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Estimates of the future burden of cancer attributable to infections in Canada

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ABSTRACT

More than 7000 incident cancers diagnosed in Canada in 2015 were attributable to infections. The future infection-associated cancer burden can be lowered by reducing the prevalence of major cancer-causing infections; hepatitis B virus (HBV), hepatitis C virus (HCV), *Helicobacter pylori* (*H. pylori*) and human papillomavirus (HPV). We modeled the future impact of (1) 10%, 25%, and 50% relative reductions in the prevalence of HBV, HCV and *H. pylori* and (2) different school-based HPV vaccination coverage levels (lower, current, higher) on Canadian cancer incidence by the year 2042. We modeled counterfactual reductions in HBV, HCV and *H. pylori* prevalence in 2018, assuming a latency period of 15-years, to estimate the impact on cancer incidence starting in 2033. The number of HPV-attributable cancers among vaccinated cohorts was a function of pre-2018 vaccine coverage levels and the 2018 counterfactuals. A 50% counterfactual reduction in the prevalence of HBV, HCV and *H. pylori* could prevent an estimated 10,585 cancers from 2018 to 2042; a 25% reduction could prevent 5293 cancers and a 10% reduction could prevent 2117 cancers. Assuming continuity of current estimated country-wide HPV vaccine coverage, 3977 anogenital and 1073 head and neck cancers could be prevented from 2018 to 2042, whereas vaccine coverage of 80% in girls and boys could prevent an additional 311 cancers. Almost 16,000 cancers could be prevented in Canada from 2018 to 2042 with a 50% relative reduction in HBV, HCV and *H. pylori* prevalence and 80% HPV vaccine coverage of girls and boys.

1. Introduction

Globally, an estimated 14.0% of cancers diagnosed in 2012 were attributable to four infectious agents; hepatitis B virus (HBV), hepatitis C virus (HCV), *Helicobacter pylori* (*H. pylori*) and human papillomavirus (HPV) (Plummer et al., 2016). Several strategies have been adopted to reduce the prevalence of cancer-causing infections and their associated cancer or pre-cancer incidence in Canada and abroad. Canadian provinces/territories introduced publicly-funded, school-based immunization programs for HBV from 1992 to 1998 and for HPV from 2007 to 2010 (Government of Canada, 2017; Shapiro et al., 2017). Due to HBV's long latency, reductions in cancer incidence have not yet been realized. However, the annual number of reported HBV infections in Canada has decreased from 10.8 per 100,000 persons in 1990 to 1.7 per 100,000 persons in 2008 (Public Health Agency of Canada, 2011). A meta-analysis of 20 ecologic population-based studies conducted in high-income countries reported a 68% decrease in the prevalence of HPV types 16 and 18 at a vaccination coverage among girls of 50% or higher (Drolet et al., 2015). A meta-analysis of randomized controlled trials reported that eradication of *H. pylori* in asymptomatic populations

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reduced the relative risk of gastric cancer by 34% (Ford et al., 2014).

Despite infections' impact on global cancer incidence, the level of public awareness of a causal role for infections in the development of cancer is low. Yet, the public plays a key role by vaccinating their children against HBV and HPV, not reusing needles and complying with antibiotic treatment for *H. pylori* infection. The range of primary prevention strategies aimed at reducing the acquisition of infections (HBV, HCV and HPV) and secondary prevention strategies for treating existing infections (HCV, *H. pylori*) provides an opportunity to lower the infection-associated cancer burden.

We estimated that > 7000 cases of cancers, representing 3.7% of all cancers diagnosed among Canadians aged 18 and older in 2015 were attributable to seven carcinogenic infections (Volesky et al., 2019). The vast majority (90.0%) of these infection-attributable cancers were due to HBV, HCV, *H. pylori* and HPV. We found that, with 3828 attributable cases, more cancers were attributed to HPV than any other infection. The infection with the next highest number of attributable cases was *H. pylori* with 2052 cases, followed by Epstein-Barr virus with 578 cases, hepatitis B and C viruses with 509 cases, human herpesvirus type 8 (i.e. Kaposi sarcoma virus) with 100 cases and finally human T-cell lymphotropic virus type 1 with 30 attributable cases in 2015.

The considerable potential to prevent carcinogenic infections highlights the importance of quantifying the impact of a variety of prevention scenarios, referred to as counterfactuals, for prioritizing strategies aimed at reducing the number of infection-associated cancers. To our knowledge, besides the impact of HPV on cancer incidence (Van de Velde et al., 2012), no study has estimated the impact of reductions in the prevalence of infections on the future Canadian cancer incidence. We estimated the future burden of infection-associated cancers by the year 2042 by modeling the impact of: 1) relative reductions in HBV, HCV and *H. pylori* infection prevalence and 2) lower, current, and higher levels of school-based HPV vaccination coverage.

2. Methods

This analysis is part of the Canadian population attributable risk of cancer (ComPARe) Study, which aimed to estimate the current and future burden of cancer attributable to modifiable risk factors in Canada (Brenner et al., 2018). Here, we estimated the future burden of cancers caused by four major infectious agents (HBV, HCV, *H. pylori* and HPV). The future burden and the potential for prevention of infection-associated cancers are reported as: the number of cancers projected and prevented in 2042 and the cumulative number of cancers prevented from 2018 to 2042 based on different counterfactuals.

We calculated potential impact fractions (PIFs) to estimate the proportion of HBV, HCV and *H. pylori*-associated incident cancers that could be avoided by 2042 under various counterfactual scenarios, using the following equation (Morgenstern and Bursic, 1982):

$$PIF = \frac{(P–P^*)(RR–1)}{P(RR–1) + 1}$$

where P is the pre-counterfactual infection prevalence, P* is the post-counterfactual infection prevalence, and RR is the relative risk or odds ratio (OR) for the association between the infection and cancer. The annual prevented cases were estimated as:

$$PC_i = I_i \times PIF$$

where I_i is the projected cancer incidence in year *i*.

For HPV, we approximated the proportion of cancers attributable to HPV by using prevalence of HPV in cancer cases and therefore did not calculate PIFs. Knowing the proportion of specific cancers attributable to HPV enabled us to estimate the number of avoidable HPV-related cancer cases. When estimating the future number of preventable cancers among vaccinated cohorts, the proportion attributable to HPV was multiplied by the relevant cancer incidence, after accounting for vaccine efficacy, protection (e.g. the proportion of HPV types contributing to cancer incidence that are covered by the vaccines), and coverage.

