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Estimating the Age of Disease-causal HPV Infection Based on the Natural History of CIN2+ Among Females in Canada

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Background. Although human papillomavirus (HPV) vaccination is approved for males and females up to 45 years of age in Canada, not all of the jurisdictions offer catch-up programs up to age 26. However, US-based modeling studies suggest a significant proportion of causal HPV infections leading to high-grade cervical intraepithelial neoplasia (CIN+) and cervical cancer occur in women older than age 26 years. To inform vaccination policies in Canada, this study estimated the age distribution of putatively causal HPV infections leading to CIN2+ based on the natural history.

Methods. We modified an existing discrete event simulation model to estimate the age of causal HPV infection for females diagnosed with CIN2+. Simulated females (n = 1000) were tracked through 3 stages while undergoing screening: causal HPV infection, CIN2+ disease onset, and diagnosis. We identified the age distribution for causal infections that best fit the observed age distribution for CIN2+ diagnosis. Ten independent model runs were conducted to assess reproducibility.

Results. The predicted median age at causal HPV infection and CIN2+ diagnosis in Canada was 24.9 (95% confidence interval, 24.3-26.1) and 29.8 years (95% confidence interval, 28.8-30.6), respectively. The model estimated that 84.1% and 47.1% of causal HPV infections occurred in women older than age 18 and 26 years, respectively. Results were stable across 10 model runs.

Conclusions. The analysis indicates a substantial percentage of causal HPV infections for CIN2+ occur among women aged 26 years or older. Extending catch-up vaccination programs to women above age 26 years should be considered to prevent these infections and reduce HPV-related cervical diseases.

Keywords. Canada; cervical intraepithelial neoplasia (CIN); disease-causal infection; human papillomavirus (HPV); median age of causal infection.

Cervical cancer is the fourth most common tumor in women worldwide and is by far the most common human papillomavirus (HPV)–related disease in females. About 99.7% of cervical cancer cases are caused by persistent genital high-risk HPV infection [1]. High-risk HPV genotypes cause precancerous cervical dysplastic lesions known as cervical intraepithelial neoplasia (CIN), which may lead to cancer [2]. In 2020, Canada's crude cervical cancer incidence rate was 7.5 per 100 000 women, with 380 cervical cancer–related deaths reported [3].

To address the risks of cervical cancer and other HPV-causing cancers, several Canadian societies have recommended HPV vaccination. In 2007, the National Advisory Committee on Immunization (NACI) originally recommended the use of the quadrivalent (4vHPV) vaccine for females aged 9 to 26 years [4, 5]. Subsequently, in 2012, the committee extended the use of the 4vHPV vaccine to males aged 9 to 26 years. Further updates to the recommendations were made in 2016, when NACI endorsed the use of the 9vHPV vaccine for both males and females [6]. In the updated recommendations, NACI states that 9vHPV vaccine may be administered to women and men 27 years of age and older at ongoing risk of exposure. No upper age limit was set by NACI. The Canadian Cancer Society recommended the use of HPV vaccination for females aged 9 to 45 years and males aged 9 to 26 years [7], whereas the Canadian Society of Otolaryngology-Head and Neck Surgery recommends the use of HPV vaccination for females and males aged 9 to 45 years [8]. Additionally, the Canadian Pediatric Society recommended using the HPV vaccine for males and females aged 13 years and older as part of a catch-up program [9].

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Although all Canadian jurisdictions offer publicly funded HPV immunization programs that cover individuals up to 18 years of age, only some cover women up to 26 years of age. As a result, vaccination rates are much lower for women above age 18 years [6]. According to the 2009 Canadian Partnership Against Cancer reports, roughly half of the high-grade cervical intraepithelial neoplasia (CIN2+) cases were diagnosed among women 30 years of age or older and 20% among women 40 years of age or older [10]. Given this information regarding the age of diagnosis, the question remains as to the extent to which causal HPV infections leading to CIN2+ occur among women above age 18 and 26 years in Canada.

Several modeling studies conducted in the United States have shown a significant proportion of causal HPV infections leading to CIN2+ and cervical cancer occur in women aged 27 to 45 years [11,12]. Similar analysis with Canadian data is still lacking. Thus, the objective of this study is to estimate the age distribution of disease-causal HPV infections for CIN2+ in Canada.

