

BMJ Open Health service utilisation for anogenital warts in Ontario, Canada prior to the human papillomavirus (HPV) vaccine programme introduction: a retrospective longitudinal population-based study

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ABSTRACT

Objective: Trends in occurrence of anogenital warts (AGWs) can provide early evidence of human papillomavirus (HPV) vaccination programme impact on preventing HPV infection and HPV-induced lesions. The objective of this study was to provide a baseline of AGW epidemiology in Ontario prior to the introduction of the publicly-funded school-based HPV vaccination programme in September 2007.

Setting and participants: As a retrospective longitudinal population-based study, we used health administrative data as a proxy to estimate incident AGWs and total health service utilisation (HSU) for AGWs for all Ontario residents 15 years and older with valid health cards between 1 April 2003 and 31 March 2007.

Outcome measures: The outcome of interest was AGW healthcare utilisation identified using the International Classification of Diseases, 10th revision (ICD-10) diagnostic code for AGWs, as well as an algorithm for identifying AGW physician office visits in a database with a unique system of diagnostic and procedural codes. An AGW case was considered incident if preceded by 12 months without HSU for AGWs. Time trends by age group and sex were analysed.

Results: Between fiscal years 2003 and 2006, we identified 123 247 health service visits for AGWs by 51 436 Ontario residents 15 years and older. Incident AGWs peaked in females and males in the 21–23 year age group, at 3.74 per 1000 and 2.81 per 1000, respectively. HSU for AGWs peaked in females and males within the 21–23 year age group, at 9.34 per 1000 and 7.22 per 1000, respectively.

Conclusions: To the best of our knowledge, this is the first population-based study of AGW incidence and HSU in Ontario. The sex and age distribution of individuals with incident and prevalent AGWs in Ontario was similar to that of other provinces before HPV vaccine programme implementation in Canada.

Most individuals will acquire human papillomavirus (HPV) at some point in their

Strengths and limitations of this study

- Anogenital warts (AGWs) are an early indicator of human papillomavirus (HPV) transmission in a population relative to cervical cancers, which take more time to develop.
- Anogenital warts incidence and health service utilisation in Ontario peaked in the 21–23 years age group for both females and males.
- In the 3 years leading up to the Ontario HPV4 program, the sex and age distribution of AGWs was found to be similar to other Canadian provinces before widespread programme implementation.

lifetime. HPV can be transmitted by vaginal, anal and oral sex, as well as non-penetrative sex including digital-vaginal or skin-to-skin contact,¹ and through vertical transmission.² Although most HPV infections are transient and resolve without treatment, HPV infection can lead to both low risk lesions and cancerous conditions. At least 150 different HPV genotypes have been described, with approximately 40 genotypes having tissue specificity for the anogenital region and oral cavity.³ HPV-6 and HPV-11 accounted for approximately 90% of anogenital warts (AGWs), while HPV-16 and HPV-18 accounted for approximately 70% of cervical cancers prior to vaccine introduction.⁴ HPV is also associated with other anogenital cancers (vaginal, vulvar, penile, anal canal) and a subset of head and neck squamous cell carcinomas. The licensing of prophylactic HPV vaccines Gardasil (referred to as HPV4 vaccine, targeting HPV types 6, 11, 16 and 18, by Merck & Co, Whitehouse Station, New Jersey, USA), Cervarix (targeting HPV types 16 and 18, by GlaxoSmithKline Biologicals,

Rixensart, Belgium) and Gardasil9 (targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, by Merck & Co, Whitehouse Station, New Jersey, USA) in countries around the world starting in 2006 introduced the possibility of primary prevention for HPV-related malignancy with all three vaccines, as well as AGWs with Gardasil and Gardasil9 vaccines.

Also known as condylomata acuminata, AGWs appear as multiple, asymmetric epithelial growths on the anogenital skin or mucous membranes. They can fluctuate in size and number, and can be flat, papular, cauliflower-like or keratotic. AGWs are associated with significant costs to the healthcare system⁵ and can cause substantial psychological distress,^{6 7} as well as pain and discomfort in some cases in the form of itching, discharge, burning or bleeding.^{8 9} Approximately 70% of HPV-6/11 infections are cleared within 12 months,^{10 11} with 10–30% of AGW cases clearing spontaneously within 3 months,¹² and approximately 6 months median time to clearance of infection.^{10 13} Treatments used in Canada include topical therapies applied by a physician or the patient, or physician administered ablative treatments such as cryotherapy, electrosurgery, CO₂ laser or surgical excision.¹⁴