2.1. Current infection prevalence

We have reported on the prevalence of chronic HBV and HCV, and *H. pylori* for the Canadian population elsewhere (Volesky et al., 2019). Briefly, chronic HBV prevalence (measured by hepatitis B surface antigen (HBsAg)), was assessed using data from two merged cycles (2007–2009 and 2009–2011) of the Canadian Health Measures Survey (CHMS) (Statistics Canada, n.d.; Statistics Canada, 2010). Since we were only able to obtain sex-specific prevalence estimates from the CHMS, HBsAg prevalence from two merged cycles of the United States' National Health and Nutrition Examination Survey (NHANES) were used to partition the HBsAg sex prevalence estimates from the CHMS by 10-year age groups (Centers for Disease Control and Prevention, 2009, 2011). To estimate chronic HCV prevalence, we partitioned the five-year birth cohort estimates from a modeling study (Trubnikov et al., 2014) according to the sex distribution reported in a study that modeled acute and chronic HCV prevalence in the Canadian population (Remis, 2010). Since we required that prevalence estimates originate from population-based data covering a range of ages, the few studies assessing *H. pylori* sero status in Canadian populations did not meet this criterion (Cheung et al., 2014; Naja et al., 2007; Sethi et al., 2013). Hence, to estimate the prevalence of *H. pylori*, we reweighted NHANES data collected from 1999 to 2000 (Centers for Disease Control and Prevention, 2001) to reflect the Canadian age, sex, and race/ethnic composition (categories available were: Black, Latin American, White, and Other). To produce summary prevalence estimates, we calculated population-weighted prevalence estimates by sex thereby aggregating prevalence across age-groups (Table 1).

Rather than estimating HPV prevalence among the Canadian population, we estimated HPV prevalence among cancer cases. Since mechanistic evidence indicates that the detection of high-risk HPV types within cancer tissue is sufficient to attribute that cancer to HPV, the population attributable risk (PAR) was approximated by the prevalence in cases. The prevalence of HPV infection was calculated by pooling, using a random effects model, the proportion of cancer cases harboring high-risk HPV types (for anogenital cancers) or HPV16 (for head and neck cancers) within the cancer tumor tissue. We restricted our analyses to studies that applied “gold standard” HPV detection techniques: polymerase chain reaction (PCR) for anogenital cancers and detection of E6 and/or E7 oncoproteins via PCR for head and neck cancers (Bishop et al., 2012; Rietbergen et al., 2013).

Table 1 summarizes the prevalence of these infections in the population (for HBV, HCV and *H. pylori*) or cancer cases (for HPV), the RRs or ORs and attributable percentages used in our analyses.

2.2. Future infection prevalence

We assumed a constant prevalence of HBV (from 2007 to 2011) and *H. pylori* (from 1999 to 2000) up till 2027. We projected the future chronic HCV prevalence based on prevalence at three time points (1999, 2004, and 2009). Chronic HCV prevalence at these time points was estimated by weighting the available five-year birth cohort data (Trubnikov et al., 2014) by Canada's population to obtain the weighted average prevalence for Canadians aged 15 to 70. To project the future chronic HCV prevalence, an exponential regression was fit between the estimated prevalence and the three time points.

For the baseline HPV prevalence projections, we also assumed no change in prevalence given the lack of evidence in support of an increasing or decreasing trend in prevalence within cases. Although the prevalence of HPV within oropharyngeal cancer has increased over time (Stein et al., 2014), mostly due to a decrease in cigarette smoking, we assumed that this trend would not continue post-2018.

Table 1
Cancer types and proportions attributable to carcinogenic infections with modifiable prevalence in Canada[a].

Infection Cancer sites (ICD-03 codes)	Prevalence of the infection in the population, %[b]	Odds ratio or relative risk	Attributable, %[c]	
			Men	Women
Hepatitis B virus (HBV), chronic infection				
Hepatocellular carcinoma (C22, 817)	0.54 (men) 0.36 (women)	20.3	9.5	6.5
Hepatitis C virus (HCV), chronic infection				
Hepatocellular carcinoma (C22, 817)	1999: 1.09 (men) and 0.73 (women)	23.4	16.0	11.3
Non-Hodgkin lymphoma (9591)	2004: 1.05 (men) and 0.70 (women) 2009: 0.99 (men) and 0.66 (women)	1.4	0.3	0.2
Helicobacter pylori (*H. pylori*)				
Gastric non-cardia (C16.1–16.9)	18.0 (men)	9.4	60.0	59.0
Gastric MALT lymphoma (9699)	17.2 (women)	6.3	48.8	47.7

Infection Cancer sites (ICD-03 codes)	Prevalence of the infection in cancer cases, %	Odds ratio or relative risk	Attributable, %[c]	
			Men	Women
Human papillomavirus (HPV), high-risk types[d]		Not applicable as the prevalence in cancer cases approximates the proportion attributable to the infection.		
Cervix (C53)	100.0			
Anus (C21)	87.6 (men) 94.5 (women)			
Penis (C60)	39.4			
Vagina (C52)	72.2			
Vulva (C51)	76.8 (aged 18–49 years) 43.2 (aged ≥50 years)			
Human papillomavirus (HPV), type 16				
Oropharynx (C10, C01, C09)[e]	60.2			
Oral cavity (C02, C03, C04, C06)[f]	8.2			
Larynx (C32)	12.7			

Abbreviations: MALT = mucosa-associated lymphoid tissue.
[a] Detailed description of the prevalence and odds ratio/relative risk estimates can be found in Volesky et al. (2019).
[b] The prevalence of the infection in the population was calculated by weighting the age-group specific prevalence estimates by the Canadian population for each sex.
[c] The attributable percent by sex was calculated by dividing the number of attributable cases by the number of cases, and hence it does not reflect the proportion attributable by specific age groups.
[d] High-risk HPV types include types classified by the International Agency for Research on Cancer as Group 1 (16, 18, 31, 33, 35, 39, 45, 51, 56, 58 and 59), Group 2A (68) and Group 2B (34, 53, 66, 70 and 73) carcinogens. HPV52 and 97 were also considered high-risk types.
[e] Oropharynx subsites: oropharynx (C10), base of the tongue (C01), and tonsil (C09).
[f] Oral cavity subsites: gum and other mouth (C03, C06), floor of mouth (C04), other and unspecified parts of tongue (C02).