METHODS

Model Structure

A discrete event simulation model previously developed by Prabhu et al [11] was used to predict the distribution for age at causal HPV infection for CIN2+, age at disease onset, and age at CIN2+ diagnosis based on the natural history of CIN2+ and screening practices in Canada. The original model was enhanced by including additional functionality by (1) increasing the maximum number of lifetime screens, (2) allowing screening inputs to be based on the probability of screening in a year by age, (3) incorporating alternative distributions for the time from causal infection to CIN2+ onset, and (4) incorporating stability and scenario analyses to test the reproducibility and robustness of the results. In addition, an automated grid search was added to identify the offset that yields the best fit between the predicted and observed age distribution for CIN2+ diagnosis.

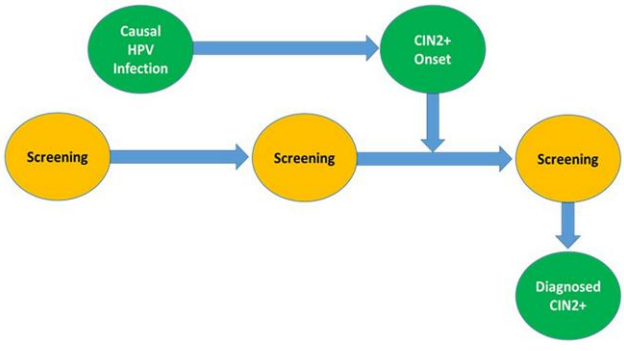

Figure 1. Discrete event simulation model structure. Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

The model simulates 1000 females who are diagnosed with CIN2+. For each female, the age at causal HPV infection, at CIN2+ onset, and at CIN2+ diagnosis is captured (Figure 1). The age at causal HPV infection is assumed to follow a distribution with shape similar to the observed age distribution for CIN2+ diagnosis, except that it is shifted to an earlier age by a fixed "offset." The shifted distribution is then used to obtain the age at causal HPV infection for the simulated females. For each simulated female, time from causal infection to CIN2+ onset is randomly drawn from a distribution based on the natural history of HPV infection.

Once CIN2+ onset occurs, local data on cervical cancer screening rates by age and sensitivity of the screening method are used to determine the age of CIN2+ diagnosis—the age at which the first true-positive screening test occurs—for each simulated female. If a simulated female reaches the maximum age for screening and has not yet been diagnosed with CIN2+, the model assumes diagnosis will occur at an unknown later age through means other than routine screening. The model records the total number of simulated females for whom diagnosis is predicted to occur after the last age of screening.

A grid search was used to identify the optimal offset that yielded the best fit (based on a χ^2 goodness-of-fit criteria) between the predicted and real-world age distribution of CIN2+ diagnosis. Based on this optimal offset, the median age of causal infection, CIN2+ onset, and CIN2+ diagnosis for the 1000 simulated females were estimated along with the corresponding 95% confidence intervals (CI). To assess the reproducibility of the base case results in terms of inter-variation between simulations, we ran the model a total of 10 times using a different set of random numbers for the simulated females.

Model Inputs

The number of incident CIN2+ cases by age was sourced from the Canadian Partnership Against Cancer Program Performance Results Report [10]. CIN2+ was defined as a diagnosis of CIN 2 (moderate dysplasia), CIN 3 (severe dysplasia), or cervical carcinoma in situ; adenocarcinoma in situ (AIS) cases were excluded. Data from 2009 were utilized because vaccination would not yet have influenced the age distribution for women who progressed to CIN2+ (see Table 1).

Table 1. Number and Cumulative Distribution of CIN2+ Cases by Age Category

Age Category, y	Number of Cases	Cumulative Distribution
20-29	3148	50.4%
30-39	1793	79.1%
40-49	876	93.1%
50-59	294	97.9%
60-69	134	100.0%

Abbreviation: CIN, cervical intraepithelial neoplasia.

Table 2. Annual Screening Rates by Age Category

Age Category	Screened During Year
18-19	35.8%
20-24	56.4%
25-34	60.8%
35-44	53.4%
45-54	48.7%
55-64	43.1%
65-69	31.9%

Abbreviations: CIN, cervical intraepithelial neoplasia.

Source: Statistics Canada—Canadian Community Health Survey, 2005 [15].

