Changing Inequalities in Cervical Cancer: Modeling the Impact of Vaccine Uptake, Vaccine Herd Effects, and Cervical Cancer Screening in the Post-Vaccination Era

Talía Malagón1,2, Mélanie Drolet1,2, Marie-Claude Boily3, Jean-François Laprise2, and Marc Brisson1,2,3

Abstract

Background: Inequalities in cervical cancer may be increased following mass vaccination against the human papillomavirus (HPV) if girls with low vaccine uptake also have low future participation in cervical cancer screening. We evaluated how vaccine uptake distribution affects inequalities in squamous cell carcinoma (SCC) incidence between groups with different screening participation.

Methods: We used an individual-based transmission dynamic model of HPV infection and disease (HPV-ADVISE). Females were stratified by routine screening frequency. We modeled the impact of vaccination on SCC incidence rate differences (absolute inequality) and incidence rate ratios (relative inequality) between women who have routine screening intervals of <5 years (frequently screened), ≥5 years (underscreened), and who are never screened. We compared simulations with uniform vaccine uptake with scenarios with unequal vaccine uptake, in which never and underscreened women have lower vaccine uptake than frequently screened women.

Results: Absolute SCC inequalities between groups with different screening rates were predicted to decrease after vaccination, even when women with the lowest screening participation had the lowest vaccine uptake. Herd effects helped reduce absolute inequalities when vaccine uptake was unequal. Conversely, relative SCC inequalities remained unchanged or increased after vaccination. Results were robust to different overall vaccination coverages and sexual mixing scenarios.

Conclusion: Though mass HPV vaccination is predicted to substantially decrease SCC incidence rates, never screened women will still have the highest disease burden after vaccination.

Impact: To reduce both absolute and relative SCC inequalities, public health initiatives will need to address inequalities in both vaccine uptake and in cervical cancer screening participation.

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Introduction

Significant inequalities exist in cervical cancer incidence and mortality in developed countries. Cervical cancer incidence and mortality rates are higher in ethnic minorities (1–6) and in individuals with low socioeconomic status, low education levels, and living in areas with high poverty (2, 7–12). An important contributor to these inequalities is the differential participation and follow-up in cervical screening programs, either because of differences in health seeking behavior or because of screening and treatment access barriers (3, 13–18).

Vaccination against the human papillomavirus (HPV), the causative agent of cervical cancer, is expected to considerably reduce the incidence of cervical cancer. However, current evidence suggests that in many settings, the sociodemographic determinants of HPV vaccine uptake are similar to those of cervical cancer screening participation. For example, lower HPV vaccine uptake has been reported for ethnic/racial minorities (19, 20) and for children of parents with low education level (21) and low household income or economic status (19, 21–23). These inequalities in vaccine uptake are more often reported for settings with opportunistic or clinic-based vaccine delivery rather than school-based delivery, though unequal vaccine initiation and/or completion is sometimes reported for school-based delivery as well (20, 24, 25). Studies also suggest that mothers with low cervical cancer screening rates are less likely to have their daughters vaccinated against HPV (19, 26), and that unvaccinated girls had lower future intentions to participate in screening (20, 27). This raises the concern that in settings with unequal vaccine uptake there may be an increase in sociodemographic inequalities in cervical cancer incidence (28, 29).

On the other hand, unvaccinated women with low screening participation may indirectly benefit from vaccination due to the reduction in HPV transmission, a phenomenon known as herd effects. For example, recent declines in genital wart diagnoses in young heterosexual Australian men are likely in part due to herd effects from vaccination in young women, as males were not
initially targeted by the Australian HPV vaccine program (30). Herd effects from vaccinated females may also extend to unvaccinated females, as suggested by recent declines in vaccine-type infection prevalence in unvaccinated adolescent girls in the United States (31), where vaccination coverage in males has until now been low (32).