2.3. Counterfactual scenarios

We projected the impact of four counterfactual scenarios: no change in the prevalence of HBV and *H. pylori* and a continuing trend for HCV, as well as 10%, 25% and 50% reductions in infection prevalence. These reductions were selected to respectively represent plausible minor, moderate and major prevalence reductions. The counterfactuals were "implemented" in the year 2018 with a 15-year latency to observe an impact on cancer incidence starting in 2033.

There is no treatment for an HPV infection; it can be cleared by the immune system rather than by an intervention (Bosch et al., 2013). We purposely ignored the impact of cervical cancer screening in achieving further cervical cancer incidence reduction and thus selected counterfactuals based on HPV vaccination coverage in girls only, and in girls and boys. Canada's National Advisory Committee on Immunization recommended HPV vaccination for girls in 2007 and for boys in 2012 (Deeks et al., 2017). We considered several plausible counterfactuals for school-based HPV vaccination starting in 2018: 1) maintenance of current coverage among girls, 2) decrease in coverage among girls (40%, 50%, and 60% coverage) and 3) increase in coverage among girls only to 80% and 4) an 80% coverage of school-aged girls and boys (which is sufficient for the elimination of HPV16 (Brisson et al., 2016)), both as direct effects (i.e. those who were vaccinated are protected and no one else) and as herd effects (i.e. vaccine protection extends beyond those directly immunized). A decrease in coverage was considered for two reasons. First, a 50% coverage, although lower than the national average, is the current coverage level in certain regions of Canada (Shapiro et al., 2017). In addition, some countries such as Denmark and Japan have experienced substantial decreases in their coverage levels due to unconfirmed reports of adverse events (Statens Serum Institut, 2017; Hanley et al., 2015). For example, in Sapporo, Japan, the reported three-dose HPV vaccination completion rate ranged from 68.4 to 74.0% and two years later it dropped to 0.6% (Hanley et al., 2015). For comparison, we also present the expected cancer incidence that could have occurred had the HPV vaccine never been administered at any point in time.

2.4. Latency period

HBV, HCV, and *H. pylori* are associated with prolonged latencies that can span decades before cancer diagnosis (El-Serag, 2012; Lingala and Ghany, 2015). For these infections, we assumed a 15-year interval between the time of prevalence reduction and its impact on the incidence of associated cancers; a shorter latency was an appropriate approach given that the data captured prevalent (recent and persistent) rather than incident infections. For HCV, the available data did not allow for direct estimation of the prevalence among individuals 70 years of age or older, so we allowed for a longer latency (between 15 and 20 years) in this age-group. For HPV-associated cancers, we did not account for a latency period because we utilized a cohort approach in which five-year age group cohorts (i.e. 20–24, 25–29, etc.) were followed through time to 2042.

Table 2
Sex-specific projected number of cancer cases and potential impact fractions for chronic hepatitis B and C viruses that could be prevented in 2042 under different counterfactuals.

Infection and associated cancer	Sex	Future burden measures	No change	Cancer burden by reductions in infection prevalence		
				10%	25%	50%
Hepatitis B virus	Men	Projected in 2042	2640	2615	2578	2516
Hepatocellular carcinoma		PIF, %	–	0.9	2.4	4.7
		Prevented in 2042	0	25	62	125
		Prevented 2018–2042	0	110	275	551
	Women	Projected in 2042	718	713	706	695
		PIF, %	–	0.6	1.6	3.2
		Prevented in 2042	0	5	12	23
		Prevented 2018–2042	0	20	50	100
	Both	Projected in 2042	3358	3329	3284	3210
		PIF, %	–	0.9	2.2	4.4
		Prevented in 2042	0	30	74	148
		Prevented 2018–2042	0	130	326	651
Hepatitis C virus	Men	Projected in 2042	2640	2598	2535	2429
Hepatocellular carcinoma		PIF, %	–	1.6	4.0	8.0
		Prevented in 2042	0	42	106	212
		Prevented 2018–2042	0	190	476	952
	Women	Projected in 2042	718	710	697	677
		PIF, %	–	1.1	2.8	5.6
		Prevented in 2042	0	8	20	41
		Prevented 2018–2042	0	36	90	179
	Both	Projected in 2042	3358	3308	3232	3106
		PIF, %	–	1.5	3.8	7.5
		Prevented in 2042	0	50	126	252
		Prevented 2018–2042	0	226	565	1131
Hepatitis C virus	Men	Projected in 2042	5850	5849	5846	5842
Non-Hodgkin lymphoma		PIF, %	–	0.0	0.1	0.1
		Prevented in 2042	0	2	4	9
		Prevented 2018–2042	0	8	19	39
	Women	Projected in 2042	4750	4749	4748	4745
		PIF, %	–	< 0.1	< 0.1	0.1
		Prevented in 2042	0	1	2	5
		Prevented 2018–2042	0	4	10	21
	Both	Projected in 2042	10,600	10,598	10,594	10,587
		PIF, %	–	0	0.1	0.1
		Prevented in 2042	0	3.0	7.0	13.0
		Prevented 2018–2042	0	12	30	59
Hepatitis C virus	Men	Projected in 2042	8491	8447	8381	8271
Total		PIF, %	–	0.5	1.3	2.6
		Prevented in 2042	0	44	110	220
		Prevented 2018–2042	0	198	495	990
	Women	Projected in 2042	5468	5459	5445	5423
		PIF, %	–	0.2	0.4	0.8
		Prevented in 2042	0	9	23	45
		Prevented 2018–2042	0	40	100	200
	Both	Projected in 2042	13,959	13,905	13,826	13,693
		PIF, %	–	0.4	1.0	1.9
		Prevented in 2042	0	53	133	265
		Prevented 2018–2042	0	238	595	1190

Abbreviations: PIF = potential impact fraction.

2.5. Human papillomavirus model parameters

2.5.1. Start date of vaccine coverage

School-based immunization of girls in grades 4 to 7 was introduced in Canadian provinces from 2007 to 2010. Specifically, Ontario (Canada's most populous province) started vaccinating grade 7 girls in 2007, whereas Quebec began vaccinating grade 4 girls in 2008 and British Columbia started vaccinating grade 6 girls in 2008 (Shapiro et al., 2017). We selected the year 2008 as the single start date for country-wide vaccination of girls, which corresponds to the median year when vaccination began. School-based catch-up HPV vaccination programs were extended to boys, first in Prince Edward Island (province with the smallest population) in 2013 and, to a few other jurisdictions (province/territory) in the following years. As we are not accounting for catch-up vaccination here, we did not consider the impact of catch-up vaccination targeted at boys prior to 2018.

