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Health service utilization for anogenital warts in Ontario prior to the human papillomavirus (HPV) vaccine program introduction

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ABSTRACT

Background: Trends in occurrence of anogenital warts (AGWs) can provide early evidence of human papillomavirus (HPV) vaccination program impact on preventing HPV infection. Therefore, baseline AGW epidemiology prior to the introduction of Ontario's HPV vaccination program is required to evaluate program impact.

Objective: To provide a baseline of AGW epidemiology in Ontario prior to the introduction of the publicly-funded school-based HPV vaccination program in fall 2007.

Methods: As a retrospective longitudinal population-based study, we used health administrative data to identify incident AGWs and total health service utilization (HSU) for AGWs for all Ontario residents 15 years and older with valid health cards between April 1 2003 and March 31 2007. An AGW case was considered incident if preceded by 12 months without HSU for AGWs. Time trends by age group and sex were analyzed.

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 in the 21-23 year age group, at 3.74 per 1000, and peaked in males in the 24-26 year age group at 2.81 per 1000. HSU for AGWs peaked in both females and males within the 21-23 age group, at 9.34 per 1000 and 7.22 per 1000, respectively.

Conclusion: To our knowledge, this is the first population-based study of HSU for AGWs in Ontario. The sex and age distribution of AGWs in Ontario was similar to that of other provinces before HPV vaccine program implementation in Canada.

STRENGTHS AND LIMITATIONS OF THE STUDY

- AGWs are an early indicator of HPV transmission. We report the baseline of AGW epidemiology in Ontario-Canada's most populous and ethnically diverse province- in the years leading up to the introduction of the publicly-funded, female-targeted school-based HPV vaccination program.
- We used health administrative data to identify incident AGWs and health service utilization (HSU) for AGWs for Ontario residents 15 years and older. These databases are consistent with administrative data used to estimate AGW burden in previous studies.
- The databases used do not capture AGW-related health visits to providers not captured by fee-for-service remuneration models without shadow billing, including sexual health clinics, public health clinics, and community health centres, nor does the data capture undiagnosed and untreated AGWs. Thus, the data are an underestimate of the true incidence of AGWs.
- The data may be impacted by changes to clinical practices in terms of compensation, coding, treatment etc., which were not accounted for here.

Most individuals will acquire human papillomavirus (HPV) at some point in their 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 benign 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 -11 accounted for approximately 90% of anogenital warts (AGWs), while HPV-16 and -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, NJ USA) and Cervarix® (targeting HPV types 16 and 18, by GlaxoSmithKline Biologicals, Rixensart, Belgium) in countries around the world starting in 2006 introduced the possibility of primary prevention for HPV-related malignancy with both vaccines, and AGWs with HPV4 vaccine.

Also known as condylomata accuminata, 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. Anogenital warts are associated with significant costs to the health care system (5) and can cause substantial psychological distress (6), as well as pain and discomfort in some cases in the form of itching, discharge, burning, or bleeding (7, 8). Approximately 70% of HPV-

6/11 infections are cleared within 12 months (9, 10), with 10-30% of AGW cases clearing spontaneously within three months (11). 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 (12).

Trends in health service utilization (HSU) for AGWs can provide an early indication of the impact of Ontario's HPV vaccine program in preventing HPV infection, by providing valuable information on the burden of AGWs pre- and post-vaccine program implementation. Other countries with HPV vaccination programs have begun reporting significant decreases in the incidence of AGWs in females targeted for vaccination since the introduction of their programs (reviewed by 13, 14). Several Canadian provinces have conducted baseline studies of AGW epidemiology in anticipation of evaluating HPV vaccine program 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, 15, 16).

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 program, 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 held at the Institute for Clinical and Evaluative Sciences. 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 (17). 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 hospitalizations 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 health care coverage. To be eligible for health care 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 health care system. The RPDB was used to determine population size, sex, and date of birth in the analysis. Ontario residents are represented in these databases by a unique, encrypted identifier, which permits linkage across databases and provides individual level HSU data. These databases are consistent with administrative data used to estimate AGWs burden in previous studies (5, 15, 16).

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 April 1 2003 and March 31 2007, which included fiscal years 2003 to 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 (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 report using similar OHIP diagnostic and procedural codes in a recent analysis of AGWs in Ontario (18). 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 ten 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 program as they age. Three-year age groups were used for 15 to 44 year olds, 10-year age groups were used for 45 to 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 i.e. every AGW-related health care visit; or, as rates of incident AGWs i.e. 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, 15, 16,19). 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 to 2006, whereas total HSU data are available for 2003 to 2006. Rates reported for multiple years are the average annual rates. Trends in AGWs were analyzed separately for OHIP, NACRS, DAD, and SDS, as these databases represent different health care 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. Anogenital warts, 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 analyzed 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 Research Ethics Board at Sunnybrook Health Sciences Centre and the Ethics Review Board at Public Health Ontario. The Public Health Ontario ERB approval number is 2014-056.01.

RESULTS

Combining physician office visits, SDS, hospitalizations, 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 health care patterns for AGWs, average annual HSU for AGWs varied across the databases (hospitalizations: 0.01 per 1000; SDS: 0.23 per 1000; ED: 0.04 per 1000; and physician office visits: 2.75 per 1000), as did the average annual rate of incident AGWs (hospitalizations: 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 utilized 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). Same day surgery accounted for 7.6% of the visits, ED accounted for 1.3% of the visits, hospitalizations accounted for 0.4% of the visits, while physician office visits accounted for 90.7% of visits (Figure 1). As physician visits accounted for the vast majority of visits and had the highest number of unique individuals, the remainder of the analysis will focus on the OHIP database.

Incident HSU for AGWs

The rate of incident AGWs in physician offices during the study period varied with age and sex. Anogenital warts incidence peaked within the 21-23 age group for both females and males at rates of 3.74 per 1000 and 2.81 per 1000, respectively (Figure 2). In the 15 to 26 age groups, incidence was higher amongst females compared to males, but between the ages of 27 to 44 years, the reverse was true, followed by similar rates between the sexes among those 45 years of age and older. The supplementary content contains the average annual rate of incident AGWs for 2004 to 2006 from the ED, hospitalization, and SDS databases (S2).

Trends by age group and sex

For females in the 15-17 age group, the rate of incident AGWs decreased from 1.21 in 2004, to 1.01 in 2005, and 0.95 in 2006 (Figure 3). In contrast, the rate of incident AGWs increased in females in the 24-26 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 age group, which changed 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 both females and males in the 21-23 age group, at a rate of 9.34 per 1000 and 7.22 per 1000, respectively (Figure 4). Health service utilization for AGWs was higher amongst females in the 15 to 26 age groups compared to males, but between the 27 to 74 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 analyzed age and sex specific trends in Z117 over the study period and compared these results to AGW trends using the full AGW case 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 (S3). 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 April 1 2003 to March 31 2007. Similar to previous studies from other regions, incident AGWs peaked in females in the 21-23 age group (5, 15, 16, 20). Although several previous studies reported peak incidence in males occurring at an older age than females (5, 16, 20), we found a similar age of peak incidence in males and females, which has been reported, but less frequently (15).

The two-fold 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.

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 program impact will be first observed and may complicate assessment of HPV vaccine program impact. The HPV4 vaccine became available for private purchase after it was launched by Merck in August 2006. It is possible the decreasing incidence in the 15-17 year age band reflects the impact of privately purchased HPV4 vaccine, however, this study was unable to investigate vaccine receipt at the individual level to explore this possibility.

Changes to cervical cancer screening policy may also 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 Program (OCSP) was launched in June 2000 and recommended Pap smears for any female who had been sexually active, with screening at one-year intervals, and after three normal Pap smears, screening was recommended every two years. The recommendations changed in 2005 to screening starting within three years of first sexual activity, with screening recommended every two to three 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.

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 does not capture AGW-related health visits to providers not captured by fee-for-service remuneration models without shadow billing, including sexual health clinics, public health clinics, and community health centres. The literature indicates that STI clinics report higher rates of AGWs than general practices (21) and that certain populations are more likely to utilize these types of services (22), 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 four 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 program. Subsequent studies of AGW epidemiology in Ontario will build on this knowledge to assess the impact of the vaccination program.

