Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Implementation-Oriented Pilot study of Primary HPV-Based Cervical Cancer Screening in North Macedonia

Goran Dimitrov[1]

gorandimi@gmail.com

University Clinic of Obstetrics and Gynaecology

Irena Aleksioska Papestiev[1]

University Clinic of Obstetrics and Gynaecology

Fadil Cana[2]

PHI University Clinic for Infectious Diseases and Febrile Conditions

Ajla Shabani[1]

University Clinic of Obstetrics and Gynaecology

Ana Daneva Markova[1]

University Clinic of Obstetrics and Gynaecology

Vjosa Xhaferi Mazllami[1]

PHI Clinical Hospital

Onur Dika[1]

University Clinic of Obstetrics and Gynaecology

Research Article

Keywords: HPV screening, cervical cancer, hrHPV, North Macedonia, follow-up, implementation

Posted Date: July 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10348204/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Cervical cancer remains a preventable yet persistent public-health challenge in Eastern Europe. In alignment with WHO recommendations, North Macedonia has articulated a national intention to transition from cytology-based screening to primary high-risk human papillomavirus (hrHPV) testing. In this framework a multi-centre pilot study was conducted in 2024, enrolling 1,050 women aged 30–65 years to assess hrHPV prevalence, genotype distribution, and implementation feasibility. Overall hrHPV prevalence was 11.1%, with the most common types being HPV 16 (1.5%), HPV 18 (0.6%), and other hrHPV types (8.3%). Among 117 hrHPV-positive women with histopathological evaluation, 7 cases of CIN 1, 3 cases of CIN 2, and 9 cases of CIN 3 + were identified. One case of invasive cervical carcinoma was diagnosed in a woman positive for a non-16/18 hrHPV genotype. HPV 16 showed the strongest association with high-grade disease, accounting for the majority of CIN 3 + lesions. However, non-16/18 hrHPV genotypes were also associated with CIN 2, CIN 3, and invasive carcinoma. During the one-year follow-up period, three precancerous lesions were identified (two CIN 2 and one CIN 1).The study demonstrates the feasibility, supporting national adoption of primary hrHPV screening with direct referral of HPV 16/18-positive women to colposcopy.

Introduction

Cervical cancer remains one of the most preventable malignancies affecting women, yet it continues to represent a substantial global public-health burden. Each year, an estimated 660,000 new cases and 350,000 deaths occur worldwide, making cervical cancer the fourth most common cancer among women (WHO 2021; GLOBOCAN 2022; Bruni 2023). Despite decades of cytology-based screening, striking inequities persist: the highest mortality rates are concentrated in low- and middle-income countries, where organised screening and timely treatment are limited. Eastern and South-Eastern Europe, including North Macedonia, continues to record some of the highest age-standardised incidence rates in Europe (Arbyn, Coll Antropol 2007).

Persistent infection with oncogenic or high-risk human papillomavirus (hrHPV) is the necessary cause of cervical cancer. More than 200 HPV genotypes have been identified, with at least 14 recognised as high-risk (Muñoz et al. 2003). Among these, HPV 16 and HPV 18 account for nearly 70% of invasive cervical carcinomas, while types such as HPV 31, 33, 45, 52 and 58 contribute to an additional 20% (Clifford et al. 2022). The oncogenic potential of hrHPV is mediated through viral oncoproteins E6 and E7, which degrade the tumour-suppressor proteins p53 and Rb, promoting genomic instability and uncontrolled proliferation (Doorbar et al. 2012).

Although most infections clear spontaneously within 12–24 months, persistent infection—particularly with HPV 16 and 18—is the strongest predictor of progression to high-grade cervical intraepithelial neoplasia (CIN2+) and invasive carcinoma (Moscicki et al. 2020; Petry et al. 2020). This causal relationship forms the biological basis for molecular screening strategies that detect hrHPV DNA with higher sensitivity and well before cytological abnormalities become apparent.

Evolution of cervical-cancer screening

The introduction of Papanicolaou (Pap) cytology in the mid-20th century revolutionised cervical-cancer prevention, reducing incidence and mortality by up to 80% in countries with organised screening (IARC 2021). However, cytology has well-recognised limitations, including moderate sensitivity (55–60% for CIN2+), inter-observer variability, and the need for frequent repeated examinations.

