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Research Article

HPV/Cervical Cancer Screening: Comparative Effectiveness of Primary HPV-Based Testing versus Cytology

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ABSTRACT

Background: Cervical cancer is a major preventable malignancy and in 2022, there were about 662,301 new cases and 348,874 deaths due to cervical cancer worldwide. In more than 99% of cases, the necessary cause is high-risk human papillomavirus (hrHPV). Cytology (Pap smear) screening has long been used and has proven effective, but its sensitivity has been identified as a limitation. HPV DNA-based primary screening has become a molecularly superior tool; however, synthesized evidence from randomized trials based on detection of CIN2+ data is limited over the last 6 years (2022-2026).

Objectives: To systematically review and metaanalyse comparative performance of HPV-based primary screening compared to cervical cytology for detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+); to appraise HPV vaccination efficacy data; to evaluate self-sampling strategies for under-screened populations; to evaluate emerging technologies such as AI-assisted colposcopy.

Methods: A systematic review and meta-analysis of peer-reviewed randomized controlled trials, systematic reviews and meta-analyses were carried out between January 2022 and June 2026, in accordance with the guidelines of the PRISMA 2020 and the Cochrane guidelines. Databases explored were PubMed/MEDLINE, Embase, CENTRAL, Scopus and Web of Science. Primary outcome: detection rate for CIN2+ (RR, 95% CI). Secondary outcomes were HPV vaccination effectiveness, self-sampling uptake, test sensitivity/specificity, and cancer burden measures at the population level.

Results: Across 8 RCTs encompassing 414,846 participants, HPV DNA-based screening detected CIN2+ lesions at a rate 61% higher than cytology (RR 1.61; 95% CI: 1.30–1.98; $p < 0.00001$). HPV mRNA testing was found to be equally sensitive (93.2% for CIN2+) but was more specific (84.0%) than HPV DNA testing (80.8%). Of the 145 RCTs included in the meta-analysis, HPV vaccination was found to be effective in decreasing the risk of developing CIN I by 85%, CIN II by 80%, and persistent HPV16/18 infection by 84%. The self-sampling strategies resulted in 2.1–3.1-fold higher screening participation rates than standard care. The risk of cervical cancer was 2.78-fold higher for vulnerable populations (RR 2.78; 95% CI: 2.32–3.32). The deep learning colposcopy models had an AUC-ROC of 95.3%.

Conclusion: HPV-based primary screening is shown to be very clearly superior in terms of sensitivity for CIN2+ detection to cytology. The WHO 90-70-90 elimination framework requires integrated vaccination, risk-stratified genotyping triage and self-sampling. AI-powered tools are a game-changer in resource-constrained environments. There is an urgent need to address the disparities between high and low-HDI countries.

Keywords: Human papillomavirus; cervical cancer screening; CIN2+; HPV DNA test; cytology; meta-analysis; vaccination; self-sampling; colposcopy; WHO elimination strategy.

INTRODUCTION

Cervical cancer is one of the most important and preventable cancers among women worldwide. Data from GLOBOCAN 2022 estimates that there were 662,301 new cases of cervical cancer and 348,874 deaths globally, of which 60% (397,082) of the cases and 57.3% (199,795 deaths) of the deaths were in Asia. The age-standardised incidence rate (ASIR) is 14.1 per 100,000 women and the age-standardised mortality rate (ASMR) is 7.1 per 100,000 women globally. The ASIR in Eastern Africa is 40.4 and in Western Asia it is 4.2 per 100,000 people, highlighting a significant geographical disparity. If the current 2022 rates continue, then the number of new reported cases will grow to 760,082 (14.8% increase) and deaths are expected to reach 411,035 (17.8% increase) by 2030. In more than 99% of the cervical cancers, the etiological agent is a high-risk human papillomavirus (hrHPV), primarily HPV16 and HPV18, which cause about 70% of cervical cancers. hrHPV infection is a well-defined oncogenic process that results in a progression of low-grade squamous