In settings where vaccine uptake is differential by sociodemographic characteristics associated with screening participation, herd effects may counterbalance the impact of unequal vaccine uptake, acting to reduce inequalities in cervical cancer incidence. However, the counterbalancing benefits of herd effects will be highly dependent on sexual mixing patterns in the population. If sexual mixing is assortative according to the sociodemographic determinants of vaccine uptake and screening participation (where individuals choose partners with similar characteristics as themselves, e.g., race/ethnicity and education; refs. 33–36), herd effects and vaccine protection may be restricted to groups with high vaccine uptake and screening participation, increasing inequalities in cervical cancer incidence.

An association between women’s screening behavior and vaccine uptake is predicted to reduce a vaccine program’s overall population-level effectiveness against cervical cancer incidence (19), but no study has yet examined how this association could affect cervical cancer incidence inequalities between groups with different screening behaviors. The objectives of this article are to examine (i) how girls-only HPV vaccination can affect absolute and relative inequalities in cervical cancer incidence between women differing by screening participation, and (ii) the potential impact of herd effects and assortative sexual mixing on inequalities in cervical cancer.

Materials and Methods
Mathematical model

We used HPV-ADVISE, an individual-based transmission-dynamic model of sequential partnership formation and dissolution and natural history of multi-type HPV infection and disease. The model structure, calibration methods, and parameter values are described in detail by Van de Velde and colleagues (37) and in the HPV-ADVISE online technical appendix (http://www.marcbrisson.net/HPVadvise.pdf).

Demographic/behavioral characteristics. The simulated population is heterosexual, open, and stable. Upon entering the population, individuals are stratified by gender, one of four sexual activity levels, and one of five screening behavior levels (S0/S1/S2/S3/S4). The routine screening intervals for respective levels are <2 years, 2 to <5 years, 5 to <10 years, ≥10 years, and never screened. Respective screening behavior levels represent 36%/33%/15%/10%/7% of the population, based on Canadian screening data (38, 39). A woman’s time to her next routine screening visit is sampled from a normal distribution with a level-specific mean and SD.

Natural history of squamous cell carcinoma. Transmission and natural history of progression to squamous cell carcinoma (SCC) are modeled for eighteen individual HPV types, including high oncogenic risk HPV-16 and 18. Individuals have a type-specific infection state: susceptible, infected, or immune. Women in the infected state can clear the infection and return to an immune or susceptible state, or progress to subsequently higher grades of cervical intraepithelial neoplasia (CIN) 1, 2, and 3. Individuals in CIN lesion states may regress to lower CIN grades or regress to the infected, susceptible, or immune states. Women with CIN3 may progress to SCC. In this study, we do not model the progression from HPV infection to adenocarcinoma because declines in invasive cervical cancer since the introduction of screening programs are mainly due to declines in SCC (40–42).

Screening algorithm. Women’s first routine screening visit occurs at an age-specific rate. The model uses Canadian guidelines for management and treatment algorithms for cytology and histology results of screened women (43, 44). The sensitivity and specificity of cytology and colposcopy are lesion grade-specific and based on literature values (45–49). Women with SCC may also develop symptoms and be diagnosed outside of routine screening.

Calibration and validation. The model has been previously calibrated and cross-validated with highly stratified Canadian data on sexual behavior, screening, and HPV natural history (37, 50). Model results were further cross-validated with the screening history of SCC cases by age in Canada (Supplementary Fig. S1; ref. 51). Results are presented as the median (interquartile range) of model predictions from the parameter sets identified through model calibration (Van de Velde and colleagues ref. 37).

Model-based analyses

Model outcomes. For the analyses, we grouped screening behavior levels S0/S1, S2/S3, and S4 and refer to these groups as “frequently screened,” “underscreened,” and “never screened” women, respectively. We analyzed the impact of girls-only vaccination on SCC incidence rates/100,000 women-years stratified by screening behavior level. We ran simulations over 70 years following vaccination to capture the full effects of vaccination on cervical cancer. In analyses, the predicted SCC incidences at 70 years after vaccination are referred to as the “postvaccination” results.

