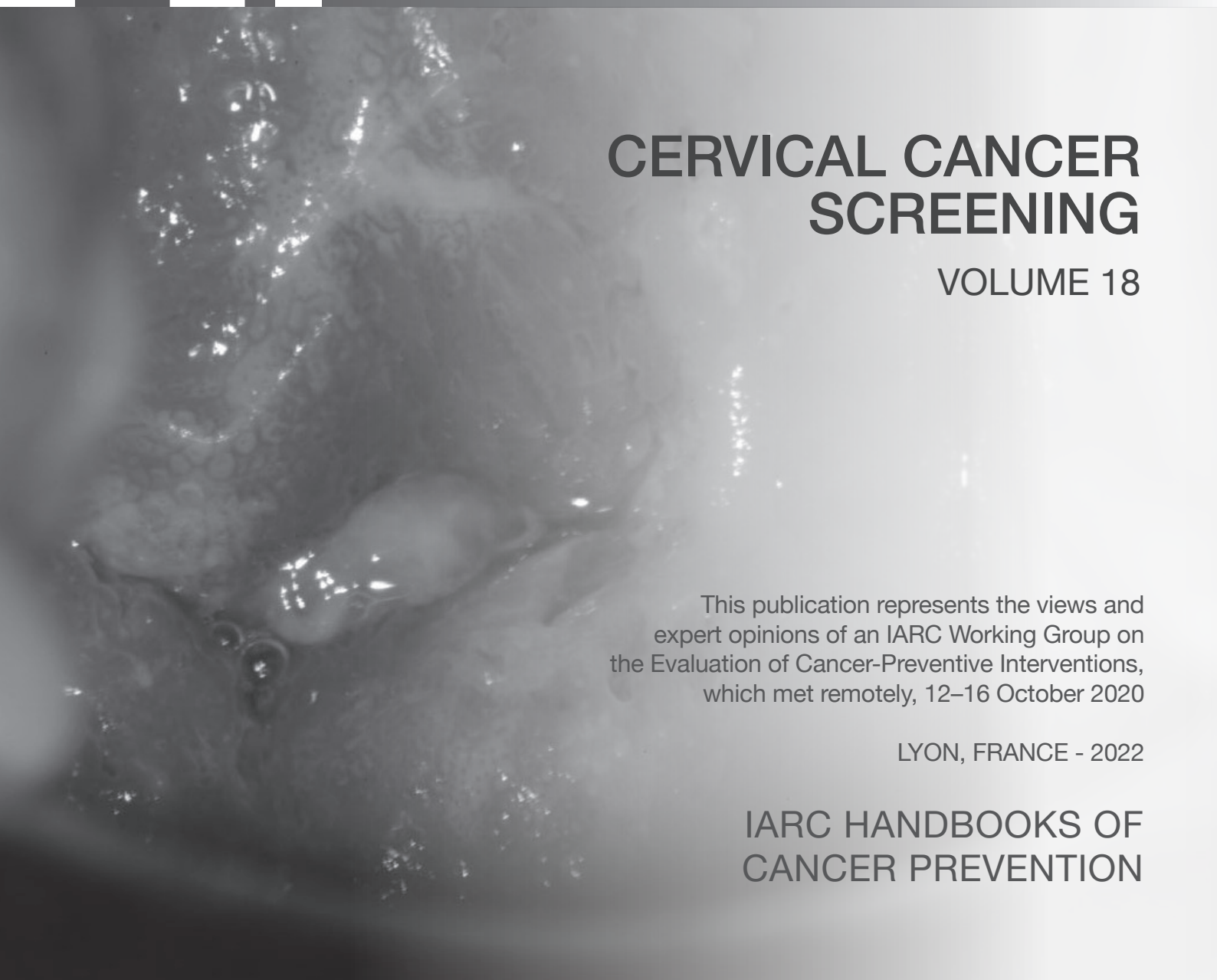
IARC HANDBOOKS



CERVICAL CANCER SCREENING

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IARC HANDBOOKS OF CANCER PREVENTION

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6. SUMMARY

6.1 Cervical cancer

6.1.1 Cervical cancer burden

Cervical cancer is the fourth most commonly diagnosed cancer type in women worldwide, with an estimated 604 000 new cases in 2020. It is also the fourth most common cause of cancer death in women, with an estimated 342 000 deaths in 2020. The burden of cervical cancer varies markedly across the world, with a 10-fold variation between the highest and lowest incidence rates and a more than 15-fold variation between the highest and lowest mortality rates. The incidence and mortality rates are highest in sub-Saharan Africa. The incidence rates are lowest in Western Asia and Australia and New Zealand, and the mortality rates are lowest in Australia and New Zealand and Western Europe. The highest cervical cancer incidence and mortality rates are generally observed in countries with the lowest levels of the Human Development Index. The incidence rates are also higher in countries that have a high prevalence of HIV infection and/or lack sustained cervical cancer screening programmes. Three patterns emerge from an analysis of trends in age-standardized incidence rates over time in different countries: (i) a decrease in rates over the years, (ii) an increase in overall rates, and (iii) an increase in rates in the younger age groups.