2.5.2. Current vaccine coverage

To estimate current Canada-wide vaccine coverage across jurisdictions, we calculated a weighted proportion based on average vaccine completion rates (receiving the last dose of a two or three dose schedule) for the available school years within each jurisdiction (Shapiro et al., 2017). The weights were represented by the proportion of girls aged 10–14 in a particular jurisdiction relative to their Canadian counterparts for the year 2014. The weights were based on the 2014 population levels because vaccine completion rates were reported for school years ranging from 2011/12 to 2015/16. Country-wide coverage was estimated because we lacked provincial level cancer incidence data for some HPV-associated cancer sites (e.g. vagina, vulva, base of tongue and tonsil), and provincial cancer incidence could only be projected to 2038 due to smaller sample size hindering stable projections past 2038. We calculated the school-based vaccination completion rate for Canada using a weighted mean based on the size of each province's proportion of the female Canadian population aged 10–14 years as weights. The

Table 3
Sex-specific projected number of cancer cases and potential impact fractions for *Helicobacter pylori* that could be prevented in 2042 under different counterfactuals.

Cancer	Sex	Future burden measures	No change	Cancer burden by reductions in infection prevalence		
				10%	25%	50%
Gastric MALT lymphoma	Men	Projected in 2042	1389	1321	1219	1050
		PIF, %	–	4.9	12.2	24.4
		Prevented in 2042	0	68	170	339
		Prevented 2018–2042	0	272	679	1358
	Women	Projected in 2042	1014	966	893	772
		PIF, %	–	4.8	11.9	23.8
		Prevented in 2042	0	48	121	242
		Prevented 2018–2042	0	198	496	992
	Both	Projected in 2042	2403	2287	2112	1822
		PIF, %	–	4.8	12.1	24.2
		Prevented in 2042	0	116	290	581
		Prevented 2018–2042	0	470	1175	2351
Gastric non-cardia cancer	Men	Projected in 2042	2823	2654	2399	1976
		PIF, %	–	6.0	15.0	30.0
		Prevented in 2042	0	170	424	848
		Prevented 2018–2042	0	717	1792	3585
	Women	Projected in 2042	2274	2140	1939	1604
		PIF, %	–	5.9	14.7	29.5
		Prevented in 2042	0	134	335	670
		Prevented 2018–2042	0	562	1404	2809
	Both	Projected in 2042	5097	4794	4338	3579
		PIF, %	–	6.0	14.9	29.8
		Prevented in 2042	0	304	759	1518
		Prevented 2018–2042	0	1279	3197	6393
Total	Men	Projected in 2042	4212	3975	3619	3025
		PIF, %	–	5.6	14.1	28.2
		Prevented in 2042	0	237	593	1187
		Prevented 2018–2042	0	989	2472	4943
	Women	Projected in 2042	3288	3105	2832	2376
		PIF, %	–	5.5	13.9	27.7
		Prevented in 2042	0	182	456	912
		Prevented 2018–2042	0	760	1900	3801
	Total	Projected in 2042	7500	7080	6450	5401
		PIF, %	–	5.6	14.0	28.0
		Prevented in 2042	0	420	1049	2099
		Prevented 2018–2042	0	1749	4372	8744

Abbreviations: PIF = potential impact fraction, MALT = mucosa-associated lymphoid tissue.

resulting estimate, 72.4% among girls, was imputed to 2008, which was approximately the median year when school-based programs were introduced.

2.5.3. Vaccine efficacy and protection

Efficacy against high-grade cervical, vaginal, and vulvar disease/cancer based on per-protocol analyses of HPV vaccination trials was reported to range from 95% to 100% in HPV-naïve populations (FUTURE II Study Group, 2007; Huh et al., 2017). To be conservative, we used 95% efficacy in our calculations. Currently, three HPV vaccines are available; the most cancer causing HPV types covered by these vaccines are 16 and 18 (in bi/quadrivalent and nonavalent), and the nonavalent also protects against types 31, 33, 45, 52 and 58. Since the nonavalent vaccine has been in use in all Canadian jurisdictions as of 2018, we modeled its use starting in 2018 for the other counterfactuals. For cohorts vaccinated prior to 2018, we assumed that the quadrivalent vaccine was administered.

With respect to cervical cancer, we utilized protection levels of 70.8% for the bi/quadrivalent and 89.5% for the nonavalent vaccines since these proportions represent the estimated relative contribution of HPV types covered by the respective vaccines (de Martel et al., 2017). Since we had previously estimated the proportion of anogenital cancers due to high-risk HPV types (Table 1), we calculated the proportion of high-risk HPV types included in the vaccines to determine their associated level of protection. For this estimation, we relied on data from a study that reported HPV type distribution in anogenital cancer specimens obtained from population-based registries in the United States (Saraiya et al., 2015). Specifically, to determine the level of vaccine protection, we estimated the proportion of the identified high-risk types covered by the bi/quadrivalent and nonavalent vaccines. We estimated that among high-risk HPV positive cancers, protection of the bi/quadrivalent vaccines ranged from 66.0% (vaginal cancer) to 87.1% (anal cancer), and nonavalent protection ranged from 94.3% (penile cancer) to 97.7% (anal cancer).

2.5.4. Herd immunity

The HPV vaccine confers different levels of herd immunity among non-vaccinated girls and boys. We extracted and interpolated herd effects from a modeling study that meta-analyzed transmission-dynamic models from high-income countries (Brisson et al., 2016). Brisson et al. calculated that 40% vaccine coverage of girls would produce 53% protection among women and 36% among men whereas for 80% coverage of girls, 93% protection among women and 83% among men would be observed (Brisson et al., 2016). For 50%, 60% and 72.4% vaccine coverage levels, we assumed that herd effects would increase by 10% increments. For example, a 50% coverage of girls would produce an estimated effect of 63% (10% higher than the 53% herd effect reported for 40% coverage of girls) and 46% coverage of boys (10% higher than the 36% herd effect for boys when 40% of girls are vaccinated). For current coverage of 72.4%, we increased the herd effect by an additional 2.4% to match the increase in coverage from 60% to 72.4%.

2.5.5. Estimating preventable cases

To determine the proportion of future cancer incidence that could be prevented under the different HPV vaccine coverage counterfactuals,

Table 4
Projected number of anogenital cancers and the number that could be prevented according to variations in school-based HPV vaccine coverage in Canada[a,b,c].

