

Adverse events following HPV vaccination, Alberta 2006–2014



Xianfang C. Liu^a, Christopher A. Bell^b, Kimberley A. Simmonds^b,
Lawrence W. Svenson^{a,b,c}, Margaret L. Russell^{a,*}

^a Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada T2N 4Z6

^b Epidemiology and Surveillance Team, Alberta Ministry of Health, 23rd fl Telus Plaza NT, 10025 Jasper Avenue, Edmonton, AB, Canada AB T5J 1S6

^c School of Public Health, University of Alberta, Edmonton, AB, Canada T6G 1C9

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ABSTRACT

Background: In Canada, private purchase of human papilloma virus (HPV) vaccines has been possible since 2006. In Alberta, Canada, a publicly funded quadrivalent HPV vaccine program began in the 2008/2009 school year. There have been concerns about adverse events, including venous thromboembolism (VTE) associated with HPV vaccines. We describe the frequencies of adverse events following HPV vaccination among Alberta females aged 9 years or older and look at VTE following HPV vaccination.

Methods: We used the Alberta Immunization and Adverse Reaction to Immunization (Imm/ARI) repository (publicly funded vaccine), the population-based Pharmaceutical Information Network (PIN) information system (dispensing of a vaccine), and the Alberta Morbidity and Ambulatory Care Abstract reporting system (MACAR) for June 1, 2006–November 19, 2014. Deterministic data linkage used unique personal identifiers. We identified all reported adverse events following immunization (AEFI) and all emergency department (ED) utilization or hospitalizations within 42 days of immunization. We calculated the frequency of AEFI by type, rates per 100,000 doses of HPV vaccine administered and the frequencies of ICD-10-CA codes for hospitalizations and emergency department visits.

Results: Over the period 195,270 females received 528,913 doses of HPV vaccine. Of those receiving at least one dose, 192 reported one or more AEFI events (198 AEFI events), i.e., 37.4/100,000 doses administered (95% CI 32.5–43.0). None were consistent with VTE. **Of the women who received HPV vaccine 958 were hospitalized and 19,351 had an ED visit within 42 days of immunization.** Four women who had an ED visit and hospitalization event were diagnosed with VTE. Three of these had other diagnoses known to be associated with VTE; the fourth woman had VTE among ED diagnoses but not among those for the hospitalization.

Conclusions: Rates of AEFI after HPV immunization in Alberta are low and consistent with types of events seen elsewhere.

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Abbreviations: WHO, World Health Organization; HPV, human papillomavirus; qHPV, quadrivalent human papillomavirus; bHPV, bivalent human papillomavirus; NACI, National Advisory Committee on Immunization; AEFI, Adverse Events Following Immunization; VTE, venous thromboembolic events; ULI, unique personal identifier; Imm/ARI, immunization and adverse reaction to immunization; PIN, Pharmaceutical Information Network; ED, Emergency Department; MACAR, (Alberta) Morbidity and Ambulatory Care Abstract Reporting; ICD-10-CA, International Classification of Diseases, 10th Revision-Canadian Adaptation.

* Corresponding author at: Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3280 Hospital Drive NW, Calgary, AB, Canada T2N 4Z6. Tel.: +1 403 220 4279; fax: +1 403 270 7307.

E-mail addresses: xcliu@ucalgary.ca (X.C. Liu), chris.bell@gov.ab.ca (C.A. Bell), kimberley.simmonds@gov.ab.ca (K.A. Simmonds), larry.svenson@gov.ab.ca (L.W. Svenson), mlrussel@ucalgary.ca (M.L. Russell).

1. Introduction

The World Health Organization (WHO) recommends the human papillomavirus (HPV) vaccine for prevention of cervical cancer and other HPV-related diseases [1]. Quadrivalent HPV (qHPV) vaccine was authorized and became available for private purchase in Canada in 2006 for females aged 9–26 years. This authorization was expanded to include females aged 9–45 years in 2011. Bivalent HPV (bHPV) vaccine was also authorized for use among females aged 10–25 years in 2010. Canada's National Advisory Committee on Immunization (NACI) has recommended both vaccines in females aged 9–26 years of age [2]. Both vaccines were initially administered in a three-dose series; however NACI now recommends a two-dose series for immunocompetent persons aged 9–14 years [2].

