



Adverse events following immunization in Ontario's female school-based HPV program



Tara Harris^{a,*}, Dawn M. Williams^a, Jill Fediurek^a, Tsui Scott^c, Shelley L. Deeks^{a,b}

^a Public Health Ontario, Toronto, ON, Canada

^b Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

^c Immunization Policy and Programs, Ontario Ministry of Health and Long-Term Care, Toronto, ON, Canada

ARTICLE INFO

Article history:

Received 25 February 2013

Received in revised form

28 November 2013

Accepted 2 January 2014

Available online 15 January 2014

Keywords:

Human papillomavirus vaccine

Vaccine safety

Adverse events

Surveillance

ABSTRACT

Background: In September 2007, a school-based human papillomavirus (HPV) vaccination program targeting grade 8 girls (approximately 13 years old) and delivered by public health was implemented in Ontario, Canada. We assessed reports of adverse events following immunization (AEFI) from the school-based program as part of quadrivalent HPV (HPV4) vaccine safety surveillance and to contribute to a comprehensive HPV vaccine program evaluation.

Methods: AEFIs following HPV4 vaccine (Gardasil[®]) administered between September 1, 2007 and December 31, 2011 were extracted from the province's reportable disease system. Confirmed AEFI reports among females 12–15 years old (i.e. assumed to have received vaccine through the program) were included. Events were grouped according to provincial AEFI case definitions. Rates were calculated using doses distributed as the denominator.

Results: Between 2007 and 2011, 133 confirmed AEFIs were reported while 691,994 HPV4 vaccine doses were distributed in the school-based program. The overall reporting rate was 19.2 HPV4 AEFI per 100,000 doses distributed. Annual reporting rates decreased from 30.0 to 18.3 per 100,000 doses distributed. Frequently reported events included 'allergic reaction—dermatologic/mucosa' (25%), 'rash' (22%), and 'local/injection site reaction' (20%); 26% of reports had a non-specific event of 'other severe/unusual events' selected. Ten serious AEFIs were reported (7.5% of reports) including 2 anaphylaxis, 2 seizures, 1 thrombocytopenia and 1 death. Further review found that the reports of anaphylaxis did not meet the Brighton anaphylaxis definition and the death was attributed to a preexisting cardiac condition.

Conclusions: Overall these findings are consistent with the safety profile of HPV4 vaccine from pre-licensure clinical trials and post-marketing surveillance reports and importantly, no new safety signals were identified, especially no reports of VTE in this younger female population. Continued assessment of HPV4 AEFI surveillance data may be important to detect and investigate safety signals.

Crown Copyright © 2014 Published by Elsevier Ltd. All rights reserved.

1. Introduction

In Canada, quadrivalent human papillomavirus (HPV4) vaccine (Gardasil[®]) was licensed in July 2006 for females between the ages of 9 and 26 years for the prevention of genital warts, as well as cervical, vulvar, and vaginal cancers and their precursors caused by HPV types 6, 11, 16, and 18. Since 2007, the National Advisory Committee on Immunization (NACI) has recommended the use of HPV4 vaccine in females between the ages of 9 and 13 years as the group for whom the potential benefit would be greatest [1,2]. By 2009, all Canadian provinces and territories had introduced school-based HPV4 vaccination programs for females between grades four to eight depending on the jurisdiction, with most also

offering catch-up programs [3]. Since 2010, Gardasil[®] has been licensed in women up to 45 years of age for the above indications, as well as males 9 to 26 years of age for the prevention of anogenital warts, anal intraepithelial neoplasia (AIN) and anal cancer [4]. HPV2 vaccine (Cervarix[®]) was also licensed for use in females 9 to 45 years of age for the prevention of CIN 1, 2 and 3 and cervical AIS due to HPV types 16/18 [5]. HPV2 vaccine is not currently indicated for the prevention of anal, vulvar/vaginal cancers or licensed for use in males. To date, routine HPV vaccination programs in Canada continue to target adolescent females using HPV4 vaccine, with the exception of one province (Prince Edward Island) which has a gender-neutral program which was announced in April 2013 [6].

In Ontario, Canada's largest province (13.5 million) [7], a voluntary, publicly funded, school-based HPV vaccination program (using HPV4 vaccine) was implemented during the 2007–2008 school year. Grade eight girls (approximately 13 years of age) are eligible to receive the three-dose schedule.

* Corresponding author. Tel.: +1 647 260 7445; fax: +1 647 260 7757.

