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EVOLVING CERVICAL CANCER SCREENING GUIDELINES AND HPV VACCINATION STATUS. A LITERATURE REVIEW

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ABSTRACT

Background: Persistent infection with high-risk types of human papillomavirus is the primary cause of cervical cancer globally. Recent decades have witnessed significant advances in prevention, with the introduction of effective prophylactic HPV vaccines and highly sensitive molecular screening methods transforming how cervical cancer is detected and managed. Aim of this review is to explore the impact of HPV vaccination programs on cervical cancer prevention strategies, focusing on how vaccination coverage influences the global shift from traditional cytology-based screening to HPV DNA testing in selected high-income countries.
Methodology: A comprehensive search was conducted across scientific databases, including PubMed, the Cochrane Library, and WHO reports, focusing on recent peer-reviewed studies.
Results: The diagnostic performance of cytology has declined in vaccinated populations due to fewer abnormal findings, prompting a shift toward primary HPV DNA testing. This method offers sensitivity rates exceeding 90% and supports longer screening intervals of five years or more. Countries like Australia, the Netherlands, Sweden, and the UK have adopted nationwide HPV-based screening, while Poland initiated pilot HPV testing programs in 2024.
However, several barriers persist, including disparities in vaccine distribution, the high cost of molecular diagnostics, and persistent public hesitancy toward vaccination.
Conclusions: Combining widespread HPV vaccination with HPV DNA-based screening offers the most promising strategy for reducing cervical cancer incidence and achieving the WHO's 2030 elimination targets. Those recommendations include expanding gender-neutral vaccination, supporting transitions to HPV testing in lagging regions, and incorporating innovations like self-sampling to improve outreach and screening participation.

KEYWORDS

HPV Vaccination, HPV DNA Test, Pap Smear, Cervical Cancer Screening, Global Guidelines, Self-Sampling

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Introduction.

Human papillomavirus (HPV) is a common sexually transmitted infection, with high-risk HPV (hrHPV) types—particularly HPV 16 and 18—accounting for approximately 70% of cervical cancer cases globally (Drolet et al, 2019). Although most HPV infections are transient and resolve spontaneously, persistent infections can lead to the development of cervical intraepithelial neoplasia (CIN), which may progress to invasive cervical cancer, if left undetected and untreated (Koshiol et al, 2008).

The World Health Organization's Global Strategy to eliminate cervical cancer as a public health concern outlines a clear framework built around the"90-70-90 goals" to be achieved by 2030, consisting of 90% of girls should be fully vaccinated against HPV by the age of 15, 70% of women should undergo cervical screening with a high-accuracy test at ages 35 and 45, and lastly 90% of those diagnosed with cervical disease should receive appropriate care—this includes 90% of women with precancerous lesions receiving treatment, and 90% of women with invasive cervical cancer receiving proper clinical management (World Health Organization, 2020).

For over six decades, cytology-based screening (Pap smears) has served as the cornerstone of cervical cancer prevention. However, conventional cytology has shown variable sensitivity, typically ranging from 55% to 75% for detecting high-grade CIN (Arbyn et al, 2022). Moreover, cytology is labor-intensive, subject to interobserver variability, and requires frequent retesting to ensure early detection (Kitchener et al, 2009).

Numerous studies and real-world evidence now support the superiority of HPV testing over cytology and consequently, many national programs have begun integrating or fully transitioning to HPV-based screening strategies, reflecting a broader shift in cervical cancer prevention efforts in the post-vaccine era.

Methodology

This review provides a summary of key information on the impact of HPV vaccination programs on cervical cancer prevention strategies. The analysis is based on peer-reviewed studies sourced from scientific databases such as PubMed, the Cochrane Library, and WHO reports prioritizing the most recent systematic reviews and meta-analyses along with studies conducted on large research groups.

A literature search using the keywords”Uterine Cervical Neoplasms"[Mesh]) AND”Early Detection of Cancer"[Mesh]) AND”Papillomavirus Vaccines"[Mesh] was conducted through MeSH (Medical Subject Headings) of NLM database, excluding case reports as they did not assure enough data to support broader conclusions. Publications were selected based on their relevance to HPV vaccine efficacy, cervical cancer screening outcomes, and national policy changes.