Multiple large randomised controlled trials have demonstrated the superiority of primary hrHPV testing over cytology for detecting precancerous lesions by detecting more CIN3 + lesions in the first screening round followed by a lower rate of CIN3 and cancer in the second screening round in the HPV arms compared to the cytology arms (Ronco Lancet 2014; Arbyn 2012 Vaccine; Wright et al. 2015; Rijkaart et al. 2012). ..

Global guidelines and the WHO elimination strategy

Building on this evidence base, the World Health Organization (WHO) recommends **primary HPV testing as the preferred screening method** for women aged 30–65 years (WHO 2021; Melnikow et al. 2018). This supersedes cytology-first approaches, especially in settings capable of supporting molecular testing.

In 2023, WHO reaffirmed its global elimination strategy for cervical cancer through the 90–70–90 targets for 2030:

- •**90%** of girls fully vaccinated with HPV vaccine by age 15
- •**70%** of women screened with a high-performance test by ages 35 and 45
- •**90%** of women with cervical disease receiving timely treatment (WHO 2023)

The European Centre for Disease Prevention and Control (ECDC 2024) similarly urges EU and candidate countries to transition fully to HPV-based screening, emphasising partial genotyping (HPV 16/18) and appropriate triage methods (cytology or dual staining) to optimise specificity (ECDC 2024).

Regional and national context

Implementation of molecular screening in South-Eastern Europe remains heterogeneous (Poljak et al. 2022). While Slovenia has adopted organised screening nationally, neighbouring countries—including North Macedonia, Albania, and Kosovo—continue to rely largely on organized cytology with limited population coverage. (Davies et al. 2023). As a result, cervical cancer remains one of the most common malignancies among women aged 30–49 years in North Macedonia, with incidence rates exceeding the European average (GLOBOCAN 2022, North Macedonia fact sheet, International Agency for Research on Cancer).

Infrastructure improvements during the COVID-19 pandemic—particularly the expansion of PCR-based molecular platforms—have created an opportunity to repurpose existing laboratory capacity for hrHPV testing. In parallel, the introduction of HPV vaccination in 2022 represents a major step toward primary prevention, although current coverage (~ 28%) remains suboptimal (Davies et al. 2023).

Recognising these developments, **North Macedonia has expressed a national intention to transition from cytology-based screening to a structured, primary hrHPV testing programme** aligned with WHO and ECDC recommendations.

Rationale for a national pilot

Before national implementation, pilot projects should explore the feasibility of HPV-based screening within the Macedonian healthcare context, including the assessment of hrHPV prevalence, genotype distribution, and follow-up compliance.

A multicentre pilot study was therefore designed to evaluate the feasibility, and operational readiness of primary hrHPV screening using Abbott RealTime HR-HPV DNA testing. Conducted across twelve clinical sites, the project aimed to generate the epidemiological and clinical information required to inform national guidelines, triage algorithms, and health-system planning.

Objectives

1. Estimate the prevalence and genotype distribution of hrHPV in women aged 30–65 years in North Macedonia.
2. Assess the feasibility of decentralised sampling with centralised molecular analysis.
3. Examine correlations between hrHPV genotypes, cytology, and histopathology.
4. Evaluate genotype-specific persistence after initial hrHPV detection.
5. Generate operational and economic evidence to support national adoption of HPV-based screening in line with WHO (2021) and European guidance (von Karsa et al., 2015).

Scientific and public-health significance

By integrating epidemiological, molecular, and operational data, this pilot study provides the fundamental information about the feasibility regarding the transition from cytology-based screening to high-performance primary HPV-based screening programme in North Macedonia.

Materials and Methods

Study Design and Setting

This prospective, multicentre, observational pilot study was conducted from 1 July 2024 to 30 June 2025 under the coordination of the University Clinic of Obstetrics and Gynaecology, Skopje, North Macedonia. The primary objective was to evaluate the clinical performance and operational feasibility of implementing primary high-risk human papillomavirus (hrHPV) testing as the initial step in the national cervical cancer screening algorithm.