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In Alberta, the publicly funded routine childhood and adolescent vaccines are administered exclusively by public health nurses. Alberta began to deliver a publicly funded three-dose qHPV vaccine series in the 2008/09 school year for females in grade 5, most of whom were aged 10–11 years [3]. A catch-up program was implemented from 2009/10 to 2011/12 for females in grade 9 (most of whom were aged 14–15 years). Both qHPV and bHPV vaccines are also available for private purchase through pharmacies.

The monitoring of adverse events following immunization (AEFI) contributes to vaccine safety surveillance and is an important component of all vaccination programs. Vaccine safety is monitored by passive surveillance in Alberta. There have been community concerns that HPV vaccines may be associated with adverse events. Venous thromboembolic events (VTE) are a particular concern, as some were reported to occur following HPV immunization in the United States [4]. The objective of this study is to describe the frequencies of adverse events among females aged 9 years or older that occurred following HPV vaccination including looking specifically at VTE following HPV vaccination.

2. Methods

2.1. Ethics and role of funding source

The study was approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID: REB 14-0598). The funding source had no role in study design, collection, analysis or interpretation of data, report writing or publication decision.

2.2. Data source and data extraction

Alberta has a publicly funded universal healthcare system in which >99% of residents are registered [5]. The registration file for this program includes a Person Health Number that serves as a unique personal identifier (ULI) [6] that permits data linkage at the level of the individual across other administrative databases. We used ULI to deterministically link data on vaccination, AEFI, and healthcare utilization.

Alberta's Immunization and Adverse Reaction to Immunization repository (Imm/ARI) contains complete vaccination records, including AEFI, for all publicly funded vaccines that were administered by public health since 2006. Vaccination records prior to 2006 comprise historical data and are entered electronically into Imm/ARI by public health nurses after review of paper vaccination records. The Pharmaceutical Information Network (PIN) contains records of all prescriptions dispensed by pharmacies, whether privately or publicly funded. In the case of HPV vaccine, this would only include privately funded vaccines. It is estimated that PIN captures over 95% of dispensed pharmacologic products [7]. We have assumed that all vaccine dispensed according to PIN was actually administered to the purchaser as the cost to purchaser of HPV vaccine is about \$150/dose [8]. Both Imm/ARI and PIN contain information on the patient, vaccine, dose, and date that vaccine was administered/dispensed [9].

In Alberta, AEFI surveillance is a passive reporting system. Individuals who experience an AEFI report to their vaccine provider, who completes a provincial AEFI reporting form; the data are entered into Imm/ARI [10]; Alberta Health then reports AEFI to the Public Health Agency of Canada. The provincial AEFI reporting form consists of a close ended checklist of types of adverse events, accompanied by an open ended text field into which a description of event is to be entered as well as an open ended comment section. The reporting form also collects time of onset following immunization, outcome, hospitalization dates, patient identifiers, vaccine antigens, vaccination date, and dose number. Alberta

policy is that providers should “Report events that do not meet specific case definitions but are felt to be significant (i.e., serious or unusual) under [checkbox] Other Severe or Unusual Events. . . When an AEFI is:

- Serious (death, hospitalization, congenital abnormality, residual abnormality, life threatening), unexpected (in terms of type or frequency),
- Of concern (to the vaccinee, his/her caregiver(s) or AEFI reporter).”

AEFI's that meet any of these criteria should be reported regardless of consistency with time period of occurrence for the event of the case definition of any such event. VTE cases are captured by the checkbox ‘other unusual events’ on the AEFI reporting form. Event codes and text descriptions on all AEFI reports are reviewed by trained nurses and coded into Imm/ARI. Information related to hospitalizations and emergency department (ED) visits are captured in the Alberta Morbidity and Ambulatory Care Abstract Reporting (MACAR) system, including dates of admission and discharge, and ICD-10-CA (International Classification of Diseases, 10th Revision-Canadian Adaptation) codes for diagnoses.

We extracted data on vaccinations, AEFI reports, hospitalizations and ED visits (within 42 days of vaccination) [4,11] for all females for whom an HPV dispense or vaccination event was recorded over June 1, 2006–November 19, 2014, using ULI to link records for unique individuals.