Trends in health service utilisation (HSU) for AGWs can provide an early indication of the impact of Ontario's HPV vaccine programme in preventing HPV infection, by providing valuable information on the burden of AGWs prevaccine and postvaccine programme implementation. Other countries with HPV vaccination programmes have begun reporting significant decreases in the incidence of AGWs in females targeted for vaccination since the introduction of their programmes (reviewed by refs. ¹⁵ and ¹⁶). Several Canadian provinces have conducted baseline studies of AGW epidemiology in anticipation of evaluating HPV vaccine programme impact, reporting peak incidence rates for males and females ranging from 3.03 to 3.92/1000 population and 3.38 to 4.66/1000 population, respectively.^{5 17 18}

The objective of our report is to provide a baseline of AGW epidemiology in Ontario in the years leading up to the introduction of the publicly-funded, female-targeted school-based HPV vaccination programme, which was introduced in the fall of 2007.

METHODS

Databases

Neither AGWs nor HPV infection are reportable diseases in Ontario, therefore there are no surveillance data to derive incidence and prevalence. Data are available on AGW-related HSU in Ontario through a variety of health administrative databases. The Ontario Health Insurance Plan (OHIP) database captures fee-for-service claims made by Ontario physicians, and represents claims from approximately 98% of physicians in the province.¹⁹ The OHIP database was used to identify

physician visits for AGWs using a combination of diagnostic and procedural codes. The Canadian Institute of Health Information (CIHI)-Discharge Abstract Database (DAD) was used to identify hospitalisations for AGWs. The CIHI National Ambulatory Care Reporting System (NACRS) covers hospital and community-based ambulatory care services, and was used to identify emergency department (ED) visits for AGWs. The same-day-surgery (SDS) database was used to identify same day surgeries and procedures for AGWs. The Registered Persons Database (RPDB) contains information on all Ontario residents who are eligible for healthcare coverage. To be eligible for healthcare coverage in Ontario residents must be Canadian citizens, landed immigrants or refugees, with Ontario as their primary or permanent home and must be present in Ontario for a minimum of 153 days over a 12-month period. Eligible Ontario residents are assigned a unique health card number which permits access to health services available through a publicly funded healthcare system. The RPDB was used to determine population size, sex and date of birth in the analysis. These data sets were linked using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences. These data sources are consistent with administrative data used to estimate AGWs burden in previous studies.^{5 17 18}

Data sharing statement

This study used health administrative databases held at the Institute for Clinical and Evaluative Sciences. Public deposition of ICES data is not permitted.

Population

Ontario is Canada's most populous and ethnically diverse province. We included all Ontario residents 15 years and older with a valid health card number between 1 April 2003 and 31 March 2007, which included fiscal years 2003–2006 hereafter referred to as simply year, based on the RPDB.

Case definition

The outcome of interest was AGW HSU. We identified AGW HSU in the CIHI-DAD, NACRS and SDS databases using the International Classification of Diseases, 10th revision (ICD-10) diagnostic code for AGWs, which is A630. There was no pre-existing validated algorithm for identifying AGW cases in the OHIP database; therefore, we identified codes with potential relevance to AGWs through the Ministry of Health and Long-Term Care (MOHLTC) Chapter 4 Claims Submissions (2003 and 2014 editions), the Ontario Medical Association Section on General & Family Practice (SGFP) Common Family Practice Codes (2011), the MOHLTC OHIP Schedule of Benefits for Physician Services (2013) and the Practice Solutions (PSS) electronic medical record system as an example of a common electronic medical record and billing system used in family practice (see online supplementary figure S1). We reviewed the list of

diagnostic and procedural codes in consultation with physicians having experience in sexual and reproductive health services and combined in algorithms for AGW case definitions. Smith *et al*²⁰ report using similar OHIP diagnostic and procedural codes in a recent analysis of AGWs in Ontario. We conducted sensitivity analyses to identify the most probable case definition for AGWs. The final algorithm to identify AGW HSU in OHIP was as follows: 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. Any of these 10 code combinations comprised of a diagnostic and/or procedural code constituted a HSU for a case of AGWs.