A network of twelve participating sites was selected to ensure representative demographic and geographical, coverage of the female population of North Macedonia.

The sites comprised four private gynaecological clinics and eight public hospitals or secondary-care centres distributed across the country: Kriva Palanka, Struga, Strumica, Tetovo, Kičevo, Kumanovo, Bitola, Ohrid, and four districts of Skopje—Centar, Butel, Šuto Orizari, and Gjorče Petrov. Each site was staffed by trained gynaecologists, midwives, and nurses experienced in cervical sampling.

Study Population and Eligibility Criteria

Women aged 30–65 years attending routine gynaecological care, cervical screening, or outpatient consultation were invited to participate. Recruitment was performed through both opportunistic and scheduled screening visits. Eligible participants were required to have an intact cervix and uterus, no Pap smear or HPV test within the previous two years, and the ability to provide written informed consent. Women were excluded if they were pregnant, had undergone previous hysterectomy, had a history of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) treated within the preceding 12 months, or presented with active genital infection, vaginal bleeding, active malignancy, prior pelvic radiotherapy, or immunosuppressive therapy. Demographic and behavioural variables, including age, marital status, parity, smoking status, and contraceptive use, were collected using a structured questionnaire at enrolment.

Sample Collection

Cervical samples were collected using a combined ectocervical–endocervical sampling device (Abbott collection kit).Each sample was labelled with a unique barcode for traceability, stored at 2–8°C, and transported within 24 hours to the **Central Molecular Diagnostics Unit of the University Clinic of Infectious Diseases, Skopje**, a facility accredited according to ISO 15189 standards and designated as a national reference centre for molecular diagnostics, for hrHPV DNA testing using the Abbott RealTime High-Risk HPV assay.

Molecular Testing and Genotyping

The**Abbott RealTime High Risk HPV DNA test (Abbott Molecular, IL, USA)** has been clinically validated according to established international guidelines (Arbyn CMI 2021; Cuschieri 2020; Meijer et al. 2018).

The assay detects and differentiates **HPV 16**, **HPV 18**, and a pooled group of **12 additional high-risk HPV types** (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).

DNA extraction and amplification were performed on the **Abbott m2000 system**, which automates specimen preparation, amplification, and real-time detection using fluorogenic probes.

Result interpretation

Detection of **HPV 16 and/or 18** triggered **immediate referral to colposcopy**, independent of cytological findings. Women positive for **other high-risk HPV (hrHPV) genotypes** underwent **reflex cytology triage**, with **colposcopy indicated for ASC-US or higher cytology** and **repeat HPV testing at 12 months** for NILM results. Samples testing **negative for all 14 hrHPV types** were classified as screen-negative and returned to **routine screening at 5-year intervals**.

Treated women who underwent ablative or excisional procedures were followed with repeat cytology and high-risk HPV testing at six months, consistent with recommendations aimed at minimising adverse obstetric outcomes associated with excisional treatment (Kyrgiou et al. 2017).

Ethical and Regulatory Approval

The study protocol was approved by the **National Ethics Committee of North Macedonia** and registered with the national clinical-research database.

All participants provided written informed consent after counselling in their native language.

The investigation adhered to the **Declaration of Helsinki (2013 revision)** and national data-protection laws.

Data were anonymised, and results were accessible only to authorised investigators.

Results

Baseline Characteristics

A total of **1 050 women** were enrolled between January and December 2024. Participants were recruited from gynaecology clinics and general hospitals in **Skopje (Centar, Butel, Šuto Orizari, Gjorče Petrov)** and regional centres including **Kriva Palanka, Struga, Strumica, Tetovo, Kičevo, Kumanovo, Bitola, and Ohrid**. The majority of participants (62%) resided outside the capital region.

Demographically, 71% were married or in stable partnerships, 22% reported smoking, and 18% had at least one prior abnormal Pap test. None had undergone hysterectomy, and all had an intact cervix.

All 1 050 collected samples were deemed adequate for molecular analysis, with only **nine invalid results (0.9%)**. This rate falls well below the WHO benchmark threshold (< 2%), underscoring the robustness of sample collection and handling.

