R E V I E W   A R T I C L E

The road ahead for cervical cancer prevention and control

J.E. Tota MSc,*† A.V. Ramana–Kumar PhD,* Z. El-Khatib PhD,* and E.L. Franco DrPH*†

ABSTRACT

Since the early 1950s, Papanicolaou ("Pap") cytology screening has dramatically reduced cervical cancer mortality in most high-income settings. Currently, human papillomavirus (HPV) vaccination has the greatest potential to reduce the global burden of cervical cancer and precancerous lesions. However, as the prevalence of precancerous lesions declines, maintaining cytology as the primary screening test in settings with established programs might become less efficient. A reduction in test performance (sensitivity, specificity, and positive predictive value) would lead to an increase in unnecessary colposcopy referrals. Fortunately, HPV DNA testing has emerged as a suitable candidate to replace cytology. Compared with the Pap test, HPV testing is less specific but much more sensitive in detecting high-grade precancerous lesions, less prone to human error, and more reproducible across settings. Linkage of HPV vaccination and screening registries could serve the added role of monitoring vaccine efficacy. As a triage test, cytology is expected to perform with sufficient accuracy because most HPV-positive smears would contain relevant abnormalities. This approach and others—for example, HPV testing followed by genotyping—are being evaluated in large population studies and have already been recommended in some settings. Other specific biomarkers that might perform well for screening and triage include HPV E6/E7 messenger RNA testing, methylation of host or viral genes, and p16^{INK4a} staining. Considering the rapid pace of major discoveries and the anticipated arrival of a nonavalent HPV vaccine (currently in phase III trials), the evidence base in this field has become an elusive target and will continue to be an obstacle for policymakers.

KEY WORDS

Cervical cancer, human papillomavirus, vaccination, screening

1. INTRODUCTION

In 1941, Georgios Nicholas Papanicolaou first reported that microscopic evaluation of vaginal smears might be a useful approach for detecting uterine cancer[1]. His work eventually led to the establishment of the Pap smear for cervical cancer screening, which is the primary reason that most high-income countries have witnessed a major decline in cervical cancer mortality[2–4]. More recently, discovery of human papillomavirus (HPV) as a necessary cause of cervical cancer[5] has resulted in new prevention fronts: HPV vaccination and molecular-based screening technologies.

In this article, we discuss current cervical cancer screening and prevention initiatives in North America and the need for a paradigm shift in the screening approach because of the negative impact that vaccination is expected to have on Pap screening performance. We make the argument that HPV testing alone should be adopted as the primary cervical screening test and might serve the added role of monitoring vaccine effectiveness. Ultimately, both HPV vaccination and HPV DNA testing should be viewed as components along the continuum of care for cervical cancer prevention.

2. PAP CYTOLOGY SCREENING

Pap cytology screening has had remarkable success in most high-income countries, but virtually no effect in lower-resource settings. As a result, cervical cancer has now become a sentinel disease of inequality, being much more common in poor countries and in aboriginal populations in Western countries[6,7]. In 2008, more than 85% of cases and of deaths attributed to cervical cancer (530,000 and 270,000 respectively) occurred in developing countries[8].

To be effective, cervical cancer cytology screening programs require complex and costly infrastructure to ensure adequate coverage, quality, and follow-up treatment of precancerous lesions. In

