Human papillomavirus tests for cervical cancer screening in low resource settings: a protocol of a diagnostic test accuracy systematic review

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Abstract

Background: Human Papillomavirus (HPV) tests for cervical cancer screening in low resource settings might improve early detection and preventive efforts. **Objectives:** To determine the diagnostic accuracy of HPV tests for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) in low resource settings. **Search strategy:** we will search the Cochrane library, MEDLINE, CINAHL, Web of Science, and Scopus. We will search references of relevant studies. **Selection criteria:** We will include diagnostic test accuracy studies if women had an HPV test for cervical cancer screening, followed by verification with colposcopy and colposcopy-directed biopsy. The primary target is CIN2+. **Data collection and analysis:** Two authors will independently screen studies, extract data, and assess methodological quality. We will use bivariate diagnostic random-effects meta-analysis. **Results:** This is a protocol of a diagnostic test accuracy systematic review. **Conclusions:** Evidence will aid in making well-informed decisions for cervical cancer screening in low resource settings. **Implications for future research** will be suggested based on the gaps identified.

Keywords

Cervical Intraepithelial Neoplasia; Early Detection of Cancer; Papillomaviridae; Papillomavirus Infections; Developing Countries; Sensitivity; Specificity; Diagnostic accuracy

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1. Introduction

Cervical cancer remains a major health concern. Currently, it ranks as the fourth most common cancer in women worldwide [1,2] with most cases affecting middle aged women living in developing countries [3,4]. Invasive cervical cancer is one of the best examples of cancer prevention by screening and treatment at the pre-invasive stage [5,6]. The detection of cytological abnormalities by microscopic examination of cervical smears with the subsequent treatment of women with high-grade cytological abnormalities, constitutes an effective prevention strategy against

the development of cervical cancer [7].

Developing countries may lack financial, technical, and human resources for repetitive cytological screening and prolonged surveillance of screen-positive women. Alternative test methods might serve as affordable, applicable, and acceptable screening tests in low resource settings [8].

DNA of high-risk human papilloma virus (hr-HPV) can be retrieved in almost all cancers of the cervical epithelium and therefore can be used as a screening test [9]. Several HPV tests, both DNA-based and RNA-based assays, are currently available and validated. The tests are executed using cells from the surface of the cervix collected in the clinic or by self-sampling [10,11].

The use of HPV testing has gained wide acceptance in developed countries with an established laboratory infrastructure. The clinical applicability of HPV tests includes its use as a primary screening, in the triage of abnormal cytology, or in the follow-up after treatment [6,8,10–12]. Evidence of test accuracy in developing countries requires a comprehensive synthesis of the best available current research. This would pave the path to its programmatic implementation.

The aim of this review is to determine the diagnostic accuracy of HPV test screening tests for detecting cervical intraepithelial neoplasia (CIN) of grade 2 or worse (CIN 2+), in low and lower-middle income countries.

2. Methods

We will conduct the systematic review using methodological approaches prespecified in this protocol. We prospectively registered the protocol in PROSPERO (CRD42020185851). We will report the review according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines [13].

2.1 Eligibility criteria

We will include published cross-sectional studies that have evaluated the diagnostic accuracy of HPV tests, followed by verification of study participants

with a reference test, for cervical cancer screening. Participants are adult women in low resource settings defined as low and lower middle-income countries. Index tests include DNA-based or RNA-based HPV assays of samples that are either clinic- or self-collected. Target conditions included CIN 2+ and CIN 3+. We will accept a colposcopy and colposcopy-directed biopsy as the reference standard for the diagnosis of the target conditions. We will exclude studies of a case-control design as these are considered to have high risk of bias due to inflated accuracy estimates.

2.2 Information sources

We will use a comprehensive search strategy to find published articles (Appendix S1). We will search the Cochrane library, MEDLINE, CINAHL, Web of Science, and Scopus. We will not apply any restrictions on language or date of publication. Strategies will utilize a combination of controlled vocabulary and keywords. Medline search strategy is (exp Cervical Intraepithelial Neoplasia/ OR CIN.mp. OR Cervical Intraepithelial Neoplasia.mp.) AND (exp human papillomavirus dna tests/ OR (papillomavirus.mp. AND test*.mp.) OR (hpv.mp. AND test*.mp.)) AND (specific*.mp. OR exp sensitivity and specificity/).

We will search the reference lists in articles retrieved from electronic databases and relevant review articles.

2.3 Study selection

Two review authors will use a reference manager to import and de-duplicate search results. They will independently screen titles and abstracts to identify potentially eligible studies for full-text retrieval. Two review authors will double check the list of potentially eligible studies. Review authors working in pairs, will independently assess the full text using the predefined eligibility criteria. They will resolve discrepancies by discussion and by consulting with the lead author.

2.4 Data collection process

For each included study, two review authors will independently extracted the following data: General

information: title, journal, year, and study design; Sample size: total number of participants included and tested; Baseline characteristics: age, index test, threshold for the definition of a positive screening result; reference test; numbers of true positive, true negative, false positive, and false negative findings. We will extract these data for both target conditions (CIN2+ and CIN3+). All numbers will be double checked by two authors. We will summarize the data from each study in 2×2 tables (true positive, false positive, false negative, true negative).

2.5 Risk of bias and applicability

Review authors, working in pairs, will independently assess the risk of bias of included studies and applicability of their results using QUADAS-2 [14]. They will resolve discrepancies by discussion and by consulting with the lead author. We will address aspects of study quality involving the participant spectrum, index tests, target conditions, reference standards, and flow and timing (Table S1). We will classify a study as having a high risk of bias if at least one of the domains of QUADAS-2 was judged as being high risk.

2.6 Synthesis of results

Each type of HPV test will be compared against the reference test. For each type of HPV test, TP, TN, FP, and FN will be computed. We will use bivariate diagnostic random-effects meta-analysis [15]. We will present the results in a summary receiver operating characteristic (ROC) curve. We will use the Markov chain Monte Carlo procedure to generate summary positive and negative likelihood ratio and diagnostic odds ratio for the bivariate model [16]. When there are three or less studies, we will use a univariate random-effects model. For each of the target condition, we will present the synthesis by the type of HPV test and by method of sample collection. We will assess the effect of risk of bias of included studies on diagnostic accuracy by performing a sensitivity analysis in which we will exclude studies classified as having high risk of bias. We will use R software version 4.0.1 and package 'mada' version 0.5.9 [17].

3. Results

We will report the results under the following headings:

1. Study selection
2. Study characteristics
3. Risk of bias and applicability
4. Results of individual studies
5. Synthesis of results
6. Additional analysis

4. Discussion

The review will assess the diagnostic accuracy of various HPV tests for cervical cancer screening in low and lower middle-income countries. We will consider only cross-sectional studies for inclusion in the review. We will compute pooled estimates of diagnostic test accuracy of various HPV tests and will present the results by type of test and sample collection procedure.

Authors' contributions All authors have made substantive intellectual contributions to the development of this protocol. AN contributed to the study conception and design and conceptualized the review approach. MK, ME, MG, YA, FE, RM, AN contributed to writing the manuscript and approved the final draft.

Competing interests The authors declare that they have no competing interests.

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