E-mail address: tara.harris@oahpp.ca (T. Harris).

The program is locally administered by the province's 36 public health units (HUs), that also provide school-based hepatitis B and quadrivalent meningococcal vaccine programs for all students in grade 7. A further expansion of the HPV4 vaccination program was announced in June 2012 to include an ongoing catch-up program for females in grades 9–12. In addition, a one-time catch-up program was offered for girls who were eligible the first year of the program (2007–2008) who have since graduated from high school, to initiate their first dose by June 2013.

The combined safety profile from five HPV4 vaccine clinical trials includes over 21,000 subjects from efficacy and immunobridging trials in females 16 to 26 years of age and males and females 9 to 15 years of age, respectively [8]. These data indicate injection site adverse events following immunization (AEFI) were significantly more frequent among vaccine recipients compared to both aluminum-containing (83% vs. 77%, $p < 0.05$) and non-aluminum-containing (83% vs. 49%, $p < 0.05$) placebo recipients, across all three doses. Similarly, vaccine recipients were also more likely to report injection site adverse events of severe intensity compared with placebo recipients (4% vs. 2%, $p < 0.05$). Among systemic adverse events, headache, fever and nausea were the most frequently reported in both vaccine and placebo groups. There were no significant differences found in the rates of serious systemic adverse events between vaccine (0.05) and placebo groups (0.02), across all three doses (risk difference = -0.16 , 95% CI = -0.44 to 0.12 , $p = 0.253$). No differences were seen in the incidence of headache and fever, the most common non-serious adverse events [8].

As of May 2013, with more than 111 million doses of HPV4 vaccine distributed worldwide [9], information from post-marketing surveillance has been consistent with the safety profile of HPV4 vaccine from pre-licensure clinical trial data. An early review of post-marketing safety data in 2009 by the Global Advisory Committee on Vaccine Safety (GACVS) noted that several signals had been observed in countries introducing HPV vaccination but none had been determined to be causally-related to the vaccine with the exception of syncope [10]. A disproportionate reporting of syncope and syncope-related injury following HPV4 vaccine was observed by passive surveillance systems in the United States (US) [11] and Australia [12–14]. This led to an updated Gardasil® product monograph to list syncope as a warning/precaution and to emphasize the importance of post-vaccine observation for a period of 15 min in a seated/lying down position to prevent injury [11,13,15–17]. In Canada, 634 reports of adverse events following HPV4 vaccine between July 2006 and May 2010 did not yield any unusual signals and were also consistent with data from pre-licensure trials [18]. A recent American study based on a large cohort of HPV4 vaccine recipients, also found an association with same-day syncope. Skin infections within two weeks following immunization were also found to be associated however these were likely the result of misclassification of local injection site reactions; while no new safety concerns were detected [19]. The Vaccine Safety Datalink (VSD) in the US did not find an association between HPV4 vaccine and pre-specified adverse events (including syncope) however further study of venous thromboembolism (VTE) was recommended to investigate a possible association [20].

The objective of our review was to summarize HPV4 vaccine AEFI reported in Ontario during the first 4.5 years of program implementation. This work was conducted as part of a comprehensive evaluation of the school-based HPV vaccination program in Ontario [21,22].

2. Materials and methods

In Ontario, reporting of AEFI by health professionals (i.e. physicians, registered nurses and pharmacists) is mandated by provincial

public health legislation however vaccine recipients or their parents may also voluntarily report an AEFI [23]. Initial reports of AEFI are received by the local HU where they are reviewed and investigated. Recommendations may be made to the vaccine recipient or their provider by the local Medical Officer of Health (MOH) regarding additional follow-up and receipt of further doses of vaccine. AEFI reports are entered into the integrated Public Health Information System (iPHIS), the passive electronic reporting system for reportable diseases and AEFI in Ontario. Reports are classified as 'confirmed', 'does not meet definition' and 'person under investigation' as per provincial surveillance guidelines. A 'confirmed' AEFI must meet the definition at least one of several specific AEFI under provincial surveillance [24]. These definitions do not specify temporal criteria (i.e. interval from vaccine administration to onset of the event) nor is causation inferred. Provincially reported AEFI are not further validated or assessed using any other source of information beyond what is available within the iPHIS application.

For this review we included all 'confirmed' reports of AEFI in iPHIS which followed HPV4 vaccine administered between September 1, 2007 and December 31, 2011 to females between 12 and 15 years of age at the time of immunization. This age range was selected as this was the age cohort assumed to have received vaccine through the school-based program. Data was extracted from iPHIS as of May 14, 2012.

