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Early impact of Ontario's human papillomavirus (HPV) vaccination program on anogenital warts (AGWs): A population-based assessment

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ABSTRACT

Introduction: This study aimed to evaluate the early population impact of Ontario's school-based human papillomavirus (HPV) vaccination program, implemented in September 2007 for grade 8 females, by comparing anogenital wart (AGW) health care utilization before and after vaccine program implementation, in program-eligible and program-ineligible cohorts, focusing on 15–26 year olds.
Methods: Using a retrospective longitudinal population-based study design, health administrative data were used to identify incident AGWs and total health service utilization (HSU) for AGWs for Ontario residents 15 years and older between April 1 2004 and March 31 2014. The study period was divided into two eras: the pre-vaccine program era and the vaccine program era. Negative binomial models were generated to analyze trends across time by age group and sex. We adjusted female rates for routine Papanicolaou (Pap) testing to address spillover effects of Pap smear policy changes on AGW diagnosis.
Results: Between fiscal years 2004 and 2013, AGW incidence decreased 2.6% on average per year in 15–17 year old females, and total HSU for AGWs decreased an average of 4.8% and 2.2% per year in 15–17 and 18–20 year old females. Comparing the vaccine era to the pre-vaccine era, AGW incidence decreased 6.5% in 18–20 year old females, and AGW HSU decreased 13.8%, 11.1%, and 10.0% in 15–17, 18–20, and 21–23 year old females respectively. In contrast, male AGW incidence rates increased an average of 4.1%, 2.8%, and 0.9% per year in 15–17, 21–23, and 24–26 year old males respectively. AGW incidence rates increased 12.2% in 15–17 year old males from the pre-vaccine to vaccine era.
Conclusion: The decline in AGW incidence and HSU in program-eligible females suggests the school-based HPV vaccination program has had an early population impact in Ontario. The increasing AGW incidence in males suggests no early evidence of herd effects in males.

1. Introduction

In September 2007, Ontario, Canada's most populated province with approximately 13.3 million residents in 2011 [1], implemented a voluntary, publicly-funded school-based human papillomavirus (HPV) vaccination program for grade 8 girls, using the HPV4 vaccine, Gardasil® [2]. Initially a three-dose schedule was used, but this was modified in the 2015/16 school year to a two-dose schedule. Evaluating the impact of the program on population-level cervical cancer incidence in Ontario will require the passage of substantial time due to the latency period from HPV infection to cervical cancer; however, health care utilization

Abbreviations: OHIP, Ontario Health Insurance Program; RPDB, Registered Persons Database; ICES, Institute for Clinical Evaluative Sciences; MOHLTC, Ministry of Health and Long-Term Care; CIHI, Canadian Institute of Health Information; HSU, health service utilization.

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for anogenital warts (AGWs) provides an early indication of the program's impact in preventing HPV-induced lesions, while also providing valuable information on the change in the AGW burden. Researchers from other countries with HPV vaccination programs, including Australia, the United States (US), Sweden, and Denmark, have begun reporting significant decreases in the incidence of AGWs among females, with the greatest reductions in settings with high vaccine uptake; however, the indirect impact on males has varied ([3–9], and reviewed by [10–13]).

Our objective was to evaluate the early population impact of Ontario's HPV school-based vaccination program on AGWs by comparing health care utilization for AGWs before and after program introduction using health administrative data. We aimed to estimate the benefits of the program at the population level by age group and sex.