intraepithelial lesions (LSIL) to cervical intraepithelial neoplasia (CIN) grades 1–3 and eventually to invasive cervical carcinoma. Each day, some 1,800 women are diagnosed with cervical cancer and nearly 1,000 women die of the disease worldwide. Cervical cancer is the fourth most prevalent and the fourth leading cause of cancer deaths in women worldwide, and is the most common type of cancer death in women in 37 countries, mainly in sub-Saharan Africa and Latin America. In November 2020, the World Health Organization (WHO) endorsed and launched the Global Strategy to Accelerate the Elimination of Cervical Cancer in collaboration with 194 member countries, with the bold 90-70-90 targets for 2030: 90% of girls fully vaccinated with HPV vaccine by the age of 15; 70% of women screened with a high-performing test by age 35 and 45; and 90% of women with cervical disease getting treatment. If these goals are met in low- and lower-middle-income countries, more than 74 million new cases of cervical cancer and over 62 million deaths will be prevented by 2120, according to mathematical modelling estimates. As of 2024, at least 144 countries have launched HPV vaccination programmes and more than 60 countries have integrated HPV testing into their cervical screening programmes, although global coverage of HPV vaccines for eligible girls is just 15%, ranging from 1% in Central and Southern Asia to 86% in Australia and New Zealand **(1-3)**.

Conventional cytology-based cervical screening (the Pap smear) has proven to be an effective method of preventing cervical cancer in countries where it is delivered in a high-quality program. Its use is, however, limited by certain intrinsic factors, such as sensitivity variation, subjectivity in interpretation, and the need for trained lab staff to use it, which pose a challenge to its widespread implementation. DNA-based primary screening uses molecular detection of viral nucleic acids, and has fundamentally higher sensitivity for identifying women who are truly at risk of developing high-grade precancerous lesions. Recently, HPV mRNA testing (based on the oncoproteins E6/E7) and self-sampling approaches have been added to the cervical cancer prevention technological toolbox, as have been artificial intelligence (AI)-assisted colposcopy. However, there were a number of evidence gaps at the end of the research period (2022-2026) **(4-11)**:

- The lack of contemporary pooled analyses limited to HPV DNA compared to cytology;
- Limited real-world long-term efficacy and durability data for HPV vaccines in diverse populations and dosing schedules;
- The lack of full characterization of optimal self-sampling implementation strategies for reaching under-screened populations;
- Insufficient evaluation of AI-assisted screening platforms in clinical validation settings. As a result of these gaps, this systematic review and meta-analysis aimed to fill these with evidence published from January 2022 to June 2026.

MATERIALS AND METHODS

Study Design and Registration

This investigation was carried out systematically following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) and the Cochrane Handbook for Systematic Reviews of Interventions (SRoI) **(14-15)**.

Eligibility Criteria

Studies were eligible for inclusion if they met the following PICO-defined criteria:

Population (P)	Women aged 20–69 undergoing cervical cancer screening; both general and high-risk populations included
Intervention (I)	HPV-based primary screening (DNA or mRNA), HPV vaccination, or self-sampling HPV strategies
Comparator (C)	Conventional or liquid-based cytology (Pap smear), placebo, or standard care
Outcomes (O)	Primary: CIN2+ detection rate (RR, 95% CI). Secondary: CIN3+, vaccine efficacy (CIN I–III reduction), screening uptake, test sensitivity/specificity, cancer incidence/mortality
Study Design (S)	Randomized controlled trials (RCTs), systematic reviews, and meta-analyses published January 2022 – June 2026

Exclusion criteria: non-randomized observational studies without control groups for primary screening comparisons; studies combining screening modalities without separable arms; duplicated cohorts (only the most complete report retained); non-English language publications; study protocols without reported outcomes; and studies published prior to January 2022.

Search Strategy

The PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science databases were searched comprehensively on April 12, 2025 (with follow-up searches through June 2026). They included the following search terms: Medical Subject Headings (MeSH), free-text keywords such as "human papillomavirus-based screening", "HPV DNA test", "HPV primary screening", "cervical cancer screening", "uterine cervical neoplasms", "CIN2+", "cervical intraepithelial neoplasia", "Papanicolaou test", "cytology", "self-sampling", "HPV vaccination", and "cervical cancer elimination", "colposcopy AI", and "deep learning cervical". Selected studies and key reviews were hand-searched in bibliographies to identify further studies **(15-18)**.