Each AEFI report represents one individual vaccine recipient and describes one or more adverse events following receipt of HPV4 vaccine. Adverse event reactions selected in iPHIS were grouped according to provincial AEFI case definitions for descriptive analysis [24]. Serious AEFI were defined as any event that resulted in death, was life-threatening, required in-patient hospitalization of 24 h or more or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or any other important medical event that may have jeopardized the patient or may have required intervention to prevent one of the outcomes above [25]. Medically important events were defined based upon national AEFI surveillance guidelines which designate anaphylaxis, seizure/convulsions, Guillain-Barré Syndrome (GBS), Bell's Palsy, paralysis other than Bell's Palsy, meningitis, encephalopathy/encephalitis, acute transverse myelitis, acute disseminated encephalomyelitis, thrombocytopenia and syncope with injury as serious AEFI. Additionally, reports of anaphylaxis were further assessed using the Brighton Collaboration case definition of anaphylaxis [26].

Reporting rates for HPV4 vaccine AEFI are calculated using doses distributed within the school-based program as the denominator and are presented to monitor reporting trends over time and for comparison to other passive surveillance systems. These should not be interpreted as incidence rates. Microsoft Excel 2010 and SPSS version 12 were utilized for all descriptive analyses.

3. Results

We identified 213 HPV4 vaccine AEFI reports during the time period of interest among eligible Ontario females. Almost two-thirds of reports were classified in iPHIS as 'confirmed' (62%, 133/213) and 28% (59/213) were 'does not meet'. The remaining 10% (21/213) were assigned other case classifications (e.g. person under investigation).

Among the 133 confirmed HPV4 vaccine AEFI, the majority occurred in females 13 years of age (72%, 96/133) with a mean age of 13.6 years (range 12.2–15.9 years). Most were following administration of HPV4 vaccine alone (98%, 131/133), while 2 were associated with concomitant administration of hepatitis B vaccine.

Over the reporting period, 691,994 publicly-funded HPV4 vaccine doses were distributed in the school-based program in Ontario

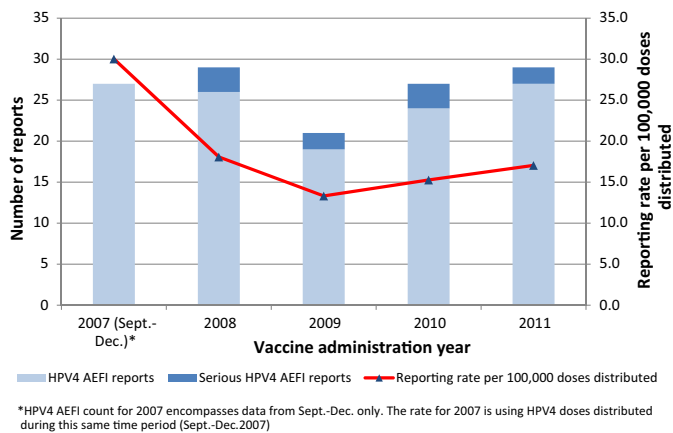


Fig. 1. Number of reports and reporting rate of confirmed adverse events following quadrivalent HPV vaccine in females 12 to 15 years of age by vaccine administration year and serious classification, September 1, 2007 to December 31, 2011.

resulting in a provincial HPV4 vaccine AEFI reporting rate of 19.2 reports per 100,000 doses distributed. Annual reporting rates decreased significantly since program introduction from 30.0 to 18.3 per 100,000 doses distributed in 2007 and 2011, respectively ($p < 0.05$) (Fig. 1).

In total there were 152 adverse events associated with the 133 individual HPV4 vaccine AEFI reports. The majority of reports included a single adverse event (114/133; 86%) and the remaining included two or more distinct events (14%, 19/133). The most frequently reported adverse events were 'allergic reaction—dermatologic/mucosa' (25%), 'rash' (22%), and 'local/injection site reaction' (20%), while 26% of reports had a non-specific event of 'other severe/unusual events' selected (Table 1).