2. Methods

2.1. Population and study period

The population included all Ontario residents 15 years and older with a valid health card number in Ontario's health care system (described below). Average annual incidence was reported for individuals 15 years and older, but our analysis of pre-vaccine and vaccine eras focused on 15–26 year olds as this is the age group where we would likely see the earliest and greatest population impact on AGWs given the age eligibility of the vaccine program. In our analysis, the year started on April 1 and ended March 31 in keeping with the fiscal calendar, and the study period was April 1 2003 to March 31 2014 (years 2003–2013). The first year of the study period was used as a wash-out year to exclude prevalent cases (see Outcome Definition). The study period was divided into two eras: the pre-vaccine program era (2004–2007), and the vaccine program era (2008–2013). Although Ontario's program was implemented in September 2007, the full first series of HPV4 vaccination would have been completed between March and May 2008, hence April 1 2008 was designated as the start of the vaccine program era. Grade 8 girls are eligible for the program, most of whom are 13 years of age by December 31 of the calendar year in which they are in grade 8. For the purposes of this study we defined the program eligible cohort during the vaccine program era as females born between January 1 1994 and December 31 2000 (aged 14–20 years in 2013). We did not have individual-level data on HPV4 vaccination status.

2.2. Data sources

Health administrative data has been used to estimate AGW burden in other studies [6,7,14–18]. Health care encounters captured by the provincial insurance plan data were used to measure AGW-related health care utilization. Ontario provides health care coverage to all residents through the Ontario Health Insurance Program (OHIP). Eligibility requires that an individual be a Canadian citizen, landed immigrant, or refugee, has Ontario as their primary or permanent home, and resides in Ontario for at least 153 days over a 12-month period. There is no parallel system of private services for routine medical care and hospitalizations. Individual-level outpatient physician visits for AGWs were captured within the OHIP database, which represents approximately 90% of AGW health service visits captured by the provincial health insurance administrative databases [16]. The Registered Persons Database (RPDB) contains information on all Ontario residents who are eligible for health care coverage and was used to determine population size, sex, and date of birth. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

2.3. Outcome definitions

Consistent with previous health services studies on AGWs, an episode of AGWs was deemed incident if it was preceded by a 12-month window without any AGW-related care utilization [9,15–18]. In addition to AGW incidence, we report total AGW HSU rates, which counted every health care encounter that fulfilled the AGW outcome definition in the numerator. As described further elsewhere, the OHIP database provides diagnostic and procedural codes from physician office visits that can be combined into algorithms to generate a probable outcome definition for AGWs [16,19]. A physician office visit was counted as an AGW visit if any of the following ten code combinations were billed: 099 only if billed with Z117; or, 079 only if billed with Z117; or, 629 only if billed with Z117; or, Z549; or, Z758; or, Z733, Z736, or Z769 only in females; or, Z767 or Z701 only in males [16].

2.4. Statistical analysis

We analyzed annual AGW HSU rates and incidence per 1000 population across the study period stratified by sex and age group among 15–26 year olds. The crude rates were calculated by dividing the numerator (number of prevalent AGW cases stratified by fiscal year, gender, and age group) by the denominator (size of the Ontario population in the same fiscal year, gender and age group). We then modeled the numerator count as the outcome and fiscal year as the independent continuous variable in the negative binomial regression models with the log link function and log (population) as the offset. Average annual rates are reported by era and are the average of the annual HSU or incidence rates for each year in a given era. A negative binomial regression model was also used to model incidence or HSU rates by year. Considering that some AGWs diagnosed at the time of routine Papanicolaou (Pap) testing might not otherwise be diagnosed, we adjusted for the impact of changes in Pap testing rates resulting from revisions to Ontario's cervical screening guidelines in 2011 and associated changes to OHIP Pap testing reimbursement for physicians in 2012. As we are examining changes over time, we wanted to ensure this potential change in outcome identification was adjusted for. We used established billing codes to identify Pap tests (Supplemental Table S1) [19,20]. Visits meeting the Pap test outcome definition occurring 12 months or more apart were considered as routine screening visits. After we calculated the Pap testing rates, they were adjusted in the negative binomial model as a continuous variable for females, with unadjusted rates explored in a sensitivity analysis. Reported percent changes were the average annual change between 2004 and 2013, relative to 2004, or between the pre-vaccine and vaccine eras (Supplemental Table S2). The threshold for statistical significance was set at $p < 0.05$. Analyses were performed using SAS, 9.3 (The SAS Institute, Cary, NC) and Microsoft Excel 2010.