Results and Discussion

1. Human Papillomavirus as a Carcinogen

Human papillomavirus (HPV) is the most widespread sexually transmitted infection globally, with around 75–80% of sexually active people contracting it during their lifetime. Most HPV infections are harmless and clear within 1–2 years, but persistent or repeated infections can lead to serious health problems. There are about 200 types of HPV, with over 20 considered carcinogenic (Serrano et al, 2018). High-risk strains, particularly HPV 16 and 18, are responsible for nearly all cervical cancer cases and also contribute to other cancers, including those of the throat, anus, penis, vagina, and vulva. Low-risk strains, like HPV 6 and 11, cause the majority of anogenital warts, which, while not life-threatening, can affect quality of life and incur healthcare costs.

HPV is linked to 4.5–5.2% of all cancers worldwide, with around 630, 000 new cases annually. Its prevalence and impact vary by region, gender, immune status, and sexual behavior (Shapiro, 2022).

2. Evidence and Effectiveness of HPV Vaccination

HPV vaccination is a highly effective and safe method of preventing several cancers caused by the human papillomavirus, especially cervical cancer. While screening can detect cervical cancer early, no equivalent exists for other HPV-related cancers like those of the head and neck, making vaccination crucial. Four main prophylactic HPV vaccines, including bivalent, quadrivalent, and nonavalent formulations—Gardasil®, Gardasil®9, Cervarix®, and Cecolin®—target various high-risk HPV strains and are most effective when given before exposure, typically to individuals aged 9–14 (González-Rodríguez et al, 2024). Studies show these vaccines reduce HPV infections, genital warts, and precancerous lesions, with protection lasting over 10 years. The World Health Organization now supports single-dose schedules for most youth, though three doses are still recommended for those with weakened immune systems. While some programs focus only on girls, gender-neutral vaccination offers broader protection, especially for groups like men who have sex with men (MSM). The vaccines are also cost-effective and have strong global health endorsements. Ongoing research continues to explore their long-term benefits, especially for non-cervical cancers. Australia and Sweden, which achieved high vaccine uptake early, are already seeing reductions in cervical cancer incidence. Despite this success, vaccine coverage remains suboptimal in some regions due to misinformation, logistical challenges, and inequities in access.

Women who develop HPV-related cervical, vaginal, and vulvar cancers represent a subgroup of patients who may be particularly sensitive to HPV infection and re-acquire infections, but there is currently no solid evidence supporting the use of prophylactic HPV vaccines in women who have already been treated for invasive cervical or other HPV-related gynecologic cancers (Bizzarri et al, 2025). A small retrospective study suggested that HPV vaccination may help reduce the risk of subsequent HPV-associated disease in some patients, but its findings are limited and not conclusive. Meta-analyses indicate potential benefits in reducing recurrence of high-grade lesions (especially those caused by HPV16/18) after local surgical treatment, though the quality of data is low and better evidence is expected from upcoming trials like NOVEL (Kechagias et al, 2022).

For patients treated for early-stage cervical cancer or with procedures like conization, vaccination might offer some protection against future HPV-related conditions in other sites such as the vagina or anus. However, for those with more advanced disease or who underwent chemo-radiation, the potential benefits remain uncertain. Some countries already support vaccination in certain patient groups post-treatment (Phillips et al, 2018).

Despite the vaccine’s good safety profile and proven immunogenicity up to age 55, the European Society of Gynecological Oncology (ESGO) states there’s insufficient evidence to formally recommend vaccination for this population. Until more research is available, clinicians should offer individualized counseling about

potential benefits and limitations, based on age, prognosis, and vulnerability to further HPV-related diseases (Bizzarri et al, 2025).