Vaccine efficacy. We based vaccine characteristics on estimates of quadrivalent vaccine efficacy and cross-protection published in a systematic review of HPV vaccine clinical trials (52), as this is the HPV vaccine most often administered in high-income countries with screening programs (53). In the base case scenario, we assumed vaccine efficacy against HPV-16/18/31/33/45/52/58 is 95%/95%/46%/29%/8%/18%/6%, respectively (52). We assumed lifetime duration of vaccine protection in the base case scenario to allow a clearer interpretation of results. However, in sensitivity analyses, we evaluated the impact of a shorter vaccine protection in which each vaccinated individual is given a specific duration of protection sampled from a normal distribution with a mean of 20 (SD, 5) years.

Vaccination strategy, coverage, and vaccine uptake distribution. We modeled a routine 10-year-old girls-only vaccination program, as not many countries yet routinely vaccinate males (53). Here, we define vaccine uptake as the yearly fraction of 10-year-old girls vaccinated in each screening behavior level, and overall vaccination coverage as the yearly fraction of all 10-year-old girls vaccinated. We compared the impact of 50% and 80% overall vaccination coverage, to represent settings with lower (e.g., U.S. 54% for ≥1 dose; ref. 32) and higher (e.g., Australia 83% for ≥1 dose; ref. 54) vaccination coverage. For each overall vaccination
coverage level, we examined three vaccine uptake distribution scenarios (Table 1): (i) uniform vaccine uptake across screening behavior levels, (ii) unequal vaccine uptake, in which women less frequently screened have lower vaccine uptake, and (iii) extremely unequal vaccine uptake, in which women less frequently screened are not vaccinated. For the unequal vaccine uptake scenarios, we calculated vaccine uptake by screening behavior level using ORs of a daughter’s odds of being vaccinated given her mother’s Pap test history (26), as a proxy for girls’ future screening behavior.

Impact of extreme assortative sexual mixing by screening behavior level. Sexual mixing can be assortative by a variety of sociodemographic characteristics (notably educational achievement and ethnicity; refs. 33–36,55), which have been associated with vaccine uptake (19–21, 32) and screening participation (14, 56, 57). Our model does not stratify individuals according to ethnicity or socioeconomic status, and sexual mixing is defined only by age and sexual activity level. Sexual mixing is, thus, independent of screening behavior level in our base case scenario. However, given the potential importance of assortative sexual mixing by sociodemographic characteristics associated with screening behavior, we conducted sensitivity analyses where women of different screening behavior levels and their partners belong to separate, nonintermixing subpopulations (extreme assortative sexual mixing scenarios). This represents an extreme case in which sexual mixing is completely assortative by the sociodemographic determinants of screening participation, and women of different screening behavior levels choose their partners in mutually exclusive pools of men. For example, this could represent an extreme scenario in which individuals only choose partners of the same ethnicity as themselves, and where ethnicity is strongly associated with screening participation. These sensitivity analyses evaluate the maximal impact of assortative mixing on vaccination effectiveness.

Impact of herd effects. To estimate the magnitude of vaccination herd effects, we modified our base model to create a counterfactual scenario, excluding the indirect effects of vaccination previously described in van De Velde and colleagues ref. 50). The impact of herd effects is measured by the difference in predicted vaccine impact between our base model and the modified counterfactual model without herd effects.

Inequality measures. Because absolute and relative measures of inequality may give different results when measuring changes in inequality over time (58, 59), we used both an absolute and relative indicator of inequality, as is recommended (59). We measured absolute SCC inequality using incidence rate differences and relative SCC inequality using incidence rate ratios, with frequently screened women as the reference category for both measures. Although the incidence rate ratio and difference are generally used as measures of association in the epidemiologic literature (60), they are also widely used as straightforward measures of inequality (59). Inequalities are presented as the median incidence rate difference and the median incidence rate ratio over predictions from all parameter sets.

Results

Prevaccination inequalities

Before vaccination, never screened women in the model had an extremely high SCC incidence rate [50.1 (32.2–63.6)/100,000 women-years] with lower incidence rates in underscreened and frequently screened women [5.8 (5.3–6.3) and 1.0 (0.7–1.1)/100,000 women-years, respectively; Fig. 1]. In absolute terms, the incidence rate of SCC among underscreened and never screened women was higher by 5.0 (4.3–5.7) and 49.1 (31.1–62.8) SCC/100,000 women-years compared with frequently screened women, respectively. This corresponds in relative terms to 6.1 (5.0–6.9) and 47.1 (27.5–55.6) times greater SCC incidence in underscreened and never screened women compared with frequently screened women, respectively.