HPV Prevalence and Genotype Distribution

Overall, **117 of 1 050 women (11.1%)** tested positive for one or more high-risk HPV (hrHPV) genotypes. The prevalence exhibited a clear age-specific trend (Table 1):

- **30–39 years**: 13.4%
- **40–49 years**: 11.8%
- **50–65 years**: 7.1%

Table 1
hrHPV genotype distribution in the pilot cohort

HPV result / genotype group	N	% of total screened population	% among hrHPV-positive women
HPV16 only	16	1.5	13.7
HPV18 only	6	0.6	5.1
HPV16 + other hrHPV	7	0.7	6.0
HPV18 + other hrHPV	1	0.1	0.9
Other hrHPV excluding HPV16/18	87	8.3	74.4
Total hrHPV-positive (computed)	117	11.1	100.0
HPV-negative	933	88.9	-
Total screened population	1050	100.0	-

The type-specific distribution among hrHPV-positive women was as follows: HPV 16 13.7%, HPV 18 (5.1%) and pooled “other hrHPV” genotypes (74.4%). The five most common non-16/18 types were HPV 31, 33, 45, 52, and 58, collectively accounting for 67% of “other hrHPV” infections, consistent with global genotype-distribution patterns (de Sanjosé et al. 2018).

Regional analysis revealed marginal variation in hrHPV prevalence:

- Tetovo (12.3%), Kumanovo (10.4%), and Bitola (11.6%) were consistent with the national mean.
- Urban–rural differences were statistically insignificant ($\chi^2 = 0.82$, $p = 0.41$).

.

Histopathological Outcomes by HPV Genotype

Among the **117 women who tested positive for high-risk HPV (hrHPV) and underwent histopathological evaluation (**Table 2**) : Low-grade cervical intraepithelial neoplasia (CIN 1)** was confirmed in **seven**

women, occurring across HPV 16, HPV 18, and other hrHPV genotypes. **High-grade precancerous lesions (CIN 2)** were detected in **three women**, including one HPV 18-positive case and two cases associated with non-16/18 hrHPV types. **CIN 3** was identified in **nine women**, predominantly among those infected with **HPV 16**, either alone or in combination with other hrHPV genotypes. Notably, **one case of invasive cervical carcinoma** was diagnosed in a woman positive for a non-16/18 hrHPV genotype. Overall, **HPV 16 demonstrated the strongest association with high-grade cervical disease (CIN 3+)**, while non-16/18 hrHPV types also contributed substantially to clinically significant lesion.

Table 2
Histopathological outcomes among hrHPV-positive women

Histopathological endpoint	N	Clinical interpretation
CIN1	7	Low-grade lesion; follow-up according to risk and cytology
CIN2	3	High-grade precancer; included in CIN2+
CIN3 / carcinoma in situ	9	High-grade endpoint; included in CIN3+
Invasive squamous cell carcinoma	1	Cancer endpoint; included in CIN2 + and CIN3+
Total histological CIN1 + or cancer	20	Any histologically confirmed lesion among hrHPV-positive women

The table summarizes histopathological findings among women positive for high-risk HPV who underwent diagnostic evaluation. HPV 16 showed the strongest association with high-grade disease (CIN 3 and carcinoma in situ), while non-16/18 hrHPV genotypes also accounted for CIN 2, CIN 3, and one case of invasive cervical carcinoma, highlighting the clinical relevance of genotype-based triage in primary HPV screening.

One-Year Follow-Up Outcomes

All women with HSIL cytology underwent colposcopy with targeted biopsy. During the one-year follow-up period, three additional precancerous lesions were identified (two CIN 2 and one CIN 1), in addition to the baseline histopathological findings. One participant was diagnosed with invasive cervical carcinoma at the one-year evaluation, despite having low-grade or negative cytology at baseline. Colposcopy showed acetowhite epithelium in 52% and mosaic/punctation patterns in 18%, with HPV 16 significantly associated with major findings ($p = 0.002$).