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Competing interests:

None.

Funding:

Funding was provided by Public Health Ontario.

Ethics:

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the Ethics Review Board at Public Health Ontario, ERB approval 2014-056.01.

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. SEW provided clinical expertise, and participated in study design, data interpretation, and writing of the manuscript. SD 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.

Key Messages Box

- Anogenital warts are an early indicator of HPV transmission in a population relative to cervical cancers, which take more time to develop.
- Anogenital warts incidence and health service utilization in Ontario peaked in the 21-23 age group for both females and males.
- In the three 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 program implementation.

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FIGURE LEGENDS

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 to 2006. Rates are average annual for indicated period of time.

[1] 2003 to 2006

[2] 2004-2006, with 2003 as a washout to exclude prevalent cases

Health service utilization, HSU

Figure 2. Average annual rate of incident AGWs captured by physician office visits, by sex and age group, fiscal years 2004 to 2006.

Figure 3. Annual incident AGWs captured by physician office visits, by fiscal year, sex, and age group, fiscal years 2004 to 2006.

Figure 4. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.

S1. Table of AGW-related diagnostic and procedural codes used by physician offices.

S2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS)(e), by sex and age group, fiscal years 2004 to 2006.

S3. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004 (a); age-specific trends in code Z117 in females (b); age-specific trends in billing code combinations that include Z117, for 21-23 year old females (c).

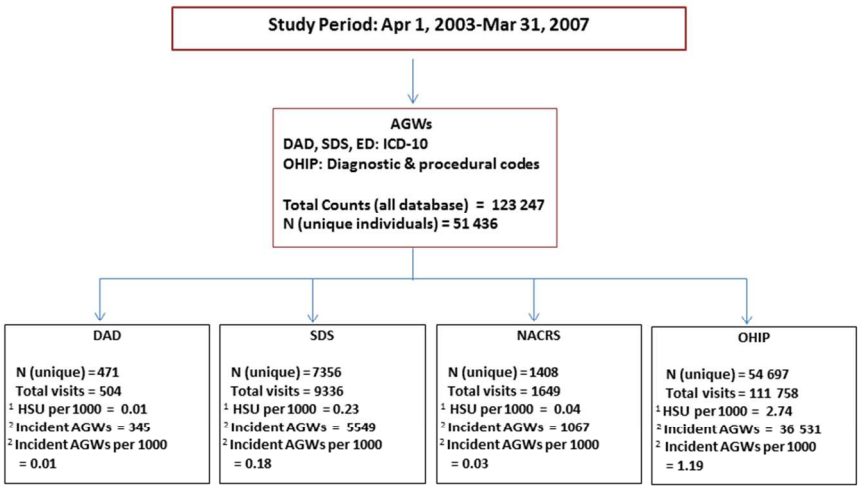


Figure 1. Counts and rates of AGWs by data source for Ontario residents 15 years and older, with a valid health card number, fiscal years 2003 to 2006. Rates are average annual for the indicated period of time. [1] 2003 to 2006, [2] 2004 to 2006, 2003 as washout to exclude prevalent cases. HSU, health service utilization.
254x190mm (96 x 96 DPI)

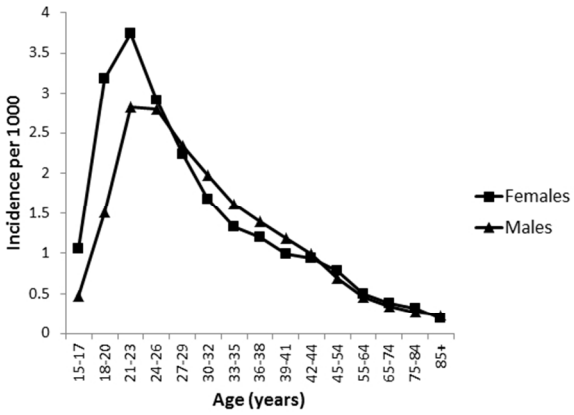


Figure 2. Average annual rate of incident AGWs captured by physician office visits, by sex and age group, fiscal years 2004 to 2006.
254x190mm (96 x 96 DPI)

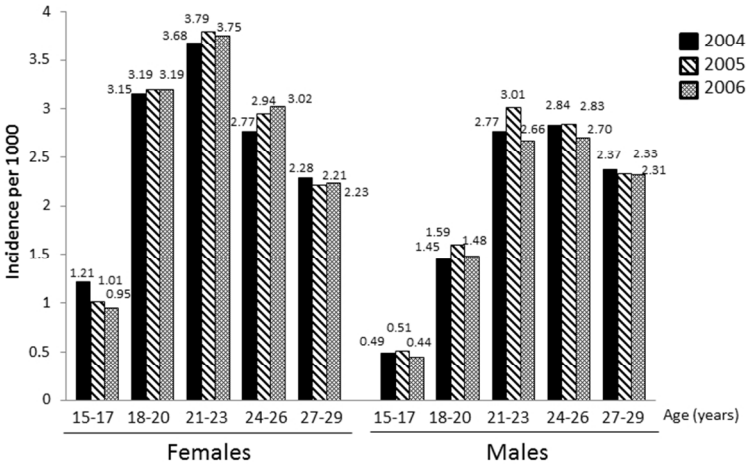


Figure 3. Annual incident AGWs captured by physician office visits, by fiscal year, sex, and age group, fiscal years 2004 to 2006.
254x190mm (96 x 96 DPI)

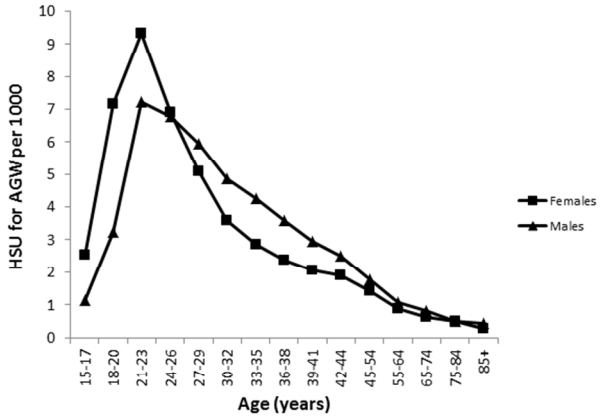
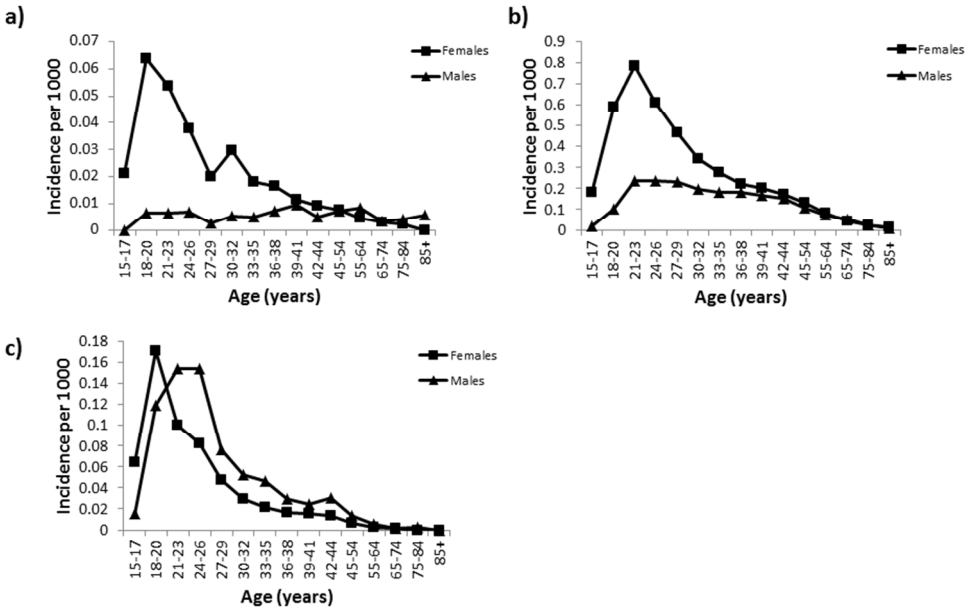