We conducted descriptive analysis of AGW-related HSU by age group, sex and fiscal year. Age groups were designed to provide sufficient granularity in the ages surrounding peak AGW HSU and incident AGWs, and to provide baseline data on age groups targeted in the provincial HPV vaccination programme as they age. Three-year age groups were used for 15–44 year olds, 10-year age groups were used for 45–84 year olds, and a separate age group was used for individuals 85 years and older, to be in line with the epidemiology of AGWs. Reported rates are either rates of total HSU for AGWs that is, every AGW-related healthcare visit; or, as rates of incident AGWs that is, AGW cases preceded by 12-months without an AGW visit divided by the number of health card holders. This is similar to definitions used for incident cases in previous studies.^{5 17 18 21} The first year of the study functioned to exclude prevalent cases when estimating the rate of incident AGWs, thus, AGWs incidence data are available for 2004–2006, whereas total HSU data are available for 2003–2006. Rates reported for multiple years are the average annual rates. Trends in AGWs were analysed separately for OHIP, NACRS, DAD and SDS, as these databases represent different healthcare settings. Rates are provided per 1000 population.

Sensitivity analysis

One procedural code used in our AGW algorithm was for in-office chemical and/or cryotherapy, Z117, in conjunction with a diagnostic code. AGWs, however, can be treated using other therapies including patient-administered topical agents. Secular changes in the treatment of AGWs towards more patient-applied therapies could skew AGW rates because there are no corresponding codes to capture such treatment in administrative databases. To examine the potential impact of this, we analysed age and sex specific trends in Z117 and compared these results to AGW trends using the full AGW case algorithm, and then with the OHIP code combinations that included Z117.

This study was approved by the Institutional Review Boards at Sunnybrook Health Sciences Centre and Public Health Ontario in Toronto, Canada. The Public Health Ontario ERB approval number is 2014-056.01.

RESULTS

Combining physician office visits, SDS, hospitalisations and ED visits for Ontario residents 15 years and older between fiscal years 2003 and 2006, 51 436 individuals had 123 247 health service visits for AGWs (figure 1). Consistent with expected healthcare patterns for AGWs, average annual HSU for AGWs varied across the databases (hospitalisations: 0.01 per 1000; SDS: 0.23 per 1000; ED: 0.04 per 1000; and physician office visits: 2.74 per 1000), as did the average annual rate of incident AGWs (hospitalisations: 0.01 per 1000; SDS: 0.18 per 1000; ED: 0.03 per 1000; physician office visits: 1.19 per 1000). As revealed by comparing the number of unique individuals overall in all four databases (51 436) with the sum of the number of unique individuals in each separate database (63 932), some individuals utilised more than one type of health service for AGW diagnosis and/or treatment. From 2004 to 2006, the total number of physician office visits for AGWs was just over double the estimated number of new cases over the same period of time (data not shown). SDS accounted for 7.6% of the visits, ED accounted for 1.3% of the visits, hospitalisations accounted for 0.4% of the visits, while physician office visits accounted for 90.7% of visits (figure 1). As physician visits captured in the OHIP database accounted for the vast majority of visits and had the highest number of unique individuals, the analysis will focus primarily on the OHIP database.

AGW incidence

The rate of incident AGWs during the study period varied with age and sex. Females in the 15–38 years age group were more frequently diagnosed with AGWs in hospitals and SDS than males in the same age group (figure 2A, B). AGW incidence rates were more similar between sexes for AGWs diagnosed in ED, however AGW incidence was higher in females <21 years and males 21–26 years compared to the opposite sex of the same age groups (figure 2C). The rate of incident AGWs in physician offices also varied with age and sex. AGWs incidence peaked within the 21–23 years age group for both females and males at rates of 3.74 per 1000 and 2.81 per 1000, respectively (figure 3). In the 15 to 26 years age groups, incidence was higher among females compared to males, but between the ages of 27–41 years, the reverse was true, followed by similar rates between the sexes among those 42 years of age and older.

Trends by age group and sex

For females in the 15–17 years age group, the rate of incident AGWs decreased from 1.21 in 2004, to 1.01 in 2005 and 0.95 in 2006 (figure 4). In contrast, the rate of incident AGWs increased in females in the 24–26 years age group from 2.77 in 2004, to 2.94 in 2005, to 3.02 in 2006. The rate of incident AGWs showed little fluctuation in males from 2004 to 2006, with the exception of males in the 21–23 years age group, which changed