the United States alone, the costs for screening and prevention programs are estimated to amount to roughly US$4 billion annually[9]. Although cytology has very high specificity (~98%), its sensitivity for the detection of cervical intraepithelial neoplasia is only slightly above 50%[10,11]. That figure implies that roughly half the slides from women with cervical lesions will erroneously be classified as negative. Liquid-based cytology (LBC) has some advantages over conventional Pap cytology, including reduced obstruction by extraneous materials and the possibility for ancillary molecular testing; however, it is more costly and still suffers from poor sensitivity. To compensate, screening guidelines in high-income countries have traditionally recommended annual Pap testing for women starting at 18 years of age or shortly after they become sexual active. Recently, U.S. consensus guidelines (issued by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology) and guidelines from the Canadian Task Force on Preventive Health Care were updated, recommending that cytology exams be repeated every 3 years starting at age 21[12] or 25[13] respectively. In women less than 25 years of age, minor cervical abnormalities are very common. However, most of those lesions will regress, and their likelihood of progressing quickly to cervical cancer is extremely low. The decision to increase the age at screening initiation and to extend the intervals between screening was therefore intended to avoid overtreatment and associated adverse outcomes in future pregnancies, and to safely reduce the burden to the health care system[14,15]. The latter point is particularly relevant, considering that roughly 10% of all specimens processed by cytotechnicians in the United States are flagged for abnormalities, requiring additional follow-up or treatment[16].

Unfortunately, the introduction of HPV vaccination in most high-income counties is not expected to immediately improve the screening situation. Rather, in settings in which screening programs are now in place, vaccination is expected to have a major negative effect on the test's positive predictive value (PPV), an important measure used by clinicians that provides a probabilistic value concerning action prompted by a positive test result. As the prevalence of squamous abnormalities (atypical squamous cells of undetermined significance and squamous intraepithelial lesions) attributable to HPV types 16 and 18 declines, the PPV will also substantially decrease[17]. In addition, the sensitivity and specificity of Pap screening might also be adversely affected because of a decrease in the "signal-to-noise" ratio (fewer true squamous abnormalities compared with cases of inflammation and reactive atypia), which could lead to less attention being paid to slides that are generally unremarkable and to more false negatives—or alternatively, to more overcalls of benign abnormalities because of

fear of the false negatives, leading to unnecessary colposcopy referrals[18]. In fact, estimates of Pap sensitivity as low as 35% have been reported in studies conducted in low-risk settings with stringent quality-control standards (Newfoundland and Labrador, and Quebec, for example), providing evidence to support the former prediction[19,20].

Previously, we modelled the expected effect on the PPV of Pap cytology of a decline in lesion prevalence from as high as 50% to as low as 1%, first assuming constant conservative values for sensitivity and specificity (70% and 98% respectively) and then varying those parameters (range: 30%–70% and 95%–98% respectively)[17]. Under both scenarios, but especially the latter (which also took into account decreases in sensitivity and specificity), we found that the vaccine-induced reduction in lesion prevalence would create a screening scenario untenably cost-effective as PPV estimates fell to below 10%. Those projections clearly indicate that, despite the phenomenal success of Pap testing since the early 1950s, we are approaching a point at which primary screening by this approach will no longer be sustainable. Despite low vaccine uptake across the United States[21], the prevalence of vaccine-targeted HPV types has already declined among young women 14–19 years of age (to 5.1% in 2007–2010 from 11.5% in 2003–2006)[22]. In addition, a substantial decline in the incidence of high-grade precancerous lesions has been observed in women 21–24 years of age living in Connecticut (to 688 per 100,000 women in 2011 from 834 per 100,000 women in 2008)[22], reflecting the urgency of adopting an alternative screening approach. The important question now is "What will be the most efficient screening approach post-vaccination?"

3. HPV-BASED AND OTHER PROMISING SCREENING TECHNOLOGIES

In the early 1980s, with investigators well aware of the remote distal connection between sexual activity and cervical cancer, a succession of molecular epidemiologic studies were launched to evaluate the putative role of HPV as the true intermediate endpoint along that casual pathway. Over the course of two decades (that is, as polymerase chain reaction protocols for the detection of HPV DNA continued to become more accurate), risk estimates rose from single to triple digits[23] until investigators were eventually able to conclude with certainty that infection with HPV is necessary for the development of cervical cancer and its precursor lesions[5]. Immediately, scientists recognized the public health implications of that discovery and proceeded with trials comparing HPV DNA testing with Pap cytology in screening for cervical cancer.