Vaccination effectiveness by vaccine uptake distribution

Figure 1A and B show the predicted impact of vaccination with different HPV vaccine uptake distributions by screening behavior level on SCC incidence rates 70 years after vaccination, assuming

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Table 1. Vaccine uptake distribution scenarios

<table>
<thead>
<tr>
<th>Vaccine uptake distribution</th>
<th>Model Screening behavior level</th>
<th>Proportion of women</th>
<th>Uptake at 50% overall vaccination coverage</th>
<th>Uptake at 80% overall vaccination coverage</th>
<th>Analysis Screening behavior level groups</th>
<th>Uptake at 50% overall vaccination coverage</th>
<th>Uptake at 80% overall vaccination coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform</td>
<td>S0 36%</td>
<td>50%</td>
<td>80%</td>
<td>Frequently screened (&lt;5 years)</td>
<td>50%</td>
<td>80%</td>
<td></td>
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<tr>
<td></td>
<td>S1 33%</td>
<td>50%</td>
<td>80%</td>
<td>Underscreened (&lt;5 years)</td>
<td>50%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S2 15%</td>
<td>50%</td>
<td>80%</td>
<td>Never screened</td>
<td>50%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S3 10%</td>
<td>50%</td>
<td>80%</td>
<td>Frequently screened (&lt;5 years)</td>
<td>55%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S4 7%</td>
<td>50%</td>
<td>80%</td>
<td>Underscreened (&lt;5 years)</td>
<td>45%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>Unequal</td>
<td>S0 36%</td>
<td>55%</td>
<td>85%</td>
<td>Never screened</td>
<td>25%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S1 33%</td>
<td>55%</td>
<td>85%</td>
<td>Frequently screened (&lt;5 years)</td>
<td>74%</td>
<td>100%</td>
<td></td>
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<tr>
<td></td>
<td>S2 15%</td>
<td>45%</td>
<td>77%</td>
<td>Underscreened (&lt;5 years)</td>
<td>0%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S3 10%</td>
<td>45%</td>
<td>77%</td>
<td>Never screened</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S4 7%</td>
<td>25%</td>
<td>57%</td>
<td>Frequently screened (&lt;5 years)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

*Group-level vaccine uptake is the weighted average of constituent screening level vaccine uptakes: \(\frac{\text{Uptake at 50% overall vaccination coverage}}{\text{Proportion of women in level}}\) and \(\frac{\text{Uptake at 80% overall vaccination coverage}}{\text{Proportion of women in level}}\).
that sexual mixing is independent of screening behavior level (not associated with sociodemographic determinants of screening). Interestingly, our model predicted that never screened women would have the largest absolute SCC incidence rate reduction out of all screening behavior levels, for all vaccine uptake distribution scenarios, even the extremely unequal vaccine uptake scenario. However, vaccination effectiveness among never screened women was greatest in the uniform vaccine uptake scenario. Compared with never screened women, the vaccine uptake distribution had smaller absolute impacts on vaccination effectiveness among underscreened and frequently screened women. Similar patterns were observed with lower (50%) and higher (80%) overall vaccination coverage.

Impact of extreme assortative sexual mixing
Our model predicted that, with unequal vaccine uptake, extreme assortative mixing by screening behavior level would result in lower vaccination effectiveness among never screened and underscreened women compared with independent mixing (Fig. 1). However, even with extreme assortative mixing by screening behavior level, unequal vaccine uptake was still predicted to produce a substantial absolute reduction in the SCC incidence rate of never screened women (Fig. 2). This was because never screened women still benefited from both direct protection and within-group herd effects. However, when vaccine uptake was extremely unequal (with only frequently screened women vaccinated), vaccination had no impact on never screened women. This was because they were not vaccinated and did not benefit from herd effects of vaccination (due to extreme assortative sexual mixing). Similarly, underscreened women did not benefit from vaccination when they had 0% vaccine uptake. Sexual mixing patterns had a similar qualitative impact with lower (50%) and higher (80%) overall vaccination coverage.

