Journal of Posthumanism
2025
Volume: 5, No: 9, pp. 658–672
ISSN: 2634-3576 (Print) | ISSN 2634-3584 (Online)
posthumanism.co.uk

DOI: https://doi.org/10.63332/joph.v5i9.3601

# Diagnostic Evaluation of HPV DNA Test in Detecting Cervical Pre-Cancer: A Systematic Review

Jannatul Ferdous[1], Ashrafunnesa[2], Saifullah Munshi[3], Md Maruf Haque Khan[4], Mohuwa Parvin[5], Hridi[6], Tanjela Bushra[7], Fariha Haseen[8]

***Abstract***

*Cervical cancer remains a significant global health challenge, particularly in low- and middle-income countries, due to limited access to effective screening programs. Persistent infection with high-risk human papillomavirus (HR-HPV) is recognized as the primary etiological factor for cervical cancer. Although cytology-based screening methods such as the Pap smear and liquid-based cytology (LBC) have historically served as the cornerstone of early detection, their sensitivity limitations have prompted the investigation of HPV DNA testing as an alternative or adjunctive screening strategy. This systematic review aimed to evaluate and compare the diagnostic accuracy of HPV DNA test, which detects HPV 16, HPV 18, and 12 other high-risk HPV genotypes, with conventional cytology methods (Pap test and LBC) and visual inspection with acetic acid (VIA) in detecting high-grade cervical intraepithelial neoplasia (CIN2+) as part of primary cervical cancer screening. The review was conducted in accordance with PRISMA guidelines. A comprehensive literature search was performed using PubMed, Google Scholar, and Medline to identify relevant studies published in English. Six studies were ultimately included, comprising one randomized controlled trial and five cross-sectional studies. The findings consistently demonstrated that HPV DNA testing, exhibits significantly higher sensitivity than cytology or VIA for detecting CIN2+ lesions, though with slightly reduced specificity. Combining cytology or VIA with HPV DNA testing further improved sensitivity but resulted in lower specificity. While these results highlight the superior detection capability of HPV-based testing, the long-term impact on reducing cervical cancer incidence and mortality requires further validation through ongoing and future randomized trials.*

***Keywords:*** *Diagnosis, HPV, DNA, Cervical Pre-Cancer.*

## Introduction

Cervical cancer is a major public health issue globally, ranking as the fourth most common cancer among women, with an estimated 660000 new cases and 350,000 deaths reported worldwide in 2022.[1] The burden of cervical cancer is disproportionately higher in low- and middle-income countries, largely due to limited access to effective screening programs and timely treatment.[2] Early detection of cervical pre-cancerous lesions offers the best opportunity to prevent progression to invasive cervical cancer and reduce mortality.

Persistent infection with oncogenic, or high-risk, human papillomavirus (HR-HPV) is now recognized as the central cause of cervical carcinogenesis.[3] Among the over 200 known HPV

[1]Professor, Department of Gynaecological Oncology, Bangladesh Medical University, Dhaka, Bangladesh, Email: jannat@bsmmu.edu.bd
[2] Professor, Department of Gynaecological Oncology, Bangladesh Medical University, Dhaka, Bangladesh
[3]Professor, Department of Virology, Bangladesh Medical University, Dhaka, Bangladesh.
[4]Assistant Professor, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh
[5]Resident, Department of Gynaecological Oncology, Bangladesh Medical University, Dhaka, Bangladesh
[6]Research Officer, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh
[7]Research Associate, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh
[8]Associate Professor, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh

types, at least 14 are considered high-risk, with HPV 16 and HPV 18 responsible for approximately 70% of cervical cancers worldwide.[4] The progression from initial HPV infection to cervical intraepithelial neoplasia (CIN) and, eventually, invasive cancer is typically slow, providing a window of opportunity for detection and intervention of pre-cancerous conditions.[5]

Traditionally, cytology-based screening, particularly the Papanicolaou (Pap) smear, has been the primary method for detecting cervical abnormalities. Although effective, cytology has well-documented limitations, including relatively low sensitivity, inter-observer variability, and the need for repeated rounds of testing to ensure effective detection.[6,7] These limitations have driven the need for more sensitive, objective, and reliable screening tools.