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the Ethics Review Board at Public Health Ontario.

3. Results

3.1. AGW counts, AGW sex and age distribution

Between April 1 2004 and March 31 2014, 113 029 individuals 15 years and older made 286 609 health care visits for AGWs through physician offices. In the pre-vaccine and vaccine eras the average annual HSU rate of physician office visits for AGWs among individuals 15 years and older was 2.74 and 2.61 per 1000 population, respectively. The average annual incidence of AGWs based on physician office visits among individuals 15 years and older was 1.17 and 1.15 per 1000 population in the pre-vaccine and vaccine eras, respectively. The average annual AGW incidence varied by age group and sex (Fig. 1), similar to our previous report [16]. AGW incidence peaked in 21–23 year old females and males. Average annual incidence was higher in females than males who were 15–23 years old, but males had a higher average annual incidence from 27 to 41 years of age, while the rate was similar between both sexes in individuals 24–26 years and 42 years and older.

3.2. AGW incidence

Between 2004 and 2013, Pap test rate-adjusted AGW incidence decreased significantly by an average of 2.6% per year in 15–17 year old females ($p = 0.04$), but decreased non-significantly in 18–20 and 21–23 year old females and increased non-significantly in 24–26 year old females. In contrast, between 2004 and 2013 male AGW incidence increased significantly by an average of 4.1%, 2.8%, and 0.9% per year in 15–17, 21–23, and 24–26 year old males respectively ($p = 0.01$, $p < 0.0001$, $p = 0.05$). Among 18–20 year old males there was a non-significant increase in AGW incidence from 2004 to 2013, however we did observe a sharp decrease from 2010 to 2013 in this age group (Fig. 2). AGW incidence between the pre-vaccine and vaccine eras differed significantly for certain age groups. Pap test rate-adjusted AGW incidence decreased significantly between the pre-vaccine and vaccine eras by 6.5% in 18–20 year old females ($p = 0.03$), and decreased non-significantly in 15–17 and 21–23 year old females, and increased non-significantly among 24–26 year old females. For males, AGW incidence increased significantly between the pre-vaccine and vaccine eras by 12% in 15–17 year olds ($p = 0.04$) and increased non-significantly among males 18 to 26 years of age.

3.3. AGW total HSU

Between 2004 and 2013, Pap rate-adjusted AGW HSU rates decreased significantly by an average of 4.8% and 2.2% per year in 15–17 and 18–20 year old females respectively ($p = 0.0003$, $p = 0.01$), and decreased non-significantly among 21–23 year old females and increased non-significantly in 24–26 year old females (Fig. 3). Among males there were no significant changes, however, AGW HSU rates decreased non-significantly in 15–17, 21–23, and 24–26 year olds, and increased in 18–20 year olds. Comparing the pre-vaccine and vaccine eras, AGW HSU rates differed significantly for certain age groups. Age specific analysis revealed Pap test rate-adjusted AGW HSU rates decreased significantly between the pre-vaccine and vaccine eras by 13.8%, 11.1%, and 10.0% in 15–17, 18–20, and 21–23 year old females respectively ($p = 0.01$, $p < 0.0001$, $p = 0.004$), and decreased non-significantly in 24–26 year old females. Among males there were no significant changes, however, AGW HSU rates decreased non-significantly between the pre-vaccine and vaccine eras in 15–17 and 21–23 year olds, and increased in 18–20 and 24–26 year olds.