In 2007, results from the first North American trial to evaluate HPV DNA testing in the context of cervical cancer screening were published, confirming the belief that this approach is much more sensitive than Pap in

detecting high-grade precancerous lesions (95% vs. 55%). The only trade-off in the equation was a minor reduction in specificity (94% vs. 97%)[24]. It is important to note that the HPV test used in this particular trial was the Hybrid Capture 2 assay (Qiagen, Gaithersburg, MD, U.S.A.), which is capable of detecting (but not distinguishing between) 13 high-oncogenic-risk (HR) HPV genotypes from cervical specimens. All HPV screening assays detect only HR-HPV genotypes, with some, such as the Cobas test (Roche Molecular Systems, Pleasanton, CA, U.S.A.) being capable of detecting HPV types 16 and 18 individually, and a pool of 12 other HR-HPV types. In recent years, a number of other randomized and nonrandomized trials have evaluated HPV testing performance relative to Pap cytology in primary screening. Results from those studies were compiled into a meta-analysis by Cuzick *et al.* in 2008[25] and later updated by Richardson *et al.* in 2011[26], demonstrating that HPV testing has superior sensitivity (ratio: 1.29; 95% confidence interval: 1.18 to 1.39), but lower specificity (ratio: 0.94; 95% confidence interval: 0.92 to 0.96) for the detection of cervical intraepithelial neoplasia grade 2 or worse[26]. To reduce costs and the psychological trauma resulting from unnecessary colposcopy referrals for false-positive HPV tests, investigators are now evaluating more specific triage tests.

One test that might serve this purpose is Pap cytology. Over the years, we have argued that this algorithm (HPV testing with Pap triage) would maximize the properties of both tests while preserving a trained workforce to review smears from an "artificially enriched" HPV-positive population. That approach would also provide cytotechnicians with a smaller case load having a higher lesion prevalence (that is, a higher signal-to-noise ratio) and an overall more rewarding reviewing experience[17,18,26]. To evaluate that approach, a randomized controlled trial (the HPV FOCAL trial) currently underway in British Columbia is comparing triage using HPV testing followed by LBC (Pap) with triage using LBC followed by HPV DNA testing[27]. Results from FOCAL, other similar comparative trials[28], and demonstration projects (implementing HPV testing alone as the primary screening test) will be useful when the time comes once again to update screening guidelines. In considering alternative secondary tests for clinical management decisions after a positive HPV test, experts will be interested in selecting an approach that preserves the high sensitivity of HPV testing (maximizes benefits) and safely leads to a reduction in unnecessary colposcopy referrals (minimizes harms).

Additional biomarkers that are now being considered as triage tests for the management of HPV-positive women include HPV genotyping (HPV 16 or HPV 16 and 18)[29,30], HPV E6 and E7 messenger RNA testing[31], methylation (and consequent silencing) of host and viral genes[32,33], and novel cytologic methods that attempt to identify proliferating cells (for example,

p16^{INK4a} staining)[34]. With the exception of genotyping[35], these molecular technologies have not been directly compared (or compared with cytology), and additional prospective studies are therefore needed to adequately assess their relative performance—for example, specificity for standard endpoints such as cervical intraepithelial neoplasia 3+. For additional information on this topic, readers are referred to a review article by Cuzick *et al.*[36] describing the potential utility of these tests.

3.1 Role of HPV Testing in Current and Future Screening Guidelines

In addition to being more sensitive than cytology, HPV testing is also much more reproducible across settings[37,38]. Testing for HPV is also less prone to human error because it does not rely on human interpretation and requires only minimal quality control and technician training. Furthermore, because persistent infection with HR-HPV types is necessary for invasive cervical cancer to develop, HPV testing safely permits an extension of the screening interval (for example, to 5 years from 3), which is supported by results from a large U.S. screening study that reported identical 5- and 3-year risks for cervical intraepithelial neoplasia 3+ after either a negative HPV test or Pap exam (both 0.17%), and an only slightly lower risk after negative co-testing (5-year risk: 0.16%)[39]. Considering the superior sensitivity, reproducibility, and long-term safety assured by a single negative HPV test, replacing Pap cytology with HPV DNA testing now seems appropriate for primary screening, and yet most professional organizations have not adopted that approach.