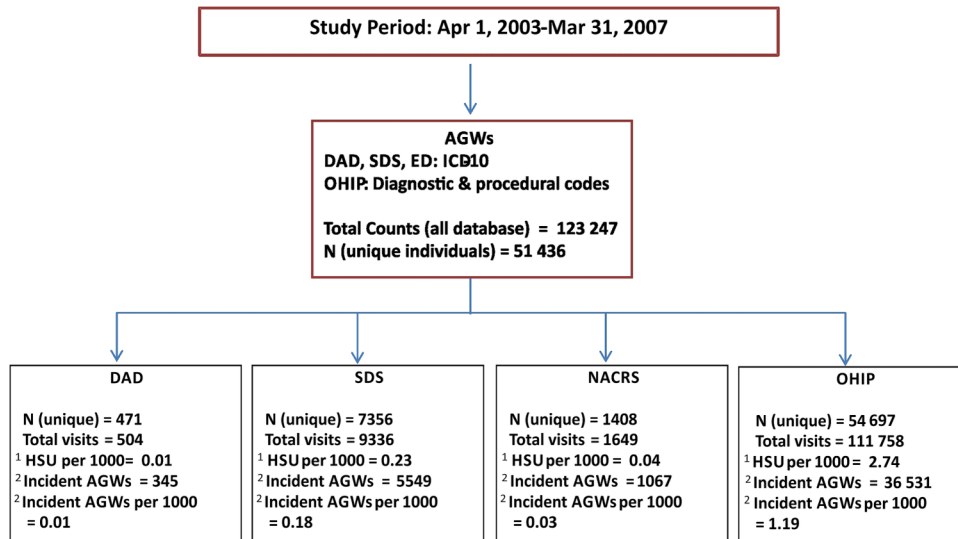


Figure 1 Counts and rates of AGWs by data source for Ontario residents 15 years and older, with a valid health card number, fiscal years 2003–2006. Rates are average annual for indicated period of time. ¹2003–2006. ²2004–2006, with 2003 as a washout to exclude prevalent cases. AGWs, anogenital warts; DAD, Discharge Abstract Database; ED, emergency department; HSU, health service utilisation; ICD 10, International Classification of Diseases 10th Edition; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; SDS, same-day-surgery.

from 2.77 in 2004, to 3.01 in 2005, to 2.66 in 2006. From 2004 to 2006, females represented a larger proportion of the new AGW cases in Ontario, but comprised a similar proportion of the total AGW-related HSU relative to males (data not shown).

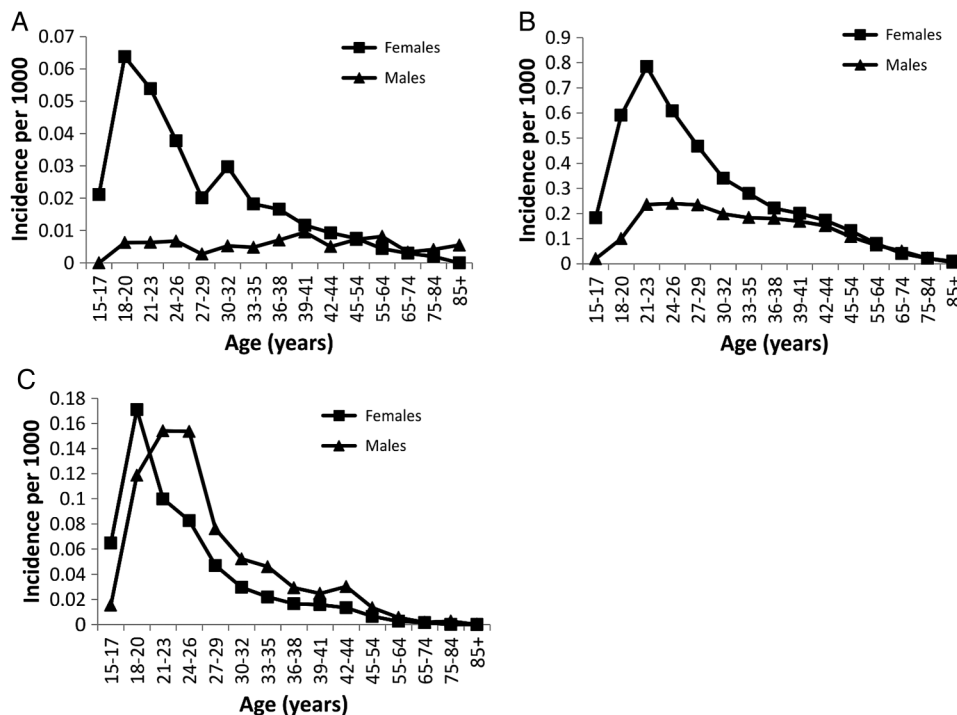
From 2003 to 2006, the total HSU for AGWs captured by the physician office visits peaked in females and males in the 21–23 years age group, at a rate of 9.34 per 1000 and 7.22 per 1000, respectively (figure 5). Health service utilisation for AGWs was higher among females

in the 15–26 years age groups compared to males, but between the 27 and 74 years age bands, the reverse was true.