3. Molecular Screening Benefits

The introduction of molecular diagnostics—particularly HPV DNA testing—has significantly improved screening quality. Primary HPV DNA testing offers substantially higher sensitivity, often exceeding 95% for detecting CIN2+ or CIN3+ lesions, with demonstrating sensitivity rates as high as 98.1% compared to only 48.5% with cytology as reported in a multicentre cross-sectional cervical cancer screening study - the ESTAMPA trial (Ramírez et al, 2023). This improved sensitivity allows for extended screening intervals and improves the negative predictive value, ultimately reducing the burden on healthcare systems while maintaining safety and efficacy. Ronco et al. analyzed data from four large European randomized controlled trials (Swedescreen, POBASCAM, NTCC, and ARTISTIC), involving 176, 464 participants who were randomized to either HPV-based experimental group or cytology-based controlling group for cervical cancer screening. The studies used different HPV testing methods and had varying intervals, with most at three years, except POBASCAM at five years. In the first 2.5 years, both screening approaches had similar detection rates for invasive cancer. (RR: 0.79; 95% CI: 0.46–1.36), but with significant decline in the experimental group after that period (RR: 0.45; 95% CI: 0.25–0.81). Among women with a negative initial test, the risk ratio was 0.30 (95% CI: 0.15–0.60), with lower cumulative incidence in the experimental arm at both 3.5 and 5.5 years. Although detection rates didn't vary by cancer stage, they were notably lower for adenocarcinoma than for squamous-cell carcinoma. Overall, HPV screening from age 30 provided 60–70% more protection than cytology, and the data suggested that screening every five years with HPV testing offers sufficient safety compared to more frequent cytology or co-testing (Ronco et al, 2013).

Additionally the analysis by Bruni et al. (2016) states that high-income countries typically implement both HPV vaccination and cervical cancer screening, describing it as the most effective methods for prevention, but the uptake of vaccination among the primary target groups remains relatively low, with global coverage rates falling below 50%.

4. Evolution of Screening Methods with a National Screening Guidelines Comparative Overview

Although cervical cancer screening protocols vary between countries—differing in recommended starting ages, test intervals, and primary methods—there is a clear trend toward adopting high-risk human papillomavirus (hrHPV) testing as the preferred approach (Wang et al, 2022). While some nations still use cytology-based or co-testing approaches, Melnikow et al. (2018) state that an emerging global consensus favors hrHPV as the foundation of screening programs, reflecting strong evidence of its superior sensitivity for detecting precancerous changes. This chapter outlines the trajectory of screening method development and compares national guidelines to show how global strategies are gradually aligning around hrHPV-based screening.

Australia launched its National Cervical Screening Program (NCSP) in 1991, advising sexually active women to undergo Pap smear testing every two years from ages 18–20 up to 69. This approach was revised in December 2017, transitioning to a five-yearly screening strategy using primary HPV testing, including HPV 16/18 genotyping and follow-up cytology for other high-risk HPV types. The 2024 updated NCSP states that screening should be conducted every 5 years in asymptomatic individuals aged 25 to 74 years with a cervix, using a primary HPV test that includes partial genotyping and triage with liquid-based cytology (LBC). Women with low risk of significant cervical abnormality should rescreen in 5 years, while those at intermediate or high risk require follow-up HPV testing in 12 months or immediate colposcopic assessment. Unsatisfactory HPV or LBC tests should be repeated within 6 weeks (Cancer Council Australia, 2014).

Separately, in 2007, Australia became the first country to implement a publicly funded national HPV vaccination initiative, focused on vaccinating girls aged 12–13, with a catch-up campaign for older females, evolving form three doses of the quadrivalent vaccine (HPV4) through two-dosage schedule of nonavalent vaccine (HPV9) with a change to 1-dose of HPV9 in 2023. The introduction of the HPV vaccination programme, coupled with the transition to 5-yearly HPV testing, is projected to significantly reduce the burden of cervical disease (Yuill et al, 2025; Velentzis et al, 2017). First-time precancer treatments may decrease by 82% and approximately 800, 400 procedures would be averted over 2010-2070 (Yuill et al, 2025).