In recent years, the HPV DNA test has gained prominence as a valuable tool for cervical cancer screening. Unlike cytology, which identifies cellular changes caused by HPV infection, the HPV DNA test detects the presence of the virus itself, allowing for earlier identification of women at risk of developing cervical pre-cancer and cancer.[8] Multiple large-scale studies and meta-analyses have demonstrated that HPV DNA testing has a significantly higher sensitivity for detecting high-grade cervical lesions (CIN2+ and CIN3+) compared to cytology, although sometimes at the expense of slightly lower specificity.[9,10]

Despite its potential advantages, the widespread adoption of HPV DNA testing raises several questions regarding its diagnostic accuracy, especially in diverse populations with varying HPV prevalence rates, screening protocols, and healthcare infrastructure.[11,12]

Given the growing emphasis on HPV-based screening strategies, particularly with the WHO's global initiative to eliminate cervical cancer as a public health problem by the end of the 21st century,[1] there is a pressing need to comprehensively evaluate the diagnostic performance of HPV DNA testing. Systematic reviews and meta-analyses of diagnostic studies are critical in providing robust, evidence-based insights into the clinical utility of HPV DNA testing in detecting cervical pre-cancer.

This review does not include other possible uses of HPV testing, which have been discussed in previous systematic reviews. Recent meta-analyses have demonstrated that HPV DNA test is more accurate than repeat cytology in managing women with ASCUS Pap smear results.[13,14] Additionally, further analyses have indicated that HPV DNA testing is more sensitive than cytology or VIA in detecting potential treatment failures following surgical management of cervical intraepithelial neoplasia.[15,16] The aim of this review is to determine the diagnostic evaluation of HPV DNA testing as a primary screening tool for cervical cancer, focusing on its performance, reliability, and accuracy in identifying cervical cancer precursors or early-stage invasive disease.

**Rationale for this review:**

Cervical cancer remains a major global health concern, with the greatest burden in low- and middle-income countries due to limited screening and treatment access. Persistent infection with high-risk HPV, especially types 16 and 18, is the primary cause of cervical carcinogenesis, and its slow progression allows for early detection. Traditional screening methods, such as cytology (Pap smear) and Visual Inspection with Acetic Acid (VIA), have reduced disease burden but are

limited by lower sensitivity, observer variability, and the need for repeated testing. HPV DNA testing offers higher sensitivity for detecting high-grade lesions, though its specificity and performance may vary across populations and settings. A systematic evaluation of its diagnostic accuracy as a primary screening tool is essential to inform effective screening strategies and advance global efforts to eliminate cervical cancer.

## Objectives

The main objective of this review was to compare the diagnostic accuracy of HPV DNA testing using the PCR platform with cytology and VIA in detecting high-grade cervical intraepithelial neoplasia (CIN2+) during primary cervical cancer screening.

## Methodology & Materials

### Study Design

This systematic review was conducted following the PRISMA 2020 guidelines. The review process comprised five steps: (1) problem identification; (2) literature searching; (3) data review and evaluation; (4) data synthesis and analysis; and (5) data presentation.

### Eligibility Criteria:

Studies were selected based on the PICO-S framework:

- **Population:** Women undergoing cervical cancer screening.
- **Intervention:** HPV DNA testing using the Cobas 4800 PCR platform (genotyping HPV 16, HPV 18, and pooled high-risk types).
- **Comparator:** Cytology (Pap smear or liquid-based cytology) and/or Visual Inspection with Acetic Acid (VIA).
- **Outcome:** Diagnostic accuracy measures, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting cervical precancerous lesions (CIN2+ or CIN3+).
- **Study design:** Diagnostic accuracy studies, including cross-sectional, cohort, and case-control designs.

### Exclusion criteria:

- Case reports, conference abstracts, letters, commentaries.
- Non-English studies (due to resource constraints and lack of translation availability).

### Search Strategy:

A comprehensive electronic search was performed in PubMed, Google Scholar, and Medline, covering publications up to April 2025. The following keywords were used with Boolean operators to maximize retrieval:

- ("HPV DNA testing" OR "HPV DNA test") AND ("cervical cancer screening" OR "cervical intraepithelial neoplasia" OR "CIN") AND ("cytology" OR "Pap smear" OR "liquid-based cytology" OR "VIA")

Additional manual searches of reference lists from included articles were conducted to identify further relevant studies. Grey literature and non-English language studies were excluded due to resource constraints and lack of translation availability.

Duplicate records were removed using EndNote reference management software and manual cross-checking.