The revised U.S. consensus guidelines recommend HPV and cytology co-testing every 5 years for women over the age of 30. But for patients who are HPV-positive and cytology-negative, follow-up with co-testing is recommended after 12 months; otherwise, immediate referral for colposcopy might be recommended if the patient is positive for HPV 16 or 18[12]. Meanwhile, the Canadian Task Force on Preventive Health Care currently makes no recommendation concerning the use of HPV testing, concluding that evidence to suggest that HPV testing will reduce the incidence of, or mortality from, cervical cancer is still lacking, and that the marginal reduction in the risk of precancerous lesions (if used in combination with cytology for co-testing) would not be sufficient to offset the high cost, despite the lengthened screening interval[13]. But not all Canadian provinces have adopted the guidelines. For example, the Ontario Cervical Screening Guideline Working Group recently recommended implementation of HPV testing (with Pap cytology triage) as the primary screening approach, with repeat testing every 5 years until age 65[40]. In Figure 1, we present a generic screening algorithm that encompasses that and other favourable
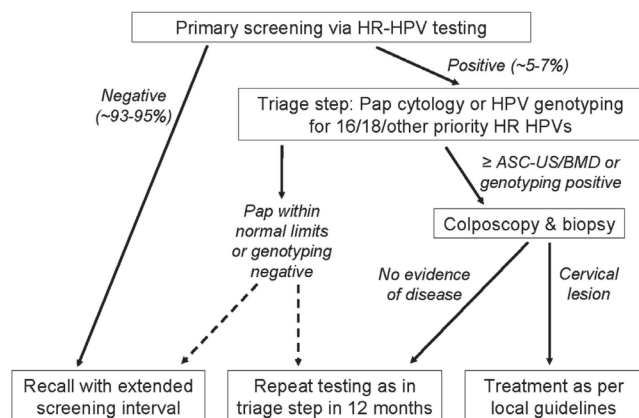
FIGURE 1 *Proposed generic algorithm for opportunistic or organized cervical cancer screening that uses human papilloma virus (HPV) testing as the primary test, followed by triage with Pap cytology or genotyping [HPV 16 and 18 and possibly other high oncogenic risk (HR) HPV types]; modified from Cuzick* et al.*, 2008[25]. The cytologic grade threshold and definition of extended screening interval may vary according to local preferences and be modified as new evidence from screening studies becomes available. ASC-US = atypical squamous cells of undetermined significance; BMD = borderline or mild dyskaryosis.*

approaches—for example, HPV testing followed by genotyping for triage.

Current guidelines present clear discrepancies with respect to the role of HPV testing in cervical screening. Although we expect that HPV testing will eventually become the primary screening approach across North America, many uncertainties still surround its implementation: for example, the most appropriate triage test; the screening interval; the management strategy for HPV-positive, Pap-negative women; and the optimal age to initiate or discontinue screening (Table I). To prevent confusion and "cherry-picking" of the recommendations to follow, policy officials should work together to evaluate the accruing evidence in an effort to harmonize future screening guidelines. Also, if we are to expect clinicians to accurately follow the guidelines, then screening algorithms should be simplified whenever possible. For instance, officials might consider adopting a universal approach that is not age-dependent—that is, an approach in which all women more than 25 years of age are tested for HPV, and cytology is reserved for triage during screening. It has already been established that screening women between the ages of 21 and 24 provides almost no benefit[41] and might actually cause more harm as a result of overdiagnosis and associated treatment[14]. But with the advent of more specific molecular markers[36] and accurate risk prediction models to guide the clinical management of patients[42], officials might decide that HPV testing can safely be initiated at an earlier age. Final results are now awaited from screening trials that included women less than 30 years of age (such as the ATHENA[43]

and FOCAL[27] trials) to help in determining whether primary HPV testing might effectively be combined with an appropriate triage test for all women undergoing screening. But unless experts decide to modify their recommendations, physicians across North America should, for the time being, continue to follow current guidelines and administer only Pap exams to women less than 30 years of age.