Cancer site, sex	Future burden measures	Lower (%)							Current (%)		Higher (%)		
	Effect:	Direct [d]	Direct	Herd	Direct	Herd	Direct	Herd	Direct	Herd	Direct	Herd	Herd
	Girls:	0.0	40.0	53.0	50.0	63.0	60.0	73.0	72.4	85.4	80.0	93.0	100.0
	Boys:	0.0	0.0	36.0	0.0	46.0	0.0	56.0	0.0	68.4	0.0	83.0	100.0
Cervix	Projected in 2042	1939	1723	1684	1693	1654	1663	1624	1626	1587	1603	1564	1543
	Prevented in 2042	0	216	255	246	285	276	315	313	352	336	375	396
	Prevented 2018–2042	0	2813	2980	2941	3108	3070	3236	3228	3395	3326	3492	3583
Anus, men[e]	Projected in 2042	345	345	345	345	345	345	344	345	344	345	344	343
	Prevented in 2042	0	0	0	0	0	0	0	0	1	0	1	1
	Prevented 2018–2042	0	0	8	0	9	0	10	0	11	0	13	25
Anus, women	Projected in 2042	775	758	757	757	756	756	755	755	754	755	754	753
	Prevented in 2042	0	17	18	18	19	19	20	20	21	20	21	22
	Prevented 2018–2042	0	130	131	131	132	132	133	133	135	134	136	136
Anus, both	Projected in 2042	1120	1103	1102	1102	1101	1101	1100	1100	1099	1100	1098	1097
	Prevented in 2042	0	17	18	18	19	19	20	20	21	20	22	23
	Prevented 2018–2042	0	130	139	131	141	132	143	133	146	134	148	161
Penis	Projected in 2042	260	260	258	260	258	260	258	260	258	260	258	258
	Prevented in 2042	0	0	2	0	2	0	2	0	2	0	2	2
	Prevented 2018–2042	0	0	13	0	14	0	14	0	14	0	15	15
Vagina	Projected in 2042	172	168	167	167	167	167	166	166	165	166	165	164
	Prevented in 2042	0	4	5	5	5	5	6	6	7	6	7	8
	Prevented 2018–2042	0	52	55	55	58	57	61	60	64	62	66	69
Vulva	Projected in 2042	987	964	960	961	956	957	953	953	949	951	947	945
	Prevented in 2042	0	23	27	27	31	30	34	34	38	36	40	42
	Prevented 2018–2042	0	296	313	309	327	323	341	340	358	350	368	384
Total, women	Projected in 2042	3873	3613	3568	3578	3533	3544	3499	3501	3456	3475	3430	3406
	Prevented in 2042	0	260	305	295	340	330	374	372	417	399	443	468
	Prevented 2018–2042	0	3291	3480	3436	3625	3582	3771	3762	3951	3873	4062	4174
Total, men	Projected in 2042	605	605	603	605	603	605	603	605	603	605	602	602
	Prevented in 2042	0	0	2	0	2	0	2	0	2	0	2	3
	Prevented 2018–2042	0	0	21	0	22	0	24	0	25	0	27	40
Total, both	Projected in 2042	4478	4218	4171	4183	4136	4149	4102	4106	4059	4080	4032	4007
	Prevented in 2042	0	260	307	295	342	330	376	372	419	399	446	471
	Prevented 2018–2042	0	3291	3501	3436	3648	3582	3794	3762	3977	3873	4089	4213

[a] We did not round numbers when performing the analysis and hence some figures do not add up.
[b] The direct effects of 80% vaccine coverage among boys was not modeled.
[c] Since cancer incidence was projected to only 2042, the first vaccinated cohort of girls vaccinated in 2008 at ages 10–14 were aged 40–44 in 2042 meaning that only cancer incidence among those up to age 45 could be impacted by vaccination.
[d] Direct effects of 0.0 among girls and boys assume that the HPV vaccination was never administered at any point in time in Canada.
[e] We estimated that 49.4% of anal cancers occur among men who have sex with men and hence are not impacted by herd effects of girls only vaccination.

we multiplied the following parameters: (1) proportion of cancer attributable to high-risk HPV types for anogenital cancers (ranging from 39.4% for penile cancer to 100.0% for cervical cancer – Table 1) and to HPV16 for head and neck cancers (ranging from 8.2% for oral cavity cancer to 60.2% for oropharyngeal cancer), (2) level of direct (40.0%–80.0%) or herd (36.0%–100.0%) vaccine coverage effects, (3) level of protection offered by the vaccines (66.0%–97.7%), and (4) vaccine efficacy (95.0%). The resulting proportion was then multiplied by the projected number of cancers to calculate the number of preventable cancers.

2.6. Cancer incidence

Supplementary Table 1 describes the modeling approach to estimate future cancer incidence (2018–2042) for each cancer. The projected number of cancers was estimated using three methods. The first method involved fitting different models with the 'Canproj' R package; this process is described in detail elsewhere (Poirier et al., 2019). The second involved applying a proportion to the Canproj projected cancer incidence to obtain the number of incident cancers for specific subsites. For example, this approach was utilized to determine the proportion of tongue cancer that is expected to be from the base of tongue and the proportion of stomach cancer that is expected to be from the non-cardia part of the stomach (Supplementary Table 1). Cancer incidence data for rare or subsite cancers were only available for two age groups (< 50 and ≥ 50 years). To approximate the number of cancers occurring in five-year age groups, we partitioned the counts in these two age groups by the five-year age distributions from other related cancers. Specifically, the cervical cancer five-year age distribution within the < 50 and ≥ 50 age groups was used to partition vaginal and vulvar cancers, and the tongue cancer five-year age distribution was used to partition tonsillar cancer, thereby allowing us to assess the impact of HPV vaccination on cancer incidence. As herd effects from girls-only vaccination do not confer protection among men who have sex with men (MSM), we estimated the proportion of anal cancers occurring among MSM. We calculated a proportion of 49.4% of anal cancers attributable to MSM by utilizing a RR of 17.3 for the association between sexual orientation and anal cancer and a 6.0% prevalence of MSM among those aged 15 to 44 in the United States (Chandra et al., 2011; Daling et al., 2004).