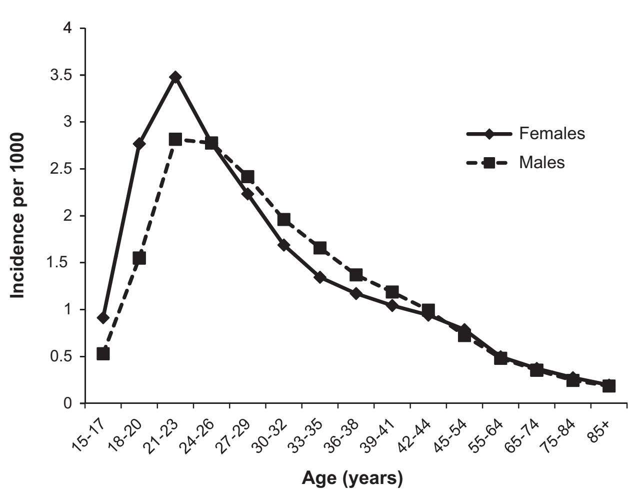

Fig. 1. Average annual incidence of AGWs captured by physician office visits 2004–2013, by sex and age group, for females (adjusted for Pap testing rate) and males (crude).

3.4. Sensitivity analysis

Without adjusting for Pap test rates there were additional significant findings. AGW incidence decreased significantly by an average of 5.8%, 4.8%, 3.0%, and 2.0% per year in 15–17, 18–20, 21–23, and 24–26 year old females respectively ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, $p = 0.008$), and between the pre-vaccine and vaccine eras AGW incidence decreased significantly by 21.2%, 18.6%, and 12.3% in 15–17, 18–20, and 21–23 year old females ($p = 0.01$, $p = 0.02$, $p = 0.01$), but decreased non-significantly in 24–26 year olds. Without adjusting for Pap test rates, AGW HSU rates decreased significantly by an average of 4.8%, 5.2%, 4.7%, and 2.4% per year in 15–17, 18–20, 21–23, and 24–26 year old females respectively ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, $p = 0.0006$), and between the pre-vaccine and vaccine eras, AGW HSU rates decreased significantly by 20.8%, 21.8%, and 20.5% in 15–17, 18–20, and 21–23 year old females respectively ($p = 0.0004$, $p = 0.001$, $p = 0.001$), but decreased non-significantly in 24–26 year old females.

4. Discussion

This study provides evidence of the early population-level impact of a school-based HPV vaccination program on AGWs in Canada's most populated province, Ontario. Our findings that AGW incidence and HSU rates have significantly decreased in some female age groups since the introduction of the HPV vaccination programs are consistent with results of similar studies and several reviews [5,9–13,21]. In contrast, incidence rates have significantly increased among similar male age groups over the same study period while no significant changes were seen in male AGW HSU.

Modeling and ecological studies have reported variable levels of impact on HPV infection in males through herd effects after implementation of female-targeted HPV vaccination programs. Estimates of HPV vaccine coverage among the target grade 8 female cohort eligible for the publicly-funded program increased from 51% in 2007/8 to 58% in 2008/9, and then remained steady at 59% and 58% for 2009/10 and 2010/11, respectively, before increasing to 70% in 2011/12 and then 80% in 2012/13 [22]. Although coverage has increased since the introduction of the program, up to the 2012/2013 school year, the program has not met its target of 90% set by the Canadian Immunization Committee [23]. Suboptimal coverage in the first several years of the program may explain why we did not observe evidence of herd effects in adolescent males in the early years of the vaccine era. In fact, AGW incidence rates increased significantly in certain male age groups in Ontario from the pre-vaccine to vaccine era, and across the study period by year. As the cohorts of vaccine eligible females get older and approach the peak age of AGW incidence and as HPV vaccine coverage increases, we may see evidence of indirect vaccine impact in Ontario males. The decreasing incidence among 18–20 year old males in the most