Contribution of vaccination herd effects
Figure 3 shows the predicted SCC incidence rate reduction attributable to direct and herd effects by screening behavior level,
assuming that sexual mixing is independent of screening behavior level. In uniform vaccine uptake scenarios at 50% overall vaccination coverage, herd effects accounted for a similar proportion of the SCC incidence rate reduction across screening behavior levels (approximately 29%). However, in unequal vaccine uptake scenarios, a larger proportion of the SCC incidence rate reduction was due to herd effects for underscreened (43%) and never screened women (66%) compared with frequently screened women (37%). In extremely unequal vaccine uptake scenarios, herd effects accounted for the entirety of the SCC incidence rate reduction in never screened women. Results were similar using 50% and 80% overall vaccination coverage, although the proportion of the rate reduction attributable to herd effects decreased with increasing coverage. This was because there were greater direct effects with higher overall vaccination coverage, and thus less potential for herd effects.

**Absolute and relative SCC inequalities**

Figure 4 contrasts the predicted change in absolute and relative inequalities postvaccination to prevaccination levels (dashed line) using the incidence rate difference and incidence rate ratio. Following vaccination, the absolute SCC incidence rate difference between never screened women and frequently screened women decreased from the prevaccination incidence rate difference in most scenarios (prevaccination incidence rate difference, 49.1/100,000 women-years; postvaccination range, 13.6–38.5/100,000 women-years; Fig. 4). The only exception was the scenarios combining extremely unequal vaccine uptake with...
extreme assortative sexual mixing by screening behavior level in which incidence rate differences did not change much (postvaccination incidence rate difference, 51.6–51.7/100,000 women-years). A similar pattern was observed for underscreened women, although the absolute effects were smaller than for never screened women. Higher overall vaccination coverage produced greater postvaccination decreases in SCC incidence rate differences between screening behavior levels, whereas a shorter duration of vaccine protection lead to smaller postvaccination decreases in SCC incidence rate differences between screening behavior levels (Supplementary Fig. S2A and S2B).

Conversely, the SCC incidence rate ratio for never screened women versus frequently screened women did not change much following vaccination in uniform vaccine uptake scenarios (prevaccination incidence rate ratio of 47.1; postvaccination incidence rate ratio range, 45.7–50.7), as all groups benefited from the same direct vaccine protection and had similar herd effects. The SCC incidence rate ratio increased in unequal and extremely unequal vaccine uptake scenarios (postvaccination incidence rate ratio range, 55.9–186.3). The SCC incidence rate ratio for underscreened women versus frequently screened women did not change much following vaccination in uniform and unequal vaccine uptake scenarios (prevaccination incidence rate ratio, 5.0; postvaccination incidence rate ratios range, 5.7–6.9), but increased with extremely unequal vaccine uptake (postvaccination range, 10.7–22.2). Higher overall vaccine coverage tended to increase SCC incidence rate ratios due to the increased effectiveness in frequently screened women. A shorter duration of vaccine protection lead to smaller increases
in relative SCC incidence rate ratios after vaccination (Supplementary Fig. S2C and S2D).

Discussion

Important sociodemographic inequalities in cervical cancer have been associated with differential participation and follow-up in cervical cancer screening (3, 13–17), and will in the long term be influenced by HPV vaccine uptake across subpopulations. Our modeling results suggest that absolute differences in SCC incidence rates between groups with different screening participation will likely decrease, as vaccination leads to strong absolute reductions in SCC incidence rates in never screened women even when they have a lower vaccine uptake. Our results also suggest that herd effects are likely to play an important role in reducing the negative impact of unequal vaccine uptake, increasing vaccination effectiveness in groups with lower vaccine uptake. However, vaccination is unlikely to completely remove absolute differences in SCC incidence rates, given the high burden of cervical cancer in never screened women and the number of cervical cancers not attributable to vaccine types HPV-16/18. Conversely, relative SCC incidence rate ratios between groups with different screening participation may increase following vaccination if vaccine uptake is unequal. This suggests that, to prevent increases in relative inequalities in cervical cancer and maximize reductions in absolute inequality, vaccination programs should strive to achieve the highest possible vaccination coverage in underscreened populations.