Among 133 confirmed HPV4 vaccine AEFI reports, 7.5% ($n = 10$) were serious including two reports of anaphylaxis, two reports of seizure, one report of thrombocytopenia and one report of death. The reported death was subject to a coroner's investigation which concluded that an underlying, previously undetected cardiac

condition was responsible. The report of thrombocytopenia was a new diagnosis made three days following receipt of HPV4 dose two (33 days following dose one) in a previously healthy female. Of the two reports of seizure, one did not have any further information available while the other noted a history of febrile seizures in infancy and a subsequent diagnosis of epilepsy. A fever of $>38.0^{\circ}\text{C}$ was observed prior to onset of the seizure which occurred on day four following immunization. In addition to two reports of anaphylaxis, further review of confirmed reports in iPHIS yielded three additional reports in which epinephrine was administered but the event was classified as 'allergic reaction'. All five reports were reviewed for additional information to determine if they met the Brighton Collaboration case definition for anaphylaxis (Table 2). Based on the information recorded in iPHIS, none met the Brighton Collaboration case definition [25].

Of the ten serious reports, there were a total of seven hospitalizations; three having 'medically important' events and four which were: treatment following a suspected hypersensitivity reaction; severe headache attributed to neurological malformation for which treatment was successful; severe headache and hallucinations; and chronic musculoskeletal pain. In addition to inpatient hospitalization, 17% of all HPV4 vaccine AEFI reports ($n = 22$) involved an emergency department visit and 62% ($n = 83$) sought medical consultation in the community.

4. Discussion

This assessment represents more than four years of passive surveillance data from adverse event reports following administration of almost 700,000 doses of HPV4 vaccine as part of the school-based HPV immunization program in Ontario. Its findings are generally consistent with the safety profile of HPV4 vaccine from pre-licensure clinical trials and post-marketing surveillance reports.

Post-marketing HPV vaccine safety through passive surveillance systems is an important component of the overall safety assessment of these vaccines as they have the potential to generate signals

Table 1

Confirmed adverse events following administration of quadrivalent human papillomavirus vaccine among females 12–15 years of age in Ontario, September 1, 2007 to December 31, 2011 ($n = 133$).

Adverse event*	Number of events†	Percent of reports (%)**	Rate (per 100,000 doses distributed)
Other severe/unusual events	34	26	5.1
Allergic reaction—dermatologic/mucosa	33‡	25	4.8
Rash	29	22	4.2
Local/injection site reaction	26	20	3.8
Allergic reaction—respiratory§§	6	5	0.9
Allergic reaction—gastrointestinal§§	5	4	0.7
Arthritis	4	3	0.6
Oculorespiratory syndrome (ORS)	3	2	0.4
Anaphylaxis	2	1	0.3
Severe vomiting and/or diarrhea††	2	1	0.3
Allergic reaction—not specified	2	1	0.3
Seizure	2	1	0.3
Thrombocytopenia	1	1	0.1
Fever of 38°C or higher	1	1	0.1
Death‡‡	1	1	0.1
Total	152§		

* Case definitions corresponding to adverse events are available from: http://www.health.gov.on.ca/english/providers/program/pubhealth/oph_standards/ophs/progstds/idprotocol/appendixb/aeft.cd.pdf.

† Includes only those events categories where the number was ≥ 1 .

‡ Includes three reports where epinephrine was administered however the event was classified as 'Allergic reaction—dermatologic/mucosa' (not 'anaphylaxis').

** Adverse event categories are not mutually exclusive. Each report may include 1 or more events. Percentages will not sum to 100%. Denominator is 133 (total number of 'confirmed' HPV4 AEFI reports).

§§ Presence of minor Brighton anaphylaxis criteria in the absence of suspected anaphylaxis (25).

†† This adverse event option was no longer available in iPHIS as of December, 2007. After this date events involving either vomiting or diarrhea may have been reported under "Other severe/unusual events" or "Allergic reaction—gastrointestinal".

‡‡ Attributed to a pre-existing cardiac condition.

§ 152 adverse events are based on 133 HPV4 AEFI reports from September 1, 2007 to December 31, 2011.

Table 2
Events managed as anaphylaxis following administration of quadrivalent human papillomavirus vaccine among females 12–15 years of age in Ontario, September 1, 2007 to December 31, 2011.