6.1.2 Cervical neoplasia

More than 90% of cases of cervical cancer are caused by persistent infection with 12 genetically related human papillomavirus (HPV) types in the alpha genus. HPV16 (in the alpha-9 species) causes about 60% of cases of squamous cell carcinoma, which comprises most of the global cervical cancer burden. HPV18 and HPV45 (in the alpha-7 species) cause 15% and 5% of cases of squamous cell carcinoma, respectively. Other closely related alpha-9 types (HPV31, HPV33, HPV35, HPV52, and HPV58) together account, with some regional variation, for 15% of cases of squamous cell carcinoma. The remaining carcinogenic types (HPV39 and HPV59 in alpha-7, HPV51 in alpha-5, and HPV56 in alpha-6) together cause about 5% of cases of squamous cell carcinoma. HPV-associated cases of adenocarcinoma are caused half by variants of HPV16 and half by HPV18 or HPV45 (and only uncommonly by other types, particularly in alpha-7).

The carcinogenicity of HPV is explained mainly by cell-cycle disruption and anti-apoptosis induced by the two major oncogenes, E6 and E7. HPV infections are very common and are usually benign. However, when they are persistent, infections with carcinogenic types may shift from the usual and common productive state (i.e. the complete life-cycle designed to produce

new virus particles). Instead, the virus can enter an abortive or transforming state characteristic of precancer, driven by interference of E6 and E7 with normal cell growth and differentiation. These changes underlie almost all cervical screening, triage, and diagnostic tests designed to detect precancer. The junction between the squamous lining of the vagina and ectocervix and the glandular lining of the endocervical canal (the squamocolumnar junction) is a ring of epithelium that is uniquely susceptible to HPV-induced carcinogenesis.

There is a well-established set of necessary intermediate states leading from normal cervical cells to invasive cancer. With a combination of microscopic and type-specific HPV test methods, the following states can be distinguished: normal cervix (uninfected), HPV infection (type-specific carcinogenic), precancer, and cancer. Precancers and cancers are subdivided into the predominant squamous pathway and the uncommon glandular pathway.

HPV infections act independently of each other, although they tend to be co-transmitted easily through direct sexual contact, leading to a peak of new infections in the decade after the age at the start of sexual activity. The odds of acquiring a given HPV infection are highly correlated with the prevalence of that type in the population. HPV16 is the most common carcinogenic type and poses the highest risk of precancer and invasive cancer. In the absence of progression to precancer, the average time to HPV clearance is similar for all HPV types. An individual woman may clear multiple types while a single causal type persists. Clearance is thought to relate mainly to cell-mediated immune control; in immunocompetent populations, most HPV infections of any type are no longer apparent within 1 year, and persistence past 2–3 years is uncommon (and is strongly linked with development of precancer). A population's prevalence of HPV infection in adult women is a critical determinant of cervical screening strategies. Women living with HIV with impaired cellular immunity have a high HPV prevalence and require separate consideration.

Precancer can develop within a few years of HPV infection and peaks in the decade after the average age of onset of sexual activity (e.g. 25–35 years in many settings). In contrast, invasive cancer typically takes decades to develop, passing through a prolonged period of non-invasive growth around the circumference of the squamocolumnar junction.

The classification of cervical cancer follows the current World Health Organization (WHO) classification, which was revised in 2020. Most cervical cancers are HPV-associated carcinomas, but a small percentage of tumours are not associated with HPV infection. The most common cervical cancer types are squamous cell carcinoma and adenocarcinoma, which account for more than 95% of all cervical cancers. Most cervical squamous cell carcinomas (93–95%) and adenocarcinomas (75–90%) are HPV-associated. Both cancer types have precursor lesions. The terminology for squamous cell carcinoma precursors has changed over time, but the two approaches currently in widespread use are the cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesion (SIL) systems. For adenocarcinoma, precursor lesions are referred to as adenocarcinoma in situ.