2.7. Statistical analysis

The calculation of attributable risks has been previously published (Volesky et al., 2019). Briefly, to estimate the proportion of cancer that is attributable to HPV, individual studies were pooled with a random effects model. A fixed effect model was used to produce a pooled measure of association between *H. pylori* and non-cardia gastric cancer. Meta-analyses were performed, and figures were produced in Stata v14 (StataCorp., College Station, TX, USA). R software (version 3.4.1) was used to calculate the future preventable burden of HBV, HCV, and *H.*

Table 5
Projected number of head and neck cancers and the number that could be prevented with variations in school-based HPV vaccine coverage in Canada[a,b,c].

Cancer site, sex	Future burden measures	Lower (%)							Current (%)		Higher (%)		
	Effect:	Direct [d]	Direct	Herd	Direct	Herd	Direct	Herd	Direct	Herd	Direct	Herd	Herd
	Girls:	0.0	40.0	53.0	50.0	63.0	60.0	73.0	72.4	85.4	80.0	93.0	100.0
	Boys:	0.0	0.0	36.0	0.0	46.0	0.0	56.0	0.0	68.4	0.0	83.0	100.0
Oropharynx, men[e]	Projected in 2042	3469	3469	3363	3469	3360	3469	3356	3469	3352	3469	3348	3342
	Prevented in 2042	0	0	106	0	109	0	113	0	117	0	121	127
	Prevented 2018–2042	0	0	742	0	760	0	778	0	800	0	826	857
Oropharynx, women[e]	Projected in 2042	914	894	892	892	890	891	889	889	887	888	885	884
	Prevented in 2042	0	20	23	22	24	24	26	26	28	27	29	30
	Prevented 2018–2042	0	186	193	192	199	198	205	205	213	210	217	227
Oropharynx, both[e]	Projected in 2042	4383	4363	4255	4361	4250	4360	4245	4358	4239	4357	4233	4226
	Prevented in 2042	0	20	129	22	134	24	138	26	145	27	151	157
	Prevented 2018–2042	0	186	935	192	959	198	983	205	1013	210	1044	1084
Oral cavity, men	Projected in 2042	761	761	760	761	760	761	759	761	759	761	759	759
	Prevented in 2042	0	0	2	0	2	0	2	0	2	0	2	2
	Prevented 2018–2042	0	0	16	0	16	0	17	0	17	0	18	19
Oral cavity, women	Projected in 2042	858	856	856	856	856	856	856	856	855	855	855	855
	Prevented in 2042	0	2	2	2	2	2	3	3	3	3	3	3
	Prevented 2018–2042	0	22	24	23	24	24	25	25	26	26	27	28
Oral cavity, both	Projected in 2042	1619	1617	1616	1617	1615	1617	1615	1617	1615	1617	1615	1614
	Prevented in 2042	0	2	4	2	4	2	4	3	5	3	5	5
	Prevented 2018–2042	0	22	40	23	41	24	42	25	44	26	45	46
Larynx, men	Projected in 2042	1230	1229	1229	1230	1228	1230	1228	1230	1228	1230	1228	1228
	Prevented in 2042	0	0	2	0	2	0	2	0	2	0	2	2
	Prevented 2018–2042	0	0	11	0	12	0	12	0	12	0	12	12
Larynx, women	Projected in 2042	187	186	186	186	186	186	186	186	186	186	186	186
	Prevented in 2042	0	0	0	0	0	0	0	0	0	0	0	1
	Prevented 2018–2042	0	4	4	4	4	4	5	5	5	5	5	5
Larynx, both	Projected in 2042	1417	1415	1415	1417	1415	1416	1415	1416	1415	1416	1415	1415
	Prevented in 2042	0	0	2	0	2	0	2	0	2	0	2	2
	Prevented 2018–2042	0	4	16	4	16	4	16	5	16	5	17	17
Total, men	Projected in 2042	5460	5459	5351	5460	5348	5460	5344	5460	5340	5460	5335	5330
	Prevented in 2042	0	0	109	0	113	0	116	0	120	0	125	131
	Prevented 2018–2042	0	0	769	0	788	0	806	0	829	0	856	888
Total, women	Projected in 2042	1959	1937	1934	1935	1932	1933	1931	1931	1928	1929	1927	1926
	Prevented in 2042	0	23	25	25	27	26	29	29	31	30	33	34
	Prevented 2018–2042	0	212	221	219	228	226	235	235	244	240	249	260
Total, both	Projected in 2042	7420	7395	7285	7395	7280	7393	7275	7391	7268	7390	7262	7255
	Prevented in 2042	0	23	135	25	140	26	145	29	151	30	158	165
	Prevented 2018–2042	0	212	990	219	1016	226	1041	235	1073	240	1105	1148

[a] We did not round numbers when performing the analysis and hence some figures do not add up.
[b] Direct effects of 80% vaccine coverage among boys was not modeled.
[c] Since cancer incidence was projected to only 2042, the first vaccinated cohort of girls vaccinated in 2008 at ages 10–14 were aged 40–44 in 2042 meaning that only cancer incidence among those up to age 45 could be impacted by vaccination.
[d] Direct effects of 0.0 among girls and boys assume that the HPV vaccination was never administered at any point in time in Canada.
[e] Included the base of the tongue and tonsils.

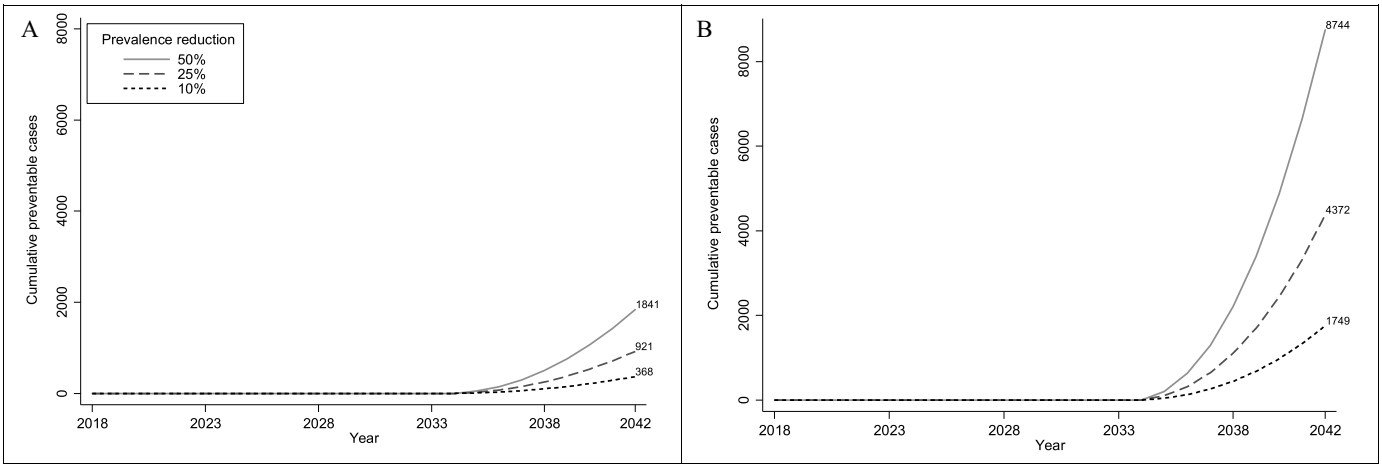

Fig. 1. Projected cumulative preventable cases attributable to hepatitis B and C viruses (A) and *Helicobacter pylori* (B) by applying counterfactual prevalence reductions.