	Adverse event classification in iPHIS	Signs and symptoms	Epinephrine administered (Y/N)	Brighton assessment
1	Anaphylaxis, local reaction	<ul style="list-style-type: none"> • Facial swelling and flushing, urticarial rash on neck and upper chest within 3 min of vaccine administration • Elevated blood pressure (162/100) after 25 min • Injection site erythema, swelling and warmth extending beyond shoulder joint after 1 h • No respiratory/cardiovascular manifestations were observed 	Y	Major dermatologic criteria met No major/minor respiratory or cardiovascular criteria met
2	Anaphylaxis	<ul style="list-style-type: none"> • Difficulty swallowing, itchiness on right cheek within 15 min vaccine administration • No respiratory or cardiovascular manifestations 	Y	No major/minor dermatologic, respiratory or cardiovascular criteria met
3	Allergic reaction—dermatologic/mucosa	<ul style="list-style-type: none"> • N/A 	Y	N/A
4	Allergic reaction—dermatologic/mucosa	<ul style="list-style-type: none"> • Immediate facial flushing, spreading to neck and arms • Swelling and redness at injection site • Sensation of “intense hot feeling” • No respiratory or cardiovascular manifestations 	Y	Major dermatologic criteria met No major/minor respiratory or cardiovascular criteria met
5	Allergic reaction—dermatologic/mucosa, rash	<ul style="list-style-type: none"> • Hive-like rash on arms and legs within 24 h of vaccine administration • No respiratory or cardiovascular manifestations 	Y	Delayed onset (12–24 h) Major dermatologic criteria met No major/minor respiratory or cardiovascular criteria met

which can be further evaluated. This is particularly important for rare adverse events which may not have been evident in clinical trials due to their limited sample size [26]. AEFI surveillance contributes to the development of relevant, credible information to address parental concerns about HPV vaccine safety—a factor which has been shown to be a key predictor of HPV vaccine acceptability and uptake [27–30].

Ontario's overall HPV4 vaccine AEFI reporting rate of 19.2 per 100,000 doses distributed between 2007 and 2011 is lower than reporting rates from both US and Australia which have reported rates of 53.9 and 24.0 per 100,000 doses distributed, respectively [11,12]. This may be attributed in part to criteria used in this analysis, which excluded AEFI occurring outside the eligible cohort and AEFI reports with a classification other than ‘confirmed’. While AEFI occurring outside the eligible cohort of females 12 to 15 years of age assumed therefore to be following doses of non-publicly funded HPV4 vaccine could have an impact on reporting rate, the lack of denominator data on non-publicly funded doses distributed necessitates exclusion from the analysis. Case classification clearly has an impact on reporting rate. Inclusion of all case classifications with or without those classified as ‘does not meet’ would result in an increased reporting rate of 30.8 and per 22.3 per 100,000 doses distributed, respectively. However, reports with classifications other than confirmed are difficult to interpret due to incomplete data entry.

The significant decline in the annual reporting rate between 2007 and 2011 is consistent with the “Weber effect” of increased reporting immediately after the licensure of a new product, which has also been observed elsewhere [31,32]. Substantial media attention regarding HPV vaccine safety in Canada at the same time the school-based program was first implemented in Ontario may have increased AEFI reporting. Rates between 2008 and 2011 were relatively steady suggesting that AEFI reporting rates for HPV4 vaccine have stabilized. The lowest annual reporting rate observed in 2009 was likely related to the impact of pandemic A/H1N1 vaccine implementation on routine AEFI reporting, including HPV4 vaccine.

The distribution of specific types of AEFI is generally comparable to HPV4 vaccine safety data from pre-licensure clinical trials and published post-marketing surveillance reports [8,11,13,17,18]. Injection site and hypersensitivity reactions were consistently among the most frequently reported events, similar to other reports. However, some variation in the distribution of reported events in these data is likely related to the presence of a high proportion (26%) of AEFI reported as ‘other severe/unusual events’ which is a non-specific event category. ‘Other severe/unusual events’ is selected when a reported event is temporally related to receipt of vaccine but does not meet a specific provincial AEFI surveillance definition. For example, frequently occurring events following HPV4 vaccine reported elsewhere such as syncope, dizziness, nausea and headache [8,11,13,17,18] do not have corresponding AEFI surveillance definitions in Ontario and are therefore likely captured under the ‘other severe/unusual events’ category, impacting the overall distribution of reported events. Of note, there were no reports of venous thromboembolism (VTE), a possible association observed in the VSD analysis by Gee and co-authors. However, it should be noted that the population of this assessment is younger overall (12 to 15 years of age) and would have substantially lower background risk of VTE compared with older adolescent and young adult females [20].