It is not unusual for absolute and relative measures of inequality to give conflicting results as to how health inequalities evolve over time (59, 61). For example, our results suggest that groups with lower screening participation and low vaccine uptake may see their relative burden of disease increase, even against a backdrop of large absolute decreases in their cervical cancer incidence rates. The choice of indicator to use for monitoring health inequalities carries implicit value judgments and is a far from straightforward decision (58). Although it is recommended to monitor both absolute and relative inequality (59), epidemiologic studies tend to predominantly report relative inequalities (62). However, an exclusive focus on relative inequalities would miss the important absolute reductions in cervical cancer inequalities that may be achieved through vaccination. Our results suggest that cervical cancer screening will remain an important determinant of cervical cancer inequalities between sociodemographic groups following vaccination. Although the proportion of women who are never or underscreened is generally not very large in countries with cervical cancer screening (56, 63, 64), they account for a large proportion of SCC cases (13, 51, 65, 66). In our simulations, vaccination did not fully eliminate absolute SCC incidence rate differences between groups with different screening participation. This reflects the importance of screening in preventing both vaccine-type- and nonvaccine-type–related cervical cancers. Increasing screening effectiveness by improving guidelines and screening methods such as HPV testing may help reduce cervical cancer incidence rates in underscreened women, but will likely have little effect on women who are never screened and have the highest risk of cervical cancer (65, 67–69).

Our scenarios are illustrative and designed to show the impacts of different vaccine uptake distributions across groups with different screening behaviors, which should be generalizable to most high-income countries with cervical cancer screening. The vaccine uptake by screening behavior level in our unequal vaccine uptake scenarios are of the same order of magnitude as has been reported for some sociodemographic groups in high-income countries where unequal vaccine uptake has been reported. For example, in England, a survey reported a three-dose vaccine uptake of 72% in white women and of 55% in black women ages 13 to 19 (70). In Belgium, 43% of women 13 to 18 from the lowest median income quintile neighborhoods compared with 57% of women from the highest median income quintile neighborhoods had initiated HPV vaccination (22). HPV vaccination programs vary in terms of targeted ages; however, it is unlikely that this would substantially affect conclusions given programs generally target individuals before their sexual debut. We limited our main analysis to the quadrivalent vaccine, but as a nonavalent vaccine may be implemented in the future, we performed a sensitivity analysis with our base case scenario using a vaccine with 95% efficacy against HPV-16/18/31/33/45/52/58 (Supplementary Fig. S3; ref. 71). A nonavalent vaccine would decrease absolute SCC inequalities slightly more than the quadrivalent vaccine. However, a nonavalent vaccine would also lead to larger increases in relative SCC inequalities with unequal vaccine uptake. This is because small incidence decreases in frequently screened women (denominator) have a strong impact on the relative burden in never screened women.

We focused our analysis on cervical SCC due to the important inequalities in its incidence (1, 6, 12), against which screening is a strong preventive factor (65, 67–69). For adenocarcinomas that are less well prevented through screening (72), both absolute and relative prevaccination incidence inequalities tend to be smaller (1, 6, 12). Because cervical carcinomas are female-specific, we focused on female-only vaccination. However, sociodemographic inequalities have also been reported for other HPV-related cancers that affect both men and women (73). We did not evaluate vaccination impact in men, but it is likely that male vaccination could also potentially help to decrease absolute inequalities in HPV-related cancers in men. For example, anal cancer has a disproportionately high burden in men who have sex with men (74), who would receive little benefit from a female-only vaccination program.