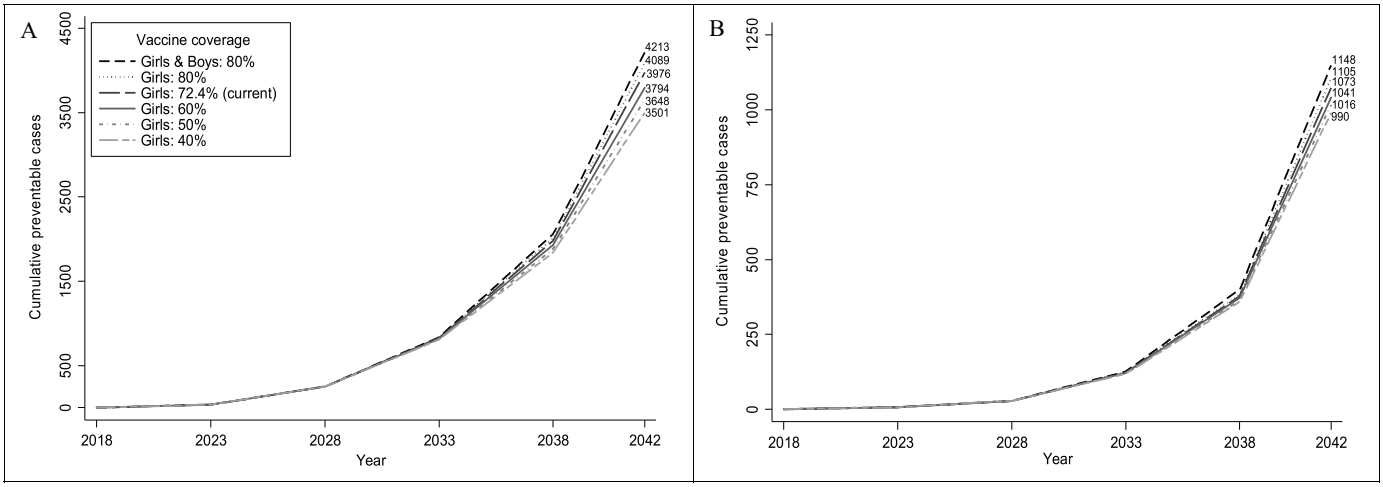

Fig. 2. Projected cumulative preventable anogenital cancers (A) and head and neck cancers (B) attributable to human papillomavirus by applying school-based HPV vaccine coverage counterfactuals[a,b].

[a]The vaccine coverage level refers to the percent of those aged 10–14 receiving the HPV vaccine.

[b]We modeled the herd effects of vaccine coverage (e.g. 40% coverage of girls produces 53% coverage of girls and 36% coverage of boys).

pylori associated cancers (R Foundation for Statistical Computing [Internet], 2017) and an electronic spreadsheet was used to estimate the future preventable burden of HPV associated cancers.

Ethics approval was granted for this project by the Health Research Ethics Board of Alberta - Cancer Committee (HREBA.CC-14-0220_REN4) and McGill University exempted this study from Research Ethics Board review.

3. Results

A 50% reduction in HBV, HCV, *H. pylori* prevalence and 80% HPV vaccine coverage of girls and boys in 2018 resulted in an estimated 15,946 cancers that could be prevented from 2018 to 2042 (Tables 2–5). Figs. 1 and 2 demonstrate the cumulative increase in the number of preventable cases over time, and for HBV, HCV and *H. pylori* after a latency period. A 50% reduction in the prevalence of HBV, HCV and *H. pylori* and 80% HPV coverage among girls and boys, could prevent an estimated 1.0% of all cancers diagnosed among men and 0.9% diagnosed among women in 2042 (data not shown).

3.1. Hepatitis B and C viruses

The future prevalence of HBV remained constant, however, that of HCV was projected as steadily decreasing to 2042. A 50% reduction in the prevalence of HBV and HCV would result in slightly fewer projected hepatocellular carcinoma cases in 2042; from 3358 to 3210 for HBV and from 3358 to 3106 for HCV (Table 2). Cumulatively from 2018 to 2042, a 10% reduction in the prevalence of HBV and HCV would prevent 356 hepatocellular carcinomas as compared to a 50% prevalence reduction that would prevent 1782 hepatocellular carcinomas.

3.2. Helicobacter pylori

A 50% prevalence reduction in *H. pylori* would lead to fewer projected non-cardia gastric cancers (3579 cases) in 2042 compared to no change in prevalence (5097 cases); and fewer gastric mucosa-associated lymphoid tissue (MALT) lymphomas, from 2403 to 1822 (Table 3). Cumulatively from 2018 to 2042, a 10% reduction in the prevalence of *H. pylori* would prevent 1749 non-cardia gastric cancers and gastric MALT lymphoma cases as compared to a 50% prevalence reduction that would result in 8744 fewer cases.

3.3. Human papillomavirus

If the estimated current Canada-wide HPV vaccine coverage of girls continued (72.4% direct coverage, but due to herd effects becoming equivalent to 85.4% coverage in girls and 68.4% in boys), an estimated total of 3976 anogenital cancers could be prevented from 2018 to 2042 (Table 4). The majority (85.4%) of these preventable cases were cervical cancers, and virtually all preventable cases occurred among women (99.4%). In contrast, continuation of current HPV vaccine coverage could prevent more head and neck cancers among men (829 cases) than women (244 cases) from 2018 to 2042 (Table 5). Among all HPV-caused cancers, 80% vaccine coverage of girls and boys could prevent 4434 cancers among women and 928 among men by 2042 (Tables 4 and 5) in those less than age 45.