**Study Selection:**

Two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible studies were retrieved and assessed against the inclusion criteria. Discrepancies between reviewers were resolved by discussion or consultation with a third reviewer to reach consensus.

**Data Extraction:**

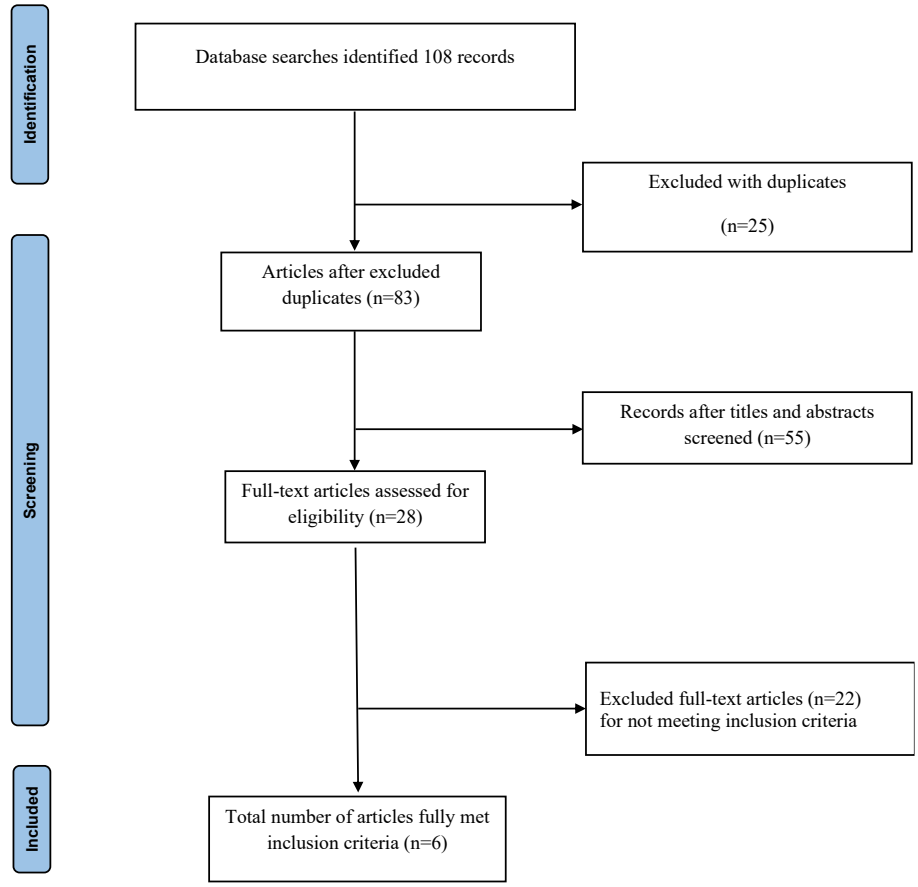
Data extraction was performed independently by two reviewers using a standardized form. Extracted information included study design, sample size, participant demographics (age range), screening methods used (HPV DNA testing, cytology, VIA), reference standard (histopathology or colposcopy), and diagnostic accuracy outcomes (sensitivity, specificity, PPV, NPV). The focus was on studies using the Cobas 4800 platform due to its genotyping capability for HPV 16, HPV 18, and pooled other high-risk HPV types.

**Risk of Bias Assessment (QUADAS-2):**

| **Domain** | **Assessment** | **Rationale** |
|---|---|---|
| Patient Selection | Low risk in most studies | Most included studies recruited large screening populations, often community-based, minimizing selection bias. However, some (e.g., small-sample cross-sectional studies like Islam et al., 2017, n=99) may not be representative of the general screening population. |
| Index Test (HPV DNA / VIA / Cytology) | Low to moderate risk | In most studies, the index tests were performed using standardized protocols (e.g., Cobas 4800, HC II). However, operator-dependent tests like VIA may have variation in application and interpretation, which could introduce observer bias if blinding to reference standard was not maintained. |

| **Domain** | **Assessment** | **Rationale** |
|---|---|---|
| Reference Standard | Low risk | Histopathology was used as the gold standard in all studies for screen-positive women. The main limitation is that not all screen-negative women received the reference standard, which may cause verification bias — particularly relevant in studies like Basu et al. (2015) where only positives underwent biopsy. |
| Flow and Timing | Moderate risk | In some studies, not all participants who screened positive underwent confirmatory testing (e.g., HC II positives with incomplete follow-up in Basu et al.), potentially introducing attrition bias. Also, the time between screening and reference standard was not consistently reported. |
| Applicability Concerns | Low risk overall | The included populations, interventions, and outcomes are consistent with the review's PICO framework, although results from small or geographically specific samples (e.g., Bangladesh, Greece) may have limited generalizability. |