Consistent with Prabhu et al [11], time from causal infection to CIN2+ onset for each simulated female was randomly draw from a gamma (1,1) distribution following a fixed 0.5-year minimum period. This distribution was based on the VIVIANE bivalent HPV (2vHPV) vaccine clinical trials [13] and the FUTURE I 4vHPV vaccine clinical trials [14], where approximately 50% of the infections progressed to CIN2+ within 1.5 years.

Detection of CIN2+ in the model requires data on the rate of screening and the sensitivity of the screening test. In 2005, the Pap test was the only method used in Canada for cervical cancer screening. The percentages of women screened are based on 2005 data from Statistics Canada (see Table 2) [15]. We assumed screening practices did not change between 2005 and 2009, when the diagnosis data were obtained. For each simulated female, the model randomly determines whether screening takes place in a given year based only on their age. If screening occurs, the fractional age in which it takes place is determined, with the constraint that a minimum of 1 year is assumed between screening tests. A sensitivity of 55.4% was used for Pap tests in the model [16].

Sensitivity Analyses

Two sets of sensitivity analyses were conducted concerning the time from causal infection to CIN2+ onset. In the first case, we noticed that not all of the persistent infections had progressed to CIN2+ or cleared by the end of the 3-year follow-up period in the FUTURE I study. Therefore, we refit the gamma distribution using data from FUTURE I [14] and assuming a proportion of females with persistent infections or CIN1 at 3 years would have progressed to CIN2+ after 3 years. The resulting distributions for the time from causal infection to CIN2+ onset included in the sensitivity analysis are as follows:

0% progress to CIN2+ after 3 years: 0.5 + gamma (0.7, 1.1),
5% progress to CIN2+ after 3 years: 0.5 + gamma (0.5, 2.0),
10% progress to CIN2+ after 3 years: 0.5 + gamma (0.5, 2.75), and
20% progress to CIN2+ after 3 years: 0.5 + gamma (0.5, 4.0).

An exponential distribution with a lambda of 1.2 was also explored to allow flexibility in choosing an alternate parametric distribution. Supplementary Appendix Figure A1 shows the alternative cumulative distributions.

In the second sensitivity analysis, we allowed the time from causal infection to CIN2+ onset to depend upon the female's age of causal infection. We assumed the gamma (1,1) distribution used in the base case applied to females with a causal infection at 20 years of age based on the mean age of females entering the FUTURE 1 study [14]. Women with causal infections earlier/later than age 20 years progressed faster/slower than women at age 20 years using the following equation: 0.5 years + gamma (a + b*age, 1) where a is calculated to ensure a gamma (1,1) distribution is assigned for a 20-year-old female, $b \geq 0$, and age is the age of causal infection. In this sensitivity analysis, the model was run using each of the following distributions to reflect an increasing influence of age on the time from infection to onset (in years):

b = 0.025: 0.5 + gamma (0.5 + 0.025*age, 1),
b = 0.05: 0.5 + gamma (0.0 + 0.05*age, 1),
b = 0.1: 0.5 + gamma (−1.0 + 0.1*age, 1), and
b = 0.2; 0.5 + gamma (−3.0 + 0.2*age, 1).

The cumulative distribution of time from causal infection to CIN2+ onset are shown for each scenario in Supplementary Appendix Figure A2.

RESULTS

Among the 1000 simulated females, the predicted median age of causal HPV infection was 24.9 years (95% CI, 24.3-26.1 years), with the best fitting offset of 5.2 years suggesting that the age of causal infections is approximately 5 years earlier than the age for CIN2+ diagnosis in Canada. About 84.1% and 47.1% of the causal infections occur in females above age 18 years and 47.1% above age 26 years, respectively (see Table 3); the percentage of causal HPV infections that occur after any given age is provided in Supplementary Appendix Figure A3. The cumulative age distribution for causal infection and the predicted and observed age distribution for CIN2+ diagnoses are shown in Figure 2*A* (see Figures 2*B* and 2*C* for graphs for the distributions by age group). The model predicted the median age of CIN2+ diagnosis of 29.8 years (95% CI, 28.8-30.6 years), which closely aligns with the real-world data for Canada where 50.4% of the CIN2+ diagnoses occurred before age 30 years. As shown in Figure 2*C*, the model appears to slightly overpredict the number of CIN2+ diagnoses among females <30 years of age (by 0.8%) and >40 years of age (by 1.1%).