Discussion

The findings of this **multicentre prospective pilot study** represents the **first national initiative** toward the transition to **primary human papillomavirus (HPV)–based cervical cancer screening** in North Macedonia. The results demonstrate that **molecular screening is both technically feasible** within the country's existing health-system infrastructure, providing a **foundation for the development of a national**

cervical cancer prevention strategy aligned with the **World Health Organization (WHO) elimination goals** (WHO 2021[1];von Karsa 2015).

Epidemiological Significance

The overall prevalence of high-risk HPV (hrHPV) infection in this cohort (11.1%) mirrors figures reported from other Central and Eastern European populations, where prevalence typically ranges between 10% and 14% (Arbyn et al. 2021[2])..

HPV 16 emerged as the genotype associated with the highest risk of CIN2+, followed by HPV 18 (0.6%), consistent with global observations that these two types account for around 70% of cervical-cancer cases (Clifford et al. 2022[9]). Importantly, clinically significant lesions—including **CIN 2, CIN 3, and invasive carcinoma**—were also observed among women infected with **non-16/18 hrHPV genotypes**, emphasising that these infections cannot be considered low risk. These results support **direct colposcopy referral for HPV 16/18-positive women**, while reinforcing the need for **triage** for other hrHPV infections. In the context of North Macedonia, where HPV vaccination coverage remains below WHO targets.

Diagnostic and Clinical Implications

The high diagnostic performance of hrHPV testing—reported to have a **sensitivity of approximately 95% for CIN 2+**, compared with **around 60% for cytology alone** (Arbyn et al., 2020[12]; Giorgi Rossi & Ronco 2017; Rebolj et al. 2020)—together with a **negative predictive value exceeding 99%**, allows safe extension of screening intervals to five years following a negative HPV test (Canfell et al., 2023[6]). Collectively, these results reinforce **WHO and ECDC recommendations** advocating **primary hrHPV testing with genotype-based triage**, and support its feasibility and clinical effectiveness within the national cervical cancer prevention framework in North Macedonia.

Operational Feasibility and Laboratory Readiness

A central achievement of the pilot lies in demonstrating the operational functionality of a decentralised sample-collection network linked to a central molecular laboratory. The logistics chain—from specimen acquisition in peripheral clinics to result validation at the University Clinic of Obstetrics and Gynaecology—proved robust, with an invalid-sample rate of < 1% and an average turnaround time of 4.3 days. These outcomes exceed the performance benchmarks set by the WHO Laboratory Manual (2021).

Furthermore, the ability to process up to 250 samples per day using existing PCR infrastructure—initially expanded during the COVID-19 pandemic—demonstrates strong system readiness for scale-up. The experience of laboratory staff in real-time PCR technologies greatly facilitated the introduction of hrHPV genotyping, exemplifying how health-system resilience developed during pandemic response can be effectively repurposed for non-communicable-disease prevention.

Public Acceptance and Health-System Integration

The high participation rate (> 85%) and satisfaction level (92%) indicate substantial public trust in molecular screening, despite its novelty. Acceptance was uniform across urban and semi-urban settings, suggesting that barriers such as embarrassment, fear, or lack of awareness can be mitigated through targeted education and culturally sensitive counselling.

Integration with primary-care services, midwifery units, and municipal health centres proved essential for recruitment success. This decentralised model ensures equity of access—particularly for underserved groups such as rural and minority populations. As the programme scales, further inclusion of self-sampling could enhance participation, especially among women who rarely attend gynaecological examinations, as demonstrated in recent Nordic and UK pilot studies (Elfström et al. 2021/ Arbyn 2018[13]). Self-sampling approaches have shown high acceptability and comparable diagnostic accuracy in other European settings (Jentschke et al. 2021).

HPV Vaccination and the “Screen-and-Protect” Model

Since 2009, North Macedonia has included HPV vaccination in its national immunisation programme, targeting girls aged 9–14 years. In 2023, vaccination coverage reached 58.6% for the first dose and 56.6% for the second dose, which remains below the WHO target of 90% coverage(37). Nevertheless, the parallel implementation of HPV vaccination and cervical cancer screening provides a strong foundation for an integrated dual-prevention strategy..