In 2017, the Netherlands transitioned from cytology to HPV-based cervical cancer screening using the PCR-based Cobas 4800 test. As part of this change, women were given the option to request a free self-sampling kit (Evalyn Brush) delivered to their homes, as an alternative to clinician-collected samples. Initially, self-sampling accounted for only 7% of all tests, primarily used by women who had never participated in

screening before and who differed in their sociodemographic profiles. Efforts to simplify access and promote self-sampling led to an increase in uptake, reaching 16% by 2020. However, HPV detection and CIN3+ diagnosis rates were lower in self-collected samples than clinician-collected ones, possibly due to dilution issues that may have reduced test sensitivity. These findings underscore the need to improve outreach, specimen processing, and testing protocols to enhance the effectiveness of self-sampling, especially for underserved populations at higher risk of cervical cancer (Arbyn et al, 2023).

Sweden's current cervical cancer screening guidelines (since 2017) recommend cytology every 3 years from age 23, switching to HPV testing at age 30 every 3 years until age 50, and then every 7 years until age 64. Women aged 23–29 with LSIL undergo HPV reflex testing, with follow-up depending on age. Women 30+ who are HPV-positive but cytology-negative are retested after 36 months, with persistent cases referred for colposcopy. At age 41, a one-time co-test (cytology + HPV) is offered. The previous guidelines used only cytology: every 3 years until age 50, then every 5 years until 60. Additionally researchers assessed alternative strategies, varying start age, testing method, interval, and follow-up timing, ensuring all included a final screen at age 60 or older. Starting screening at age 30, as done in some countries, was found to be less effective for Sweden. Instead, beginning primary HPV screening at age 23 showed the best balance of cost-effectiveness and risk-benefit balance (Fogelberg et al, 2020).

The British NHS cervical screening programme, launched in 1988, initially offered cytology-based tests to women aged 20–64 every 3 to 5 years. However, following evidence that screening women under 25 had limited impact on cancer prevention, the age range was revised. Currently, women aged 25–49 are screened every three years, and those aged 50–64 every five years. Wales and Scotland have since moved to five-year intervals for all eligible age groups. The programme has significantly reduced cervical cancer incidence and mortality. Today, the primary focus is on detecting high-risk HPV, which has proven more effective than cytology in identifying precancerous changes (CIN). Women with abnormal HPV results undergo cytology, and if cellular atypia is found, they may be referred for colposcopy and potentially treated with procedures like Large Loop Excision of Transformation Zone (LLETZ) to remove abnormal tissue. Annual data from NHS Digital shows steady upward trends in screening uptake since March 2021, following a 6.8% decrease in screening participation compared to the previous year, attributed to the impact of the global COVID-19 pandemic (Choi et al, 2023).

Scotland implemented a national cervical screening system database in 2007, which captures data on invitations, cytology, HPV testing, colposcopy, and histology. The use of a unique personal health identifier across healthcare services enables seamless integration with systems such as the National Colposcopy Clinical Information and Audit System (NCCIAS) and national databases like the Cancer Registry. Over the years, the screening programme has undergone significant updates, transitioning from traditional smears to liquid-based cytology and, more recently, to HPV testing as the primary method. Alongside these technical changes, the screening age range and recall intervals have also been revised. Initially set for women aged 20–60 with a three-year interval, the criteria shifted in 2016 to ages 25–65, with three-year intervals for those under 50 and five years for older women. In 2020, the recall frequency was unified to five years for all age groups and self-sampling trials were started as part of the transition to primary HPV screening (Cameron et al, 2024).

In Poland the HIPPO study provided compelling evidence for the adoption of hrHPV testing in national screening programmes. This study involved 33, 495 women aged 30–59, randomly assigned to either the hrHPV testing group or the cytology group. The primary endpoint was the detection rate of histologically confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+). The hrHPV testing group demonstrated a nearly twofold higher detection rate of CIN2+ compared to the cytology group. However, successful implementation of the new screening methods in a still primarily cytology-based region will depend on systemic reforms, including updating screening protocols, training healthcare providers, and enhancing public awareness. Addressing these factors is crucial to improving the effectiveness of cervical cancer prevention in Poland (Glinska et al, 2023).

