Quantifying the Impact of Dissimilar HPV Vaccination Uptake among Manitoban School Girls by Ethnicity using a Transmission Dynamic Model

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Word count: 3,842

Abstract word count: 239

Introduction

Human papillomavirus (HPV) is a risk factor for many cancers [1-5] and is a necessary condition for cervical cancer[6-8]. Health Canada approved a new HPV vaccine, Gardasil, in 2006[9]. Gardasil has been shown to be highly effective at preventing transmission of HPV types 6, 11, 16, and 18.[10] In Manitoba, Canada, Gardasil vaccination for grade 6 girls began in 2008[11]. There are many HPV genotypes, but only 15 are considered high cancer risk[12-14], with types 16 and 18 accounting for approximately 70% of cervical cancers[15, 16]. In Manitoba, two studies found types 16 and/or 18 present in 17.4% [17] and 18.0% [18] of HPV infections among women aged 15-39 years, and 18 and above, respectively.

Heterogeneity in behaviour may affect HPV transmission. Several models of HPV transmission incorporate heterogeneous sexual behaviour[19-22], such as varying partner formation rates. In Manitoba, however, there is also likely heterogeneous uptake of screening and/or vaccination. First Nations (FN) women likely have lower cervical cancer screening rates (42.6% per year among FN compared to 60.4% among AOM)[23] and higher invasive cervical cancer (ICC) incidence than all other Manitobans (AOM). In a retrospective study spanning 1984-1997, FN ICC incidence was estimated at 34.1 per 100,000 person-years, while corresponding AOM incidence was 9.5[23]. The other Manitoba-based study spanned 1970-1979 and found the FNMI/AOM ICC incidence rate ratio to be 1.34[24]. Although these studies are not recent, health disparities between FNMI and AOM continue to exist. Importantly, recent evidence suggests unequal vaccination coverage between FN and AOM girls, during the first year after Gardasil distribution in grade 6[25]. This lack of equity in health care may impact the health status of all sectors of the population, even the sector which appears to have better health care.

Because FNMI comprise approximately 15.5% of the Manitoban population[26], vaccination rates among FNMI will have less impact on cervical cancer among AOM than vaccination rates among AOM will have on cervical cancer among FNMI.

Mathematical models have been used, both within[19, 20, 27] and outside of Canada[21, 22, 28-31], to examine the potential impact of vaccination on HPV infection and cervical cancer incidence. Our work enhances upon these previous studies. We developed a model of the transmission dynamics of HPV suitable for use in a setting such as Manitoba, in which different groups of people may have different cervical cancer screening and HPV vaccination uptake. Using this model, we assessed the impact that dissimilar vaccination coverage may have on HPV prevalence and ICC incidence among FNMI and AOM, assuming screening uptake remained unchanged.

Methods

Empirical Data

Demers et al[17] estimated HPV prevalence in Manitoba in 2008 by FNMI status and age, separately for some HPV types. Young et al (1997)[18] estimated HPV type 16/18 and all-type prevalence in 1994 by First Nations status among women aged 15-39. Annual cervical cancer incidence rates were obtained from CancerCare Manitoba registry data. From Young et al (2000)[23], we obtained 1991 ICC incidence estimates by age and First Nations status. Some literature provided results by First Nations status, while other literature by FNMI status. For

consistency in model fitting, we considered published estimates by First Nations to be a proxy for FNMI, so in the remainder of our work, we refer to FNMI.

Model

A full description of the model is provided in Appendix I. The model is stratified by age, gender, sexual activity group defined by annual partner formation rate, and vaccination/screening group defined by vaccination coverage and screening rates. Four HPV types are represented, including types 16 and 18. People transit through three vaccination states representing unvaccinated, partially vaccinated, or fully vaccinated, and four cervical cancer states, representing cancer free, low grade lesions (LSIL), HSIL, and ICC. The sexual mixing in the model allows those with similar behaviour to preferentially partner with each other. Those in the same sexual activity group may preferentially partner with each other, and those with similar vaccination and screening uptake may also be more likely to partner with each other (assortative sexual mixing with respect to vaccination/screening behaviour). In the current work, the vaccination/screening groups represent FNMI and AOM.