Tumour staging assesses the extent of tumour spread and is the most important determinant of clinical management. The International Federation of Gynecology and Obstetrics (FIGO) staging system is most commonly used clinically, in conjunction with the tumour–node–metastasis (TNM) staging system to provide assessment particularly of lymph node metastasis, which has not traditionally been included in the FIGO system. The revised FIGO staging system published in 2018 added lymph node metastasis and pathological and radiological investigation to clinical assessment, and there is early evidence of improved patient stratification using

the 2018 system. In some countries, cervical cancer is diagnosed predominantly at an early stage (localized or FIGO stage I), but in others it is diagnosed at a more advanced stage (predominantly regional or FIGO stage II). In all countries, survival is strongly stage-dependent, with 5-year survival ranging from more than 90% for localized disease to less than 10% where distant disease is present.

Treatment options for precancer include excisional techniques, such as large loop excision of the transformation zone and cold-knife conization, and ablative techniques, such as cryotherapy and thermal coagulation. Squamous precancerous lesions can be treated with any of the above-mentioned techniques, whereas glandular precancer (adenocarcinoma in situ) is treated with excisional techniques. Treatment modalities for precancer have similar and high rates of success, although cryotherapy has varied outcomes compared with other treatment modalities. Recurrence of precancer after treatment may occur. Harms of treatment, primarily related to excisional techniques, include bleeding, infection, cervical stenosis, and premature delivery.

Treatment of invasive cervical cancer is based on the stage and size of the tumour. Surgical management is recommended for early cervical cancers, whereas advanced cervical cancers are treated with chemotherapy and radiation.

6.2 Cervical cancer screening programmes

The purpose of cervical cancer screening and treatment is to reduce the incidence of and mortality from cervical cancer by identifying women with precancerous cervical lesions and early invasive cancer and treating them appropriately. Adherence to and high quality of the entire screening and management pathway are central to the effectiveness of a screening programme; measures should be in place to ensure high coverage of the target population, high quality of the primary screening test, effective follow-up of women with positive screening test results, and appropriate subsequent treatment and care.

Various national and international guidelines on cervical cancer screening and treatment have been produced and/or updated, based on available resources and prevention approaches. Existing screening initiatives are not always reported properly, which hinders assessment of the availability of cervical cancer screening worldwide and prevents comparison between countries.

6.2.1 WHO African Region

Most countries in the WHO African Region have not implemented multistep cervical cancer screening with sufficient population coverage, because of meagre existing health-service infrastructure, a lack of human resources, and the low level of investment in health services. However, many countries in the region have implemented pilot or investigational screening programmes based on the screen-and-treat approach, using the visual inspection with acetic acid (VIA) test coupled with ablative procedures for precancerous lesions on the same day. These programmes are often integrated into the existing infrastructure dedicated to HIV care and reproductive health services.

6.2.2 WHO Eastern Mediterranean Region

In the WHO Eastern Mediterranean Region, most countries practise opportunistic screening based on cytology. Only Morocco, the Syrian Arab Republic, and Tunisia have implemented a screening programme within a national cancer control plan. In Morocco, VIA is the main test used in the public sector; in the other two countries, cytology is used. However, none of these three countries have an active invitation mechanism for screening; women are typically offered

cervical cancer screening when they visit a primary health-care unit or their gynaecologist. Therefore, participation rates remain low.

6.2.3 WHO European Region

In the European Union, the Council recommendations on cancer screening have contributed to the development of a common framework for the implementation of organized population-based cervical cancer screening programmes. European Union guidelines provide evidence-based recommendations for quality-assured screening programmes and key performance indicators. By July 2016, 22 European Union Member States had implemented, piloted, or planned population-based cervical cancer screening programmes. However, only nine of these countries had completed nationwide rollout. Outside the European Union, national organized population-based programmes have been implemented in Iceland, North Macedonia, Norway, and Turkey. In the countries of the former Soviet Union, cervical screening is mostly opportunistic, and those countries that have screening programmes lack widespread call–recall systems, have low coverage, and do not have quality assurance systems. Cytology remains the primary screening method in most countries in the European region, but HPV primary screening is being introduced in an increasing number of countries.

6.2.4 WHO Region of the Americas: North America

Canada and the USA have substantial differences with respect to the structure of their health systems and delivery of cervical cancer screening. Although cervical cancer screening is well established in Canada and the USA, an overlap of organized and opportunistic screening exists, particularly in the USA; in Canada, cervical cancer screening is provided mostly through organized programmes with invitation and reminder systems. In Canada, cytology remains the primary screening test, although some provinces are starting the transition to HPV primary screening. In the USA, guidelines recommend HPV testing either as a stand-alone test or as a co-test with cytology. There is high coverage in both countries.