Sensitivity analysis

To investigate whether secular changes in the treatment of AGWs towards more patient-applied therapies could be skewing AGW rates we analysed age and sex-specific trends in Z117 over the study period and compared these results to AGW trends using the full AGW case

Figure 2 Average annual rate of incident AGWs captured by hospitalisations (DAD) (A); same day surgery (B); and emergency department visits (NACRS) (C), by sex and age group, fiscal years 2004–2006. AGWs, anogenital warts.



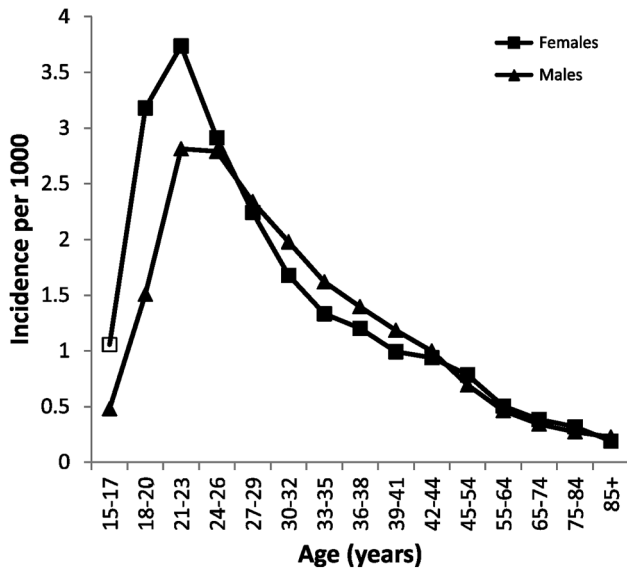


Figure 3 Average annual rate of incident AGWs captured by physician office visits, by sex and age group, fiscal years 2004–2006. AGWs, anogenital warts.

algorithm, and then with the OHIP code combinations that included Z117 for case identification. The results of the sensitivity analysis among 21–23-year-old females is provided as this was the age of peak AGW incidence for females (see online supplementary figure S2a–c). The results revealed that Z117 age distribution and rates for 15–38-year olds exhibited different rates and trends than those observed in our AGW cases, thus our observed AGW trends were unlikely a reflection of trends in Z117 treatment or coding practices.

DISCUSSION

This is the first population-based study of HSU for AGWs in Ontario, and was conducted using individual-level health administrative data from 1 April 2003 to 31 March 2007. Similar to previous studies from other regions, incident AGWs peaked in females in the

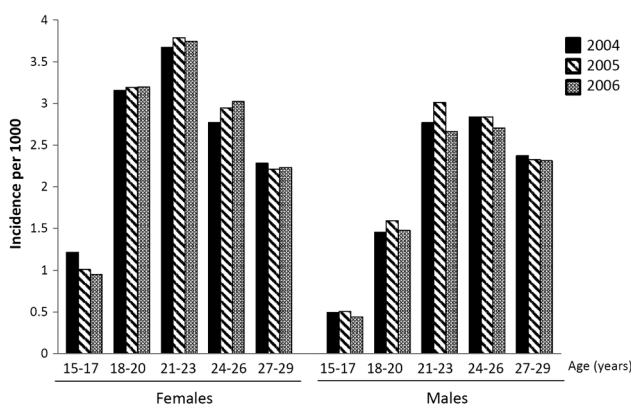


Figure 4 Annual incident AGWs captured by physician office visits, by fiscal year, sex, and age group, fiscal years 2004–2006. AGWs, anogenital warts.

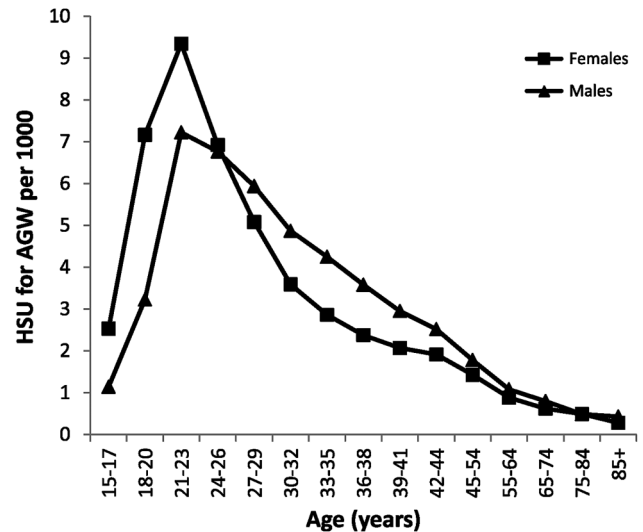


Figure 5 Average annual health service utilisation (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003–2006. AGWs, anogenital warts.