Assortative sexual mixing according to screening participation could occur where sexual mixing is assortative according to its sociodemographic determinants. Our extreme assortative sexual mixing scenarios reflect the maximum negative impact on vaccination effectiveness of assortativity according to the sociodemographic determinants of cervical cancer screening. These scenarios represent an extreme situation where, for example, members of a racial/ethnic or religious community only have sexual contacts with each other. Such extreme assortativity is unlikely to occur in actual settings, except in the case of communities with strong social prohibitions against exogamy. The impact of vaccination on inequalities is likely to be closer to that predicted assuming independent mixing than assuming extreme assortativity. The sociodemographic factors most well documented as being assortative and thus potentially having the highest likelihood of influencing vaccination effectiveness are ethnicity and education (33–35,55). In high-income countries with growing ethnic diversity, ethnic and religious homogamy has been decreasing in the
past decades (35, 75). Cervical cancer inequalities could also increase if the sociodemographic determinants of vaccine uptake and screening are also determinants of sexual behavior (76).

There are limitations to our analysis. First, as our model does not stratify individuals by socioeconomic strata, we compared groups of women stratified by their screening participation. The advantage of this approach is that it evaluates the direct interaction between vaccination and screening, a fundamental driver of cervical cancer inequalities. However, cervical cancer inequalities between sociodemographic groups instead reflect differences in the distribution of individuals’ screening participation; thus, the impact of vaccination on inequalities between sociodemographic groups will be more moderate than that predicted between screening behavior levels. Second, cervical cancer incidence rates by screening behavior categories are hard to measure empirically; thus, it is difficult to cross-validate our model’s prevaccination SCC incidence rates and inequalities with empirical data. Although the model has been previously cross-validated using cytologic outcomes (see online technical Appendix), for this analysis we also cross-validated model SCC predictions with empirical data on screening histories of SCC cases in Canada (Supplementary Fig. S1; ref. 51). Though model predictions were consistent with SCC cases’ screening histories, the model slightly underestimates the proportion of SCC diagnosed in women with a recent Pap test (<3 years), suggesting that the model might have overestimated prevaccination inequalities due to an underestimation of the SCC incidence rate in frequently screened women. The SCC incidence rate estimated in never screened women is in the range generally reported for cervical cancer incidence rates in developed countries before cytologic screening (77, 78). This suggests that estimated prevaccination SCC inequalities between screening behavior levels, though overestimated, are of the correct order of magnitude.

In conclusion, our model suggests that even if sociodemographic groups with low screening participation rates have a lower vaccine uptake, vaccination is predicted to reduce absolute SCC incidence rate differences between groups with different screening participation. This is because the high absolute SCC burden in women who are underscreened or never screened is predicted to be substantially reduced through direct vaccine protection and herd effects. Nevertheless, women with low screening participation are still predicted to have an important burden of SCC after vaccination even if they have the same vaccine uptake as other women. Relative SCC inequalities may increase in settings in which groups with lower screening participation also have lower vaccine uptake. Preventing increases in relative inequality will require vaccination programs to achieve high vaccination coverage in groups that are underscreened. Because absolute and relative inequalities in cervical cancer may evolve differently over time, public health officials should look at the impact of vaccination on both absolute and relative measures of inequality. Women with low screening participation represent an important proportion of diagnosed SCC cases and are still predicted to have high SCC incidence rates after vaccination. Public health initiatives seeking to profoundly reduce both absolute and relative cervical cancer inequalities will, thus, need to address inequalities both in vaccine uptake and in cervical cancer screening participation.

Disclosure of Potential Conflicts of Interest

In the past 3 years, M. Brisson received an unrestricted grant from Merck Frost related to Zoster burden of illness (no grants ongoing). M. Drolet has consulted for GlaxoSmithKline for the herpes zoster vaccine. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Authors’ Contributions

Conception and design: T. Malagón, M. Brisson
Development of methodology: M. Drolet, M.-C. Boily, M. Brisson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Malagón, M. Brisson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Malagón, M. Drolet, M.-C. Boily, J.-F. Laprise, M. Brisson
Writing, review, and/or revision of the manuscript: T. Malagón, M. Drolet, M.-C. Boily, J.-F. Laprise, M. Brisson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Brisson
Study supervision: M. Brisson

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