Study Selection and Data Extraction

All titles, abstracts, and full texts were screened by two independent reviewers (blinded) with a standardized Excel template having pre-defined eligibility criteria. To resolve discrepancies at each step, discussions were held with a third reviewer. Variables extracted were: first author and year, country, study design, sample size (intervention and control), age range and mean age of participants, HPV test type (DNA/mRNA/self-sampling), cytology method, follow-up period, detection rates of CIN2+ (intervention and control), relative risk (RR) and 95% confidence interval (CI), sensitivity, specificity, and screening uptake rates. In studies with more than one arm, data were collected for each arm that was applicable. Only last, full reports were kept for overlapping cohorts **(19-22)**.

Quality and Risk of Bias Assessment

The Cochrane RoB 2 tool was used to evaluate the risk of bias in RCTs. The QUADAS-C (Quality Assessment of Diagnostic Accuracy Studies – Comparative) was used for diagnostic accuracy studies.

The overall certainty of evidence for each primary outcome was rated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework. Visual inspection of funnel plots and Egger's regression test were used to evaluate publication bias, if 10 or more studies were available.

Statistical Analysis

Data were analysed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 14. Relative risks (RR) with 95% confidence intervals (CI) were estimated for binary variables. A random-effects model (DerSimonian-Laird method) was used to account for between-study heterogeneity that was anticipated. The Cochran Q test and the I^2 statistic were used to describe the heterogeneity and were set at $I^2 > 50\%$ for substantial heterogeneity. Subgroup analyses were pre-specified by HPV testing type (DNA or mRNA), cytology testing method (conventional or liquid-based), age group (< 30, 30-49, ≥ 50 years), triage (direct colposcopy or cytology triage), geographic region (high-income vs. low/middle-income countries), and HIV status. Primary outcomes of the study were subjected to leave one out sensitivity analysis. Individual patient data simulation was not conducted if the only study effect measure reported was adjusted; summary statistics were pooled if methodologically appropriate.

RESULTS

Study Selection and Characteristics

A total of 1,707 articles were identified in the database searches for the primary HPV versus cytology comparison stream, 8,453 records were identified for the HPV vaccination meta-analysis stream, and other records were identified for self-sampling and AI-assisted screening. The 145 RCTs included for the comprehensive HPV vaccination efficacy analysis were obtained after the removal of 3,045 duplicate and systematic screening based on predefined eligibility criteria, leaving 8 RCTs (414,846 participants) for the primary analysis of HPV detection for CIN2+ screening. The PRISMA 2020 flow diagram defines the selection process with respect to streams. Eight RCTs were included in the primary screening meta-analysis, all from Japan, Sweden, Canada (2), Finland, Mexico, Norway and China. The age groups eligible for the study were 20-69 years. The follow-up time was 16 to 48 months. Self-collected HPV DNA testing was used in three studies. In control arms, five used conventional cytology and three used liquid-based cytology. Total participants: 215,505 in the HPV DNA arm and 199,341 in the cytology arm.

Primary Outcome: CIN2+ Detection Rate — HPV DNA vs. Cytology

The HPV DNA-based primary screening showed superior performance over cytology in terms of detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+), statistically and clinically significant, in a pooled meta-analysis of eight RCTs, including 414,846 participants (per-protocol assessment). The HPV DNA group included 215,505 people, with 2,614 (1.21%) pooled cases of CIN2+ diagnosed. There were 199,341 participants and 1,582 cytology cases diagnosed as CIN2+ (0.79% detection rate) in the cytology group. The pooled relative risk was RR 1.61 (95% CI: 1.30–1.98; $p < 0.00001$), showing that HPV DNA-based screening found CIN2+ at 61% more frequently than conventional or liquid-based cytology. The heterogeneity was significant ($I^2 = 86\%$, $p < 0.0001$), which may have been due to variations in post-positive triage procedures among the studies. When HPV-positive women were referred for colposcopy after cytology (cytology-based triage), the superiority of HPV DNA screening was still observed (RR 1.36; 95% CI: 1.05–1.75; $p = 0.02$). The superiority was greater (RR 2.37; 95% CI: 1.69–3.33; $p < 0.00001$) for studies that referred HPV-positive women directly to colposcopy. Exclusion of studies including women under age 30 did not materially alter results (RR 1.56; 95% CI: 1.25–1.96; $p < 0.00001$). The primary outcome was consistent across and robust to leave one out sensitivity analysis. Certainty of evidence (GRADE): very low, because of risk of bias from differential participation rates and loss to follow-up.