4. HPV VACCINATION: A NEW PARADIGM IN CERVICAL CANCER PREVENTION

The International Agency for Research on Cancer has now classified 13 HPV genotypes as definite or probable carcinogens[44]. However, only 2 of them (HPV 16 and 18) are responsible for approximately 70% of the cervical cancer burden worldwide and are targeted by current vaccines[45,46]. Both Cervarix (GlaxoSmithKline, London, U.K.) and Gardasil (Merck and Co., Whitehouse Station, NJ, U.S.A.) were evaluated in randomized controlled trials and found to be nearly 100% effective in preventing new infections from the target types—that is, HPV 16 and 18, or HPV 6, 11, 16, and 18 respectively—and from precancer associated with the two oncogenic types[47,48]. Gardasil was also 100% effective in preventing genital warts, which are normally caused by HPV 6 and 11[48]. Because both vaccines are exclusively prophylactic, routine vaccination is recommended for pre-teen girls before sexual debut (ages 9–12 years), with "catch-up" vaccination for women 13–26 years of age[49,50]. However, considering that most government-funded HPV immunization programs target only pre-teen girls and that the latency between HR-HPV infection and development of invasive cancer is long, we expect that more than a decade will pass before a reduction in mortality is observed in most countries[7]. A notable exception might become evident in countries with successful "catch-up" programs in place. For example, Australia was the first country to introduce a fully-funded national immunization program for women up to the age of 26, and as a result of high vaccine uptake in the "catch-up" age range, it was also the first country to report a significant decline in the rate of high-grade precancerous lesions[51]. Recently, a decline in the rate of high-grade cervical lesions was also observed in the state of Connecticut[52], which represents the first report of a reduction in cervical neoplasia in North America since vaccines were introduced. Connecticut also happens to be among the leaders in vaccine coverage, with reports estimating that 61% of adolescent girls (13–17 years) received at least 1 dose of the vaccine in 2011[53]. Although uptake among young women more than 17 years of age is still very low across North America[54], British Columbia became, in 2013, the first province to offer free vaccination to women up to age 26, which is expected to lead to higher uptake and a reduction in cervical cancer mortality even sooner in that province.

TABLE I   Uncertainties surrounding implementation of testing for the human papilloma virus (HPV) as the primary cervical cancer screening test

Question	*Reasonable options or possibilities being explored (non-exhaustive list)*
What is the best age to start screening with HPV testing?[a]	25, 30,[b] or >30 years
What is the best age to stop screening with HPV testing?[a]	60, 65,[b] 70, or >70 years
What triage test or tests should be used to guide colposcopy referrals after a positive HPV test?[a]	Pap cytology,[b] HPV 16 or 16 and 18 genotyping,[b] HPV E6/E7 messenger RNA testing, methylation (and consequent silencing) of host and viral genes, or p16^{INK4a} staining
What is the most appropriate interval for HPV screening tests?[a]	5,[b] 7, 10, >10 years
Should we expect HPV testing to become more affordable or cost-effective in the future?	Yes, because of market expansion and high-volume testing if adopted for primary screening
Is reliance on industry (HPV test manufacturers) an important concern?	Yes, because of clear commercial and financial interests that might not be in line with the public's best interests

[a]   Question directly related to the development of cervical cancer screening algorithms.
[b]   Approach recommended in screening guidelines or currently the most widely accepted.