2.3. Data analysis

We counted the number of females who received one or more doses of HPV vaccine by number of doses received and age at first dose. We described the frequencies of occurrence of AEFIs by type of AEFI, and dose number associated with the AEFI. We calculated rates of AEFI per 100,000 doses of HPV vaccine dispensed/administered by dividing counts of AEFIs by the number of vaccine doses received among the population of interest over the period. We described hospitalizations within 42 days of HPV vaccinations by ICD-10-CA diagnostic codes for the most responsible diagnoses for all hospitalizations within 42 days of immunization. “Most responsible diagnosis” is recorded by the health care provider at discharge, using general coding standards that define the most responsible diagnostic ICD code as that responsible for the greatest portion of the length of stay or greatest use of resources [12]. A hospitalization event is defined as a hospital visit where a person was admitted and discharged from a hospital. Some hospitalization events were recorded twice because the person had one hospital visit that was temporally associated with receipt of two different vaccine doses (e.g., was hospitalized within 42 days of receiving both dose 1 and dose 2). For these, we removed the duplicate event and counted it as a single hospitalization event. For each person, we assumed that a transfer from one hospital to another had occurred if the date of discharge from the first hospital was the same as the date of admission to a second hospital. We counted each hospital transfer as a separate event. However, for the purpose of describing the frequency of the most responsible diagnoses (the diagnosis that contributed the greatest to length of stay) for such persons, we counted each most responsible diagnosis if they differed between hospitalization events. We operationally defined ‘serious’ AEFI as those that resulted in hospitalization and counted the number of ‘serious’ AEFI. We linked hospitalizations and ED visits to identify those who reported both events within 42 days of vaccination. Data analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC 2011).

2.4. AEFI review to identify VTE

One investigator (MLR), a physician, reviewed all text descriptions for AEFIs coded as 'other unusual events' for evidence that the AEFI might have been VTE.

2.5. Identification of VTE not captured by AEFI reports

In order to maximize the chances of finding a VTE that was not captured by an AEFI report within Imm/ARI, we identified within MACAR all females who were hospitalized or visited the ED within 42 days of vaccination by deterministically linking Imm/ARI, PIN and MACAR using the ULI. Our definition of VTE for this study was the occurrence of an ICD-10-CA diagnostic code of I80.x or I82.x in any of the potential diagnostic code fields (25) for a hospitalization or ED (10) visit. For any woman who had such an ICD-10-CA code for a hospitalization or ED visit, one investigator (MLR) reviewed all ICD codes for that event to assess if they were consistent with any other condition for which VTE is known to occur as per Spencer and colleagues [13].

3. Results

3.1. Source population

As can be seen from Table 1, from June 1, 2006 to November 19, 2014, 195,270 females received one or more doses of HPV vaccine. They received a total of 528,913 publicly and privately funded doses of vaccine over the study period. Nearly all of the vaccine was qHPV (99.2% of doses). The majority of women received three doses of HPV vaccine (82.4%), while a smaller proportion received only two doses (9.9%) or only one dose (6.4%). Most were aged 9–14 years (79.5%) when their first dose of HPV vaccine was received, followed by age groups 15–19 years (10.0%), 20–24 years (5.9%), or 25–29 years (2.7%).

Table 1
Distribution of HPV vaccine by numbers of women aged 9+ years immunized, by attributes of recipients and vaccine.

Characteristic	Number of women (%)
N women immunized	195,270 (100)
Number of doses received per individual	
1	12,473 (6.4)
2	19,280 (9.9)
3	160,950 (82.4)
4+	2567 (0.1)
Age (years) at which first dose of vaccine received	
9–14	155,300 (79.5)
15–19	19,483 (10.0)
20–24	11,551 (5.9)
25–29	5351 (2.7)
30–34	1725 (0.9)
35–39	874 (0.4)
40–44	583 (0.3)
45+	403 (0.2)
Type of vaccine funding	
Public	164,743 (84.4)
Private	29,025 (14.9)
Mixed ^a	1502 (0.8)
Total number of doses dispensed/administered	528,913 (100)
Type of vaccine dispensed/administered	
qHPV	524,645 (99.2)
bHPV	4193 (0.8)
Unknown	75 (<0.1)

^a Mixed funding: some doses were publicly funded, some were privately purchased.