4. Discussion

4.1. Hepatitis B and C viruses

The World Health Organization developed a global strategy to eliminate viral hepatitis with a focus on HBV and HCV by 2030 (World Health Organization, 2016); Canada is a signatory to this strategy. For HBV, the major prevention measure is vaccination, which began as early as 1982 in Canada (Government of Canada, 2017). The Canadian government encourages health care providers to assess HBV status and immunize persons immigrating to Canada (Government of Canada, 2017), although this immunization does not appear to be systematic. The future incidence of hepatocellular carcinoma would be impacted by school- or infant- based universal immunization making a 50% reduction in the prevalence plausible. Approximately 12% of hepatocellular carcinoma cases could be prevented in 2042 with a 50% reduction in the prevalence of the hepatitis viruses in 2018; a 10% reduction would prevent only 2.4% of hepatocellular carcinoma cases in 2042. However, incorporating a 15-year latency for HBV and HCV provided only a 10-year window (from 2032 to 2042) where cancer incidence could be changed by prevalence reductions.

4.2. Helicobacter pylori

H. pylori was the infectious agent responsible for the most preventable cancer cases from 2018 to 2042 (8744 cancers with a 50% prevalence reduction). Although *H. pylori* is associated with a prolonged latency thereby expanding the opportunity to detect and deliver

quadruple antibiotic therapy, there are challenges around determining who needs to be screened and concerns over increasing antibiotic resistance (Fallone et al., 2016). A 50% prevalence reduction may be more aspirational than attainable; however, the more achievable 25% prevalence reduction could prevent > 4000 cancers from 2018 to 2042. When we projected the future prevalence of *H. pylori*, we assumed a constant trend. Nonetheless, a decreasing trend in its prevalence would have resulted in fewer prevented cases, and an increasing trend would have resulted in more.

4.3. Human papillomavirus

A 40% vaccination coverage of girls (herd effects lead to 53% coverage equivalents among girls and 36% among boys) achieved a notable number of preventable cases, with 4491 potentially preventable cancers from 2018 to 2042. Since we used a birth cohort approach, the first two five-year cohorts were vaccinated prior to the application of counterfactual vaccine coverage in 2018, and thus the counterfactuals' impact on cancer incidence in these two cohorts was not modeled.

By projecting cancer incidence to only 2042, the first cohort of girls vaccinated in 2008 at ages 10 to 14 was then aged 40 to 44 in 2042, therefore only cancer incidence among individuals up to age 45 could be impacted. For boys, this constraint was even more pronounced as the vaccine was assumed to have been delivered starting in 2018. This restriction greatly influenced our results since only the first two cohorts could be followed to ages 35 to 44, whereas the remaining cohorts could only be followed to ages 30 to 34. Specifically, the impact of HPV vaccination counterfactuals was confined to cancers occurring in individuals under age 35 in 2042 and therefore differences between the counterfactual interventions are minimized as these only apply to younger cohorts. The impact of HPV vaccine coverage was limited to cancers occurring among individuals less than age 45, yet the majority of HPV-related cancers occurred in individuals over age 45. Hence, our analysis provided a short-term assessment of the impact of school-based vaccination on cancer incidence among young Canadians.

Modeling the impact of HPV vaccine coverage counterfactuals involved several assumptions. First, the estimated herd effects relied on informed assumptions about the level of protection (40% and 80% direct coverage) among non-vaccinated individuals (Brisson et al., 2016) but had to be interpolated for other coverage levels modeled here (i.e. 50%, 60%, 72.4%). Second, we used a more conservative approach to estimate current country-wide vaccine coverage by utilizing data on the completion of recommended number of doses; yet, one dose has been shown to offer considerable protection against HPV-related diseases (Kreimer et al., 2015). Third, we assumed that the vaccine confers long-term protection (up to 30 years in our calculations) against the HPV types it protects against.

There are several limitations of our analysis. First, we did not account for immigration in our calculations; for example, new arrivals not vaccinated through school-based or catch-up vaccination programs were not accounted for by the counterfactuals and they have a greater risk of developing HPV-associated cancers than the remaining Canadian population; however, herd effects are anticipated to minimize this concern. Second, although our estimate of country-wide vaccination was conservative (72.4%), there is substantial variation in the level of HPV vaccine coverage, hence some Canadian jurisdictions might not realize the reductions in cancer incidence that are possible with the counterfactual coverage levels. For example, receiving the recommended number of vaccine doses ranges from approximately 50% in Nunavut to 90% in Newfoundland and Labrador (Shapiro et al., 2017). Conservatively, the impact of catch-up vaccination was not modeled, yet it would result in more preventable cancers in the future. Third, improvements in cervical cancer screening technology coupled with vaccination coverage are likely to result in improved and more efficient cervical cancer prevention in the future, potentially leading to elimination of this disease (El-Zein et al., 2016; Franco, 2017). Finally, we focused our analysis on the four infections that cause the most cancers in Canada and for which there are proven prevention strategies; however, other infections such as Epstein-Barr virus and human immunodeficiency virus also cause cancer and a reduction in their prevalence could lessen the future infection-associated cancer burden.

4.4. Implications for cancer prevention

With an aging population, the future burden of cancer in Canada is expected to substantially increase to 2032 (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). Changes in major cancer risk factors such as infections will have varying impacts on the future burden of cancer; we identified the impact of four preventable and/or treatable infections on the future cancer burden. Even the short-term view presented here reveals that different interventions have differing impacts on future incidence.

5. Conclusion

By modeling the impact of 10%, 25%, and 50% relative reductions in the prevalence of infections – HBV, HCV, and *H. pylori* – we estimated that > 10,000 cancers could be prevented from 2018 to 2042 with a 50% prevalence reduction. The impact of 80% school-based HPV vaccine coverage among girls and boys would potentially prevent 5360 cancer cases from 2018 to 2042. Despite only capturing the impact of school-based HPV vaccination on cancers occurring among those less than age 45, our results indicate that increases in HPV coverage can result in meaningful decreases in HPV-related cancer incidence. With Canada's current cancer prevention resources, there is a substantial opportunity to reduce the future infection-associated cancer burden.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.04.006.

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Competing interests

None.

Disclosure

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E.L.F. is Editor-in-Chief at Preventive Medicine and K.D.V. is an Assistant Editor at Preventive Medicine. The process of soliciting the special issue, sending out manuscripts for review, the peer-review process and editorial decision making was conducted entirely outside of the Preventive Medicine online system (for which E.L.F. and K.D.V. have access to through their regular Preventive Medicine duties).

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