Despite our expectation that HPV vaccination will eventually lead to declines in cervical cancer incidence and mortality, the quick approval and rollout of the vaccines has prompted considerable criticism[55]. Aside from reservations related to cost and the need for HPV vaccination in settings with low cervical cancer mortality already, some policy analysts are concerned about the duration of HPV protection, the possibility of type replacement, and the safety of the vaccines in general. Fortunately, among vaccinated individuals, the rates of reported adverse events have been comparable to rates among placebo recipients and within expected background rates in the general population[56]. In addition, the latest trial results indicate that protection has endured unabated for nearly a decade (for licensed HPV vaccines) and longer (approximately 13 years for the prototype HPV 16 vaccine) without any indication of waning antibodies[57–59]. Finally, epidemiology studies investigating the potential for HPV type replacement (that is, the scenario in which other HPV types take over the niches vacated by the eradication of vaccine target types) have so far provided no strong evidence of natural type competition, which is considered a requirement for type replacement to occur in vaccinated populations[60]. Meanwhile, evidence of cross-type protection (primarily for phylogenetically related types 31, 33, and 45) suggests that the benefit of vaccination might ultimately be greater than expected[61,62].

Following from the decision to invest in HPV vaccination programs, officials have to decide which vaccine to purchase, the required number of doses, the age groups to target, and whether young men should also be included. Despite the large amount of literature addressing those issues, such decisions will ultimately depend on the objectives and available resources of each program. For instance, if an important objective is to reduce the prevalence of anogenital warts, then the quadrivalent vaccine would be the best choice; however, if prevention of cervical cancer and high-grade lesions is the main priority, then either the bivalent or the quadrivalent vaccine might be equally suitable[63]. With regard to number of doses, current evidence suggests administering 2 rather than the recommended 3 immunizations might be sufficient, and that protocol has already been implemented in some settings, including Quebec[64]. Furthermore, according to a recent trial comparing alternative dosing schedules, nonadherence with the manufacturers' recommended schedule of 0, 2, and 6 months is not expected to have a major effect on vaccine efficacy[65]. There is also now strong evidence that supports vaccination for the prevention of anogenital HPV infection and related lesions in men[66], which has led the U.S. Advisory Committee on Immunization Practices to update their recommendations to include routine use of the quadrivalent vaccine for boys 11–12 years of age, with "catch-up" vaccination up to age 21[67]. However, according to recent modelling studies, the most cost-effective approach to reduce the burden of HPV in both sexes is to attain high vaccine coverage among girls 9–13 years of age and to rely on herd immunity to protect heterosexual boys and men[68,69].

Unfortunately, rates of HPV vaccination coverage are still very low across the United States and in some parts of Canada. Although coverage rates among Grade 8 girls have steadily increased in Ontario since introduction of the vaccine in 2007, Ontario still had the lowest coverage rate in Canada: 59% as of 2010[70]. Meanwhile, among girls targeted across Eastern Canada and Quebec, coverage rates are generally above 85%, which represents a huge contrast with the situation in the United States, where only 32% of girls 13–17 years of age received the vaccine in

2010[21]. As expected, the lowest coverage rates in the United States were among the uninsured (just 14% nationally) and in poorer areas where cervical cancer rates are the highest and Pap testing prevalence is the lowest—that is, the regions that could benefit the most from vaccination. In addition to the high cost, one of the major obstacles that countries now face in implementing wide-scale HPV vaccination is anti-vaccine activism, propagated mainly through the Internet by illegitimate Web sites posing as authoritative sources. To help dispel the myths or misperceptions spread by those sites concerning vaccination safety and importance, health care providers should be armed with correct information that they can use to educate their patients[71].