The overall reporting rate of hypersensitivity reactions if both urticarial and anaphylactic reactions are combined (5.1 per 100,000 doses distributed) is elevated compared with reports from the US and Australia (2.5 and 3.1 per 100,000 doses distributed, respectively) [11,13]. However within the Ontario data, the presence of urticaria is captured within the category “Other allergic reactions—dermatologic/mucosa” which also includes generalized pruritus, prickle sensation and red, itchy eyes, therefore is not directly comparable to other systems which capture urticarial reactions more specifically. The proportion of serious HPV4 vaccine AEFI in this report is similar to the proportion that were classified as serious using a similar definition in an HPV vaccine AEFI assessment from the Vaccine Associated Adverse Event reporting System (VAERS) in the US (7.5% vs. 6.2%, respectively) [11]. The

slightly elevated reporting rate of anaphylaxis; 0.3 per 100,000 doses distributed compared with 0.27 and 0.10 per 100,000 doses distributed in Australia and the US, respectively; [11,13] is difficult to interpret as it is based on only two reports. Limited descriptive information about the events reported as anaphylaxis, as well as the identification of three misclassified reports where epinephrine was administered highlights the challenge assessing a report of suspected anaphylaxis retrospectively using surveillance data. It is difficult to ascertain if any of these reports would have progressed to a true anaphylactic reaction (and thus meet the case definition) since epinephrine was administered and subsequently altered the progression of the event. In a community setting such as a school, best practice recommendations from the Canadian National Advisory Committee on Immunization support the availability of an epinephrine kit at all sites where vaccines are administered, prompt administration of epinephrine in cases of suspected anaphylaxis and arrangement for rapid transport to an emergency department via ambulance [33].

Limitations of this analysis include those which are shared with other passive AEFI surveillance systems including under-reporting, inconsistent quality and completeness of AEFI reports and reporting bias [34]. As such, some variables may be either missing and/or incomplete including dose number, time to onset and duration of the event, as well as description of the reaction, treatment and outcome. As a result of this HPV4 safety assessment revised provincial AEFI case definitions and guidelines for iPHIS entry have been implemented to improve the overall quality and completeness of AEFI surveillance information available in Ontario [35].

Another limitation of this analysis is the lack of comparison to background rates which would further contextualize this safety assessment based on AEFI reports, which have been temporally associated with HPV4 vaccine. Siegrist and co-authors have calculated background rates of specific autoimmune diseases among adolescent females to assist with assessment of HPV4 vaccine post-marketing safety data, including emergency care for asthma/allergy (3 per 100,000 adolescents within 24 h), diabetes (2 per 100,000 within 1 week of an injection) and hospitalization for autoimmune diseases (10 per 100,000 within 6 weeks of an injection) [36]. However, direct comparison of our data to these background rates is challenging due to variations in the definitions of specific events (e.g. allergic reaction) and the lack of a comparable denominator.

Finally, Ontario does not currently have a comprehensive population-based immunization registry to estimate the total cohort of vaccine recipients and subsequently the population-based rate of specific HPV4 vaccine AEFI in the school-based program [37]. Instead, AEFI reporting rate is calculated using doses distributed to the publicly funded program as the denominator which enables comparison of rates over time and to other post-marketing surveillance reports [11,13]. We have confirmed that the use of doses distributed is a good approximation of doses administered as vaccine wastage is estimated to be less than 1% for publicly funded HPV vaccine program in Ontario (2012 email from T. Scott, Ontario Ministry of Health & Long-Term Care).

5. Conclusions

This Canadian provincial analysis further contributes to the large post-marketing surveillance data already establishing notable safety of HPV4 vaccine safety in over 111 million doses. Overall, reports of adverse events following administration of HPV4 vaccine in Ontario were consistent with the safety profile of HPV4 vaccine from pre-licensure clinical trials and post-marketing surveillance reports from elsewhere in the world. Importantly, no new safety signals were identified especially no reports of VTE in this younger female population. Some variations in reporting

rate and distribution of reported events may be attributed to differences in classification of AEFI reports within the current provincial AEFI surveillance system.

Continued assessment of HPV4 AEFI surveillance data may be important to detect and investigate safety signals, generate hypotheses for further research as well as inform comprehensive evaluation of immunization programs and maintain professional and public confidence in vaccine safety.

Acknowledgments

We would like to extend our sincere thanks to public health unit staff across the province for their efforts in investigation and reporting of adverse events following immunization which are essential to the assessment of HPV4 vaccine safety in Ontario.

Conflict of interest: The authors have no conflicts of interest to disclose.