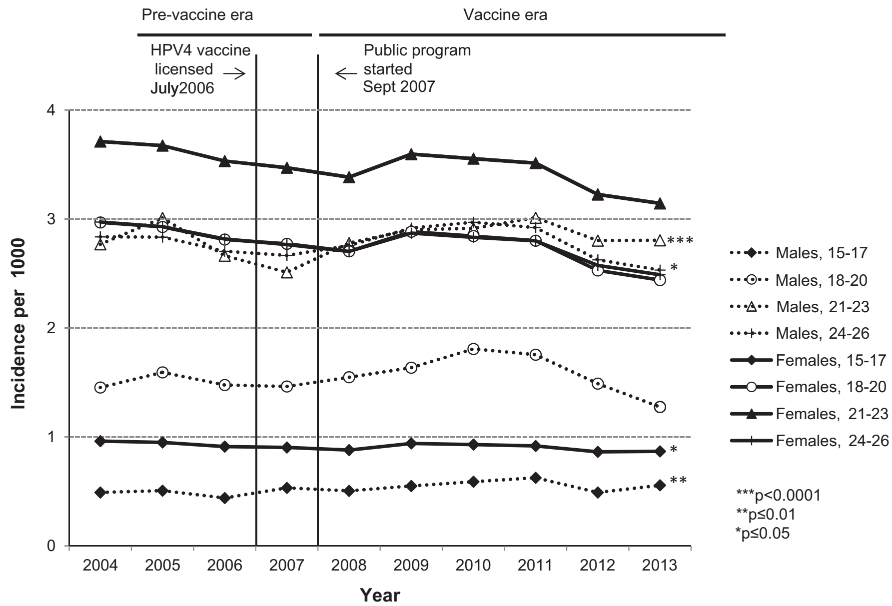

Fig. 2. Annual incident AGWs captured by physician office visits in 15–26 year olds, 2004–2013, for females (adjusted for Pap testing rate) and males (crude). Statistical significance reflects average annual changes in incidence relative to 2004.

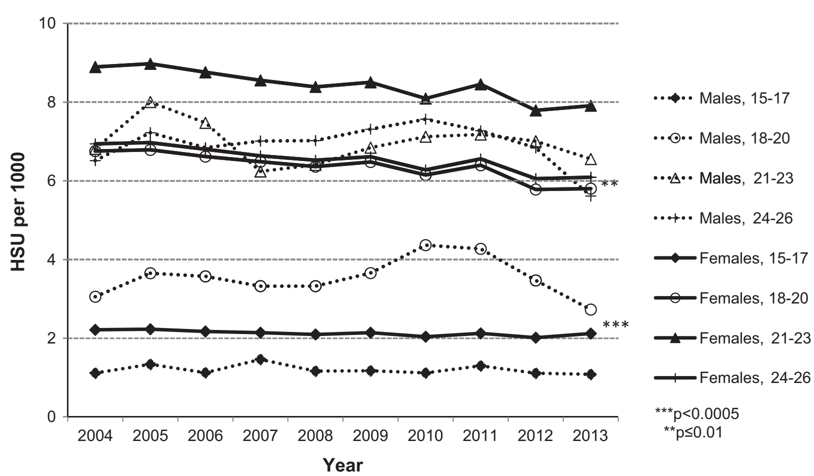

Fig. 3. Annual health service utilization (HSU) for AGWs captured by physician office visits in 15–26 year olds, 2004–2013, for females (adjusted for Pap testing rate) and males (crude). Statistical significance reflects average annual changes in HSU relative to 2004.

recent years requires further investigation to determine if it is a sustained effect. One explanation is that this decrease is an early reflection of herd effects as female and male sexual partnering tends to involve partnering between younger females and slightly older males [24–26]. It is interesting to note that we did not observe a similar decrease in 15–17 year old males in recent years.

The HPV vaccine was recommended by Canada's National Advisory Committee on Immunization (NACI) for females 9–26 years of age in the early years of licensure, which extends beyond the age group targeted in the publicly funded program [27]. The significant decrease in AGW HSU rate in 21–23 year old females, who would not have been eligible for the publicly-funded program, may reflect private HPV vaccine purchase. From the launch of Gardasil® in August 2006 to December 2013, it is estimated that 523 160 doses were privately purchased (personal communication with Merck Canada).

Smith et al. recently reported early benefits of the Ontario HPV vaccination program on cervical dysplasia and also explored AGWs [28]. In contrast to our study, that study reported impact based on program eligibility and individual-level vaccination status, and observed statistically significant protective effects of program eligibility and vaccination on cervical dysplasia, but no statistically significant impact on AGWs. Our study differs by providing a population-level assessment with age bands corresponding to the program eligible cohort without considering individual level vaccination data in order to reflect population impact. In Ontario, AGW incidence peaks among 21–23 year olds, and this could explain the non-significant effect on AGWs reported by Smith and colleagues, who studied a younger population with lower AGW incidence.