HPV mRNA Testing: Sensitivity, Specificity, and Longitudinal Performance

The sensitivity, specificity, and longitudinal performance of HPV mRNA testing methods will be presented.The sensitivity, specificity and longitudinal performance of HPV mRNA testing methods will be discussed. The detailed accuracy data of the Aptima HPV mRNA assay compared to HPV DNA assays were provided by a systematic review and meta-analysis published in The Lancet Oncology (Arbyn et al., 2022), and from the CERVIVA HPV primary screening study in Ireland (2023/2024). In these studies, HPV mRNA testing was

Table 1: Characteristics of Included RCTs — HPV-Based vs. Cytology Screening

Study (Year)	*Country*	*N Total*	*Age (years)*	*Intervention*	*Follow-up (months)*
Fujita et al. (2024)	Japan	7,337 / 7,772	30–58	Self-sampling HPV DNA vs. Cytology	30
Gustavsson et al. (2018)	Sweden	14,361	30–49	HPV DNA (self-sampling) vs. Cytology	18
Ogilvie et al. (2018)	Canada	19,009	25–65	Primary HPV DNA vs. LB Cytology	48
Isidean et al. (2016)	Canada	20,111	30–69	HPV DNA vs. Cytology	16.6
Leinonen et al. (2012)	Finland	132,195	25–67	HPV DNA vs. Cytology	43.2
Lazcano-Ponce et al.	Mexico	20,256	25–66	Self-sampling HPV DNA vs. Cytology	NA
Nygård et al. (2022)	Norway	157,447	34–69	Primary HPV DNA vs. LB Cytology	18
Zhang et al. (2020)	China	60,732	35–64	High-risk HPV DNA vs. Cytology	24
TOTAL		414,846	20–69	—	16.6–48

Table 2. Meta-Analysis Summary — HPV DNA vs. Cytology for CIN2+ Detection

Analysis	*Studies (n)*	*Participants*	*RR (95% CI)*	*p-value / I^2*
Main analysis (all RCTs)	8	414,846	1.61 (1.30–1.98)	$p < 0.00001$ / $I^2 = 86\%$
Cytology triage subgroup	—	—	1.36 (1.05–1.75)	$p = 0.02$ / High
Direct colposcopy subgroup	—	—	2.37 (1.69–3.33)	$p < 0.00001$ / High
Excluding women <30 years	—	—	1.56 (1.25–1.96)	$p < 0.00001$ / High
HPV mRNA vs. HPV DNA (CERVIVA, 2023)	1 study	N/A	Sensitivity equiv. (93.2% vs. 92.8% for CIN2+)	Specificity: 84.0% vs. 80.8%

found to be as sensitive as HPV DNA assays on clinician-collected samples for the detection of CIN2+ (relative sensitivity 0.98; 95% CI: 0.95–1.01) and CIN3+ (0.98; 95% CI: 0.95–1.01); it was slightly more specific (relative specificity 1.03; 95% CI: 1.02–1.04). The LRSS for CIN3+ in 4-7 year intervals ranged from 0.91 to 1.05, with the pooled estimates not being significantly different from one. HPV E6/E7 mRNA (Aptima HPV assay) was compared to HPV DNA (Cobas 4800) for a 42-month follow-up period in the CERVIVA study. HPV mRNA had similar sensitivity to HPV DNA for CIN2+ (93.2% vs. 92.8%) and CIN3+ (94.6% vs. 94.6%), and significantly higher specificity (84.0% vs. 80.8% for CIN2+ and 88.4% vs. 85.6% for CIN3+). For women who tested negative for HPV, the proportion of women with more severe lesions (CIN2+ and CIN3+) detected over 3 years was similar for mRNA vs. DNA methods (CIN2+: 0.20% RNA vs. 0.22% DNA, and CIN3+: 0.10% RNA vs. 0.11% DNA), which supports screening intervals of 5 years for HPV mRNA-negative women. Interestingly, Aptima was less sensitive on samples collected by the clinician (relative cross-sectional sensitivity 0.84; 95% CI: 0.74–0.96) than on samples collected by the patient, reflecting the influence that sample type has on performance.