References

- [1] National Advisory Committee on Immunization (NACI). Statement on human papillomavirus vaccine. An advisory committee statement (ACS). *Can Commun Dis Rep* 2007;33:1–31.
- [2] National Advisory Committee on Immunisation (NACI). Update on human papillomavirus (HPV) vaccines. An advisory committee statement (ACS). *Can Commun Dis Rep* 2012;28 (ACS-1).
- [3] Government of Canada. Publicly funded immunization programs in Canada—routine schedule for infants and children including special programs and catch-up programs (as of March 2013) [Internet]. Ottawa, ON: Government of Canada; 2013 [updated March 2013; cited May 22, 2013]. Available from: <http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php>.
- [4] Notice of Compliance Online Query: Gardasil®. [Internet]. Notice of Compliance Online Query: Gardasil®. [Internet]. Ottawa, ON: Health Canada; 2013 [updated May 7, 2013; cited May 22, 2013]. Available from: <http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp>.
- [5] GlaxoSmithKline Inc. CERVARIX® human papillomavirus vaccine types 16 and 18 (recombinant, AS04 adjuvanted) [Internet]. Mississauga, ON: GlaxoSmithKline Inc.; 2013 [updated May 2, 2013; cited May 22, 2013]. Available from: <http://www.gsk.ca/english/docs-pdf/product-monographs/Cervarix.pdf>.
- [6] Prince Edward Island Cancer Treatment Centre. HPV vaccine program expands to include boys [Internet]. Charlottetown, PE: Prince Edward Island Cancer Treatment Centre; 2013 [updated April 18, 2013; cited June 3, 2013]. Available from: <http://www.cancercentre.pe.ca/index.php3?number=news&dept=&newsnumber=8937&lang=E>.
- [7] Statistics Canada. Population estimates and projections. Population by year, by province and territory. [Internet]. Ottawa, ON: Statistics Canada; 2012 [updated Sept. 27, 2012; cited May 22, 2013]. Available from: <http://www.statcan.gc.ca/tables-tableaux/sum-som/101/cst01/demo02a-eng.htm>.
- [8] Block SL, Brown DR, Chatterjee A, Gold MA, Sings HL, Meibohm A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) I1 virus-like particle vaccine. *Pediatr Infect Dis J* 2010;29(2):95–101.
- [9] Gardasil®. Gardasil® [Human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck's HPV vaccine, available to developing countries through UNICEF tender. [Internet]. Whitehouse Station, NJ: Merck & Co.; 2013 [updated May 9, 2013; cited May 22, 2013]. Available from: <http://www.mercknewsroom.com/press-release/prescription-medicine-news/gardasil-human-papillomavirus-quadrivalent-types-6-11-16-an>.
- [10] Global Advisory Committee on Vaccine Safety. Report of meeting held 17–18 June 2009. *Wkly Epidemiol Rec* 2009;84(32):325–32.
- [11] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302(7):750–7.
- [12] Gold MS, McIntyre P. Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance. *Sex Health* 2010;7(3):320–4.
- [13] Gardasil®. Gardasil® (Human papillomavirus vaccine). Safety information. [Internet]. Symonston, Australia: Therapeutic Good Administration; 2010 [updated June 24, 2010; cited May 22, 2013]. Available from: <http://www.tga.gov.au/safety/alerts-medicine-gardasil-070624.htm>.
- [14] Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, et al. Mass psychogenic response to human papillomavirus vaccination. *Med J Aust* 2008;189(5):261–2.
- [15] Gardasil®. Package Insert—Gardasil®. [Internet]. Whitehouse Station, NJ: Merck & Co.; 2013 [updated March 2013; cited May 22, 2013]. Available from: http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf.
- [16] Gardasil®. Information Pertaining to Labeling Revision for Gardasil®. Reminder to healthcare providers: 15 m observation period needed after vaccination. [Internet]. Silver Spring, MD: US Food & Drug Administration; 2009 [updated