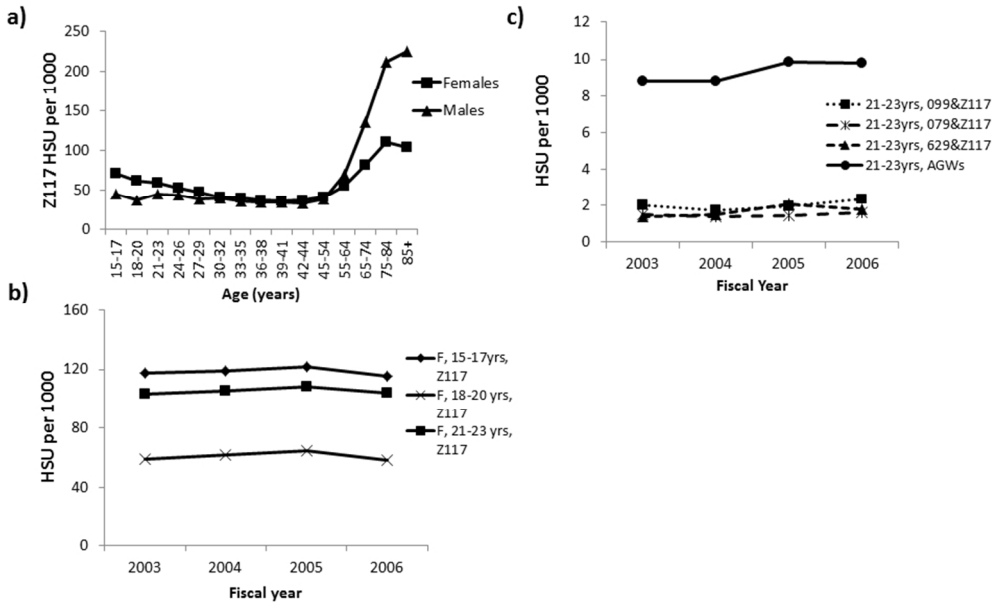
Figure 4. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.
254x190mm (96 x 96 DPI)

Code	Description
ICD-10	
A630	Anogenital (venereal) warts
OHIP	
Diagnostic Codes	
099	venereal disease, TD, condyloma, Duchennes, herpes genitalis, chlamydia,
079	condyloma accuminata, rabies, viral disease, other viral disease, viral illness
629	Warts, venereal, other disorders, Other diseases or disorders not specified elsewhere-genital organs female, other disorders of female genital organs, condylomata, leukorrhea
078	verruca(plantar wart), warts, all types, other viral disease, warts
K028	STD, BBD mgmt
Procedural Codes	
Z117	Chemical Rx wart (plantar, genital)
Z549	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (local anaesthesia)
Z701	Male genital surgical procedures: Excision: condylomata (local anaesthesia)
Z733	Female genital surgical procedures: Excision: condylomata (chem or cryo surgery)
Z736	Female genital surgical procedures: Excision: condylomata (local anaesthesia, surgical excision OR electrodessication OR CO2 laser)
Z758	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (general anaesthesia)
Z767	Male genital surgical procedures: Excision: condylomata (general anaesthesia)
Z769	Female genital surgical procedures: Excision: condylomata (general anaesthesia, surgical excision OR electrodessication OR CO2 laser)

S1. Table of AGW-related diagnostic and procedural codes used by physician offices.
254x190mm (96 x 96 DPI)



S2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS) (e), by sex and age group, fiscal years 2004 to 2006.
254x190mm (96 x 96 DPI)



S3. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004 (a); age-specific trends in code Z117 in females (b); age-specific trends in billing code combinations that include Z117, for 21-23 year old females (c). 254x190mm (96 x 96 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any pre-specified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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

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Key Words: genital warts; anogenital warts; human papillomavirus; HPV; epidemiology of genital warts; health service utilization

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ABSTRACT

Objective: Trends in occurrence of anogenital warts (AGWs) can provide early evidence of human papillomavirus (HPV) vaccination program 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 program 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 utilization (HSU) for AGWs for all Ontario residents 15 years and older with valid health cards between April 1 2003 and March 31 2007.

Outcome Measures: The outcome of interest was AGW health care utilization 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 analyzed.

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 both females and males within the 21-23 age group, at 9.34 per 1000 and 7.22 per 1000, respectively.

Conclusions: To 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 program implementation in Canada.

ARTICLE SUMMARY

- AGW is considered the first clinical endpoint to evaluate an HPV vaccination program. We report the baseline of AGW epidemiology in Ontario-Canada's most populous and ethnically diverse province- in the years leading up to the introduction of the publicly-funded, female-targeted school-based HPV vaccination program.
- We used health administrative data to identify incident AGWs and health service utilization (HSU) for AGWs for Ontario residents 15 years and older. These databases are consistent with administrative data used to estimate AGW burden in previous studies.
- The databases capture only AGW-related health visits to providers working in remuneration models that submit billing data to the province and exclude visits to some sexual health clinics, public health clinics, and community health centres, nor does the data capture undiagnosed and untreated AGWs. Thus, the data are an underestimate of the true incidence of AGWs.
- The data may be impacted by changes to clinical practices in terms of compensation, coding, treatment etc., which were not accounted for here.

Most individuals will acquire human papillomavirus (HPV) at some point in their 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 benign 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 -11 accounted for approximately 90% of anogenital warts (AGWs), while HPV-16 and -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, NJ USA) and Cervarix® (targeting HPV types 16 and 18, by GlaxoSmithKline Biologicals, Rixensart, Belgium) in countries around the world starting in 2006 introduced the possibility of primary prevention for HPV-related malignancy with both vaccines, and AGWs with HPV4 vaccine.

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. Anogenital warts are associated with significant costs to the health care system (5) 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 three months (12). 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 (13).

Trends in health service utilization (HSU) for AGWs can provide an early indication of the impact of Ontario's HPV vaccine program in preventing HPV infection, by providing valuable information on the burden of AGWs pre- and post-vaccine program implementation. Other countries with HPV vaccination programs have begun reporting significant decreases in the incidence of AGWs in females targeted for vaccination since the introduction of their programs (reviewed by 14, 15). Several Canadian provinces have conducted baseline studies of AGW epidemiology in anticipation of evaluating HPV vaccine program 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, 16, 17).

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 program, 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 (18). 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 hospitalizations 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 health care coverage. To be eligible for health care 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 health care system. The RPDB was used to determine population size, sex, and date of birth in the analysis. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. These data sources are consistent with administrative data used to estimate AGWs burden in previous studies (5, 16, 17).

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 April 1 2003 and March 31 2007, which included fiscal years 2003 to 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 (supplementary figure 1). 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 report using similar OHIP diagnostic and procedural codes in a recent analysis of AGWs in Ontario (19). 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 ten 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 program as they age. Three-year age groups were used for 15 to 44 year olds, 10-year age groups were used for 45 to 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 i.e. every AGW-related health care visit; or, as rates of incident AGWs i.e. 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, 16, 17, 20). 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 to 2006, whereas total HSU data are available for 2003 to 2006. Rates reported for multiple years are the average annual rates. Trends in AGWs were analyzed separately for OHIP, NACRS, DAD, and SDS, as these databases represent different health care 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. Anogenital warts, 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 analyzed 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, hospitalizations, 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 health care patterns for AGWs, average annual HSU for AGWs varied across the databases (hospitalizations: 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 (hospitalizations: 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 utilized 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). Same day surgery accounted for 7.6% of the visits, ED accounted for 1.3% of the visits, hospitalizations 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 age group were more frequently diagnosed with AGWs in hospitals and SDS than males in the same age group (Figure 2 a, 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 2 c). The rate of incident AGWs in physician offices also varied with age and sex. Anogenital warts incidence peaked within the 21-23 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 age groups, incidence was higher amongst females compared to males, but between the ages of 27 to 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 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 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 age group, which changed 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 both females and males in the 21-23 age group, at a rate of 9.34 per 1000 and 7.22 per 1000, respectively (Figure 5). Health service utilization for AGWs was higher amongst females in the 15 to 26 age groups compared to males, but between the 27 to 74 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 analyzed age and sex specific trends in Z117 over the study period and compared these results to AGW trends using the full AGW case 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 (supplementary figure 2a, 2b, 2c). 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 April 1 2003 to March 31 2007. Similar to previous studies from other regions, incident AGWs peaked in females in the 21-23 age group (5, 16, 17). Although several previous studies reported peak incidence in males occurring at an older age than females (5, 17, 21), we found a similar age of peak incidence in males and females, which has been reported, but less frequently (16). However, incidence in males remained stable from the 21-23 and 24-26 age groups (2.81/1000 and 2.79/1000, respectively), thus peak incidence spanned the 21-26 age group in males (Figure 3).