3.2. Frequency of occurrence of AEFI & serious AEFI events

Of the 195,270 women who received HPV vaccine, 192 (<0.1%) reported one or more AEFI events (198 AEFI events). Of the 192, 186 reported one AEFI event, while six reported two different AEFI events. All AEFI events occurred after receipt of the qHPV vaccine. Six persons who experienced an AEFI had received one or more vaccines in addition to HPV on the same day as they received HPV vaccine. Table 2 displays the frequency of occurrence of types of AEFI by dose of HPV vaccine in series received that corresponded to the AEFI event. Among the 198 events, the most commonly reported events were allergic reaction ($n=90$), other unusual events ($n=34$), other rash ($n=32$), and pain and/or swelling ($n=23$) (Table 2). Most AEFI events occurred after receipt of the first dose of vaccine ($n=117$), followed by second ($n=55$) and third ($n=25$) doses. Review of the text fields for 'other unusual events' found none of these events to be consistent with VTE.

Of the 192 persons reporting AEFI events, five had a serious AEFI, (all classified as 'serious' because of hospitalization); however only 4 of them were hospitalized within 42 days of immunization. The fifth person was hospitalized on day 110, well outside of the 42 day window.

3.3. Rate of occurrence & outcome of AEFI events

Over the study period, the rate of AEFI events was 37.4 per 100,000 doses of HPV vaccine administered (95% CI: 32.5–43.0). The rate varied over time: no events were reported for 2006 or 2007, however only about 5000 doses of vaccine were dispensed in those years (data not shown). For the period January 1, 2008–November 19, 2014, the rate was 37.7 per 100,000 doses (95% CI: 32.8–43.3). AEFI rates varied over time, peaking in 2011 (Fig. 1).

Of the 198 AEFI events, the outcomes were known for 171, all of which were full recovery.

3.4. Hospitalization within 42 days of vaccination

Among the 195,270 females who received HPV vaccine, 958 were hospitalized (1053 hospitalization events) within 42 days of immunization; however only 4 of those hospitalized had a reported AEFI (see above). Of the 958 who were hospitalized, most (861, 89.8%) had only one hospitalization event within 42 days of immunization. The large majority of those hospitalized were aged 9–14 years (66.0%) or 15–19 years (22.0%). The proportion of hospitalizations that occurred on the same day as vaccination was 0.7%, 34.6% within 1–14 days, 32.8% within 15–28 days, and 31.9% within 29–42 days (data not shown).

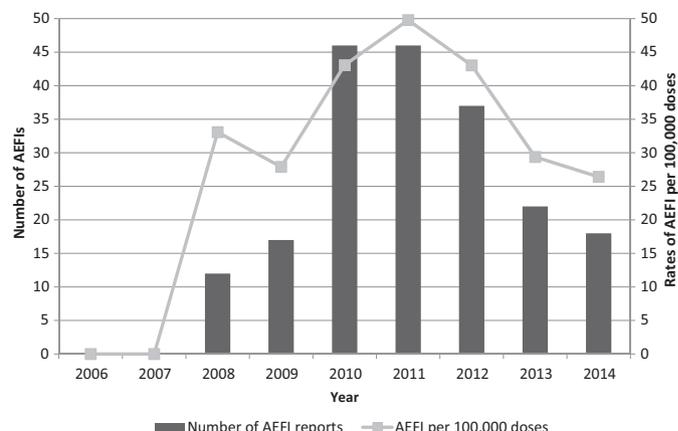


Fig. 1. Numbers of AEFI and AEFI rates/100,000 doses dispensed 2006–2014.

Table 2
Distribution of types of AEFI by dose of vaccine for which AEFI event reported.^a

	Number of doses of HPV vaccine received at time of occurrence of AEFI				N persons
	1	2	3	5	
Allergic reaction	54	32	4	0	90
Other unusual events	20	10	4	0	34
Other rash	23	3	6	0	32
Pain and/or swelling	12	5	5	1	23
Fever	1	2	1	0	4
Severe diarrhea	1	2	1	0	4
Anaphylaxis	2	0	1	0	3
Adenopathy	1	1	0	0	2
Convulsion/seizure	1	0	1	0	2
Anesthesia/paraesthesia	1	0	0	0	1
Arthralgia/arthritis	0	0	1	0	1
Erythema multiforme	0	0	1	0	1
Sterile abscess	1	0	0	0	1
Total	117	55	25	1	198

^a Six of the 192 persons who experienced an AEFI had an AEFI on two occasions.