We fit model estimated HPV prevalence and cervical cancer incidence to corresponding empirical estimates, separately, for three different values of the vaccination/screening group assortativity parameter. The values were 0.33, representing scenarios with little sexual partnership mixing between FNMIs and AOMs, 0.67 representing more mixing but still retaining some within-ethnic preference, and 1.00 representing the extreme case in which partnerships are chosen solely based on partnerships available with no ethnic preference.

For each of the three assortativity values, maximum likelihood was used in two stages to find the best fitting parameter sets. We first ran 200,000 simulation scenarios with varying parameter values and used maximum likelihood to fit model estimated to empirically estimated HPV prevalence. Using our best fit to HPV prevalence, we then ran 20,000 scenarios with varying cancer progression parameter values. We used maximum likelihood again at this stage in order to fit to detected HSIL and ICC incidence, under the constraint that between 65% to 75% of ICC incidence was attributable to HPV type 16/18, and that no more than 90% of ICC incidence was attributable to HPV type 16/18 among those aged 15-34, and no less than 60% among those aged 35-79. Though literature on age- and HPV type-specific ICC is scarce, in one study, it was estimated that 86% of ICC among women aged < 35 was attributable to type 16/18, while 67% of ICC among women aged 35+ was attributable to type 16/18[32]. Empirically estimated HSIL incidence is among those screened and detected, so we fit to screened and detected model estimates, even though the model can provide estimates of true incidence. We conducted this process in two stages because the sample sizes from CancerCare for estimated cancer incidence were immensely larger than the sample sizes used in published literature to estimate HPV prevalence. If both HPV prevalence and ICC incidence were fit simultaneously, the HPV prevalence values would, therefore, have negligible impact on the overall best fits.

Under the assumption of an ethnic mixing assortativity value of 0.33, we further explored the 12 best fitting scenarios. We did this by first identifying the top 12 fits to HPV prevalence among the 200,000 scenarios run, using maximum likelihood. For each of these 12, we then ran 20,000 simulations with varying cancer progression parameter values and used maximum likelihood to identify each of the 12 respective best fits, as described above.

Vaccination Impact

The age groups used for fitting varied, depending on estimates available from literature. Once the best fitting parameter set to HPV prevalence, ICC incidence, and detected HSIL incidence before vaccination was found, we used this set in order to examine different combinations of vaccination coverage and efficacy. When examining vaccination impact, some vaccination-related parameters were fixed. It was assumed that only 11 and 12-year-old girls may be vaccinated, and no vaccination of boys. This simplifying assumption was used in order to reduce the potential number of vaccination scenarios examined. During the first year of the vaccination program in Manitoba, >80% of vaccinations were among 11 and 12-year-olds.[25]

We modelled no vaccination prior to 2008. From 2008 to 2012, 2-year vaccination coverage, representing vaccination of 11-12 year olds, was consistent with that found during the first two years (2008-2009) of the publicly funded vaccination program.[25] Among AOM, the 2-year coverage for initial vaccination (first dose) was 39%, and 95% of those with a first dose vaccination would receive all three doses required for full vaccination. Among FNMI, the corresponding coverage was 36% for first dose, and 93% of those with a first dose vaccination would receive all three doses.

The main results are provided with 14 scenarios of varying first dose vaccination coverage among FNMI and AOM from 2013 on, and the following fixed: 90% of girls with first dose vaccination receive full vaccination, no vaccine waning, full vaccination efficacy is 100% and partial vaccination efficacy 50%. In supplementary table S2, the interested reader will find

results that include vaccine waning. The partial vaccination efficacy was based on a combination of 1-dose efficacy which is likely lower and 2-dose efficacy which is likely higher than that modelled[33].