**Figure 1.** Flow chart of systematic review of literature selection process for the present research




## Result

### Study Characteristics:

In the present review, we included 6 papers: one was a randomized controlled[15] and five was cross-sectional (Table 1).[14,16-20]

The initial search identified 108 articles. After removing duplicates, 83 articles remained. Of these, 55 were excluded after screening titles and abstracts, and 22 full-text articles were excluded for not meeting inclusion criteria. Finally, 6 studies met the criteria and were included in this review.

The studies included in this review were conducted across diverse geographical regions, primarily in low- and middle-income countries, as well as in Europe. Basu et al. (2015) conducted a large-scale cross-sectional study in India involving 39,729 women, evaluating visual inspection with acetic acid (VIA) and HPV testing (HC II) for cervical cancer screening, using biopsy in VIA-positive or HPV-positive cases as the gold standard.[14] Similarly, Sankaranarayanan et al.

(2005) carried out a large randomized controlled trial in Osmanabad, India, involving over 70,000 women, comparing VIA, Pap smear, and HPV testing for CIN2+ detection with biopsy confirmation.[15] In Switzerland, Bigras and Marval (2005) performed a cross-sectional study on 13,842 women using liquid-based cytology and HPV DNA testing (HC2) with biopsy in screen-positive cases.[16] Islam et al. (2017) conducted a smaller cross-sectional study in Bangladesh involving 99 women, assessing the performance of Pap smear and HPV DNA (HC2 assay) with biopsy as the gold standard.[17] Sarian et al. (2005) carried out a multi-center cross-sectional study in Brazil and Argentina with over 14,000 women screened using cytology, HPV (HC2), VIA, and VILI, with abnormal findings leading to biopsy.[18] Agorastos et al. (2005) conducted a cross-sectional study in Greece involving 1,296 women screened with conventional cytology and HPV PCR, with histopathological confirmation for abnormal cases.[19] Finally, Cuzick et al. (2003) conducted a large cross-sectional study in the United Kingdom on 10,358 women using conventional cytology and HPV testing (HC2), with colposcopy and biopsy for abnormal findings.[20]

**Cervical Cancer Screening:**

Basu et al. (2015)[14] reported a VIA positivity rate of 7.1%, while HPV detection using Hybrid Capture II (HC II) was 4.7%. The detection of cervical intraepithelial neoplasia grade 3 or higher (CIN 3+) was notably higher with HPV testing compared to VIA. After adjusting for verification bias, VIA showed a sensitivity of 67.9%, whereas HC II demonstrated a markedly superior sensitivity of 91.2%. Specificity was also better for HPV testing (96.9%) than VIA (93.2%). Additionally, using HPV testing to triage VIA-positive women significantly increased the positive predictive value from 4.0% to 37.5%, without compromising sensitivity. Treatment adherence was excellent, and cancers identified through screening were more likely to be diagnosed at an early stage.

In a study by Sankaranarayanan et al. (2005),[15] test positivity varied across methods: 14.0% for VIA, 7.0% for cytology, and 10.3% for HPV. Detection rates of high-grade lesions (CIN 2/3 or worse) were similar across VIA (0.7%), cytology (1.0%), and HPV testing (0.9%). However, the detection rate for VIA declined over time, potentially due to decreasing positivity rates. Over 85% of women diagnosed with high-grade lesions received proper treatment. While cytology and HPV testing showed consistent diagnostic performance, VIA required stringent quality control to maintain accuracy.

Bigras & Marval (2005)[16] found that HPV testing had a much higher sensitivity (97%) than cytology (59%) for detecting high-grade cervical lesions. While cytology had slightly better specificity (97% vs. 92% for HPV), 14% of cytology-negative samples associated with histologically confirmed HSIL did not display abnormal cells, revealing cytology's limitations. The study also observed that higher HPV viral loads correlated with abnormal Pap results, reinforcing the superior sensitivity of HPV testing for detecting significant lesions.