The finding that adjustment by Pap test rate changed the size and statistical significance of AGW trends suggests that AGWs may be diagnosed incidentally through a pelvic exam conducted during a Pap test visit. The sensitivity analysis suggests that analyses unadjusted for Pap test rates may overestimate the change in AGW burden and that adjusted rates may underestimate the changes. As Pap testing is part of the clinical care pathway that results in a diagnosis, analyses evaluating the HPV program need to consider the role, if any, that changes in Pap testing could have on their findings.

There are several limitations to consider when interpreting the results of this study, including those described previously [16]. As a population-based assessment, there are a number of factors that could have influenced the observed trends aside from the HPV vaccine program. For example, the increasing use of urine screening for chlamydia as opposed to gynecological exam with swabs may have reduced the number of AGW cases diagnosed incidentally. Secondly, our reliance on cryotherapy and chemical therapy codes for the AGW case definition underestimated the true burden of AGWs because topical, patient-applied treatments are not captured in the health administrative data. If treatment practices changed during the study period to incorporate more topical, patient-applied treatments, then this would contribute to a reduction in AGW cases and HSU, because individuals with AGW who self-treat would not be captured through cryotherapy and chemical codes. Decreasing sexual activity with concomitant lower risk of sexually-transmitted infection among our target age groups could explain some of our results. Data from nationally representative surveys of adolescent sexual behavior demonstrated that the percentage of 15–19 year old Canadians reporting at least one act of sexual intercourse declined from 47% in 1996/1997 to 43% in 2005 entirely due to behavior of the female population [29]. We do not know if this trend continued through our study period, although this would unlikely account for the magnitude of the changes we have observed in AGWs, and the discordant sex-specific changes. It is important to note that the HPV vaccine itself, however, has not been identified as a potential driver of changes to sexual practices [19,30,31]. Reporting AGW incidence and HSU rates based on records in the OHIP database is an underestimate of total AGW rates in Ontario, where individuals can be diagnosed and treated at emergency departments (ED), hospitals, same day surgery (SDS) clinics, sexual health clinics, community health centres, and public health clinics, none of which are captured in the database used in our study. We did look at AGW HSU at ED, hospitals, and SDS clinics, but these comprised only an additional 9% of visits. As this limitation applies to the whole study period, it should not affect inferences regarding trends across the study period as there is no known reason for a shift in an individual's choice in type of health services sought for AGWs during this period. However, if people attending these alternate clinics have a different probability of either being vaccinated or having AGWs, we could have over- or under-estimated that population effect. Finally, we did not have access to individual level HPV vaccination data, so we were not able to assess if any of the individuals with AGWs were vaccinated.

5. Conclusions

By comparing AGW incidence and HSU rates by age group and sex over time, this study estimates the impact of the HPV vaccination program in Ontario at the population level and provides preliminary insight into the benefits of the current program and potential indirect effects among males. Our analysis suggests a significant impact of the Ontario HPV vaccination program on AGW rates in young adult females, but no evidence of herd effects on males. Continued assessment is needed to provide further evidence of program impact, especially as boys will be eligible to receive the HPV vaccine through the school-based program beginning in the 2016/17 school year.

Competing interests

None.

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Contributorship statement

SLD conceived of the study, participated in study design, data interpretation, and writing of the manuscript. FMG participated in study design, data analysis and interpretation, supervised the statistical analysis, and wrote the first draft of the manuscript and revised drafts. CC had full access to the data and performed data analysis. SD provided clinical expertise and participated in data interpretation and writing of the manuscript. SEW and LCR participated in study design, data analysis and interpretation, and writing of the manuscript. All authors approved of the final manuscript.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.08.020.

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