Results

Model Fitting

We established a set of parameter values from ranges obtained through literature (supplementary table S1) that fit the model estimates to the two years of empirical HPV prevalence estimates and nearly 40 years of HSIL and ICC incidence. We present the best fitting values to HPV prevalence (figure 1) and to HSIL and ICC incidence (figure 2) in the scenario of tendancy toward within-ethnic mixing, assortativity 0.33. The best fitting values in the scenarios of assortativity 0.66 and 1.00 appeared similar (not shown). Among 15-39 year old sexually active women, empirically estimated type 16 or 18 prevalence in 1994 differed from 2008 estimates. Estimated all-type HPV prevalence (figure 1, panel B) among 15-39 year olds in 1994 was very similar between FNMI and AOM. By contrast, the 2008 all-type prevalence estimate was much higher than the 1994 estimate among FNMI, but much lower than the 1994 estimate among AOM.

None of the simulation scenarios derived from our parameter value ranges produced model-estimated prevalence that varied as much over time as corresponding empirical estimates. Our best fit, however, produced model-estimated prevalence that passed through 5 of the 6 empirically estimated 95% C.I.s for all-type prevalence, and 4 of the 6 empirically estimated

95% C.I.s for type 16 or 18 prevalence. Although we could only fit to HPV prevalence among age ranges for which empirical estimates were available, we present model estimated prevalence for more narrowly defined age ranges in figure 3 panel C (HPV type 16/18) and panel D (all HPV type).

A visual inspection of our best fitting model estimated ICC incidence shows a close fit with ICC incidence data among all women (figure 2). Cervical cancer incidence showed a consistent decline over time among all women and our model estimates fit this well (figure 2, panel A). We also fit closely to HSIL incidence among the age group 40-79. Empirically estimated HSIL incidence among women < 30 years rose over time, while that among women aged 30-39 fell over time. Although our best fitting scenario produced detected HSIL incidence within the correct range and a less pronounced rise in incidence among young women than seen empirically, we did not match the steeply rising incidence among young women and falling incidence among middle aged women. This is likely due to changing screening patterns over time. Our best fitting model scenarios assumed that low grade lesions (LSIL) were unlikely to be detected or treated in a woman, even if she were screened (supplementary table S1).

Only one year of incidence by FNMI status was found in the literature (figure 2, panels C and D). The model estimated incidence did not have as much disparity by FNMI status as empirically estimated incidence. For example, the 1990 empirical estimate of incidence among women aged 35-64 was 3.2 times higher among FNMI than AOM (48.2 per 100,000 person-years and 14.9 per 100,000 person-years, respectively). By contrast, the 1990 model estimated

incidence in the same age group was just 1.8 times higher among FNMI than AOM (36.6 and 19.9 per 100,000 person-years).

Vaccination Uptake

In table 1, we present the impact of vaccination coverage among 11-12 year old school girls by 2059, by FNMI status. The scenarios represented are categorized by initial (first dose) 2-year vaccination coverage among FNMI and AOM girls. The first dose vaccination coverage scenarios among FNMI were chosen to represent 57%, 75%, and 93% of the AOM coverage. An additional fixed FNMI coverage of 37% is shown so that we can assess the impact of changing AOM coverage on FNMI ICC incidence, when FNMI coverage is held constant.

By 2059, the impact of vaccination is pronounced, not only among the young women, but also among older women, aged 35-79 (table 1). ICC incidence among women aged 35-79 may fall by as much as 68% by 2059, if we can achieve very high percentages of vaccination coverage – 93% among FNMI and 99% among AOM. For example, in our scenarios with assortativity 0.33 (a tendency to prefer within-ethnic partnerships), our model estimated ICC incidence fell from 15.42 per 100,000 person years with no vaccination to 5.66 per 100,000 person years with the highest vaccination coverage that we modeled. Similarly, under the scenarios with assortativity 0.67, ICC incidence could fall from as high as 15.24 to as low as 4.91, and under assortativity 1.00 (partners chosen without regard for ethnicity), ICC incidence could fall from as high as 15.26 to as low as 4.88 per 100,000 person years.