From the stability analysis, the median age of causal infection ranged from 24.5 to 26.0 years across 10 independent runs of

Table 3. Base Case and Sensitivity Analysis Results: Predicted Median Age of Causal Infection and CIN2+ Diagnosis for Canada (Years)

Scenario	Causal Infection		CIN2+ Diagnosis
	Median (95% CI)	% Older Than Age 26 y	Median (95% CI)
Base case	24.9 (24.3-26.1)	47.1%	29.8 (28.8-30.6)
Sensitivity analysis: time to CIN2+ onset by % of censoring of CIN2+ cases in FUTURE I			
0% censoring: 0.5 + gamma (0.7-1.1)	25.0 (24.4-26.2)	47.4%	29.7 (28.7-30.4)
5% censoring: 0.5 + gamma (0.5-2.0)	24.6 (24.0-25.8)	46.2%	29.8 (28.8-30.6)
10% censoring: 0.5 + gamma (0.5-2.75)	23.7 (23.1-24.9)	44.3%	29.3 (28.3-30.3)
20% censoring: 0.5 + gamma (0.5, 4.0)	22.9 (22.3-24.0)	42.0%	29.0 (28.0-30.0)
Sensitivity analysis: 0.5 + exponential (1.2)	25.1 (24.2-26.2)	47.5%	29.8 (28.8-30.6)
Sensitivity analysis: time to CIN2+ onset dependence on age of infection			
b = 0.025: 0.5 + gamma (0.5 + 0.025*age, 1)	25.1 (24.6-26.2)	47.4%	30.0 (29.6-30.9)
b = 0.05: 0.5 + gamma (0 + 0.05*age, 1)	25.0 (24.5-26.1)	47.0%	30.0 (29.6-30.9)
b = 0.1: 0.5 + gamma (−1.0 + 0.1*age, 1)	24.8 (24.2-25.8)	45.7%	30.1 (29.7-30.9)
b = 0.2: 0.5 + gamma (−3.0 + 0.2*age, 1)	24.1 (23.6-25.0)	43.9%	29.9 (28.9-30.7)

Abbreviation: CI, confidence interval.

the model, with the percentage of causal infections occurring among females aged 26 years or older ranging from 46.3% to 49.9% (see Supplementary Table A1 in the Supplementary Appendix). Supplementary Figures A4A and A4B in the Supplementary Appendix show the cumulative distributions for the age of causal infection and of CIN2+ diagnosis for the 10 runs.

Sensitivity analyses explored the impact of uncertainty in the distribution of time from causal infection to CIN2+ onset on the median age of causal infection. In the first analysis, the distributions used to model time from infection to CIN2+ onset were varied based on the assumed degree of censoring of CIN2+ cases in the FUTURE I trial. As the assumed percentage of censoring increased, the median time from causal infection to CIN2+ onset also increased (see Supplementary Appendix Figure A1). Consequently, the median age of causal infection decreased as censoring increased, with the median youngest age of HPV infection was 22.9 years, when assuming 20% censoring (see Table 3). Even in this case, 42% of the infections occurred in females aged 26 years or older. Results based on the exponential distribution were similar to the scenario with 0% censoring.

Finally, the sensitivity analysis incorporating age dependence on the time from causal infection to CIN2+ onset showed improvement in the model fit (Supplementary Figure A5 in the Supplementary Appendix), particularly in the scenario with b = 0.05. As the degree of dependence on age increased, the median age of causal infection decreased from 25.1 to 24.1 years, and the percentage of causal infections among females aged 26 years of age or older decreased from 47.4% to 43.9% (see Table 3).

DISCUSSION

A discrete event simulation model developed by Prabhu et al (2021) was extended and used to estimate the age distribution and median age of causal HPV infection for CIN2+ in Canada during the prevaccine era [11]. Based on the Canadian inputs, our model predicted the median age of causal infection and CIN2+ diagnosis was 24.9 and 29.8 years, respectively, with 84.1% of the infections that progress to CIN2+ occurring in females aged 18 years or older and 47.1% occurring after 26 years of age. The results from the model were reproducible when running the model multiple times with independent sets of 1000 simulated females. With each run of the model, results for the median age of causal infection, median age of CIN2+ diagnosis, and the percentage of causal infections occurring in females 26 years or older all fell within the corresponding 95% CI from the base case analysis.