Islam et al. (2017)[17] demonstrated that HPV DNA detection via the Hybrid Capture 2 (HC-2) assay was positive in 28.28% of cases, with positivity increasing alongside lesion severity. HPV viral loads were particularly elevated in invasive squamous cell carcinoma cases. Statistically significant associations were observed between HPV positivity and both histological findings

and Pap smear results ($p<0.005$ for both). The study concluded that combining HPV DNA testing with Pap cytology improves detection rates and follow-up for cervical precancer and cancer.

According to Sarian et al. (2005),[18] VIA had a positivity rate of 11.6%, whereas Pap smear positivity was much lower: 2.2% at the LSIL threshold and 1.1% at the HSIL threshold. HPV testing produced a positivity rate of 17.1%. The sensitivity of VIA and VILI in detecting CIN 2/3 lesions was relatively limited, and approximately 10% of women with normal histology had false-positive VIA results. However, when VIA was combined with Pap smears or HPV DNA, both sensitivity and specificity significantly improved, supporting the advantage of combined screening strategies over individual tests.

Agorastos et al. (2005)[19] conducted a cross-sectional study in Northern Greece involving 1,296 women, revealing that HPV DNA testing was considerably more sensitive than cytology for detecting cervical intraepithelial neoplasia (CIN), with sensitivity rates of 75% versus 50%, respectively, for high-grade lesions. Specificity and predictive values were similar for both tests, although a slight drop in specificity for women more than 30 years of age.

**Table 1:** Summary of the published articles

| **Author-Year** | **Study design** | **Sample size (n)** | **Screening tests** | **Criteria for gold standard application** | **Outcome** |
|---|---|---|---|---|---|
| Basu et al.,[14] 2015, India | Cross-sectional | n= 39 729 | VIA, HPV (HC II) | Abnormal VIA, positive HPV followed by histopathology confirmation | Test positivity: 7.1% (VIA), 4.7% (HC II); Sensitivity: VIA 67.9%, HC II 91.2%; Specificity: VIA 93.2%, HC II 96.9%; Triaging of VIA+ with HPV increased PPV from 4.0% to 37.5%; High compliance to treatment; Shift towards early-stage cancer detection. |
| Sankaranarayanan et al.,[15] 2005, India (Osmanabad district) | Randomized controlled (Baseline data) | 35,193 cyto, 36,938 HPV | VIA, Cytology (Pap), HPV | Positive screening test (>ASCUS, positive HPV, positive VIA, clinical suspicion) referred for colposcopy and histopathology | Test positivity: VIA 14.0%, Cytology 7.0%, HPV 10.3%; Detection of CIN2+: VIA 0.7%, Cytology 1.0%, HPV 0.9%; Over 85% treatment compliance; VIA detection rate decreased over time. |
| Bigras & Marval,[16] 2005, Switzerland (Geneve, Vaud, Neuchatel, Fribourg, Valais, Tessin) | Cross-sectional | n= 13,842 | Liquid-based cytology, HC2 | Abnormal cytology or positive HPV, confirmed by colposcopy-guided biopsy (histopathology) | Test positivity in 1334 women; 1031 biopsied positive cases + 502 biopsied negatives; 82 histologic HSIL detected; HPV more sensitive than cytology; HPV viral load correlated with abnormal Pap |

| | | | | | |
|---|---|---|---|---|---|
| Islam et al.,[17] 2017, Bangladesh | Cross-sectional | n= 99 | Pap smear, HPV-DNA (HC-2 assay) | Biopsy in colposcopically positive cases; histopathology as gold standard | 28.28% positive with HPV-DNA (HC-2); significant association between HPV-DNA positivity and histological diagnosis (P<0.005); high viral load in invasive SCC |
| Sarian,[18] 2005, Brazil (Sao Paolo, Campinas, Porto Alegre), Argentina (Buenos Aires) | Cross-sectional | n= 10,138 cyto, 4195 HPV | Conventional cytology, HC2, VIA, VILI | Abnormal VIA/VILI, smear >LSIL, positive HPV referred for histopathology confirmation | VIA positivity: 11.6%, VILI: 23%, Pap (LSIL): 2.2%, Pap (HSIL): 1.1%, HCII: 17.1%. Combined VIA/VILI + Pap/HCII improved sensitivity up to 100%, specificity up to 99.8%. |
| Agorastos et al.,[19] 2005, Greece (Thessaloniki Thermi, Corfu Veria, Serres) | Cross-sectional | n= 1296 | Conventional cytology, PCR (MY09/MY11, 18 HR types) | >ASCUS or positive HPV followed by histopathology confirmation | HPV DNA testing showed significantly better sensitivity than Pap smear for detecting CIN (75% vs 50% for high-grade lesions; 81.2% vs 50% for any grade). Specificity and predictive values similar. Sensitivity of HPV DNA higher regardless of age. |