Among our 12 best fitting sets of parameter values, under the scenarios of assortativity 0.33, the trend in estimated impact of vaccination on subsequent cancer incidence was similar across all 12 well-fitting parameter value sets. Surprisingly, our model results indicate that it is not clear that ICC incidence among the older women (age group 35-79) will fall with vaccination if waning exists and there are no boosters (supplementary table S2). With a mild annual waning rate of 0.05 from full to partial and from partial to no vaccination, vaccination among 11-12 year old school girls consistently reduced estimated ICC incidence among young women aged 15-34 by 2059, but did not consistently reduce estimated ICC incidence among older women. In our model, we assumed that infection with a specific HPV type conferred lifetime immunity to that type. With waning, once the vaccination efficacy wore off and the woman had not yet been infected with the type-specific HPV, she was then susceptible at a later age.

Cross-Ethnic Impact of Vaccination Uptake

Vaccination coverage by FNMI status may impact not only that ethnic group, but the other group as well (figure 4). For example, given a fixed first dose vaccination coverage among FNMI of 37%, a change in first dose coverage among AOM from 40% to 99% results in an estimated change in ICC incidence among 35-79 year old FNMIs by 2059 from 12.46 to 10.17 per 100,000 person years under assortativity 0.33, from 11.37 to 8.67 under assortativity 0.67, and from 12.40 to 8.20 under assortativity 1.00 (Table 1). That is, assuming ethnic mixing assortativity of 0.33, ICC incidence among FNMI if AOM coverage is 99% may be 18.4% lower than if AOM coverage is just 40% (Figure 4). The greater the cross-ethnic mixing, the larger the impact that vaccination coverage among one group has on estimated ICC incidence in the other. For example, assuming ethnic mixing assortativity of 1.00 (no preference by ethnicity), ICC

incidence among FNMI if AOM coverage is 99% may be almost 40% lower than if AOM coverage is just 40% (Figure 4). The impact of FNMI vaccination coverage on AOM ICC incidence is not as great as the reverse. Despite this, under assortativity 1.00, ICC incidence among AOM 35-79 year olds if FNMI coverage is 84% may be nearly 10% lower by 2059 than if FNMI coverage is just 37% (Figure 4, right panel).

Discussion

The novel focus of our study was to explore the impact of vaccination coverage in one ethnic group in Manitoba on ICC incidence in the other. Broadly, however, our results are in line with modelling estimates from other studies. Van de Velde and colleagues estimated that in Canada, a quadrivalent vaccine with 70% coverage among 12-year-old girls would reduce ICC by 31% over 70 years[34]. We estimated that 60% coverage among 11- and 12-year-old FNMI girls and 65% coverage among AOM girls would reduce ICC by 38% among AOM 35-79 year olds and 40% among FNMI 35-79 year olds over 47 years, assuming a mixing assortativity of 0.33 and a high (90%) full vaccination rate among those with first dose (Table 1). In another Canada-based study, Tully and colleagues estimate an approximate 70% reduction in ICC incidence among women of all ages (from 10 to 3 per 100,000 person years) by 2057 if 80% of 12-year-old girls are immunized[35]. We estimate that 84% coverage among FNMI and 90% coverage among AOM girls would reduce ICC by 58-64% among FNMI 35-79 year olds and 51-57% among AOM 35-79 year olds by 2059, depending on ethnic mixing assortativity (Table 1). In a second Van de Velde and colleagues study, they detail the importance of assumptions about waning

when assessing the likely impact of vaccination on future cervical cancer incidence[36]. Indeed, we found that with a waning rate of 0.05 per year among school girls, older women by 2059 may experience higher ICC incidence than with no vaccination (Supplementary Table S2). Whether this occurs would depend on both the coverage of vaccinations among school girls, as well as booster vaccination. In summary, assuming no waning, we estimated a slightly larger impact of vaccination than Van de Velde and colleages but a lower impact than Tully and colleagues.

Although our model estimated cancer incidence among all women combined appeared to fit observed data well, our model estimates did not have as much disparity between FNMI and AOM populations as empirically estimated incidence. We only fit to one year of incidence data by ethnicity. Another study that compared ICC incidence in Manitoba between FNMI and AOM did not present actual incidence but did estimate the incidence rate ratio estimate of 1.34[24]. Our model estimated disparity is therefore in line with all of the available empirical data. If we have under-estimated the incidence disparity, however, this means that our results may be conservative. That is, the impact that disparate vaccination coverage by FNMI status may have on future expected differences in ICC incidence between FNMI and AOM women may be larger than our estimate.

