Vaccine 34 (2016) 172–178

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females

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ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form
24 September 2015
Accepted 25 September 2015
Available online 6 November 2015

Keywords:
HPV vaccine
Vaccine safety
Postmarketing product safety
Venous thromboembolism
Research design

ABSTRACT

After the Food and Drug Administration (FDA) licensed quadrivalent human papillomavirus vaccine (HPV4) in 2006, reports suggesting a possible association with venous thromboembolism (VTE) emerged from the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink. Our objective was to determine whether HPV4 increased VTE risk.

The subjects were 9–26-year-old female members of five data partners in the FDA's Mini-Sentinel pilot project receiving HPV4 during 2006–2013. The outcome was radiologically confirmed first-ever VTE among potential cases identified by diagnosis codes in administrative data during Days 1–77 after HPV4 vaccination. With a self-controlled risk interval design, we compared counts of first-ever VTE in risk intervals (Days 1–28 and Days 1–7 post-vaccination) and control intervals (Days 36–56 for Dose 1 and Days 36–63 for Doses 2 and 3). Combined hormonal contraceptive use was treated as a potential confounder. The main analyses were: (1) unadjusted for time-varying VTE risk from contraceptive use, (2) unadjusted but restricted to cases without such time-varying risk, and (3) adjusted by incorporating the modeled risk of VTE by week of contraceptive use in the analysis.

Of 279 potential VTE cases identified following 1,423,399 HPV4 doses administered, 225 had obtainable charts, and 53 were confirmed first-ever VTE. All 30 with onsets in risk or control intervals had known risk factors for VTE. VTE risk was not elevated in the first 7 or 28 days following any dose of HPV in any analysis (e.g. relative risk estimate (95% CI) from both unrestricted analyses, for all-doses, 28-day risk interval: 0.7 (0.3–1.4)). Temporal scan statistics found no clustering of VTE onsets after any dose.

Thus, we found no evidence of an increased risk of VTE associated with HPV4 among 9–26-year-old females. A particular strength of this evaluation was its control for both time-invariant and contraceptive-related time-varying potential confounding.

1. Introduction

In June 2006, the Food and Drug Administration (FDA) approved the quadrivalent human papillomavirus vaccine (HPV4; Gardasil; Merck) for the prevention of anogenital cancers, associated precancerous lesions, and genital warts caused by human papillomavirus types 6, 11, 16, and 18. HPV4 is routinely recommended as a

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http://dx.doi.org/10.1016/j.vaccine.2015.09.087

three-dose series (0, 1–2, and 6 months) for those aged 11–12 years but can be administered as young as age 9 years; catch-up vaccination is recommended for females aged 13–26 years and males aged 13–21 years who have not been previously vaccinated [1]. No safety issues were identified in pre-licensure studies involving approximately 21,000 subjects aged 9–26 years [2].

Post-licensure surveillance identified a possible increased risk of venous thromboembolism (VTE) after HPV4 vaccination. In the first 2.5 years of passive surveillance in the Vaccine Adverse Events Reporting System (VAERS), VTE was reported more frequently following HPV4 than expected using other vaccines for comparison [3]. However, 90% of the reported cases had at least one pre-existing known risk factor, and most of the comparison vaccines were childhood vaccines, suggesting that the prevalence of VTE risk factors among adolescents may have explained the disproportionate reporting. To supplement passive surveillance, in the first 3 years after licensure, the Vaccine Safety Datalink (VSD) monitored 600,558 HPV4 doses administered to females aged 9–26 years, checking for increased risks of eight outcomes using sequential analysis methods [4]. No safety signals were detected. However, there was a statistically non-significant relative risk of 1.98 for VTE after HPV4 administration among females aged 9–17 years using a historical comparison group. (If the incidence of adolescent VTE has been increasing [5], historical controls could have produced bias.) The eight post-HPV4 VTE cases producing this estimate were chart-reviewed, and five were confirmed. The VTE diagnosis in four of the five confirmed cases occurred within 7 days after vaccination; the fifth occurred on Day 32. All five cases had at least one known risk factor—contraceptive use, coagulation disorders, smoking, obesity, or prolonged hospitalization. No elevated risk was detected after HPV4 vaccination among females aged 18–26 years.