The distribution for the predicted age of CIN2+ diagnosis was found to fit well with the observed data in Canada. Comparison versus estimates from Prabhu et al 2021 [11] suggests the age of causal infection and CIN2+ diagnosis were slightly higher in Canada than in the United States (median age of 24.9 vs 23.9 years for causal infection and 29.8 vs 28.0 years for CIN2+ diagnosis). This difference of about 1 to 2 years between the United States and Canada is not unexpected due, in part, to differences in sexual practices. According to the 2015/2016 Canadian Community Health Survey, 55.2% of females were sexually active in the 15- to 24-year age group [17]. In the United States, 74% of females have their sexual debut by age 17 years [18]. Consequently, females in the United States would be more likely to become infected with HPV at an earlier age and thus more likely to have a persistent infection that progresses to CIN2+ at an earlier age.

The median age at causal HPV infection resulting in CIN2+ in Canada study is slightly lower than the estimate by Burger et al [12] of 25.1, 25.4, and 27.9 years for the UMN-HPV CA, Harvard, and Policy 1-Cervix simulation models, respectively, when imperfect compliance (more representative with real world) with the US screening guidelines was assumed [12]. However, these estimates were consistent with Prabhu et al.

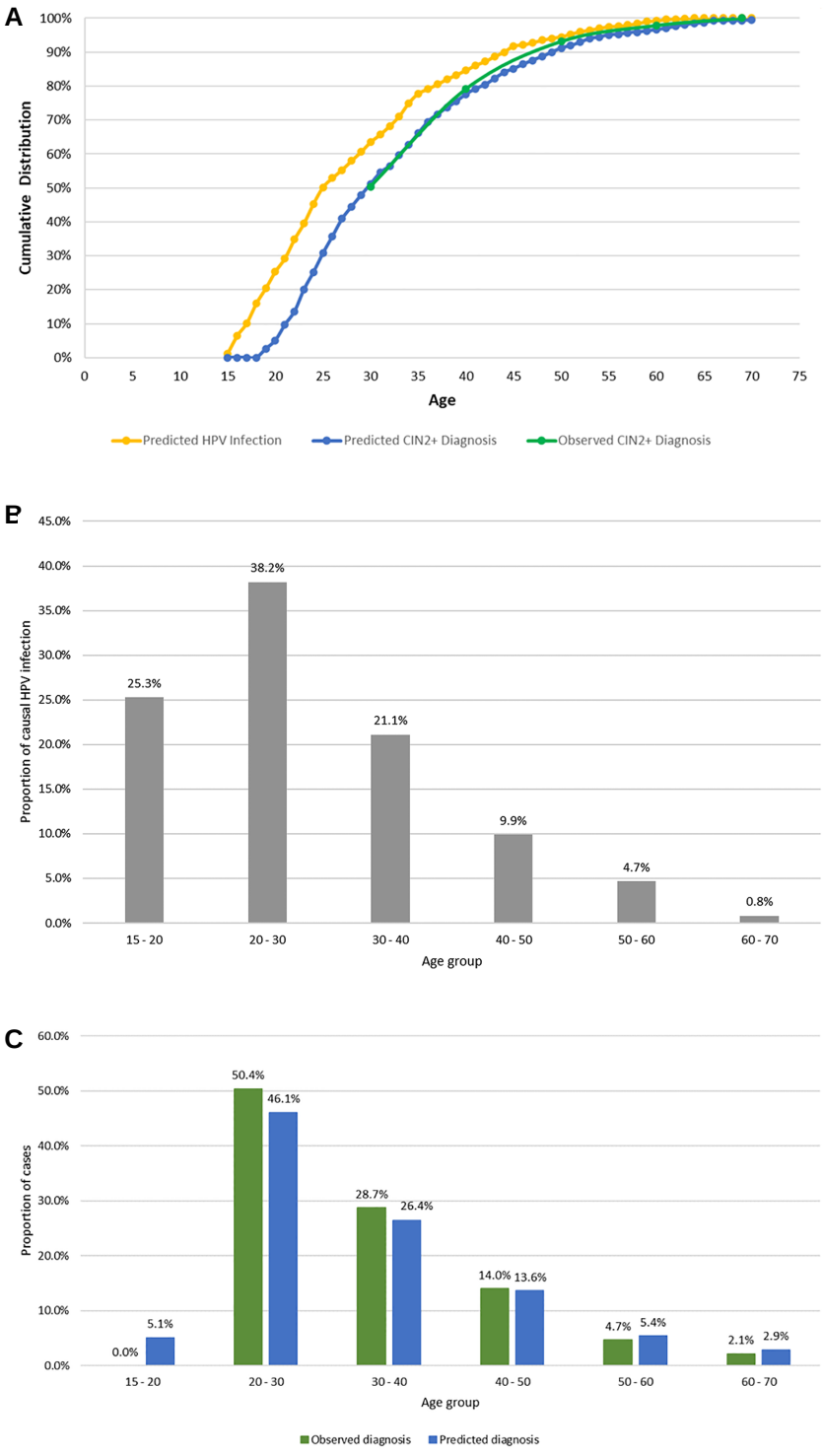

Figure 2. Base case results for age of causal infection and CIN2+ diagnosis. (*A*) Cumulative distribution for age of causal HPV infection and CIN2+ diagnosis. Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus. (*B*) Predicted proportion of causal HPV infections acquired by age category. (*C*) Predicted and observed proportion of CIN2+ diagnoses by age category*. *0.5% of the predicted diagnoses occur after age 70 years.

The key difference is that Burger et al estimated the median age at causal HPV infection resulting in cervical cancer instead of CIN2+ Additionally, a common definition for CIN2+ was not used in the real-world studies where the age distribution of CIN2+ cases were obtained. In Canada, CIN2+ included CIN2, CIN3, and cervical carcinoma in situ (excluding AIS) cases,

whereas CIN2+ included CIN2, CIN2/3, CIN3, and AIS cases in the United States. It could also lead to differences in the median age between the United States and Canada.