HPV Self-Sampling: Uptake and Effectiveness

The use of HPV self-sampling has been recognized as an important pathway to reach and engage under-screened and never-screened individuals, who are at the highest risk for cervical cancer. In a new meta-analysis (Costa et al., British Journal of Cancer, 2022/2023), which comprised of randomized controlled trials, screening uptake was found to be significantly higher among women who were offered HPV self-sampling than those who were offered standard screening. Another meta-analysis was published in 2022 by Frontiers in Public Health which also revealed that HPV self-sampling significantly boosted uptake of cervical cancer screening as compared to traditional methods. In the ACCESS randomized controlled trial conducted in Japan (Fujita et al., 2024), a total of 7,337 women in the self-sampling intervention group and 7,772 in the control group had screening uptake of 20.0% and 6.4%, respectively (RR: 3.10; 95% CI: 2.82–3.42; $p < 0.001$). This is a 3.1 times higher participation rate for women who were not screened for ≥3 years. The success rate of HPV-positive women that were offered follow-up cytology was 46.8%, reducing the gains in detecting CIN2 +. To help advance the goal of greater cervical cancer screening uptake, a mailed HPV self-collection kit with scheduling assistance was used to screen women from low-income backgrounds in a Phase 3 RCT (MBMT-3, The Lancet Public Health, 2023) and showed to increase screening uptake compared to scheduling assistance alone.

HPV Vaccination Efficacy — Comprehensive Meta-Analysis

A comprehensive meta-analysis of 145 RCTs (Wang et al., Frontiers in Immunology, January 2026), following PRISMA 2020 guidelines and PROSPERO registration, provided the most extensive synthesis of prophylactic HPV vaccine efficacy, immunogenicity, and safety across bivalent, quadrivalent, and nonavalent formulations. The studies were conducted between 2010 and 2024, with follow-up periods ranging from 6 to 136 months. Key efficacy findings were:

- CIN Grade 1: 85% risk reduction (RR 0.15; 95% CI: 0.09–0.24; $p < 0.00001$; $I^2 = 91\%$); most pronounced in individuals ≤20 years (88% reduction)
- CIN Grade 2: 80% risk reduction (RR 0.20; 95% CI: 0.13–0.30; $I^2 = 74\%$); highest with three-dose (0/1/6) regimen; bivalent vaccine most effective for CIN II associated with HPV16/18
- CIN Grade 3: 52% significant risk reduction (RR 0.48; 95% CI: 0.23–0.98; $p = 0.04$; $I^2 = 69\%$)
- Persistent HPV16/18 infections: 84% risk reduction (RR 0.16; 95% CI: 0.12–0.21; $I^2 = 95\%$)
- Incident HPV16/18 infections: 75% risk reduction (RR 0.25; 95% CI: 0.19–0.34; $I^2 = 92\%$); greatest in HIV-negative group (94%)
- Atypical Squamous Cells of Undetermined Significance (ASC-US): 69% reduction ($I^2 = 94\%$)
- Low-Grade Squamous Intraepithelial Lesion (LSIL): 37% reduction (RR 0.63; 95% CI: 0.49–0.81; $p = 0.0003$)
- Serious adverse events: modest 10% reduction (RR 0.90; 95% CI: 0.82–0.99; $p = 0.03$); injection-site adverse events modestly increased (RR 1.26; $p = 0.007$) but no increase in systemic adverse events
- Pregnancy outcomes: no significant differences across seven pregnancy-related endpoints (live birth, spontaneous abortion, congenital anomalies, preterm birth)

Two Cochrane reviews (Henschke et al., 2025), synthesizing evidence from 60 RCTs (157,414 participants) and 225 observational studies (>132 million people), confirmed that HPV vaccination is safe and highly effective at preventing cervical cancer. Girls vaccinated at or before age 16 were 80% less likely to develop cervical cancer than unvaccinated girls, with substantial reductions in CIN2+ and CIN3+. The Vaccine Integrity Project review (University of Minnesota, 2026), drawing on 121 new peer-reviewed studies published between September 2024 and January 2026, found that vaccinated individuals were approximately 65% less likely to develop cervical cancer, with even greater protection in those vaccinated at age ≤16. Single-dose

Table 3: Self-Sampling HPV Strategies — Key Outcomes (2022–2026)

Study / Source	*Year*	*Participants*	***Strategy***	***Key Outcome***
ACCESS RCT (Fujita et al.)	2024	15,109	Opt-in self-sampling kit	RR uptake: 3.10 (2.82–3.42)
Costa et al. (meta-analysis)	2022–23	Multiple RCTs	HPV self-sampling kits	Significant ↑ screening uptake
MBMT-3 RCT (Lancet Public Health)	2023	Low-income US women	Mailed HPV self-collection + scheduling	Greater uptake vs. scheduling alone
Frontiers Public Health (meta-analysis)	2022	Multiple RCTs & obs.	Self-sampling proposal	↑ Cervical cancer screening (CCS) uptake

vaccination was found to offer comparable protection to multi-dose schedules for persistent HPV infection and cervical pre-cancers over five years of follow-up.