The two-fold 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 program impact will be first observed and may complicate future assessment of HPV vaccine program 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 Program (OCSP) was launched in June 2000 and recommended Pap smears for any female who had been sexually active, with screening at one-year intervals, and after three normal Pap smears, screening was recommended every two years. The recommendations changed in 2005 to screening starting within three years of first sexual activity, with screening recommended every two to three 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 30's) 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 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 STI clinics report higher rates of AGWs than general practices and that certain populations are more likely to utilize these types of services (22, 23), 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 four 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 program. Subsequent studies of AGW epidemiology in Ontario will build on this knowledge to assess the impact of the vaccination program.

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Competing interests:

None.

Funding:

Funding was provided by Public Health Ontario.

Ethics:

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the Ethics Review Board at Public Health Ontario, ERB approval 2014-056.01.

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. SEW provided clinical expertise, and participated in study design, data interpretation, and writing of the manuscript. SD 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.

Data sharing:

No additional data available.

Key Messages Box

- Anogenital warts are an early indicator of HPV transmission in a population relative to cervical cancers, which take more time to develop.
- Anogenital warts incidence and health service utilization in Ontario peaked in the 21-23 age group for both females and males.
- In the three 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 program implementation.

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Licence for Publication

FIGURE LEGENDS

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 to 2006. Rates are average annual for indicated period of time.

[1] 2003 to 2006

[2] 2004-2006, with 2003 as a washout to exclude prevalent cases

Health service utilization, HSU

Figure 2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS)(c), by sex and age group, fiscal years 2004 to 2006.

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

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

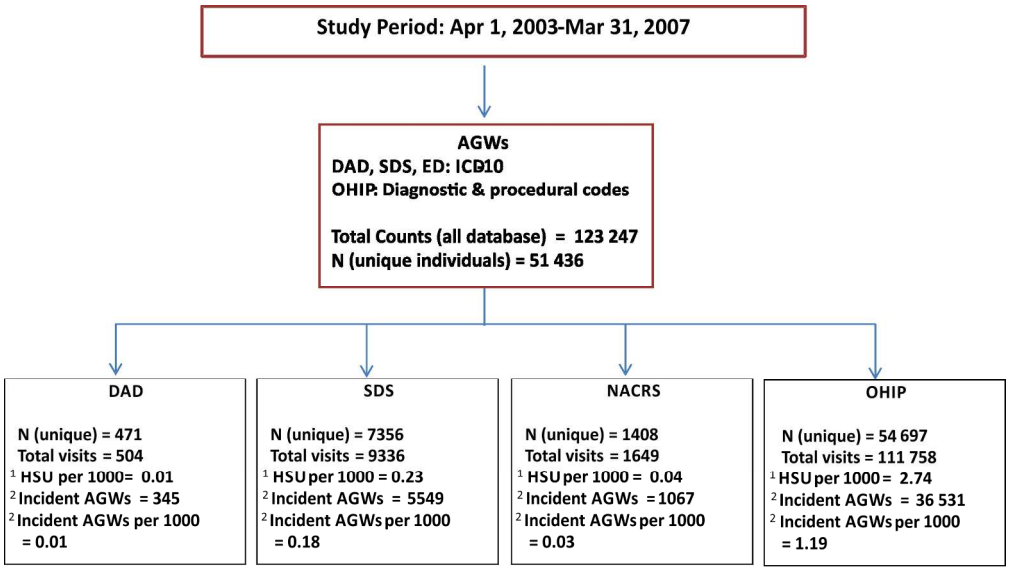
Figure 5. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.

Supplementary figure 1. Table of AGW-related diagnostic and procedural codes used by physician offices.

Supplementary figure 2a. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004.

Supplementary figure 2b. Age-specific trends in code Z117 in females.

Supplementary figure 2c. Age-specific trends in billing code combinations that include Z117, for 21-23 year old females.



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1 2003 to 2006
2 2004-2006, with 2003 as a washout to exclude prevalent cases
Health service utilization, HSU

215x120mm (300 x 300 DPI)

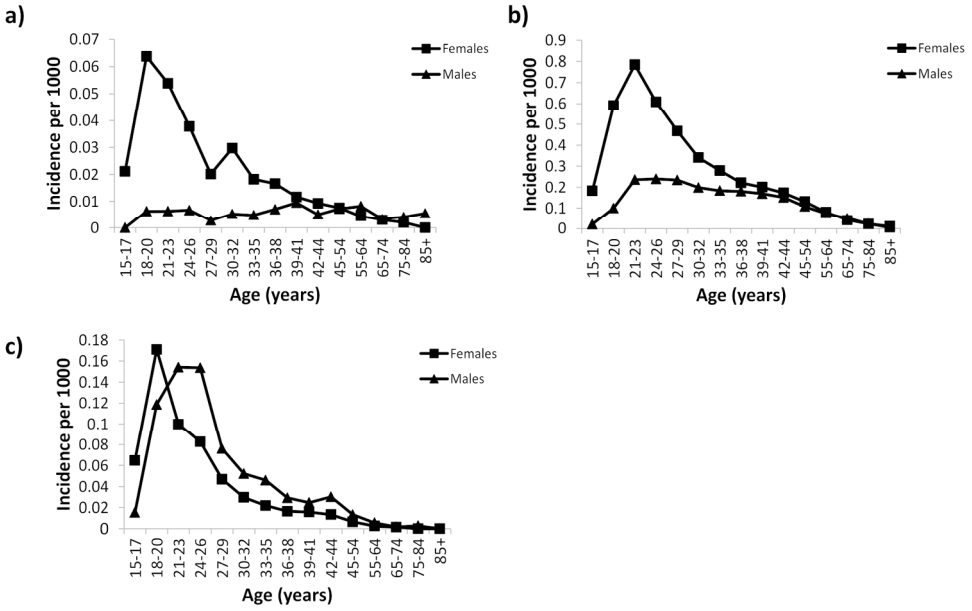


Figure 2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS)(c), by sex and age group, fiscal years 2004 to 2006.
173x130mm (300 x 300 DPI)