A critical component in estimating the age of causal infections is the distribution of time from causal infection to CIN2+ onset. Although the base analysis utilized the placebo arm from 2 reputable studies—VIVIANE and FUTURE 1 [13, 14]—to estimate this distribution, 2 sets of sensitivity analyses around this parameter were conducted. In the first sensitivity analysis, the potential impact of censoring in the FUTURE 1 trial was explored. Here, the distribution was refit under alternative assumptions regarding the percentage of females at risk of progression at the end of follow-up (eg, who had a persistent infection that had not yet cleared or progressed within 3 years) who would have progressed to CIN2+ had they continued to be followed. Although the percentage is unknown, the model was rerun with values ranging from 0% to 20% to reflect increasing time from causal infection to CIN2+ onset. Results of the analysis showed the median age of causal infection decreased as the censoring percentage increased, shifting from 25.0 to 22.9 years of age. Although the percentage of causal infection to occur in females aged 26 years or older also decreased, the percentage remained fairly high (at 42%) even when assuming 20% censoring.

We also relaxed the simplifying assumption that time from causal infection to CIN2+ onset does not depend on the age of causal infection. Although there is evidence to suggest the time from causal infection to onset might be longer for females whose causal infection occurs at a later age, the strength of this relationship is not well understood [13]. Consequently, we explored several cases where the impact of age on the time from causal infection to CIN2+ onset increased. In the base case, the time from causal infection to CIN2+ onset was the same for females regardless of whether the causal infection was at ages 20 or age 40 years, for example. By incorporating age dependence in the scenario analysis, the time to CIN2+ onset now differs for causal infections at ages 20 and 40 years by a median of 0.5, 1, 2, and 4 years (for values of $b = 0.025$, 0.05, 0.10, and 0.20, respectively). Results from this analysis suggested that as the strength of the relationship increased, the median age of causal infection decreased (shifting from 25.1 years to 24.1 years). In addition, we found a shift to a higher concentration of causal infections were predicted to have occurred between the ages of 20 and 30 years, with fewer causal infections occurring among females 40 years of age or older (see Supplementary Appendix Figure A6). Nevertheless, more than 40% of the predicted causal infections continue to occur among females older than 26 years of age.