A large Swedish nationwide cohort study (BMJ, 2026) tracked approximately 1 million girls and women born 1985–2001 for up to 18 years post-vaccination. Women vaccinated before age 17 showed a 79% lower risk of invasive cervical cancer compared with unvaccinated women. No waning of protection was observed; even 13–15 years after vaccination, risk remained approximately 77% lower. US state-by-state analysis (Journal of the National Cancer Institute, 2026) demonstrated a 27% national decline in cervical cancer incidence among women aged 20–31 since HPV vaccine introduction, with states recording >50% declines in Washington DC, Rhode Island, Michigan, and Hawaii correlating with higher vaccination rates.

Vulnerable Populations and Equity in Cervical Cancer Risk

Following a systematic review and meta-analysis of 127 studies across high and upper-middle-income countries, the pooled relative risk of cervical cancer in vulnerable populations (women with low socioeconomic status, migrants, prisoners, sex workers, substance use disorders, mental illness, and HIV-positive women) was estimated and published in Nature Communications (2026). The main results were highly significant: women at risk were found to be at a substantially higher risk of cervical cancer (RR 2.78; 95% CI 2.32–3.32), and high-grade cervical lesions (RR 2.5; 95% CI 2.05–3.04), particularly when comparing subgroups and showing very high levels of heterogeneity. HIV infected women are 6 times more likely to get cervical cancer than HIV un-infected women. In sub-Saharan Africa, the incidence rates for countries like Eswatini (65 per 100,000), Zambia (65 per 100,000), Malawi (72 per 100,000), Zimbabwe (96 per 100,000) and Tanzania (10 per 100,000) are 10 to 16 times higher than in the United States (6 per 100,000). The cervical cancer screening rate among women worldwide is 36%, and there are extreme disparities, with only 4% in Ethiopia and almost 100% in the Netherlands and Sweden. On 2020, 200,000 new cases (32% of global burden) and 100,000 deaths (34% of global fatalities) occurred in the South-East Asia Region (WHO-SEARO), highlighting the disproportionate burden of the region.

AI-Assisted Colposcopy and Digital Screening

In recent years, artificial intelligence (AI) and deep learning (DL) technologies have also been utilized for automated interpretation of cytology, colposcopy and associated imaging as a means to enhance early detection of cervical cancer, especially in low- and middle-income countries. A systematic review of AI in colposcopic and cytological image analysis (2026) compiled advances in this rapidly evolving area, highlighting the potential of AI to improve the inter-observer variability in the interpretation of colposcopic images. The multimodal DL model that combines clinical history and colposcopy images for CIN2+ prediction showed: AUC-ROC = 95.3%; accuracy = 90.8%; positive predictive value (PPV) = 94.1%; negative predictive value (NPV) = 87.9% (development and internal validation using 6,356 LEEP-conization/cone-biopsy cases). The model proved to be more effective than the clinical impression alone by the clinicians. Up to 35% of colposcopy referrals for conisation could be avoided if the 10% expected probability decision threshold for recommendation for colposcopy is implemented without sacrificing any true CIN2+ cases. Based on the cervical cancer screening and diagnosis criteria, a Swin Transformer-based ensemble DL model was proposed to further improve the accuracy of cervical cancer screening

Table 4: HPV Vaccination Efficacy — Key Meta-Analytic Outcomes (2022–2026)

Outcome	*Studies (n)*	*RR (95% CI)*	*I^2*	*GRADE Certainty*
CIN Grade 1 reduction	21	0.15 (0.09–0.24)	I^2 = 91%	Low
CIN Grade 2 reduction	24	0.20 (0.13–0.30)	I^2 = 74%	Moderate
CIN Grade 3 reduction	5	0.48 (0.23–0.98)	I^2 = 69%	Moderate
Persistent HPV16/18 infections	51	0.16 (0.12–0.21)	I^2 = 95%	Low
Incident HPV16/18 infections	24	0.25 (0.19–0.34)	I^2 = 92%	Low
ASC-US	10	0.31 (reduction 69%)	I^2 = 94%	Low
Serious adverse events	27	0.90 (0.82–0.99)	I^2 = 39%	High
Cervical cancer (obs. studies; age ≤16)	225	RR ~0.20 (79–80% reduction)	Varies	High
Cervical cancer incidence (US, 2026)	State-level	27% national decline	—	Moderate

from colposcopy images (Scientific Reports, 2025). An AI-assisted analysis software that detects CIN (Scientific Reports, 2024) has been developed and validated, including for helping to screen for CIN, particularly in areas with limited pathology resources.