Thirty-two women had hospital transfers. Thirty-one women had one hospital transfer and one woman had two transfers, resulting in 69 hospitalization events. Of these, six transfers (12 events) had the same most responsible diagnosis. Fourteen women had multiple hospitalization records because they received two doses of HPV vaccine within 42 days, and thus both doses were temporally associated with the hospitalization. Fifty-two persons had more than one hospitalization event because they were hospitalized on separate occasions (i.e., these were not hospital transfers). From the 1053 hospitalization events, after accounting for transfers, we counted 1047 most responsible diagnoses.

The frequencies of the 1047 most responsible diagnoses are shown in Table 3. Mental, behavioral and neurodevelopmental disorders (19.4%) were the most frequently coded most responsible diagnoses, followed by diseases of the digestive system (15.8%), and injury, poisoning and certain other consequences of external causes (13.8%).

3.5. Identification of VTE among those hospitalized

In addition to assessing frequencies of the most responsible diagnoses we examined all ICD-10-CA diagnostic codes (in any of the fields possible for hospitalizations) for codes corresponding to our case definition of VTE. There were three women who had such codes. The first had a most responsible diagnosis of Z50.1 (other physical therapy), and an I80.2 other diagnosis. She was 26 years of age and received the first dose of HPV vaccine 23 days prior to hospitalization. The other ICD-10-CA codes were consistent with having incurred an injury.

The second, aged 11 years, had a most responsible diagnosis of R07.4 (chest pain unspecified), and an I80.1 other diagnosis. She had received the third dose of HPV vaccine 14 days prior to hospitalization. The other ICD-10-CA codes for this hospitalization indicated the presence of a congenital heart defect known to be associated with VTE.

The third was hospitalized for most responsible diagnosis of I80.2 (phlebitis and thrombophlebitis of other deep vessels of lower extremities). She was 14 years of age and received the third dose of HPV vaccine 11 days prior to hospitalization. Review of the other ICD 10 codes for this hospitalization indicated that the VTE was classified as a complication of other diagnoses (sepsis) that caused the hospitalization.

Two of these three persons had received one or more vaccines in addition to HPV on the same days as they received HPV vaccine. None of those hospitalized with a VTE diagnosis died.

Table 3
Frequency of most responsible diagnoses among women hospitalized within 42 days of immunization.

ICD 10 Chapter codes	Count (%)
Certain infectious and parasitic diseases (A00-B99)	29 (2.8)
Neoplasms (C00-D49)	22 (2.1)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	12 (1.1)
Endocrine, nutritional and metabolic diseases (E00-E89)	35 (3.3)
Mental, Behavioral and Neurodevelopmental disorders (F01-F99)	204 (19.4)
Diseases of the nervous system (G00-G99)	35 (3.3)
Diseases of the eye and adnexa (H00-H59)	4 (0.4)
Diseases of the ear and mastoid process (H60-H95)	8 (0.8)
Diseases of the circulatory system (I00-I99)	15 (1.4)
Diseases of the respiratory system (J00-J99)	104 (9.9)
Diseases of the digestive system (K00-K95)	165 (15.8)
Diseases of the skin and subcutaneous tissue (L00-L99)	8 (0.8)
Diseases of the musculoskeletal system and connective tissue (M00-M99)	73 (7.0)
Diseases of the genitourinary system (N00-N99)	54 (5.2)
Pregnancy, childbirth and the puerperium (O00-O9A)	8 (0.8)
Certain conditions originating in the perinatal period (P00-P96)	1 (0.1)
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	19 (1.8)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	66 (6.3)
Injury, poisoning and certain other consequences of external causes (S00-T88)	144 (13.8)
External causes of morbidity (V00-Y99)	0 (0)
Factors influencing health status and contact with health services (Z00-Z99)	41 (3.9)
Total	1047 (100)

3.6. ED visits within 42 days of immunization

Among those who received HPV vaccine, 19,351 had an ED visit within 42 days of immunization (26,849 events). Of these, 713 also had a hospitalization within 42 days. Among those with an ED visit and hospitalization event, 4 were diagnosed with VTE (including the 3 hospitalized with a VTE diagnosis described above). One person visited the ED and was diagnosed with VTE, but did not have any ICD-10-CA codes consistent with VTE among the discharge diagnoses for the hospitalization.