In our study, we explored vaccination coverage among FNMI school girls ranging from 57% to 93% of that among AOM school girls. During the first few years of the vaccination program in Manitoba, the discrepancy in vaccination coverage between FNMI and AOM school girls was 8%. By contrast, among older women, the first dose vaccination coverage among FNMI may be as much as 1/4 to 1/3 lower than among AOM women[25]. We have an obligation to ensure that

the discrepancy in coverage among school girls not only does not widen to similar values as found among older women, but that it even narrows or disappears.

Our study results indicate that vaccination coverage among FNMI has the greatest impact on ICC incidence among FNMI, and similarly, coverage among AOM has the greatest impact on ICC incidence among AOM. However, unequal vaccination coverage in school girls by FNMI status can impact not only the respective groups, but can also have a cross-over impact on the other group. The amount of cross-over impact depends partly on sexual partnership mixing between the groups. We assessed the impact of vaccination coverage among one group on ICC incidence among the other, under three different scenarios of cross-ethnic mixing.

There is no empirical data that we are aware of that assesses the degree to which FNMI and AOM in Manitoba mix with respect to sexual partnerships. However, studies among other ethnicities and settings do indicate some cross-ethnic mixing. For example, in a study among adolescents in the United States, sexual partnerships with a different ethnicity were reported in 42% of Latinos, 14% of whites, and 15% of blacks[32]. Among men who have sex with men in a San Francisco study, 83% of Asians, 74% of blacks, 34% of whites, and 83% of Latinos had a partner of a different race or ethnicity[37]. As 14% of the study population were Asian, 9% black, 56% white, and 21% Latino, this showed some assortativity by race/ethnicity, but a significant proportion of partnerships chosen randomly (proportional to the number of partnerships on offer from the different races or ethnicities). In a study among Canadian immigrants from the Middle East, 42% reported non Middle Eastern sexual partners[38]. Results from these studies do not directly translate to the propensity for First Nations, Métis,

Inuit, and All other Manitobans to inter-mix and a better understanding of these mixing patterns would help us better judge the impact of unequal vaccination uptake on cervical cancer incidence across ethnic groups. Studies such as these, however, do indicate that although there is some assortativity with respect to ethnic groups, most ethnic groups do cross-mix to some degree.

Limitations

In addition to vaccination coverage, sexual risk taking, cancer screening, and different HPV and cancer biology by FNMI status may contribute to cervical cancer incidence. In this study, we did not directly examine the potential role of these factors in estimating plausible future cancer incidence. We assumed that only vaccination impacted HPV transmission probability and only HPV infection type impacted cancer progression. We also did not examine the role of changes in future screening uptake or changes in future sexual behaviour on ICC incidence.

Because we fit our model separately for each of the three ethnic-mixing assortativity parameter values, one may reasonably expect that baseline ICC incidence across the three parameter values would be very similar. This held true among the older age group, but less so among the younger age group (table 1). Perhaps a larger number of simulation scenarios for fitting would have resulted in more similar baseline ICC incidence. However, the focus of our work was not to estimate the absolute ICC incidence value by 2059, but rather to estimate the relative value. For example, what impact might we expect ethnic-mixing assortitivity to have on the percent reduction in ICC incidence? This was the purpose of Figure 4.

Our best fitting model scenarios assumed that low grade lesions (LSIL) were unlikely to be detected or treated. This may explain why we did not observe the same pattern of HSIL incidence over time as was estimated empirically. Further investigation into this may be warranted for future work.

We made a conscious choice to confine vaccinations to 11-12 year old girls, limiting the scope of this work to only examining the impact of vaccination programs among grade 6 girls. However, more work is warranted exploring the impact of catch-up vaccinations among older girls, or booster vaccinations. Finally, we did not examine the impact of vaccinating boys.