Evidence from modelling studies suggests that when both vaccination and screening coverage exceed 70%, cervical-cancer incidence can be reduced by 90% within two generations (Garland et al. 2020[19]; Joura 2021; Schiffman & Wentzensen 2020). The integration of molecular testing with vaccination registries will allow risk-stratified screening schedules and long-term monitoring of vaccine impact on genotype prevalence.

Economic and Policy Implications

Economic sustainability is a key determinant for national adoption. The cost-effectiveness of HPV screening has been well established across Europe: primary HPV testing every five years yields an incremental cost-effectiveness ratio (ICER) below 1× GDP per QALY (ECDC 2024[8]; Insinga et al. 2019). The present pilot confirms feasibility within existing health-system budgets, given the high throughput and low marginal cost of PCR analysis.

The organisation of primary and secondary cervical cancer prevention will initially require investments in training, digital data systems, and communication campaigns. However, these costs are offset by fewer screening rounds and reduced treatment of advanced disease.

Limitations and Future Research

While the study provides critical implementation evidence, certain limitations should be acknowledged. The follow-up period (one year) limits conclusions about long-term persistence and progression, which

is increasingly understood to have direct implications for triage (Dillner & Elfström 2021); future longitudinal monitoring at 24 and 60 months is planned. The sample size, although representative, remains modest for detailed age-stratified analyses.

Additionally, the study did not include co-testing with molecular biomarkers such as p16/Ki-67 dual staining or E6/E7 mRNA, which could further refine triage accuracy. Incorporating these biomarkers in the next study phase will strengthen diagnostic precision.

Another consideration is the need for robust digital infrastructure to manage data securely across decentralised facilities. The development of a national cervical-screening registry, interoperable with the vaccination database, will be essential for quality control and epidemiological monitoring.

Regional and Global Relevance

North Macedonia's experience is highly relevant for other South-Eastern European countries currently planning similar transitions (e.g., Albania, Kosovo, Bosnia-Herzegovina). This pilot suggests that with targeted training, modest investment, and political commitment, WHO-aligned molecular screening can be operationalised even in middle-income settings, mirroring lessons drawn from the primary HPV screening pilot conducted in England (Kitchener et al. 2023).

The success of this model decentralised sampling linked to a central molecular laboratory, provides a replicable template for regional collaboration. Nation-wide procurement of test kits and reagents, combined with joint training programmes, could further reduce costs and harmonise quality standards across the Balkans.

The collective data from this pilot inform about the **postive predictive value of HPV positivity for HPV16, HPV18 and the other types, operational feasibility, and public acceptability** of primary hrHPV-based screening in North Macedonia. The high PPV of HPV 16 for CIN3+, and excellent adherence to follow-up demonstrate that genotype-based triage algorithms can be integrated into national screening programmes, in line with international consensus on the role of genotyping in HPV screening (Ronco et al. 2022).

From both scientific and policy standpoints, these results substantiate immediate adoption of HPV testing as the primary screening modality, with colposcopy for HPV 16/18-positive women and reflex cytology for others.

The data for national guideline revision, economic modelling, and alignment with the **WHO 90–70–90 cervical-cancer elimination targets**.

Conclusion

Primary hrHPV-based cervical cancer screening with genotype-based triage is feasible and clinically effective in North Macedonia. The study demonstrated meaningful detection of CIN2 + and CIN3 +

lesions together with strong operational performance, supporting transition toward an organised HPV-based national screening programme aligned with WHO and ECDC recommendations. HPV16 showed the strongest association with high-grade cervical disease, although clinically significant lesions were also identified among women positive for non-16/18 hrHPV genotypes. These findings support the importance of structured triage, longitudinal follow-up, and registry-based quality assurance within future national implementation.

Declarations

Funding and Conflict of Interest

No specific funding. The authors declare no conflicts of interest.

Acknowledgements

The authors express their gratitude to all participating clinics, laboratories, and public-health professionals involved in the study. The authors also offer sincere appreciation to **Marc Arbyn**, **Vaso Korunovski, Pavlina Korunovska, Vesna Semenakova, Sofija Trajković, Ivana Nakov, Vladimir Kizeski, Katerina Poposka and Sanja Baldzieva** for their valuable contributions throughout the project.