4. Discussion

In this study, we linked vaccination data with AEFI reports, hospitalization records, and ED visit records, at a population-level, to describe AEFI type as well as to identify VTEs that may be related to HPV vaccination among women aged 9 years or older. We found an AEFI rate (37.4/100,000 doses) that was substantially less than that from reports from the American Vaccine Adverse Event Reporting System (VAERS) (53.9/100,000 doses) [14]. The most common types of adverse events that we observed (e.g., allergic reactions, 'other unusual events', rash) were similar to those found from analysis of the VAERS data [14] and similar to those seen in the province of Ontario [15]. Our results are consistent with other large post-licensure safety and surveillance studies that found that HPV vaccines are safe [11,16].

While we observed three cases of VTE among those hospitalized within 42 days of immunization, all three had other health conditions known to be associated with VTE. While one additional person had an ED visit with a VTE code, this code was not among the discharge diagnoses for the immediately following hospitalization. We think it likely that the VTE diagnosis from the ED visit was a tentative diagnosis that was not substantiated by further investigations during hospitalization. While Gee and colleagues [4] noted an association with VTE after HPV immunization, this association was not statistically significant, only five confirmed cases were observed and all of those cases had other known risk factors for VTE. Other investigators have found no association between HPV vaccination and the occurrence of VTE [11,16–18].

In Alberta, AEFI events are reportable if they meet case definitions outlined by Alberta Health [10]. AEFI reports are reviewed by public health nurses who ensure AEFIs meet case definitions and enter the data into Imm/ARI. We found a higher rate of AEFI events (37.4/100,000) than that reported for the Ontario schoolgirl HPV immunization program over 2007–2011 (19.2/100,000 doses dispensed) [15]. These differences are almost certainly due to the use of stricter guidelines for the classification of AEFI in Ontario. Harris and colleagues identified 213 qHPV AEFI reports for Ontario, of whom only the 133 classified as 'confirmed' were used in their analyses. If all 213 reports had been used, the Ontario rate of AEFI would have been 30.7/100,000; a rate much closer to that which we observed. However, as was also seen in Ontario, AEFI rates varied by year. Passive surveillance data may be affected by numerous factors, including "biased reporting, underreporting and the inability to determine whether a vaccine caused the adverse event in any individual report" [19]. Changes in reporting may result from changes in the reporting practices of healthcare personnel, or by community concerns (resulting in increased reporting to healthcare personnel) [20,21]. It is possible that the 2011 publication of the report of Gee and colleagues [4] might have affected reporting rates elsewhere, including in Ontario and in Alberta. However it is also possible that a longer follow-up time for HPV immunizations administered in the earlier years of the study period may also have contributed to the observed pattern of reporting.

The strengths of this study included capturing women who had received either publicly funded or privately purchased HPV vaccines. Similarly, in addition to the passively reported AEFI data, our design overcame the limitations of passive reporting in our search for VTE by accessing the records of all hospitalizations for the entire population of women immunized regardless of types of vaccine received or modes of vaccine funding. However, our study also has limitations. Residents of Alberta who were hospitalized within Alberta but immunized out of province would not have been captured. Similarly, those who were immunized within Alberta but hospitalized out of province would not have been captured. We do not know how many women this would be, but posit that the numbers are small. We did not validate the ICD codes for

hospitalizations or emergency department visits by chart review. As the predictive value of ICD codes for VTE is variable [17] this may have led to misclassification of outcome. Even in the absence of misclassification, it is possible that VTE identified during hospitalization might have had symptom onset prior to hospitalization. Finally, the women in our study received 528,913 doses of vaccine: thus AEFI that occur very rarely but which are truly associated with immunization with HPV vaccine would not be detected.

5. Conclusion

Adverse events following HPV immunization in Alberta are low, consistent with those seen elsewhere, and consistent in the types of event seen elsewhere.

Authors' contribution

XCL participated in data analysis, data interpretation and drafted the manuscript. CAB participated in study conceptualization, study design, acquired the data and participated in data analysis, data interpretation and drafting the manuscript. KAS participated in study conceptualization, study design, data interpretation and drafting the manuscript. MLR participated in study conceptualization, study design, data interpretation and drafting the manuscript. LWS participated in study conceptualization, study design, data interpretation and drafting the manuscript. All authors critically reviewed the manuscript.

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Conflicts of interest: None of the authors have any competing interests.

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