Conclusion

There is no question that extreme effort must be made to equally encourage girls of all backgrounds and their families to participate in publicly-funded HPV school vaccination programs. This is an ethical consideration and the present study has provided no evidence to further support this already clear mandate. However, we have shown that without equal vaccination uptake among school girls of all backgrounds, the expected impact of vaccination on cervical cancer incidence may be lower than it would have been with equal vaccination. Even with effort, policy alone may not be able to ensure equal vaccination uptake, since families play a role by agreeing or not to have their daughters vaccinated. Policy makers should be prepared for higher rates of cervical cancer if we are unable to equalize vaccination uptake among all sectors of society.

Conflicts of Interest

None of the authors have conflict of interests. We have no financial or personal relationships with other people or organizations that could bias our work.

Acknowledgement

This work was supported by the University of Manitoba Research Grants Program [grant #36954].

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Table 1. Impact of Vaccination Coverage on ICC Incidence by 2059[1]

		Model Estimated ICC Incidence per 100,000 Person-Years											
1st Dose Vax Coverage		Ethnic Mixing Assortativity 0.33[4]				Ethnic Mixing Assortativity 0.67[4]				Ethnic Mixing Assortativity 1.00[4] (no ethnic preference)			
Among AOM[2]	*Among FNMI[3]*	Age 15-34		Age 35-79		Age 15-34		Age 35-79		Age 15-34		Age 35-79	
		AOM[2]	FNMI[3]	AOM[2]	FNMI[3]	AOM[2]	FNMI[3]	AOM[2]	FNMI[3]	AOM[2]	FNMI[3]	AOM[2]	FNMI[3]
Baseline – no vaccination		3.80	6.58	8.69	15.42	3.52	5.94	8.53	15.24	4.78	8.02	8.51	15.26
40%	*23%*	3.42	6.25	6.91	13.78	3.12	5.29	6.44	12.55	4.38	7.80	7.29	14.08
	30%	3.18	5.51	6.87	13.16	2.97	4.95	6.34	11.97	4.11	7.08	7.19	13.28
	37%	2.90	4.74	6.81	12.46	2.83	4.59	6.22	11.37	3.82	6.30	7.08	12.40
65%	*37%*	2.08	4.22	5.65	11.66	1.90	4.28	5.04	10.28	2.30	4.88	5.53	10.43
	49%	1.77	2.97	5.52	10.39	1.72	3.74	4.88	9.36	1.96	3.92	5.31	9.67
	60%	1.52	2.08	5.40	9.25	1.57	2.77	4.74	8.55	1.67	2.67	5.12	8.50
90%	*37%*	1.12	4.04	4.60	10.69	1.48	3.34	4.02	9.01	1.39	3.02	4.25	9.09
	51%	0.97	2.70	4.48	9.19	1.36	2.71	3.90	8.13	1.20	2.21	4.11	7.99
	68%	0.76	1.62	4.36	7.71	1.27	2.20	3.79	6.37	0.99	1.57	3.97	6.94
	84%	0.64	0.90	4.24	6.49	1.18	1.80	3.64	5.48	0.84	1.17	3.83	6.01
99%	*37%*	0.77	3.95	4.11	10.17	1.07	3.28	3.55	8.67	0.86	2.49	3.62	8.20
	56%	0.63	2.11	3.99	8.21	0.97	2.54	3.42	6.81	0.74	1.67	3.48	6.77
	74%	0.49	1.20	3.90	6.81	0.88	2.03	3.31	5.74	0.65	1.23	3.35	5.25
	92%	0.44	0.79	3.81	5.66	0.83	1.62	3.02	4.91	0.60	1.01	3.17	4.88

[1]Full vaccination among those with 1st dose – 90%. No Waning. Full dose efficacy = 100%. 1-2 dose vaccine efficacy = 50%.

[2] AOM = All other Manitobans

[3] FNMI = First Nations, Métis, and Inuit

[4] This assortativity refers to the degree of sexual mixing between ethnic groups. Value is between 0-1. 0 represents no cross-mixing, 1 represents no partnership preference by ethnicity, values between 0 and 1 represent some cross-mixing and some within-ethnic preference.