- June 18, 2009; cited May 22, 2013]. Available from: <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm165145.htm>.
- [17] Gardasil®. Product Monograph. Gardasil® [quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine. [Internet]. Kirkland: Merck Canada Inc.; 2011 [updated July 14, 2011; cited May 22, 2013]. Available from: <http://www.merck.ca/assets/en/pdf/products/GARDASIL-PM.E.pdf>.
- [18] Nkanza J, Lafleche J, Anyoti H, Law B. Profile of adverse events following immunization with human papillomavirus vaccine and hepatitis B vaccine in females aged 9 to 26 years in Canada (July, 2006 to May, 2010). In: International Society for Pharmacovigilance: Annual Meeting. 2010.
- [19] Klein NP, Hansen J, Chao C, Velicer C, Emery M, Slezak J, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. *Arch Pediatr Adolesc Med* 2012;116(1):1–9.
- [20] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the vaccine safety datalink. *Vaccine* 2011;29(46):8279–84.
- [21] Wilson SE, Karas E, Crowcroft NS, Bontovics E, Deeks SL. Ontario's school-based HPV immunization program: school board assent and parental consent. *Can J Public Health* 2012;103(1):34–9.
- [22] Wilson S, Harris T, Sethi P, Fediurek J, Deeks S. Vaccine coverage assessment for Ontario's school-based human papillomavirus vaccination program. In: 10th Canadian Immunization Conference. 2012.
- [23] Health Protection and Promotion Act (HPPA). Health Protection and Promotion Act (HPPA). R.S.O. 1990, c. H.7, s. 38 (3); 1998, c. 18, Sched. G, s. 55 (4). [Internet]. Toronto, ON: Ministry of Health & Long-Term Care; 2011 [updated Dec. 31, 2011; cited May 22, 2013]. Available from: http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90h07_e.htm.
- [24] Infectious Diseases Protocol. Infectious Diseases Protocol, 2009. Appendix B: Provincial case definitions for reportable diseases. Disease: Adverse events following immunization (AEFIs). [archived]. Ministry of Health and Long-Term Care; 2009.
- [25] Council for International Organizations of Medical Sciences. Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance [Internet]. Geneva: Council for International Organizations of Medical Sciences; 2012 [updated 2012; cited May 22, 2013]. Available from: <http://www.cioms.ch/index.php/publications/available-publications?task=view&id=40&catid=54>.
- [26] Rugeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5675–84.
- [27] Ogilvie G, Anderson M, Marra F, McNeil S, Pielak K, Dawar M, et al. A population-based evaluation of a publicly funded, school-based HPV vaccine program in British Columbia, Canada: parental factors associated with HPV vaccine receipt. *PLoS Med* 2010;7(5):e1000270.
- [28] Haesebaert J, Lutringer-Magnin D, Kalecinski J, Barone G, Jacquard A, Regnier V. French women's knowledge of and attitudes towards cervical cancer prevention and the acceptability of HPV vaccination among those with 14–18 year old daughters: a quantitative-qualitative study. *BMC Public Health* (1):1034.
- [29] Constantine NA, Jerman P. Acceptance of human papillomavirus vaccination among Californian parents of daughters: a representative statewide analysis. *J Adolesc Health* 2007;40(2):108–15.
- [30] Dahlstrom LA, Tran TN, Lundholm C, Young C, Sundstrom K, Sparen P. Attitudes to HPV vaccination among parents of children aged 12–15 years—a population-based survey in Sweden. *Int J Cancer* 2010;126(2):500–7.
- [31] Weber JC. Epidemiology of adverse reactions to non-steroidal anti-inflammatory drugs. *Adv Inflammation Res* 1984;6:1–7.
- [32] Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS)—United States, 1991–2001. *MMWR Surveill Summ* 2003;52(1):1–24.
- [33] National Advisory Committee on Immunisation (NACI). Vaccine safety and adverse events following immunization. Anaphylaxis: initial management in non-hospital settings. In: Canadian immunization guide. 7th ed. Ottawa, ON: Public Health Agency of Canada (PHAC); 2006. p. 80.
- [34] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the vaccine adverse event reporting system. *Pediatr Infect Dis J* 2004;23(4):287–94.
- [35] Infectious Diseases Protocol. Infectious Diseases Protocol, 2013. Appendix B: provincial case definitions for reportable diseases. disease: adverse events following immunization (AEFIs) [Internet]. Toronto, ON: Ministry of Health & Long-Term Care; 2013 [updated Jan.1, 2013; cited May 22, 2013]. Available from: http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/aefi_cd.pdf.
- [36] Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. *Pediatr Infect Dis J* 2007;26(11):979–84.
- [37] Wilson SE, Harris T, Sethi P, Fediurek J, Macdonald L, Deeks SL. Coverage from Ontario, Canada's school-based HPV vaccine program: the first three years. *Vaccine* 2013;31(5):757–62.