV doses distributed for all reports, and 19 per million for serious reports. Among 29 verified reports of death, there was no pattern of clustering of deaths by diagnosis, co-morbidities, age, or interval from vaccination to death.

Interpretation: No new or unexpected safety concerns or reporting patterns of 4vHPV with clinically important AEs were detected. Safety profile of 4vHPV is consistent with data from pre-licensure trials and postmarketing safety data.

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1. Introduction

Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine, Gardasil® (4vHPV), was licensed by the US Food and Drug Administration (FDA) in 2006 and approved for females 9–26 years old [1]. In 2009, 4vHPV was approved for males 9–26 years old [2,3]. 4vHPV is indicated for prevention of vaccine type-associated cervical and other anogenital cancers, neoplasias and warts and was recommended as a three dose series over a 6-month period [4–6]. In pre-licensure clinical trials, injection site pain and mild systemic reactions occurred most commonly [4]. The Advisory Committee on Immunization Practices recommends routine HPV vaccination beginning at 11 or 12 years of age, since 2006 for females and since 2011 for males [5,6].

A review of the first 2.5 years (June 2006 through December 2008) of 4vHPV post-licensure safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), after approximately 23 million doses had been distributed, revealed higher than expected

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reporting for venous thromboembolism and syncope [7]; but generally, no other potential safety signals were observed. Subsequent epidemiologic studies in the United States and Europe did not detect an increased risk of venous thromboembolism following 4vHPV [8–10]. Studies assessing autoimmune and neurological conditions after 4vHPV have also been consistent with prelicensure data [8–13]. A study in France found an apparently increased risk of Guillain-Barré syndrome (GBS) following 4vHPV vaccination [14]. However, a recent study in the US vaccine safety datalink found no evidence of an increased risk of GBS following 4vHPV [15]. Syncope has been previously reported and the National Academy of Medicine concluded that syncope can result from any injected vaccine [16].

From 2009 through 2015, 4vHPV accounted for most (over 90%) of the human papillomavirus vaccine distributed in the United States [17,18]. We analyzed reports submitted to VAERS following 4vHPV from 2009 through 2015 to provide updated safety information, assessed selected rare adverse events (AE) that have more recently emerged as alleged safety concerns, and included data for males, which was lacking in the first VAERS review.

2. Methods

2.1. Study population

VAERS is a national spontaneous reporting system for AEs following US-licensed vaccines [19]. It is co-administered by the Centers for Disease Control and Prevention (CDC) and the FDA. VAERS accepts reports from patients, parents, healthcare providers, vaccine manufacturers, and others. The VAERS reporting form collects information on the vaccinated individual, vaccines administered and the AE itself. Signs and symptoms of the AE are coded using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [20]. A single VAERS report may be assigned more than one MedDRA Preferred Term. Preferred terms are not necessarily medically-confirmed diagnoses. Reports are classified as "serious" based on the US Code of Federal Regulations if any of the following are documented: hospitalization, prolongation of existing hospitalization, permanent disability, life-threatening illness, or death [21]. Except for reports submitted by vaccine manufacturers, medical records are requested for reports designated as serious; for reports of death, autopsy reports and death certificates are also requested to ascertain cause of death. Manufacturers are responsible for conducting appropriate follow-up on their reports.

We included VAERS reports following 4vHPV for persons vaccinated from 2009 through 2015 and received by January 31, 2016, to account for reporting and data lags. For reports with missing vaccination date, we included those received from 2009 through 2015 and imputed vaccination date based on historical lag times. We excluded foreign source (non-US) reports. VAERS is used to conduct routine surveillance as a public health function; therefore, it is not subject to Institutional Review Board review and informed consent requirements.

2.2. Study design

We conducted descriptive analyses of VAERS data, calculated crude 4vHPV AE reporting rates based on vaccine doses distributed, performed clinical review of reports for selected pre-specified conditions of interest, and conducted empirical Bayesian data mining to identify AEs reported more frequently than expected following 4vHPV compared to other US-licensed vaccines. Dose number in a vaccination series is often missing or inconsistently reported in VAERS; therefore, we did not analyze 4vHPV data by dose number.

2.3. Outcome measures and statistical methods

2.3.1. Data analysis

We summarized basic characteristics of reports by severity, type of reporter, patient age and AE onset interval. We stratified by sex and assessed the most common MedDRA Preferred Terms for all 4vHPV reports and for reports where 4vHPV was administered alone. Pre-specified conditions for clinical review were chosen based on information from previous post-licensure studies and surveillance, and from public concern about specific AEs [7–15]. We calculated crude AE reporting rates for the following pre-specified conditions: syncope, venous thromboembolism, anaphylaxis, a composite of selected autoimmune disorders, postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS), Guillain-Barré syndrome (GBS), and death (Appendix).

2.3.2. 4vHPV adverse event reporting rates

We calculated crude 4vHPV AE reporting rates for all reports and serious reports by dividing the number of reports by 4vHPV doses distributed in the United States from 2009 through 2015; we also graphically depicted annual crude reporting rates from 2006 through 2015 to display historical reporting trends. Crude reporting rates were calculated for the pre-specified conditions. Because we were not able to determine doses distributed for a particular sex, we could not calculate a reporting rate by sex for any diagnosis or for any sex-specific conditions.

2.3.3. Clinical review of reports of selected pre-specified conditions

Physicians reviewed all reports of GBS, anaphylaxis, CRPS, primary ovarian insufficiency (POI), POTS, and death (Appendix). Reports suggestive of GBS and anaphylaxis were classified according to Brighton Collaboration criteria [22,23]. Cause of death was determined by autopsy report, death certificate or medical records. Syncope, venous thromboembolism, and reports in pregnant women and of infants born to mothers who were pregnant at the time of 4vHPV receipt have been previously published, and selected autoimmune disorders have been extensively studied in databases that allow for calculation of incidence rates [7–13,15,16,24–27]; therefore, this summary will not focus on those conditions.

2.3.4. Empirical Bayesian data mining

We used published methods and criteria [28–30] to identify 4vHPV-AE pairs reported at least twice as frequently as expected (i.e., lower bound of the 90% confidence interval surrounding the empirical Bayesian geometric mean [EB05 $\geq$ 2]) compared to all other US-licensed vaccines. After assessing findings for biological plausibility and clinical significance, we reviewed reports with AEs that exceeded this data mining threshold and had not previously been assessed or identified and characterized in the prelicensure clinical trials or other post-marketing studies.

3. Results

From 2009 through 2015, VAERS received 19,760 US reports following 4vHPV (Table 1). Females accounted for 11,894 (60.2%) reports, males 3391 (17.2%), and in 4475 (22.6%) sex was unknown or not reported. Overall, 94.2% of reports were non-serious; most reports (40.7%) were in the persons aged 11–17 years. Most reports came from vaccine manufacturers (56.6%) followed by healthcare providers (28.1%). Median time from receipt of 4vHPV to start of symptoms was on the day of vaccination and ranged up to 5 years. The 90th percentile for symptom onset for all reports was within 2 weeks of vaccination. In 28.3% of reports other vaccines were

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