5. Self-sampling methods

Self-sampling for high-risk human papillomavirus (hrHPV) is an increasingly viable alternative to clinician-collected cervical specimens in screening programs. This method allows women to collect their own vaginal sample using a swab or brush, eliminating the need for a pelvic exam performed by medical professionals. Dry brush is preferred over a wet brush, with no difference in the detection of hrHPV, as it improves safety in home settings with reducing the risk of exposure to potentially harmful transport media chemicals from wet brushes (Jun et al, 2016; Wolfrum et al, 2012). Additionally during the COVID-19

pandemic the global adoption of self-sampling (SS) accelerated due to disruptions in traditional clinician-based screening. With social distancing, clinic closures, and resource reallocation it emerged as a practical and adaptable alternative (Poljak et al, 2021). Given these benefits, self-sampling is generally well accepted by women and has the potential to enhance participation in cervical screening programs, particularly among those reluctant to undergo clinical exams (Shiraz et al, 2023).

The samples are typically analyzed using either polymerase chain reaction (PCR)-based or signal amplification (SA)-based assays. Self-collected samples tend to yield lower sensitivity and specificity compared to clinician-collected ones when signal amplification-based hrHPV tests are used. However, response rates are generally higher for self-sampling kits than for traditional screening invitations. When hrHPV detection relies on PCR-based methods, self-sampling maintains comparable sensitivity with only a slight reduction in specificity in detecting high-grade cervical lesions (CIN2+ or CIN3+), while still achieving better participation rates than conventional approaches (Arbyn et al, 2018).

Pendersen et al. (2025) conducted a large, pragmatic randomized study to inform strategies for implementing HPV self-sampling. The study compared two invitation methods - direct mailing of self-sampling kits and an opt-in system. The results showed that directly sending the kits to women who had not recently attended screening significantly improved participation compared to requiring them to request a kit. Engagement was higher among older women in both groups and declined with increasing time since last screening. For women who had missed screening for a short duration, the direct-mail method led to higher response rates. However, for those who had not been screened for an extended period, both approaches produced similar participation levels.

Rebolj, Sargent, Njor & Cuschieri (2023) highlight the adaptability of self-sampling (SS) in reaching under-screened women. They discuss innovative delivery methods, including offering SS kits during unrelated primary care visits, distributing kits through local pharmacies, conducting home visits by healthcare workers, and engaging women through community outreach and public health campaigns.

One limitation of current self-sampling pathways is the requirement for follow-up clinician visits when hrHPV is detected, as cytology (LBC) remains the standard triage method. However, emerging molecular approaches—such as HPV genotyping and methylation marker analysis—may allow for risk stratification using the same self-collected sample (Del Mistro et al, 2017). This innovation could be especially impactful in low- and middle-income settings, where shortages of trained cytopathologists and laboratory resources pose major challenges (Shiraz et al, 2023).

For the integration of hrHPV self-sampling into national screening frameworks, further research is needed to evaluate delivery models, improve access, and understand the impact on program coverage across diverse healthcare settings.

Conclusions and Future Directions

The integration of widespread prophylactic HPV vaccinations with high-sensitivity HPV DNA screening represents the most effective and sustainable strategy for reducing the global burden of cervical cancer. Countries that have implemented gender-neutral immunization programs alongside the adoption of molecular-based screening protocols are already demonstrating measurable declines in precancerous lesions and cervical cancer incidence.

Evidence from randomized controlled trials and real-world surveillance consistently supports the superior diagnostic accuracy and clinical value of HPV DNA testing compared to conventional pap smear. As vaccinated cohorts enter screening age, the decreasing prevalence of cytological abnormalities necessitates a shift toward more precise and clinically relevant approaches. Primary HPV testing, supported by extended screening intervals, allows for better risk assessment and more efficient resource use.

To align with the WHO's 2030 cervical cancer elimination targets, efforts must now focus on scaling up HPV testing, addressing inequities in vaccine access, and implementing context-appropriate solutions in lower-resource settings. Self-sampling kits and community outreach can support this transformation by increasing participation and lowering access barriers.

Overcoming barriers such as vaccine hesitancy, limited financial resources, and insufficient healthcare infrastructure remains essential for the effective implementation of molecular HPV screening. However, with the right policies, education, and health system investments, it is possible to build adaptable and robust prophylactic programs. The future of cervical cancer prevention will depend on adaptable strategies that evolve with changing population needs and technological progress.

Disclosure

Author's contribution:

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