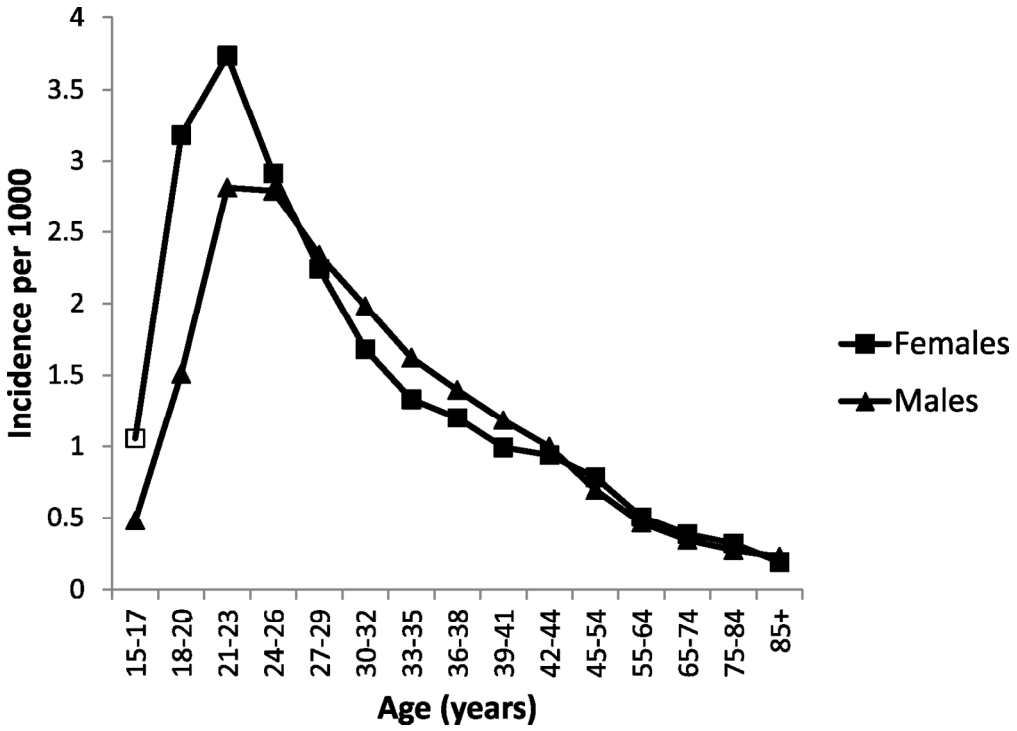


Figure 3. Average annual rate of incident AGWs captured by physician office visits, by sex and age group, fiscal years 2004 to 2006.
142x102mm (300 x 300 DPI)

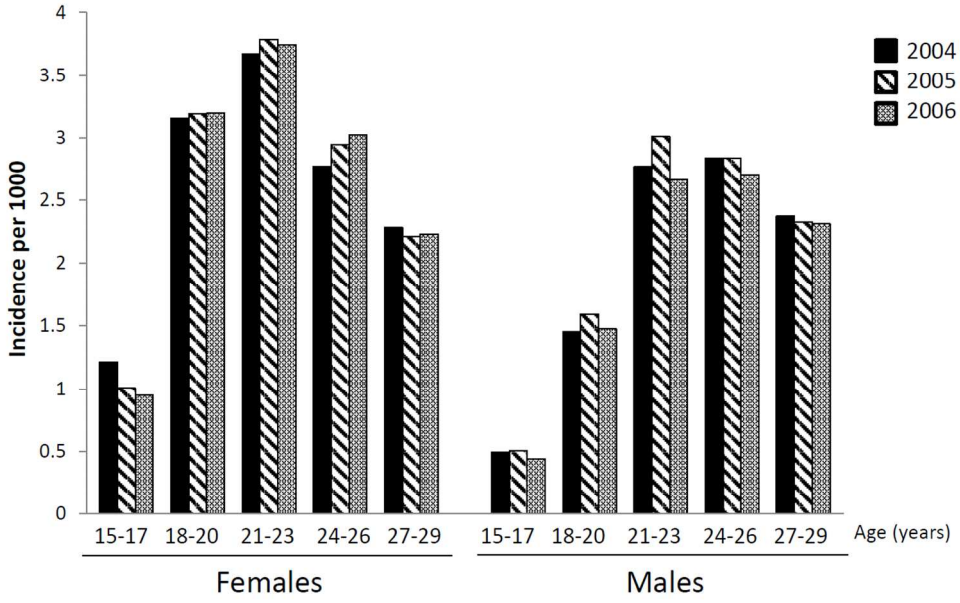


Figure 4. Annual incident AGWs captured by physician office visits, by fiscal year, sex, and age group, fiscal years 2004 to 2006.
173x109mm (300 x 300 DPI)

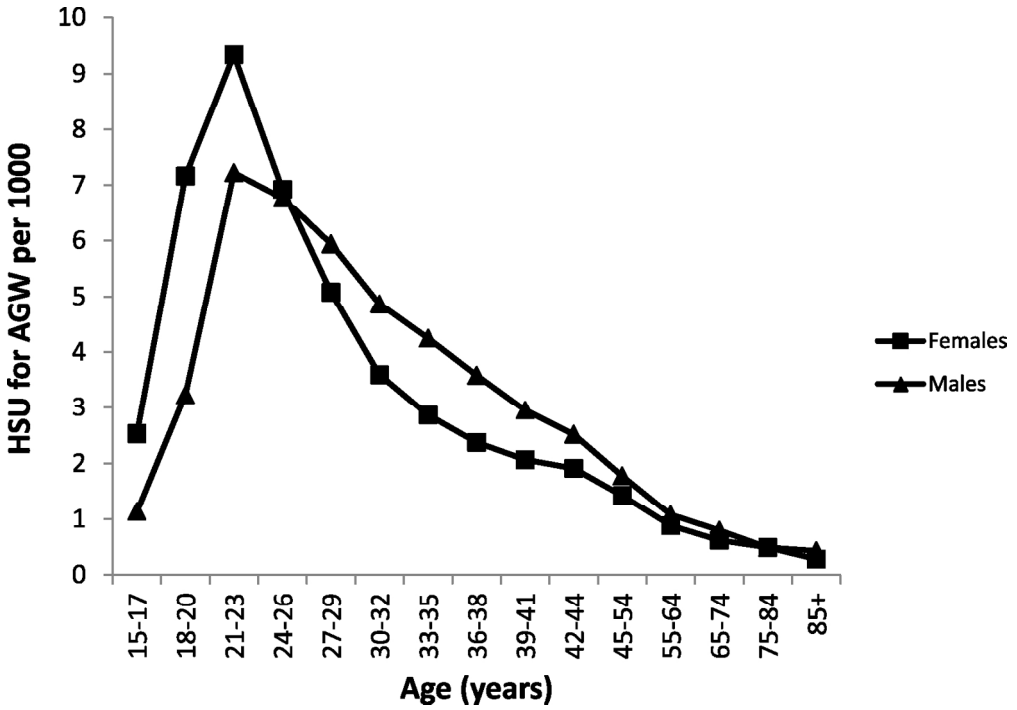
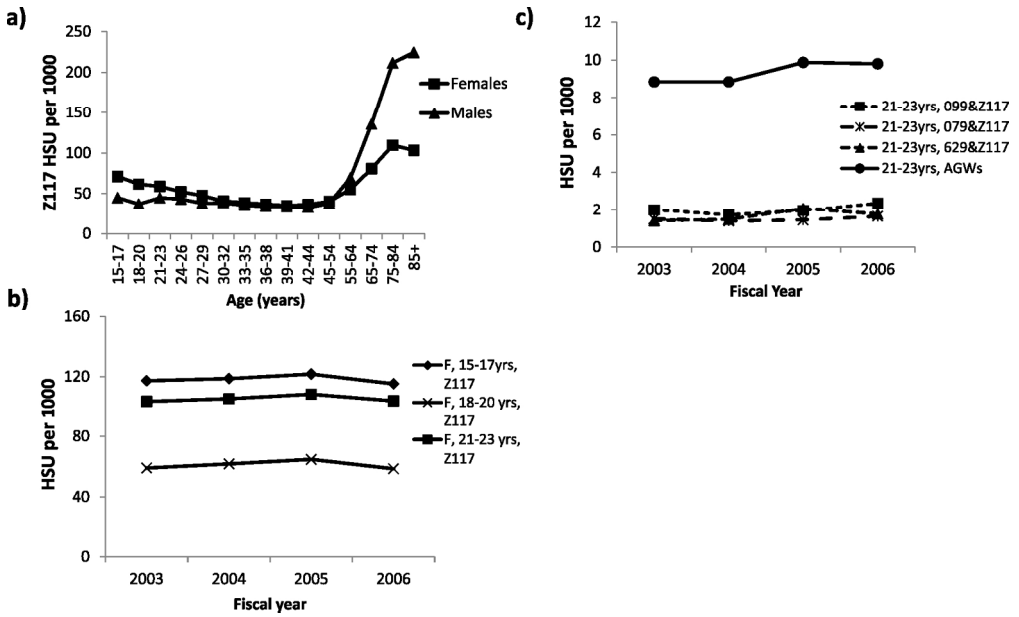


Figure 5. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.
148x103mm (300 x 300 DPI)

Code	Description
ICD-10	
A630	
OHIP	
Diagnostic Codes	
099	venereal disease, TD, condyloma, Duchennes, herpes genitalis, chlamydia,
079	condyloma accuminata, rabies, viral disease, other viral disease, viral illness
629	Warts, venereal, other disorders, Other diseases or disorders not specified elsewhere-genital organs female, other disorders of female genital organs, condylomata, leukorrhea
078	verruca(plantar wart), warts, all types, other viral disease, warts
K028	STD, BBD mgmt
Procedural Codes	
Z117	Chemical Rx wart (plantar, genital)
Z549	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (local anaesthesia)
Z701	Male genital surgical procedures: Excision: condylomata (local anaesthesia)
Z733	Female genital surgical procedures: Excision: condylomata (chem or cryo surgery)
Z736	Female genital surgical procedures: Excision: condylomata (local anaesthesia, surgical excision OR electrodessication OR CO2 laser)
Z758	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (general anaesthesia)
Z767	Male genital surgical procedures: Excision: condylomata (general anaesthesia)
Z769	Female genital surgical procedures: Excision: condylomata (general anaesthesia, surgical excision OR electrodessication OR CO2 laser)

Supplementary figure 1. Table of AGW-related diagnostic and procedural codes used by physician offices.
173x163mm (300 x 300 DPI)



Supplementary figure 2. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004 (a); age-specific trends in code Z117 in females (b); age-specific trends in billing code combinations that include Z117, for 21-23 year old females (c).
173x104mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review See Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number N/A
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author See Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review See Page 14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments N/A
Support:		
Sources	5a	Indicate sources of financial or other support for the review See Page 14
Sponsor	5b	Provide name for the review funder and/or sponsor See Page 14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol See Page 14
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known See Pages 4 & 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) See Page 5
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review N/A
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage See Pages 5-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated N/A
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review See Pages 5 & 6

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	N/A
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	N/A
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	See Pages 5-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	See Page 8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

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

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

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Key Words: genital warts; anogenital warts; human papillomavirus; HPV; epidemiology of genital warts; health service utilization

Word Count: 3260

ABSTRACT

Objective: Trends in occurrence of anogenital warts (AGWs) can provide early evidence of human papillomavirus (HPV) vaccination program 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 program 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 utilization (HSU) for AGWs for all Ontario residents 15 years and older with valid health cards between April 1 2003 and March 31 2007.

Outcome Measures: The outcome of interest was AGW health care utilization 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 analyzed.

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 both females and males within the 21-23 age group, at 9.34 per 1000 and 7.22 per 1000, respectively.

Conclusions: To 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 program implementation in Canada.

ARTICLE SUMMARY

- AGW is considered the first clinical endpoint to evaluate an HPV vaccination program. We report the baseline of AGW epidemiology in Ontario-Canada's most populous and ethnically diverse province- in the years leading up to the introduction of the publicly-funded, female-targeted school-based HPV vaccination program.
- We used health administrative data to identify incident AGWs and health service utilization (HSU) for AGWs for Ontario residents 15 years and older. These databases are consistent with administrative data used to estimate AGW burden in previous studies.
- The databases capture only AGW-related health visits to providers working in remuneration models that submit billing data to the province and exclude visits to some sexual health clinics, public health clinics, and community health centres, nor does the data capture undiagnosed and untreated AGWs. Thus, the data are an underestimate of the true incidence of AGWs.
- The data may be impacted by changes to clinical practices in terms of compensation, coding, treatment etc., which were not accounted for here.

Most individuals will acquire human papillomavirus (HPV) at some point in their 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 -11 accounted for approximately 90% of anogenital warts (AGWs), while HPV-16 and -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, NJ 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, NJ USA) in countries around the world starting in 2006 introduced the possibility of primary prevention for HPV-related malignancy with both vaccines, and AGWs with HPV4 vaccine.

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. Anogenital warts are associated with significant costs to the health care system (5) 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 three months (12), and approximately six 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 utilization (HSU) for AGWs can provide an early indication of the impact of Ontario's HPV vaccine program in preventing HPV infection, by providing valuable information on the burden of AGWs pre- and post-vaccine program implementation. Other countries with HPV vaccination programs have begun reporting significant decreases in the incidence of AGWs in females targeted for vaccination since the introduction of their programs (reviewed by 15, 16). Several Canadian provinces have conducted baseline studies of AGW epidemiology in anticipation of evaluating HPV vaccine program 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 program, 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 hospitalizations 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 health care coverage. To be eligible for health care 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 health care system. The RPDB was used to determine population size, sex, and date of birth in the analysis. These datasets were linked using unique encoded identifiers and analyzed 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

No additional data available.

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 April 1 2003 and March 31 2007, which included fiscal years 2003 to 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 (supplementary figure 1). 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 report using similar OHIP diagnostic and procedural codes in a recent analysis of AGWs in Ontario (20). 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 ten 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 program as they age. Three-year age groups were used for 15 to 44 year olds, 10-year age groups were used for 45 to 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 i.e. every AGW-related health care visit; or, as rates of

incident AGWs i.e. 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 to 2006, whereas total HSU data are available for 2003 to 2006. Rates reported for multiple years are the average annual rates. Trends in AGWs were analyzed separately for OHIP, NACRS, DAD, and SDS, as these databases represent different health care 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. Anogenital warts, 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 analyzed 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, hospitalizations, 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 health care patterns for AGWs, average annual HSU for AGWs varied across the databases (hospitalizations: 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 (hospitalizations: 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 utilized 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). Same day surgery accounted for 7.6% of the visits, ED accounted for 1.3% of the visits, hospitalizations 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 age group were more frequently diagnosed with AGWs in hospitals and SDS than males in the same age group (Figure 2 a, 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 2 c). The rate of incident AGWs in physician offices also varied with age and sex. Anogenital warts incidence peaked within the 21-23 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 age groups, incidence was higher amongst females compared to males, but between the ages of 27 to 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 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 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 age group, which changed 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 both females and males in the 21-23 age group, at a rate of 9.34 per 1000 and 7.22 per 1000, respectively (Figure 5). Health service utilization for AGWs was higher amongst females in the 15 to 26 age groups compared to males, but between the 27 to 74 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 analyzed age and sex specific trends in Z117 over the study period and compared these results to AGW trends using the full AGW case 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 (supplementary figure 2a, 2b, 2c). 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 April 1 2003 to March 31 2007. Similar to previous studies from other regions, incident AGWs peaked in females in the 21-23 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 and 24-26 age groups (2.81/1000 and 2.79/1000, respectively), thus peak incidence spanned the 21-26 age group in males (Figure 3).

The two-fold 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 program impact will be first observed and may complicate future assessment of HPV vaccine program 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 Program (OCSP) was launched in June 2000 and recommended Pap smears for any female who had been sexually active, with screening at one-year intervals, and after three normal Pap smears, screening was recommended every two years. The recommendations changed in 2005 to screening starting within three years of

first sexual activity, with screening recommended every two to three 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 30's) 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 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 STI clinics report higher rates of AGWs than general practices and that certain populations are more likely to utilize 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 four 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 program. Subsequent studies of AGW epidemiology in Ontario will build on this knowledge to assess the impact of the vaccination program.

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Competing interests:

None.

Funding:

Funding was provided by Public Health Ontario.

Ethics:

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the Ethics Review Board at Public Health Ontario, ERB approval 2014-056.01.

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. SEW provided clinical expertise, and participated in study design, data interpretation, and writing of the manuscript. SD 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.

Key Messages Box

- Anogenital warts are an early indicator of HPV transmission in a population relative to cervical cancers, which take more time to develop.
- Anogenital warts incidence and health service utilization in Ontario peaked in the 21-23 age group for both females and males.
- In the three 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 program implementation.

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Licence for Publication

FIGURE LEGENDS

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 to 2006. Rates are average annual for indicated period of time.

[1] 2003 to 2006

[2] 2004-2006, with 2003 as a washout to exclude prevalent cases

Health service utilization, HSU

Figure 2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS)(c), by sex and age group, fiscal years 2004 to 2006.

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

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

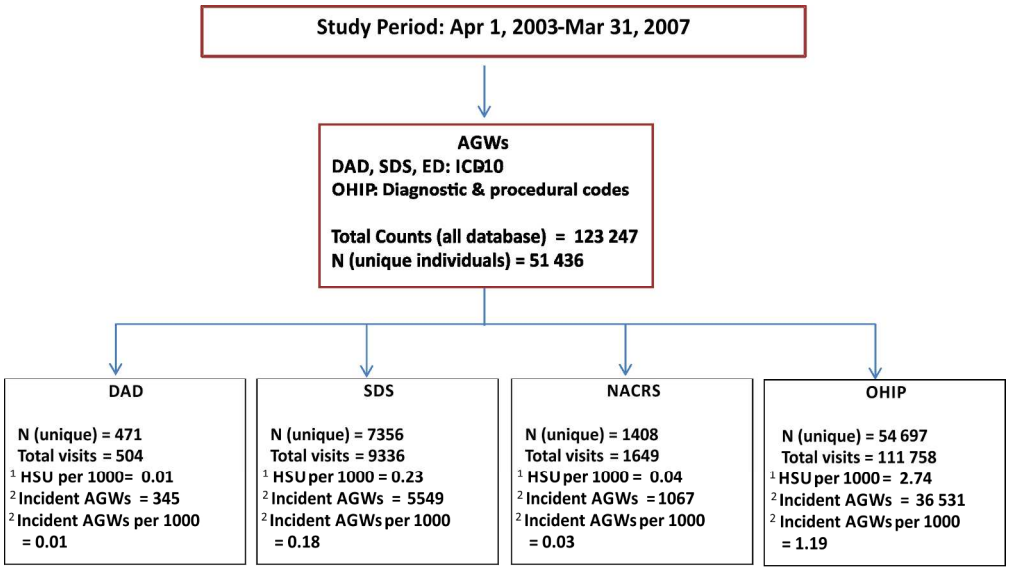
Figure 5. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.

Supplementary figure 1. Table of AGW-related diagnostic and procedural codes used by physician offices.

Supplementary figure 2a. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004.

Supplementary figure 2b. Age-specific trends in code Z117 in females.

Supplementary figure 2c. Age-specific trends in billing code combinations that include Z117, for 21-23 year old females.



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1 2003 to 2006
2 2004-2006, with 2003 as a washout to exclude prevalent cases
Health service utilization, HSU

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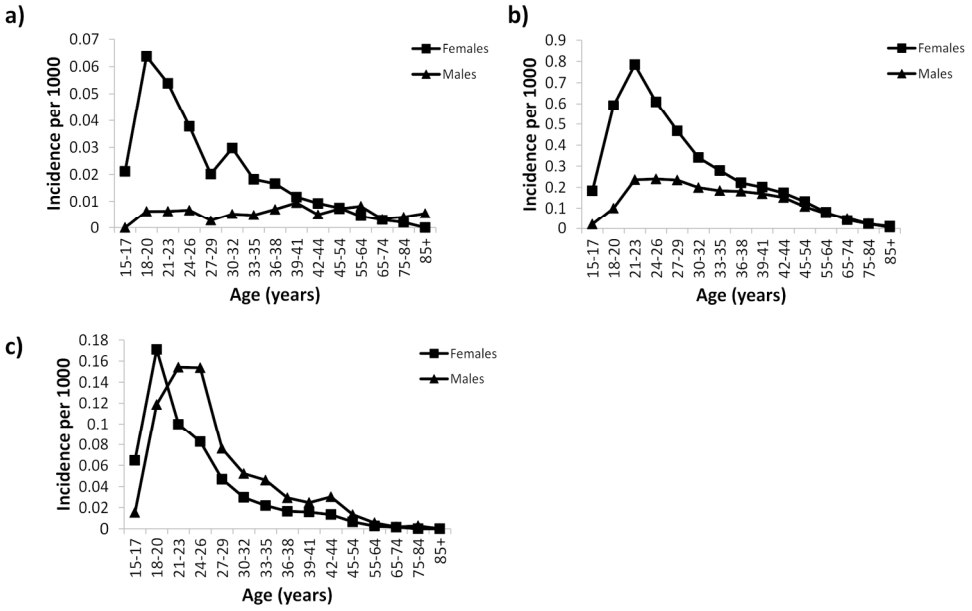

Figure 2. Average annual rate of incident AGWs captured by hospitalizations (DAD)(a); same day surgery (b); and emergency department visits (NACRS)(c), by sex and age group, fiscal years 2004 to 2006.
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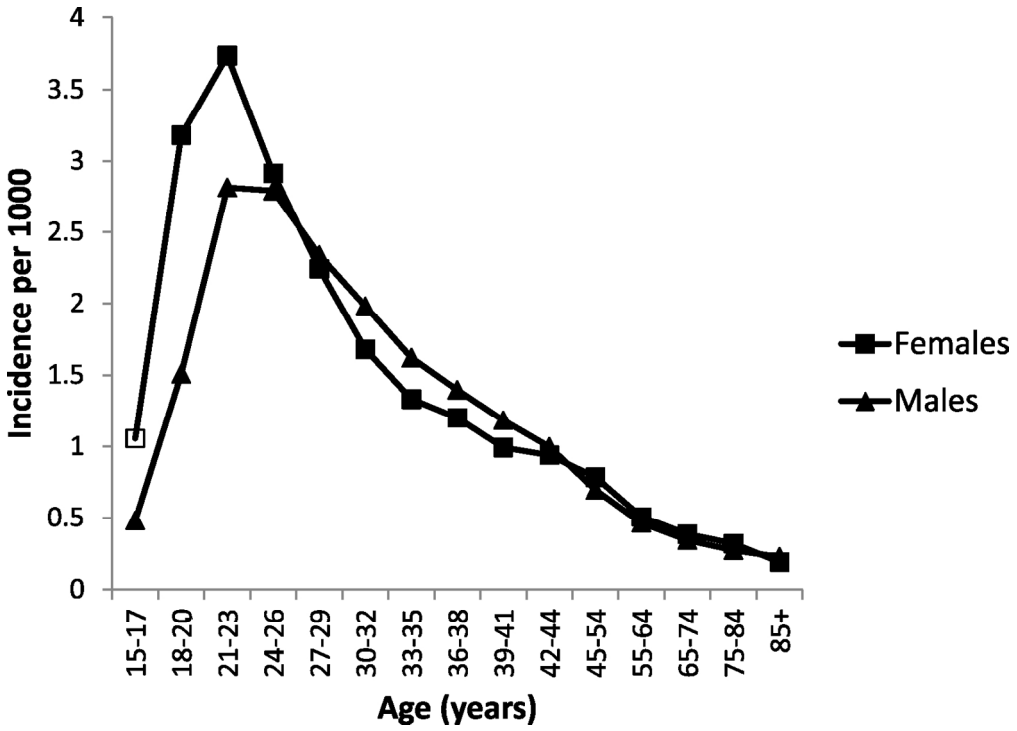