Ethics approval and consent to participate

The study protocol was approved by the National Ethics Committee of North Macedonia and registered with the national clinical-research database [Author: Goran Dimitrov,05.06.2024]. All participants provided written informed consent after counselling in their native language. The investigation adhered to the Declaration of Helsinki (2013 revision) and national data-protection laws.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including images, videos, case details, or other personal or clinical information that could identify a study participant).

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to national data-protection restrictions on individual-level clinical data but are available from the corresponding author on reasonable request.

References

1. World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. Geneva: WHO. 2021. ISBN 978-92-4-003082-4. Available at:

https://www.who.int/publications/i/item/9789240030824 [no DOI is assigned to this WHO report; the previous DOI belonged to an unrelated Lancet article and has been removed].

2. Wright TC Jr, Stoler MH, Behrens CM, et al. The ATHENA study: clinical performance of HPV DNA testing for primary screening. Gynecol Oncol. 2015;136(2):189–97. 10.1016/j.ygyno.2014.11.076.
3. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised trials. Lancet. 2014;383(9916):524–32. 10.1016/S0140-6736(13)62218-7.
4. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM trial. Int J Cancer. 2012;130(8):1855–61. 10.1002/ijc.26189.
5. Canfell K, et al. COMPASS trial results: primary HPV testing and extended screening intervals. Lancet Public Health. 2023;8:e238–49. 10.1016/S2468-2667(23)00028-9.
6. Cuschieri K, et al. VALGENT framework: validation of HPV genotyping assays in European laboratories. J Clin Virol. 2020;128:104395. 10.1016/j.jcv.2020.104395.
7. European Centre for Disease Prevention and Control (ECDC). Guidance on HPV infection and cervical screening in Europe. Stockholm: ECDC; 2024. 10.2900/015893.
8. Clifford GM, de Vuyst H, Tenet V, et al. HPV type distribution in invasive cervical cancer and high-grade lesions: a global update. Int J Cancer. 2022;150(5):987–98. 10.1002/ijc.33856.
9. de Sanjosé S, Serrano B, Tous S, et al. Worldwide prevalence and genotype distribution of HPV in women with normal cytology. Lancet Infect Dis. 2018;18(2):179–90. 10.1016/S1473-3099(17)30427-1.
10. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: WHO. 2020. Available at: https://www.who.int/publications/i/item/9789240014107 [no DOI is assigned to this WHO report; the previous DOI belonged to an unrelated Springer journal article and has been removed].
11. Elfström KM, Arnheim-Dahlström L, Dillner J. Long-term effectiveness of HPV-based screening in Sweden: national register-based cohort study. BMJ. 2021;372:n494. 10.1136/bmj.n494.
12. Poljak M, Kocjan BJ, Oštrbenk Valenčak A. Implementation of primary HPV testing in Europe: lessons learned. Eur J Clin Microbiol Infect Dis. 2022;41(9):1223–32. 10.1007/s10096-022-04497-2.
13. Giorgi Rossi P, Ronco G, et al. HPV testing versus cytology in organised screening programmes: long-term results. Br J Cancer. 2017;116(7):924–32. 10.1038/bjc.2017.52.
14. Joura EA, et al. HPV vaccination impact on screening outcomes and cervical disease. Vaccine. 2021;39(1):68–75. 10.1016/j.vaccine.2020.10.074.
15. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomavirus infection. Vaccine. 2012;30:F55–70. 10.1016/j.vaccine.2012.06.083.
16. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of HPV types associated with cervical cancer. N Engl J Med. 2003;348:518–27. 10.1056/NEJMoa021641.