Although the model provides a unique way to combine clinical data on the time from causal infection to CIN2+ onset and Canadian-specific data on screening behavior and the age distribution of CIN2+ diagnosis, the current model does have certain limitations. First, the model does not incorporate HPV genotypes in the analysis. Thus, geographic differences in the distribution of HPV genotypes could not be accounted for; therefore, questions remain regarding the potential impact this might have on the speed at which causal infections progress to CIN2+. This explains, in part, the reason to not use the model in the postvaccine era, where the distribution of HPV genotypes is likely to shift away from the vaccine types over time. In addition, we conducted extensive sensitivity analyses around the time from causal infection to CIN2+ onset, including the option to allow the time from causal infection to CIN2+ onset to depend upon the female's age of causal infection.

The model assumes cases of CIN2+ are diagnosed only via regular screening. To the extent diagnoses are made through other means for some females such as medical monitoring, the time from CIN2+ onset to diagnosis may be shorter than simulated in this model. Because the method of detection does not impact the underlying time from causal infection to CIN2+ onset, a shorter time from CIN2+ onset to diagnosis would suggest the causal infections are taking place at an older age. Thus, by assuming diagnosis only occurs through regular screening, our model is likely to result in a conservative (lower) estimate of the percentage of infections occurring among females 26 years of age or older. The model also assumes that future screening behavior does not depend on prior screening behavior. Although input data used for screening rates in the model should reflect heterogeneity among women, differences among risk groups or sexual behaviors are not explicitly incorporated.

The model estimates the age of infection for persistent infections that progress to CIN2+ without clearing. Although the present study refers to this as the "causal" infection, the model is not able to determine whether this is the first cervical HPV infection or if the female had prior infection(s) that cleared. And, if the female had a prior infection, the model is not able to determine whether the causal infection was the result of a new infection or a reactivation of an earlier infection. This highlights a gap in our understanding of the natural history of HPV infection. Unfortunately, screening does not differentiate between lesions that result from new acquisition of infection, reinfection from recent sexual experience, and reactivation of an infection after a period of latency [19, 20], necessitating further research in this area.

There are, however, several studies that suggest women older than age 26 years can acquire new HPV infections or may become reinfected after a prior infection clears [21,22]. Even among women who were previously infected, natural infection only provides modest protection against subsequent infection [23] and vaccination in females who are seropositive, but DNA negative, receive significant protection from vaccination [24]. Thus, preventing these infections through vaccination could have a significant impact on decreasing the number of females diagnosed with CIN2+. Based on the present model, we

estimate that as many as 47% of the infections that progress to CIN2+ in Canada occur in females 26 years of age and older, whereas 37% of the causal infections occur between the ages of 18 and 26 years.

Although vaccination of school-aged individuals remains critical to the prevention of cervical cancer, results from our model suggest efforts to strengthen and/or adopt public catch-up programs for females up to age 26 years should be encouraged across all Canadian provinces. In addition, consistent with the NACI recommendation [5], public policy decision makers and private health care providers across Canada should consider extending catch-up vaccination programs to women older than 26 years of age in an effort to further reduce HPV-related cervical diseases.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. A. C., X. Y., Y.-T. C., and C. R. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. E. H., R. S., and B. M. are employees of Merck Canada Inc., Kirkland, QC, Canada, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. M. R., is an employee of Merck Sharp & Dohme GmbH, Munich, GER, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. A. C., X. Y., E. H., R. S., B. M., M. R., Y.-T. C., and C. R. may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. G. B., M. Y., S. G., J. C., and E. F. served as consultants for Merck & Co., Inc., Rahway, NJ, USA.

Author Contributions. All authors contributed to the study conception and design. J. C., G. B., M. Y., and S. G. modified the model developed by Prabhu et al. 2021 [11]. X. Y., A. C., and E. H. provided guidance towards the collection of Canada-specific inputs. The model adaptation for Canada was performed by J. C., G. B., M. Y., and S. G. S. G. and M. Y. wrote the first draft of the manuscript. E. F. reviewed it extensively for coherence with HPV epidemiology. All authors provided strategic guidance to the model adaptation and reviewed and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Data availability. Not all the datasets generated during and/or analyzed during the current study are publicly available due to its proprietary nature. However, the diagnosis data could be validated from publicly available source Canadian Partnership Against Cancer Program Performance Results Report, 2009-2011 [10]. The screening rates can be obtained from Statistics Canada—Canadian Community Health Survey, 2005 [15]. Further information about the data and conditions for access can be obtained from the corresponding author.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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