DISCUSSION

Superiority of HPV DNA Screening over Cytology

The results of this meta-analysis clearly show that HPV DNA-based primary screening for cervical cancer has higher sensitivity for detecting CIN2+ precancerous lesions than the conventional or liquid-based cytology. This pooled RR of 1.61 (95% CI 1.30-1.98) for 414,846 women across eight RCTs is statistically highly significant and substantial. This advantage is supported by a mechanistic argument: HPV DNA testing identifies women with high-risk oncogenic HPV types, which are the necessary causal factor for HPV infection and are directly associated to the onset of cancer, and not based on cytomorphological changes that can take years to occur after the molecular changes. There is the inherent advantage of HPV testing for the subgroup analysis of HPV-positive women where HPV testing was directly referred to colposcopy (RR 2.37) compared to HPV testing and then cytology triage (RR 1.36): Cytology, if used as a second screening step after HPV testing, will inevitably miss a percentage of high-grade lesions that would have been detected only during primary screening using cytology. But referral for direct colposcopy can lead to a rise in overtreatment and overdiagnosis because transient infections with HPV are most common in women under 30 years of age and may not develop into high grade lesions. There is a delicate balance between maximizing sensitivity and specificity, which is at the heart of the current controversy over best screening algorithms **(18-24)**. The data of the CERVIVA study and the meta-analysis by Arbyn et al. strongly suggest that HPV mRNA testing (Aptima) is an appealing alternative to HPV DNA testing, given the comparable sensitivity and the (non-trivially) higher specificity (84.0% vs. 80.8% for CIN2+), which helps minimize false-positive results and overtreatment. However, Aptima is less sensitive for self-collected samples requiring methodological adaptations to be used in self-sampling programs. Clinically feasible and evidence-based refinement of primary screening algorithms is provided by validated HPV mRNA testing available on clinician collected samples at 5-year intervals.

HPV Vaccination: Toward Cervical Cancer Elimination

The 2022–2026 meta-analysis of existing evidence confirms the efficacy, immunogenicity and safety of HPV vaccines regardless of vaccine formulation, dosage or subgroups of populations. The 84% reduction in persistent HPV16/18 infections and 80% in CIN II over follow-up up to 18 years (Sweden cohort), makes HPV vaccination one of the most effective cancer prevention interventions in the public health history. The evidence of protection from single dose vaccination versus multi-dose vaccination for several outcomes is important for programmatic implications as it is likely to make the scheduling easier in low-resource settings and could provide access to more people.

The nonavalent HPV vaccine (Gardasil-9, covering HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58) is the most comprehensive vaccine to protect against oncogenic HPV types accounting for about 90% of all cervical cancers, and the three-dose (0/1/6 months) regimen was shown to be the most effective in the Wang et al. (2026) meta-analysis. Vaccination had the highest level of protection for people under the age of 16, and the actual reduction in the incidence of cervical cancer in real-world cohorts was 79-80%.The highest level of protection was achieved when vaccination was done before the first sexual encounter, with a reduction in the incidence of CIN I up to 88% and a reduction in the incidence of cervical cancer up to 79-80% in real-world cohorts. Most importantly, no increased risk of serious adverse events, pregnancy complications, or other long-term health outcomes was found for HPV vaccines, which further supports their safety profile in population-level programs **(15-21)**.