5. SUMMARY AND OTHER ISSUES TO CONSIDER

Discovery of HPV as the necessary cause of cervical cancer and subsequent studies to evaluate HPV vaccination and molecular-based screening technologies are among the best examples of multi- and interdisciplinary research on cancer causes and prevention. Vaccination against HPV now holds tremendous potential to reduce global mortality, and yet many challenges for equitable implementation in high- and low-resource settings remain. Also, because current vaccines protect against only a fraction of the oncogenic HPV types, cervical cancer screening will continue to be needed in the post-vaccination era. As we have discussed here, the effect of vaccination on the prevalence of precancerous cervical lesions means that the current paradigm for screening must change. Fortunately, sensitive HPV-based technologies have emerged, and we expect that policymakers will soon decide to implement HPV testing as the sole primary screening test based on favourable results from ongoing demonstration projects and cost-effectiveness analyses revealing improved performance and safety, and based on projected lowered costs because of lengthened screening intervals, market expansion, and high-volume HPV testing[18]. However, adoption of HPV testing will result in many more women becoming aware of their HPV status, which could result in psychological trauma. It is therefore important for clinicians to educate their patients about HPV and to inform them that although most infections will clear on their own, additional follow-up care (monitoring, testing, and treatment) might be required to reduce their risk of cervical cancer.

In the post-vaccination era, linkage of vaccine registries with HPV screening and other disease registries (for example, using medical records) might provide a low-cost method of monitoring vaccine efficacy, including type replacement, cross-protection, and protection duration. Such linkages might also help in the evaluation of long-term safety or adverse events that are too rare to be evaluated in clinical trial populations. Ultimately, integration of primary and secondary prevention strategies inherently lends itself to acting as a single prevention strategy through record linkage and shared resources. By adopting this sort of life-course approach to cervical cancer prevention, young women or their parents might also be able to easily identify where they or their child fit into the continuum and to understand why they are being targeted for vaccination or screening (Figure 2).

Another important issue that we have not touched on is the possibility that HPV vaccination might affect the behaviour of young women by conveying a false sense of security and promoting risky sexual behaviour. This sort of "risk compensation"[72] could result in an increase in other HPV genotypes not targeted by vaccination[60] and in other sexually transmitted infections. This concern is shared by many parents and health officials, but fortunately, studies from the United States and the United Kingdom focussing on this topic have not found any association between HPV vaccination and increased risky sexual behaviour—for example, a higher number of sexual partners or lesser condom use[73,74].