21–23 years age group.^{5 17 18} Although several previous studies reported peak incidence in males occurring at an older age than females,^{5 18 22} we found a similar age of peak incidence in males and females, which has been reported, but less frequently.¹⁷ However, incidence in males remained stable from the 21–23 years and 24–26 years age groups (2.81/1000 and 2.79/1000, respectively), thus peak incidence spanned the 21–26 years age group in males (figure 3).

The twofold higher total number of health service visits compared with incident AGW visits for cases from 2004 to 2006 likely reflects multiple treatments for a single episode or recurrence of AGWs within the 12-month window. This difference may also reflect the continued treatment of prevalent cases from the start of the study period, which could contribute to total visits but not total new cases as the 12-month washout removed prevalent cases from the estimation of new cases.

The decreasing incidence of AGWs in females in the 15–17-year age band is important to consider as this is the age group where potential HPV vaccine programme impact will be first observed and may complicate future assessment of HPV vaccine programme impact.

Changes to cervical cancer screening policy may account for the decrease in AGWs in the 15–17-year age band because some cases of AGWs may be picked up incidentally during a cervical screening. The Ontario Cervical Screening Programme (OCSPP) was launched in June 2000 and recommended Pap smears for any female who had been sexually active, with screening at 1-year intervals, and after three normal Pap smears, screening was recommended every 2 years. The recommendations changed in 2005 to screening starting within 3 years of first sexual activity, with screening recommended every 2–3 years after three consecutive normal Pap smears.

Thus, from 2005, Pap smears would have been conducted less frequently and age of first Pap may have been later. These changes could impact the rate of AGW diagnosis in females if the Pap smear procedure was a significant means of identifying AGWs; unfortunately investigation of how changes to Pap smear policy relate to AGWs diagnosis and treatment rates was beyond the scope of this study.

The observation that females are more frequently diagnosed with AGWs in hospitals and SDS settings than males likely reflects gynecological and pregnancy-related services rendered in these settings, which presents the opportunity for AGW diagnosis. This is supported by the observation that the frequency of AGW visits in these sites is much higher for females of reproductive age (late teens to late 30s) compared to males of the same age, whereas there is little difference between the sexes beyond 39 years of age. The same argument can be made for physician office visits, where females also seek reproductive health services. The higher rate of AGW diagnosis in ED in the male 21–26 years age group compared to females of the same age is interesting and may reflect sex differences in health-seeking behaviour in Ontario more generally and requires further study.

Relying on health administrative data does not capture undiagnosed and untreated AGWs, thereby underestimating the true incidence of AGWs; although this would also be a limitation if surveillance data were available. The OHIP database captures only AGW-related health visits to providers working in remuneration models that submit billing data and excludes visits to some sexual health clinics, public health clinics and community health centres. The literature indicates that sexually transmitted infection clinics report higher rates of AGWs than general practices and that certain populations are more likely to utilise these types of services,^{23 24} including individuals without valid health card numbers. Thus, the findings reported here are likely an underestimate of incidence and HSU for AGWs in Ontario. As described in the sensitivity analysis, we were unable to identify AGWs treated topically by the patient, thus, such cases may be missing from the counts. Although the study period spans a relatively short window of 4 years, the data may be impacted by changes to clinical practices in terms of compensation, coding, treatment, etc, which have not been accounted for here. Conversely, this study is not limited by self-reporting.

Unlike cervical cancer, which develops over years, AGWs are an early indicator of HPV transmission. The objective of our report was to provide a baseline of AGW epidemiology in Ontario in the years leading up to the introduction of the publicly-funded, female-targeted school-based HPV vaccination programme. Subsequent studies of AGW epidemiology in Ontario will build on this knowledge to assess the impact of the vaccination programme.

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Contributors SLD conceived 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. SEW provided clinical expertise and participated in study design, data interpretation, and writing of the manuscript. SLD provided clinical expertise and participated in data interpretation and writing of the manuscript. LCR participated in study design, data analysis and interpretation, and writing of the manuscript.

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Competing interests None declared.

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Data sharing statement No additional data available.

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