Table 2: Summary of the published articles- Diagnostic Outcomes

| Author-Year | Test positivity | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Basu et al.,[14] 2015, India | VIA: 7.1, HC II: 4.7 | VIA: 67.9, HC II: 91.2 | VIA: 93.2, HC II: 96.9 | VIA: 4.0 → 37.5 (with HPV triaging) | Not provided |
| Sankaranarayanan et al.,[15] 2005, India (Osmanabad district) | VIA: 14.0, Cytology: 7.0, HPV: 10.3 | Not provided | Not provided | Not provided | Not provided |
| Bigras & Marval,[16] 2005, Switzerland (Geneve, Vaud, Neuchatel, Fribourg, Valais, Tessin) | 1334 women; 1031 biopsy positives, 502 biopsy negatives; 82 HSIL cases | HPV more sensitive than Cytology | Not provided | Not provided | Not provided |
| Islam et al.,[17] 2017, Bangladesh | 28.28 | Not provided | Not provided | Not provided | Not provided |
| Sarian,[18] 2005, Brazil (Sao Paolo, Campinas, Porto Alegre), Argentina (Buenos Aires) | VIA: 11.6, VILI: 23, Pap LSIL: 2.2, Pap HSIL: | Combined tests: up to 100 | Combined tests: up to 99.8 | Not provided | Not provided |

| | | | | | |
|---|---|---|---|---|---|
| | 1.1, HCII: 17.1 | | | | |
| Agorastos et al.,[19] 2005, Greece (Thessaloniki Thermi, Corfu Veria, Serres) | Not provided | CIN any grade: HPV 81.2 vs Pap 50 CIN high grade: HPV 75 vs Pap 50 | Similar | Similar | Similar |

## Discussion

The screening for precancerous cervical lesions is one of the three objectives set by the World Health Organization (WHO) to achieve the global goal of eliminating cervical cancer by the year 2030. Cervical cancer screening with HPV DNA testing is a proven and recommended method. Recent evidence from the International Agency for Research on Cancer suggests that HPV DNA testing is the most effective technique for lowering the cervical cancer incidence and mortality when compared to other screening methods such as cytologic analysis and VIA. In this review, we analyzed and to compare the diagnostic accuracy of HPV DNA testing (using Cobas 4800) with cytology and VIA in detecting high-grade cervical intraepithelial neoplasia (CIN2+) during primary cervical cancer screening. Our focus was primarily on evaluating the sensitivity and specificity of these screening methods, as well as other diagnostic performance measures including positive predictive value (PPV), negative predictive value (NPV), accuracy, positive and negative likelihood ratios, diagnostic odds ratio, and area under the receiver operating characteristic curve (AUC). Although predictive values often vary with the prevalence of disease in specific populations, generalization of our findings is more applicable here since the included studies were largely conducted on primary screening populations.

We observed substantial interstudy variation in the sensitivity and specificity of different screening tests. This heterogeneity was expected for cytology, as interpretation of cytological smears is known to have reproducibility challenges across different laboratories and technicians.[20,21] For HPV testing, variation was likely influenced by differences in laboratory techniques, types of primers used for PCR, and thresholds employed for positivity in HC2 assays.[22] Interestingly, a few studies, particularly those conducted in resource-limited settings, showed lower sensitivities for HPV testing, potentially due to sample collection methods, quality assurance issues, or local epidemiological factors.[23,24] Furthermore, potential misclassification bias in the gold standard (histopathology following colposcopy) may also have contributed to these discrepancies.