As policy officials struggle to address unresolved issues surrounding implementation of HPV vaccination and screening, it will be important, because of obvious commercial interests, to monitor the involvement of biotechnology and pharmaceutical companies in influencing policy decisions. For instance, recommending vaccination to broader age groups of men and women, and reducing screening intervals in redesigned algorithms would certainly be in the interest of industry, but maybe not of the public. The necessary monitoring might be challenging, because until recently, no commercial interests had been involved in the policy process. The only screening method available was conventional Pap cytology (a technology in the public domain), and therefore countries simply needed to decide whether they were going to assign the resources necessary to attain adequate quality and coverage[75]. Some practical issues also surround the introduction of HPV testing in primary screening; those issues must be addressed before wide-scale implementation. For example, delays from notification of HPV results to appropriate triage testing might pose a serious threat if they last long enough to allow precancerous lesions to progress. To avoid that possibility, officials should consider specimen co-collection to permit HR-HPV testing with reflex cytology, using banked cervical specimens collected at the initial screening visit. Adopting this approach might also help to preserve another advantage of HPV testing over conventional cytology—that is, increased coverage of women in remote areas by self-collection of specimens outside of clinic, and use of the same specimen for both HPV testing and LBC for triage of HPV-positive samples.
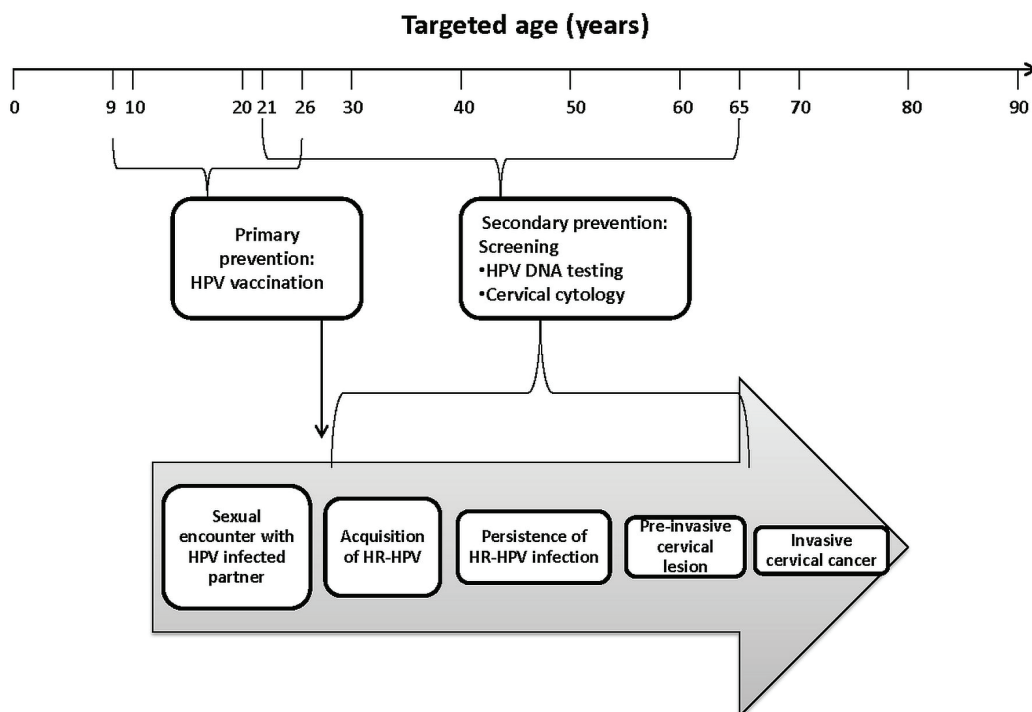
FIGURE 2   *Opportunities for prevention at various ages and times along the pathway from exposure, acquisition, and persistence of the human papilloma virus (HPV) to development of preinvasive lesions. The boxes within the large arrow depict the natural history of cervical carcinogenesis. At each step during this process, most cases will regress. In the absence of screening, only a very small fraction would be expected to progress to invasive cervical cancer. Targeted age groups for vaccination (9–26 years, including "catch-up") and screening (21–65 years) presented here are based on current recommendations in the United States. In Canada, the only difference is that women less than 25 years of age are not advised to initiate screening, according to guidelines from the Canadian Task Force on Preventive Health Care. HR-HPV = high oncogenic risk HPV.*

Because of the rapid pace of technological change and new discoveries, the evidence base in the area of cervical cancer prevention remains an elusive target, making it difficult to predict what lies ahead. Inability to predict will continue to be an obstacle for policymaking in this field. For example, if a second generation of HPV vaccines that extend protection to other HR-HPV types comes to market, policymakers might once again need to readjust screening guidelines[76], reinforcing the need for an innovative risk-assessment strategy that is flexible with respect to the growth of the new technologies[42]. Recently, ground-breaking discoveries have also occurred in the field of HPV microbicides and therapeutic vaccines research that might once again transform the landscape of cervical cancer prevention and control strategies to include novel treatment options for HPV and associated malignancies[76–78]. Since introduction of the first clinical HPV tests roughly 20 years ago, the field of HPV research has experienced tremendous growth (reflected by a 400% increase in the annual number of articles on papillomavirus in Medline's PubMed database over that time period) marked by all the key events outlined here and ultimately capped with a Nobel prize to Dr. zur Hausen in 2008 for his pioneering

role in establishing HPV as the main causal agent in cervical cancer[75]. We expect that the next 20 years will continue to be an important period for discovery for this field, but with a more concerted effort placed on evaluation of novel HPV prevention technologies and policy decisions surrounding their implementation.

6.   CONFLICT OF INTEREST DISCLOSURES

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Correspondence to: Joseph E. Tota, McGill University, Division of Cancer Epidemiology, 546 Pine Avenue West, Montreal, Quebec H2W 1S6.
E-mail: joseph.tota@mail.mcgill.ca

* Department of Oncology, McGill University, Montreal, QC.
† Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC.