Background

Human papillomavirus (HPV) is the most common sexually-transmitted infection among Canadians (1). The causal link between specific serotypes of HPV and cervical cancer is well-established (2). HPV infections lead to more than 500,000 cases of cervical cancer worldwide each year (3), and have motivated a strong research campaign to develop rigorous screening tests and prophylactic HPV vaccines (2). Gardasil was first approved in 2007 as a quadrivalent vaccine to prevent HPV infection in young women (4). This vaccine has proven to be safe and effective, with significant reductions in genital warts and cervical lesions in vaccinated females (3). In 2007, Australia became the first country to implement
a national HPV vaccination program, administering Gardasil through a school-based program targeting females aged 12 and 13 years while implementing a catch-up program for females aged 13 to 26 in a school or community setting (5, 6). In 2009, the World Health Organization (WHO) recommended the implementation of a national HPV vaccine program aimed at countries with high levels of HPV infection and cervical cancer (7). Since then, many other countries have followed Australia’s path and implemented similar programs.

In addition to the causal link between HPV and cervical cancer, HPV is also associated with anogenital warts and cancers of the penis, anus, oral cavity and oropharynx (1), and 40,000 men develop HPV-associated cancers worldwide each year (3). In 2014, the pharmaceutical company Merck released a 9-valent version of the HPV vaccine to expand coverage against additional HPV serotypes that cause cervical, vaginal, vulvar, anal, penile, head, and neck cancers (3, 8). Despite the efficacy of Gardasil, the prevalence of HPV-associated cancers in men continues to rise (1). In response to this phenomenon, Australia also became the first country to implement a gender-neutral HPV vaccination strategy: in 2013, the country began vaccinating males between 12 to 13 years old in the school-based program, and then ran a catch-up program for males between the ages of 14 to 15 years (1). Since then, other countries such as the U.S., Austria, and Canada have also recommended vaccination in males. Globally, there are now more than 70 governments taking part in the HPV vaccination program, though only 14 of those include the male population in their program (9).

In 2015, Prince Edward Island, Alberta, Nova Scotia, Quebec and Manitoba were the only provinces that had implemented a gender neutral vaccination program (1). Other provinces, such as British Columbia had implemented male vaccination for the men who have sex with men (MSM) population (1). As of 2017, all provinces and territories have adopted gender-neutral vaccination programs for pre-adolescents. The many benefits of a gender-neutral HPV vaccine, however, do not come without risks and costs. The objective of this case study is to assess all aspects of a gender-neutral approach to the HPV vaccine, and to demonstrate the impact of vaccination in both males and females on the improvement of overall HPV-related outcomes compared to female-only vaccination regimens. HPV-related outcomes assessed include health outcomes, cost effectiveness, and gender equality.

Methods

A literature search was performed on PubMed, Google Scholar and Medline using the search terms such as “HPV vaccination,” “Gender-neutral”, “cost-effectiveness” and
“immunization scale-up programs.” Favored articles included both cross-sectional studies, meta-analyses, and studies relying on models for cost-effectiveness.

**Results**

**Health outcomes**

The effectiveness of the HPV vaccine can be evaluated by analyzing HPV-related health outcomes, such as the rates of HPV infection, genital warts, precancerous lesions, and cancer (10). To determine whether the inclusion of males in vaccination programs will improve these outcomes, we must first evaluate the advantages and shortcomings of female-only vaccine campaigns. In a meta-analysis of 20 studies in high-income countries where vaccine coverage rates were above 50% in girls, rates of infection with HPV types 16 and 18 were found to decrease by 68% in young women compared to the pre-vaccine era (11). Furthermore, the prevalence of anogenital warts decreased by 61% and infections with serotypes of HPV not included in the vaccine (HPV 31, 33, and 45) also decreased, suggesting that the vaccine provides cross-protection for these strains (11). Herd effects were also observed: rates of anogenital warts in boys below 20 years of age, and in women who were not vaccinated, decreased after the introduction of the vaccine (11). In countries where vaccine coverage was below 50% in girls, positive effects were seen in the prevalence of HPV infection and anogenital warts, but these effects were limited to the vaccinated population, indicating a lack of cross-protection or herd immunity (11). Together, these data demonstrate that attaining majority female vaccination has positive health outcomes in the greater population.

After the implementation of female-only vaccination in Australia, a national sentinel surveillance network collected data on the effects of vaccination on various populations (10). Consistent with the meta-analysis discussed above, a 59% reduction in genital warts was found in the female cohort targeted by the vaccine program (10). A smaller decline in the rates of genital warts was seen in men who have sex with women. Notably, no decline was observed in the rates of genital warts in MSM (10). These data demonstrate that female-only vaccination campaigns are effective in protecting women, but ignore vulnerable populations such as the MSM community.

Considering this shortcoming, it is relevant to investigate whether vaccinating males would substantially increase coverage in the population. As stated, only recently have all Canadian provinces and territories adopted gender-neutral vaccination programs, and few other countries have implemented these programs with high uptake. As
such, in this case study, prospective studies were used to assess the potential benefits of administering the vaccine to both boys and girls. In one such study, Marty et al. performed epidemiological estimates for HPV-related disease, considering HPV transmission, cervical cancer development, and occurrence of genital warts as health outcomes (12). The analysis compared vaccinations in only 12-year old girls to vaccination in both 12-year old boys and girls. The results demonstrated that the introduction of a gender-neutral HPV vaccination as opposed to a female-only vaccination would decrease the incidence of HPV health-related outcomes such as genital warts in both males and females, as well as head, neck, anal, and penile cancers in males. Furthermore, this study estimated that men’s immunization would increase protection for women (12, 13). In conclusion, although arguments have been made to favour the female-only vaccination strategy due to attained herd immunity, this study demonstrates that vaccinating males can allow for further protection for both genders as well as the currently vulnerable MSM population.

Cost effectiveness

The cost-effectiveness of implementing HPV vaccination in males in addition to females has been highly debated since the beginning of mass vaccination with the quadrivalent HPV vaccine. The main economic argument against gender-neutral vaccination is that the cost-effectiveness of vaccinating males decreases as vaccine coverage in females increases. Some researchers have argued that even in populations where uptake levels are as low as 50% in females, focusing efforts on increasing female coverage rates is more cost-effective than implementing a vaccination program that targets males as well (14, 15). For example, a 2012 study found that the cost-effectiveness of implementing a gender-neutral vaccine program in Quebec would amount to CAD $434,000 per quality-adjusted life year (QALY), greatly exceeding the province’s cost-effectiveness threshold typically set at CAD $50,000 per QALY (16). The cost of the vaccine would therefore have to be lowered to CAD $12 per dose to reach this threshold (16). However, this and many other cost-effectiveness projections do not consider several key factors, such as lower-than-expected vaccination rates in females (1), the marginal administrative costs of vaccinating men, and the recent shift from three to two doses of the vaccine. They also often fail to account for the economic burden of genital warts, the rise of non-cervical HPV related cancers, as well as the health risks facing the MSM population and individuals who engage in sexual activity outside their region of immunization (1).
The dosing schedule of a vaccination program must also be taken into account in cost-effectiveness assessments. At the time of licensing, the HPV vaccine was given in three doses over six months (17). However, in 2014, the WHO revised the immunization schedule and now recommends a two-dose regimen (17). A recent study comparing the two regimens found that, if the two-dose schedule provides protection for at least 20 years, the benefits of including a third dose are small, rendering the two-dose schedule as the more cost-effective option (17).

Another factor that must be incorporated in assessing the cost-effectiveness of vaccinating males against HPV is the burden of non-cervical HPV-related cancers, such as oropharyngeal cancers (OPC). It has been estimated that, by 2020, OPC rates will surpass that of cervical cancer and become the most common HPV-related cancer in the U.S. (18). Moreover, the rates of HPV-related diseases in men in developed countries have increased in recent years, accounting for 38.8% of the direct costs of HPV-related diseases (19). Given these trends and considering that herd immunity takes decades to materialize, it is questionable whether protecting males solely through herd immunity is sufficient (19).

In a study conducted in 2015, it was estimated that the implementation of the quadrivalent HPV vaccine in males for the prevention of OPC would save Canadians between CAD $90 and $144 per individual compared to having no vaccine program in males (19). When this finding was applied to a theoretical cohort of 12-year old boys over their lifetime, vaccinating males was found to result in estimated savings of CAD $8 to $28 million. However, this study could not evaluate herd immunity from females to males, and as a result, the cost-effectiveness of male vaccination may have been overestimated (19). A Denmark study highlighted the high economic burden of genital warts, estimating that the country spends a total treatment cost of €8 million per year on treating the disease (20). The study concluded that vaccinating males in Denmark is “a cost effective preventive intervention that would lead to a faster prevention of cancers, cancer precursors and genital warts in men and women” (20). Altogether, these studies show that in high-income countries such as Canada, the increasing burden of non-cervical HPV-related diseases in the male population results in the cost-effectiveness of gender-neutral HPV vaccination programs.

**Gender equality & inclusivity**

The inclusion of males in HPV vaccination is a crucial step towards non-discriminatory prevention of significant diseases related to HPV. Despite the evidence and support for the vaccination of both boys and girls, there are many social constructs and inequities
that continue to halt the progress of gender-neutral vaccination programming. Targeting only girls conveys the messages that HPV-related diseases are limited to girls, that girls are “more prone to promiscuous behavior,” or even that girls bear the responsibility for transmitting HPV (21). The over-identification of HPV with females has in fact been referred to as the “feminization of HPV” (22), and overall narrowed the lens for HPV prevention, creating stigma in communities.

Moreover, as discussed earlier, many vaccination policies in Canada have historically looked at the issue through heteronormative conventions, ignoring MSM populations who in fact bear high rates and incidence of HPV (22, 23). In July 2015, British Columbia announced its plan to provide the HPV vaccine for boys, MSM, and men who are “street-involved” (24). Although a step forward to protecting all individuals, this policy created further ethical conflict. The school-based HPV vaccination program offered the vaccine to eleven-year-old boys, requiring these children to identify their sexual identity at a young age in order to receive health services. This requirement could have possibly delayed boys’ access to the vaccine until they were comfortable in identifying as homosexual, and had an overall stigmatizing effect by only targeting homosexual men and excluding heterosexual ones (25). As of January 2017, British Columbia has adopted a truly gender-neutral HPV vaccination program. In conclusion, including all males in the HPV vaccination programs will counteract the feminization of HPV and contribute to a non-discriminatory and inclusive approach to public health in Canada.

Scale-up & Implementation

The results reviewed above indicate that vaccinating both boys and girls against HPV is a cost-effective strategy to improve HPV-related health outcomes and promote inclusive, ethical practices in the Canadian health care system. As to scale-up and implementation, an important consideration pertains to the structure and governance of health care in Canada. Under the Canada Health Act (CHA), provinces and territories have jurisdiction over the management, organization, and delivery of healthcare, including immunization. In a 2012 report on HPV vaccination, the National Advisory Committee on Immunization (NACI) included five updated immunization recommendations, two of which targeted males specifically (26). Subsequently, as of July 2016, the Public Health Agency of Canada (PHAC) has updated its recommendations to include the quadrivalent and nonavalent HPV vaccines for males 9 to 26 years of age for the prevention of anal cancers (26). These recommendations have informed provincial legislations in introducing gender-neutral
vaccination regimens. In Ontario, for example, approximately 150,000 school-aged youth will now be eligible to receive the vaccine every year (27).

The outlook for gender-neutral vaccination scale-up within provinces is promising. Importantly, the existing healthcare facilities and institutions, such as hospitals, pharmacies, schools, and private clinics involved in the distribution of the vaccines can alleviate some of the hurdles in scaling up the program. For instance, given the existing school-based delivery programs, accessing a new target population of young men would be relatively easy to orchestrate. In addition, the favourable public opinion surrounding male vaccination against HPV can make communication and social mobilization easier (28). In fact, public advocacy and support has been and will be critical in the inclusion of males in HPV vaccination programs. In 2015, the Canadian Pharmacists Association released a statement urging the federal government to enhance the current immunization policy as it “[puts] the health of Canadians at risk” (29). This type of advocacy was critical for the emergence of gender-neutral vaccination programs across all Canadian provinces and territories (30).

Finally, given the successful administration of the female-only vaccination schedules in Canada, public health policy makers can draw on the lessons learned in the past decade for further improving provincial gender-neutral vaccination programs. Canada also stands to benefit from modeling after approaches to gender-neutral HPV vaccination in countries with a similar GDP per capita and health system capacity, such as Australia.

Conclusion

The objective of this case study was to demonstrate improvements in overall HPV-related outcomes as a result of the implementation of HPV vaccination programs in both males and females. Gender-neutral HPV vaccination is beneficial in terms of the burden of HPV-related disease, cost-effectiveness, and gender inclusivity. The lessons learned in the implementation of the gender-neutral HPV vaccine across Canadian provinces and territories could also inform the scale-up of similar programs to other similar socio-economic settings with universal health coverage.

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