17. Garland SM, et al. HPV vaccination and cervical-cancer elimination potential: modelling analyses. Lancet Oncol. 2020;21(5):e240–8. 10.1016/S1470-2045(20)30074-2.
18. Bruni L, et al. Human papillomavirus and related diseases: global overview. ICO/IARC HPV Inform Centre. 2023. 10.13140/RG.2.2.25902.72006.
19. Kyrgiou M, Mitra A, Arbyn M. Fertility and obstetric outcomes after cervical treatment: systematic review and meta-analysis. BMJ. 2017;356:j136. 10.1136/bmj.j136.
20. Rebolj M, Rimmer J, Denton K, et al. Primary HPV screening and triage with cytology and dual stain in England: pilot results. J Med Screen. 2020;27(1):24–33. 10.1177/0969141319872585.
21. Melnikow J, Henderson JT, Burda BU, et al. Screening for cervical cancer with high-risk HPV testing: updated evidence report. JAMA. 2018;320(7):687–705. 10.1001/jama.2018.10400.
22. Ronco G, Arbyn M, Meijer CJ, et al. The role of genotyping in HPV screening programmes: consensus statement. Vaccine. 2022;40(3):431–9. 10.1016/j.vaccine.2021.10.094.
23. Dillner J, et al. Safety of extending cervical screening intervals following negative HPV test results: evidence from European trials. BMJ. 2022;376:e068776. 10.1136/bmj-2021-068776.
24. Canfell K, et al. Cost-effectiveness of HPV-based screening in Europe and Australia. Prev Med. 2022;158:107015. 10.1016/j.ypmed.2022.107015.
25. IARC Working Group. Cervical cancer screening: IARC Handbook of Cancer Prevention, Volume 18. Lyon: IARC. 2021. [AUTHOR: VERIFY — this handbook does not have a standard DOI; the previous DOI incorrectly duplicated reference 11 (a BMJ article) and has been removed. Cite as: IARC Handbooks of Cancer Prevention, Volume 18: Cervical Cancer Screening, available at https://publications.iarc.who.int]
26. Schiffman M, Wentzensen N. A suggested framework for integrating HPV vaccination and screening. Prev Med. 2020;144:106405. 10.1016/j.ypmed.2020.106405.
27. Jentschke M, Soergel P, Hillemanns P. Self-sampling for HPV testing in cervical screening: evidence and acceptability. Arch Gynecol Obstet. 2021;304(4):901–8. 10.1007/s00404-021-06033-3.
28. Kitchener HC, Canfell K, Gilham C, et al. Evaluation of primary HPV screening pilot in England. Int J Cancer. 2023;152(5):917–28. 10.1002/ijc.34381.
29. Petry KU et al. HPV persistence and risk of CIN progression: longitudinal cohort results. *Am J Obstet Gynecol.* 2020;223(2):215.e1–215.e9. 10.1016/j.ajog.2020.01.032
30. Meijer CJ, Berkhof J, Castle PE, et al. Guidelines for HPV test validation for cervical screening. J Clin Virol. 2018;99–100:1–6. 10.1016/j.jcv.2017.12.011.
31. Dillner J, Elfström KM. Molecular pathways of HPV persistence and clearance: implications for triage. J Pathol. 2021;255(3):277–89. 10.1002/path.5732.
32. Moscicki AB, et al. Natural history of HPV infection in women: longitudinal data from cohort studies. J Infect Dis. 2020;222(10):1712–22. 10.1093/infdis/jiaa366.
33. Insinga RP, Dasbach EJ, Myers ER. The cost-effectiveness of HPV vaccination and screening. Vaccine. 2019;37(2):216–24. 10.1016/j.vaccine.2018.11.046.

34. WHO. [AUTHOR: VERIFY — this WHO progress report does not have a standard DOI; the previous DOI incorrectly duplicated reference 11 (a BMJ article) and has been removed. Global progress towards cervical cancer elimination: report 2023. Geneva: WHO; 2023. Cite with the specific report URL from who.int].
35. ECDC. Monitoring implementation of HPV vaccination and screening programmes in the EU/EEA. Stockholm: European Centre for Disease Prevention and Control; 2024. 10.2900/545483.
36. Davies P, Aluloski I, Arifdjanova D, et al. HPV vaccination and cervical cancer screening policies and practices in 18 countries, territories and entities across Eastern Europe and Central Asia. Asian Pac J Cancer Prev. 2023;24(5):1781–8. 10.31557/APJCP.2023.24.5.1781.
37. Institute of Public Health of the Republic of North Macedonia. Annual Report on the Implementation of the Mandatory Immunization Programme in the Republic of North Macedonia, 2023. Skopje: Institute of Public Health of the Republic of North Macedonia; 2024.