In December 2010, this information was presented to the FDA Pediatric Advisory Committee as part of a routine safety review [6]. The committee recommended that additional surveillance studies be conducted to further evaluate the risk of VTE, leading to the current study by the Mini-Sentinel/Post-licensure Rapid Immunization Safety Monitoring (PRISM) program [7]. Our objective was to evaluate the risk of VTE following HPV4 vaccination, considering the role of combined hormonal contraceptives (called "contraceptives" below) as a potential confounder or effect modifier.

Three studies finding no association between HPV4 and VTE were published after the launch of our investigation [8–10]. These are discussed later.

2. Methods

2.1. Study population and data sources

The study population consisted of female HPV4 vaccinees 9–26 years of age from five Mini-Sentinel Data Partners (Aetna, HealthCore, Humana, Optum, and Tennessee Medicaid) during a maximum period of June 2006–June 2013. Inclusion required continuous enrollment, with medical and pharmacy coverage, from 4 months before through at least 70 days after the first dose of HPV4.

Sources of immunization records were claims data from the Data Partners and data from eight participating state/city immunization registries. The source of VTE diagnosis records was insurance claims. Medical records were used to confirm both HPV4 exposure and VTE outcome.

2.2. Study design and null hypothesis

A self-controlled risk interval (SCRI) design [11,12] was used. This design uses only vaccinated cases occurring in a pre-specified risk or comparison interval, and it controls for all potential time-invariant confounders, e.g. genetic factors. Days 1–28 post-vaccination was chosen as the primary risk interval and Days 1–7 as the secondary risk interval. The comparison ("control") interval, considered unexposed, was designated as Days 36–56 post-vaccination for Dose 1 and Days 36–63 for Doses 2 and 3. The control interval for Dose 1 was specified to end earlier to avoid potential bias due to Dose 2 frequently being given during Days 57–63 after Dose 1.

The null hypothesis was that the average daily risk of VTE onset during the risk interval was the same as during the control interval.

Table 1
VTE case validation criteria [13].

	Pulmonary Embolism	Deep Vein Thrombosis
Definite	Confirmed by pulmonary angiography, spiral CT scan/CT pulmonary angiography, MRI scan, or pathology	Confirmed by venography, compression/duplex ultrasound, CT scan, MRI scan, or at autopsy
Probable	If above tests not performed, or were indeterminate, but ventilation-perfusion scan findings were of high probability	If above tests not performed, or were indeterminate, but impedance plethysomography, radionuclide venography, or radiolabelled fibrinogen scan test results were reported as positive
Possible	If all of the above tests were not performed, or were indeterminate, and two of the following criteria were satisfied: medical record indicates physician-diagnosed PE, signs or symptoms of PE were documented, and the patient underwent therapy with anticoagulants, or an IVC filter was placed	If all of the above tests were not performed, or were indeterminate, and two of the following criteria were satisfied: medical record indicates physician-diagnosed DVT, signs or symptoms of DVT were documented, and the patient underwent therapy with anticoagulants, or an IVC filter was placed

2.3. Exposures

HPV4 vaccination was identified by means of CPT code 90649 and CVX code 62. Both administrative and medical record data were used to establish HPV4 timing and dose number.

2.4. Outcomes

We used ICD-9 codes 415.1x (pulmonary embolism, and infarction), 451.x (phlebitis, and thrombophlebitis), and 453.x (other venous embolism, and thrombosis) associated with claims in outpatient, emergency department, and inpatient settings to identify potential cases of VTE. We considered only the first VTE diagnosis found in a patient's claims since enrollment and excluded potential cases with a history of VTE by chart review.

VTE cases were classified using the criteria developed by the Worcester Venous Thromboembolism Study (Table 1) [13]. The main analyses were conducted using only definite, i.e. radiologically confirmed, VTE cases. Probable and possible cases were included in secondary analyses. In all analyses, adjudicated symptom onset dates were used, not VTE diagnosis dates based on claims data.

2.5. VTE risk factors

We collected data from both claims and medical records on potential cases' VTE risk factors for descriptive purposes and to