Figure 3. Average annual rate of incident AGWs captured by physician office visits, by sex and age group, fiscal years 2004 to 2006.
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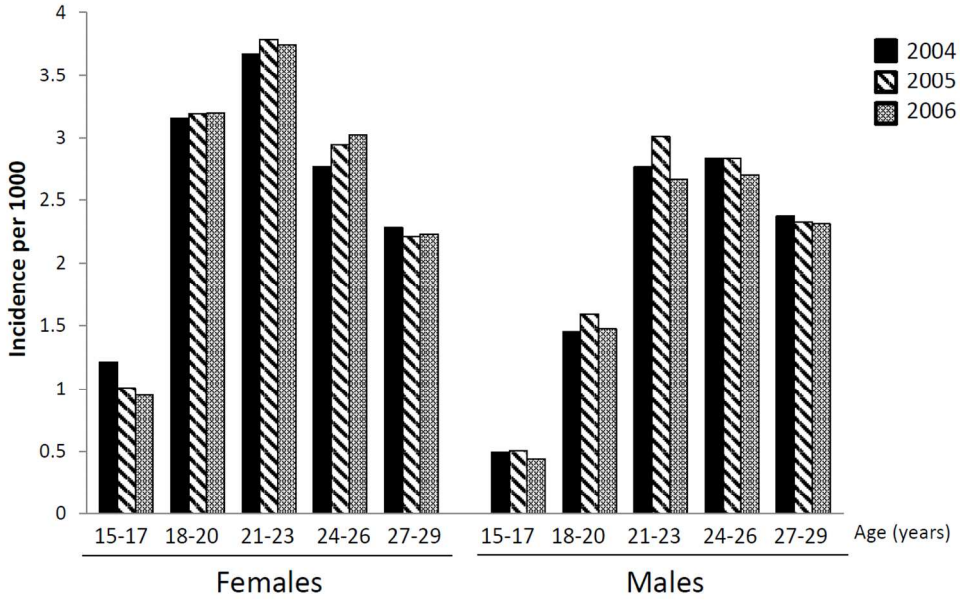

Figure 4. Annual incident AGWs captured by physician office visits, by fiscal year, sex, and age group, fiscal years 2004 to 2006.
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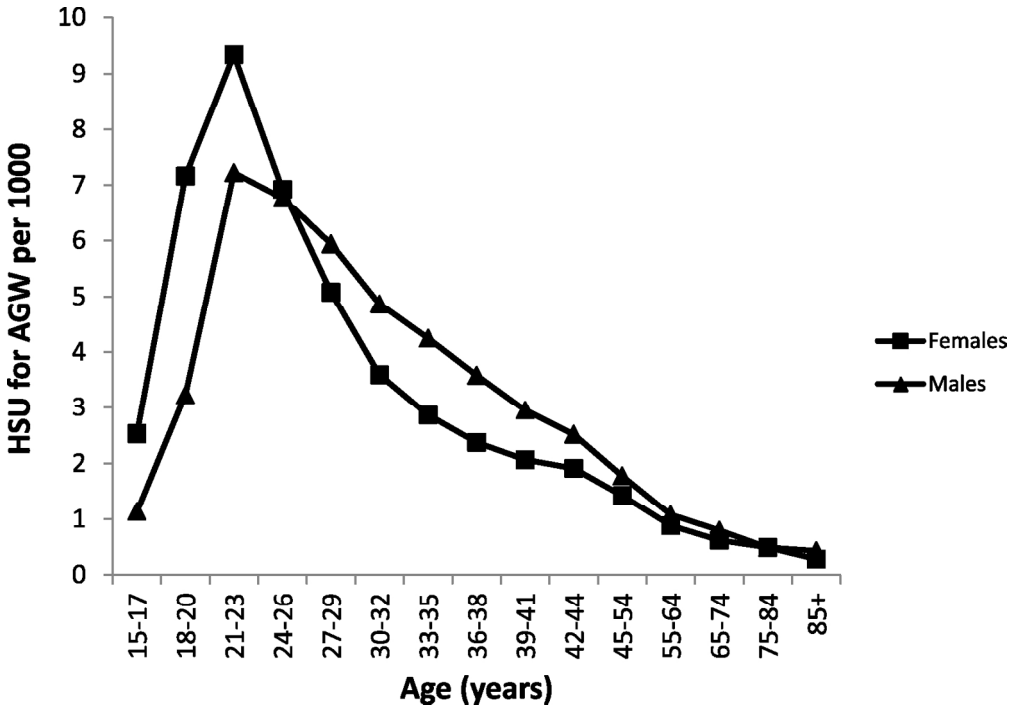
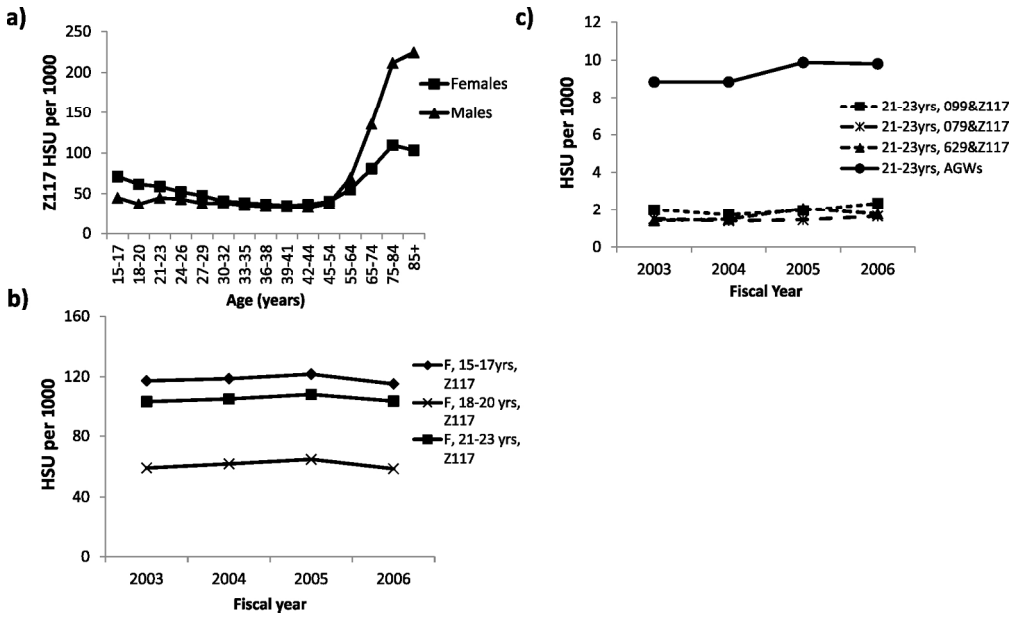


Figure 5. Average annual health service utilization (HSU) for AGWs captured by physician office visits, by sex and age group, fiscal years 2003 to 2006.
148x103mm (300 x 300 DPI)

Code	Description
ICD-10	
A630	
OHIP	
Diagnostic Codes	
099	venereal disease, TD, condyloma, Duchennes, herpes genitalis, chlamydia,
079	condyloma accuminata, rabies, viral disease, other viral disease, viral illness
629	Warts, venereal, other disorders, Other diseases or disorders not specified elsewhere-genital organs female, other disorders of female genital organs, condylomata, leukorrhea
078	verruca(plantar wart), warts, all types, other viral disease, warts
K028	STD, BBD mgmt
Procedural Codes	
Z117	Chemical Rx wart (plantar, genital)
Z549	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (local anaesthesia)
Z701	Male genital surgical procedures: Excision: condylomata (local anaesthesia)
Z733	Female genital surgical procedures: Excision: condylomata (chem or cryo surgery)
Z736	Female genital surgical procedures: Excision: condylomata (local anaesthesia, surgical excision OR electrodessication OR CO2 laser)
Z758	Digestive system surgical procedures: Rectum: Destruction: Fulguration of condylomata (general anaesthesia)
Z767	Male genital surgical procedures: Excision: condylomata (general anaesthesia)
Z769	Female genital surgical procedures: Excision: condylomata (general anaesthesia, surgical excision OR electrodessication OR CO2 laser)

Supplementary figure 1. Table of AGW-related diagnostic and procedural codes used by physician offices.
173x163mm (300 x 300 DPI)



Supplementary figure 2. Sensitivity analysis of billing code for physician-administered, in-office chemical or cryotherapy, Z117. Age distribution of HSU with code Z117 for fiscal year 2004 (a); age-specific trends in code Z117 in females (b); age-specific trends in billing code combinations that include Z117, for 21-23 year old females (c).
173x104mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review See Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number N/A
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author See Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review See Page 14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments N/A
Support:		
Sources	5a	Indicate sources of financial or other support for the review See Page 14
Sponsor	5b	Provide name for the review funder and/or sponsor See Page 14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol See Page 14
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known See Pages 4 & 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) See Page 5
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review N/A
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage See Pages 5-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated N/A
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review See Pages 5 & 6

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	N/A
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	N/A
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	See Pages 5-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	See Page 8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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