Self-Sampling as an Equity Strategy

The 3.1-fold increase in screening uptake observed in the ACCESS RCT, and consistent evidence from multiple RCTs and meta-analyses, establishes HPV self-sampling as a powerful tool for reaching under-screened and never-screened women who bear the highest burden of cervical cancer. The most effective dissemination strategy is direct mailing of kits to women's homes (opt-out or opt-in approaches), which removes procedural barriers — including clinical appointment scheduling, transportation, and discomfort with invasive examination — that disproportionately affect marginalized populations. However, the 46.8% cytology triage compliance rate among HPV-positive women in the ACCESS trial identifies a critical implementation gap: increased detection of HPV-positive women is only clinically beneficial if followed by appropriate diagnostic workup and treatment. Systems-level interventions to improve triage follow-up are essential to translate screening uptake into cancer prevention.

WHO 90-70-90 Strategy: Progress and Gaps

As of November 2024, the global elimination initiative showed significant institutional momentum: at least 144 countries have introduced HPV vaccines, over 60 countries include HPV testing in cervical screening programmes, and 83 countries include surgical-care services in health benefit packages. Rwanda announced its goal to reach 90-70-90 targets by 2027, three years ahead of the WHO goal. Ireland launched a national Action Plan targeting elimination by 2040. The World Bank and GFF announced at least US$400 million in HPV-related investments at the 2024 International Women's Day pledging event.

Nonetheless, progress toward the 70% screening coverage target remains severely lagging: globally, only 36% of eligible women have undergone any cervical cancer screening, with dramatic geographic disparities. GLOBOCAN 2022 projections indicate that without significantly accelerated action, global cervical cancer burden will increase to 760,082 new cases (+14.8%) and 411,035 deaths (+17.8%) by 2030. Countries with medium and low Human Development Index (HDI) scores are unlikely to reach the WHO elimination threshold of 4 per 100,000 women-years even with a 5% annual decline in age-standardized incidence rates, underscoring the inequitable distribution of prevention resources globally **(25-30)**.

LIMITATIONS

Several limitations of this meta-analysis warrant acknowledgment. First, the high between-study heterogeneity observed for the primary outcome (I^2 = 86%) limits the precision of pooled estimates; this is largely attributable to clinically meaningful variations in post-positive triage protocols, follow-up duration, cytology methods, and geographic healthcare contexts across included studies. Second, the number of RCTs available for the primary HPV vs. cytology comparison remains limited (n = 8), constraining definitive conclusions and increasing sensitivity to individual study characteristics. Third, GRADE certainty of evidence for the primary CIN2+ detection outcome was rated very low, primarily due to differential loss to follow-up and lack of blinding in included trials (5,25-32). Fourth, indirect comparison limitations apply when synthesizing vaccine efficacy data alongside screening performance data from heterogeneous study designs. Fifth, most evidence originates from high-income countries, potentially limiting generalizability to low- and middle-income settings where cervical cancer burden is greatest and evidence is most urgently needed.

CONCLUSIONS AND RECOMMENDATIONS

Overall, the body of evidence accumulated from 2022–2026 shows that HPV screening using primary HPV testing is significantly more sensitive than cytology for detecting HPV-related precancerous lesions (CIN2+), with substantial sensitivity increases as high as 60% (RR 1.61; 95% CI: 1.30–1.98); HPV vaccination is highly and persistently protective against all HPV infection and cervical neoplasia regardless of the grade. In particular, the nonavalent vaccine (9 vaccines) is the gold standard for prevention, as there is 84% reduction in persistent HPV16/18 infections and no signs of reduced effectiveness after 18 years. A comprehensive, integrated cervical cancer prevention strategy over the 2026–30 period should contain the following evidence-based elements: (1) universal primary HPV DNA or mRNA-based screening as the first-line test; (2) HPV DNA genotyping triage to balance with high sensitivity and specificity, a very small proportion of HPV DNA type 16/18 (2.3%) cases will require colposcopy; (3) expanded use of HPV self-sampling programmes with home mailed kits and robust follow-up systems, as these will be needed to reach the under-screened population with high cervical cancer risk; (4) acceleration of gender-neutral HPV vaccination programmes with single-dose schedules in low-resource settings; (5) deployment of AI-assisted platforms for colposcopy and cytology to address pathology workforce gaps in high-burden low-resource settings; and (6) interventions aimed at individuals in vulnerable populations who are at 2.78 times higher risk of developing cervical cancer. The tools are available to meet the WHO 90-70-90 targets by 2030; the main challenge is equitable access and use of these tools in low-HDI countries. The global community will meet its historic goal of ending cervical cancer as a public health problem if there is a coordinated effort to implement integrated national strategies, international financial commitments and enhanced primary healthcare infrastructure.

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