Consistent with previous research, the present review confirmed that HPV DNA testing performed on the Cobas 4800 PCR platform — which identifies HPV 16, HPV 18, and 12 other high-risk HPV types — demonstrates superior sensitivity for detecting high-grade cervical intraepithelial neoplasia (CIN2+) compared to cytology-based screening and VIA. In addition, other diagnostic performance measures, including specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, were evaluated in the included studies to comprehensively assess the diagnostic value of HPV DNA testing in primary cervical cancer screening.[25,26] This heightened sensitivity is valuable in reducing false-negative results and potentially lowering cervical cancer incidence and mortality in the long term. However, this advantage comes at the expense of reduced specificity, particularly in younger women where

transient HPV infections are more common.[28] The increased number of false positives leads to higher rates of referral for colposcopy and treatment for cervical pre-cancer, which may strain healthcare resources and cause unnecessary anxiety and psychological morbidity for affected women.[27,28]

Studies evaluating the combination of cytology with HPV testing have reported significantly increased sensitivity, often approaching 100%, but with an associated decline in specificity.[29] While this dual strategy might be appealing for high-resource settings aiming for maximal cancer prevention, its utility in low-resource settings is questionable given cost implications and the infrastructure required for managing follow-up care.[30]

The specificity of HPV testing has been proposed to increase with age, making it a potentially more suitable screening tool for women above 30 years of age.[31] Although our analysis did not confirm a significant age-related specificity increase, the limited age-stratified data might have affected the power to detect such differences. Cytological triage of HPV-positive women has been suggested as a viable solution to improve specificity and reduce unnecessary colposcopies.[32]

Importantly, several studies have demonstrated that a negative HPV test provides longer-lasting reassurance against cervical cancer than a negative cytology result, with some suggesting that screening intervals could be safely extended up to five years following a negative HPV test.[33,34] Extending screening intervals could improve program cost-effectiveness, particularly in organized screening programs in high-income countries.

While cross-sectional diagnostic accuracy data strongly favor HPV testing over cytology, the ultimate goal of cervical screening is not only to detect precancerous lesions but also to reduce cervical cancer incidence and mortality. Evidence from long-term randomized controlled trials (RCTs) is crucial to support any major shift in screening recommendations. Several large RCTs are ongoing or recently completed, including Swedescreen (Sweden), POBASCAM (The Netherlands), ARTISTIC (UK), NTCC (Italy), and trials in India, Canada, and Finland, enrolling hundreds of thousands of women collectively.[35,36] These trials will provide critical data on long-term outcomes, including cancer incidence reduction and potential harms of screening programs.

Based on the currently available data, agencies such as the US Food and Drug Administration (FDA) have approved HPV testing as a co-test alongside cytology for women aged 30 years and older,[37] with some organizations advocating for primary HPV testing alone.[38] In Europe, while HPV-based screening is being progressively introduced, recommendations vary by country.[26]

Despite promising early findings, the authors of this review agree with other experts that strong evidence from longitudinal studies is required before recommending the universal adoption of HPV testing as the primary modality for cervical cancer screening, especially in low-resource settings. Although the World Health Organization (WHO) and many international guidelines already recommend HPV DNA testing as the preferred primary screening method, its large-scale implementation still faces practical challenges related to cost, infrastructure, and follow-up systems in resource-limited regions. The risks of overdiagnosis, unnecessary interventions for regressive CIN lesions, and the economic and psychological impact of widespread HPV positivity must be carefully balanced against the benefits. Considering that cytology-based

screening programs have significantly reduced cervical cancer incidence even without randomized trial evidence, any substantial shift in paradigm must adhere to the highest standards of modern evidence-based medicine.[39]

**Limitations of the study**

The present review has some limitations that are worth mentioning. The number of included studies was small, which may affect the generalizability of results. Only English-language publications were considered, potentially introducing language bias. A formal risk of bias or certainty assessment (e.g., QUADAS-2 or GRADE) was not performed. Significant heterogeneity among studies was observed due to differences in methods and populations. Finally, findings may not fully apply to low-resource settings due to practical implementation challenges.

**Conclusion**

This systematic review has clearly demonstrated that HPV DNA test exhibits superior sensitivity compared to both conventional and liquid-based cytology and VIA, suggesting its potential to enhance the overall sensitivity of cervical cancer screening programs. The results of ongoing longitudinal randomized controlled trials are essential to determine the true impact of HPV-based screening on long-term cancer prevention outcomes. Moreover, caution must be exercised when generalizing these findings across different populations and healthcare settings. Further comprehensive economic evaluations are also required to assess the cost-effectiveness of implementing HPV testing—either alone or in combination with cytology—in various screening strategies, particularly in resource-limited settings.

**Other Considerations:**

**Funding sources** – No external funding was received for this review.

**Conflicts of interest** – The authors declare no conflicts of interest.

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