6.2.5 WHO Region of the Americas: Latin America and the Caribbean

Up to 2019, all countries in the Latin American region and 12 out of 21 countries in the Caribbean had defined recommendations or policies for cervical cancer screening. Latin American countries have a long-standing tradition in cervical cancer screening, and most have updated their screening recommendations during the past decade. HPV testing is part of national recommendations in 13 countries in Latin America and the Caribbean, with self-sampling considered in four countries. Screen-and-treat approaches are recommended in eight Latin American and four Caribbean countries, and VIA is recommended as the screening test in most of them. Comprehensive programme reports are not available, and the coverage varies between countries.

6.2.6 WHO South-East Asia Region

In the countries in the WHO South-East Asia Region, organized population-based cervical cancer screening using cytology has been implemented in Bhutan, Sri Lanka, and Thailand, and Thailand introduced HPV-based testing in 2020. India, Indonesia, Myanmar, and Nepal have national guidelines for cervical cancer screening and policies using VIA; however, the screening coverage in these countries is low.

6.2.7 WHO Western Pacific Region

In the WHO Western Pacific Region, Hong Kong Special Administrative Region, New Zealand, the Republic of Korea, and Taiwan, China, have well-established population-based cervical screening programmes using cytology-based screening. HPV testing replaced conventional cytology for primary screening in Australia starting in 2017 and in Singapore in 2019. New Zealand is transitioning to HPV-based screening. China has a national cervical screening programme, but the coverage is low; cervical cancer screening is mostly opportunistic and varies between the different provinces. Japan and Malaysia have national cytology-based screening programmes; however, the coverage is low. Other countries in this region also have some recommendations and strategies in place, but there is little published information on the screening activities.

6.2.8 Quality assurance of screening programmes

Quality assurance measures the quality of service delivered and enables variability in service to be identified and adjustments to be made so that uniform care is provided to the participants in screening programmes. Screening programmes establish agreed-upon performance standards and desired targets to improve outcomes. Performance indicators (also known as quality measures) are measurable evaluations of the ability of a screening programme to deliver high-quality care. Health information systems provide support for the monitoring and evaluation of screening programmes; however, these demand additional resources and thus may be challenging to implement. WHO has provided global, core, and optional quality indicators, which many international programmes have adapted into local screening programmes. Indicators are generally organized into screening, screening test results, treatment, service delivery, facility and laboratory linkages, and HIV service integration.

6.3 Participation in screening for cervical cancer

Participation in screening for cervical cancer is influenced by socioeconomic structural determinants and by intermediate determinants that operate at both an individual level and a health system level. The main determinants of participation are socioeconomic status, ethnicity, health insurance status, and education level, as well as the differential access of women to structural resources, power, authority, and control (gender inequality). Broad contextual and policy factors mediate the process and can act as buffers that modify the effect of social inequalities on participation in screening. Intermediate factors include women's lack of knowledge and awareness of cervical cancer and screening, fatalistic beliefs about cervical cancer and negative previous experiences with screening services, fear of cancer, stigma and shame associated with gynaecological procedures, and lack of social and family support. Screening performed as part of an organized population-based programme tends to improve the access of socially disadvantaged women to screening and diagnosis services.

At the provider level, barriers to participation in cervical cancer screening include fee-paid services and screening performed by male health-care providers. Facilitators of screening include encouragement from health-care providers to get screened, health-care providers having the same sociocultural background as the women, and health institutions that are organized to meet women's needs. Other factors that positively influence participation are the use of communication strategies or tools between health-care providers and women, and navigation services.

Interventions such as invitation letters, telephone calls, or text messages, as well as various educational modalities, increased screening participation. With regard to strategies targeting health-care providers, evidence from high-income countries concluded that evaluating provider performance in offering and/or delivering screening and giving feedback increased screening participation. The effectiveness of provider incentives in increasing screening participation is unclear.

Programmes that offered HPV self-sampling kits to women, either through opt-out strategies or via the general practitioner's practice, along with outreach activities, increased screening participation compared with cytology-based strategies. Opt-in strategies in which women had to request the HPV self-sampling kit were not more effective than other ways of inviting women to cytology-based screening.

Strategies using HPV self-sampling were more effective in increasing participation compared with approaches using VIA or those offering clinician-collected HPV testing. HPV self-sampling offered through periodic community health campaigns had higher screening participation rates compared with HPV self-sampling offered at government health facilities.

6.4 Preventive and adverse effects of cervical cancer screening methods

6.4.1 Visual screening methods

(a) Technical description

Visual examination after the application of acetic acid or Lugol's iodine was developed because of the suboptimal performance of the screening methods used in high-income countries when used in low- and middle-income countries. After application of acetic acid or Lugol's iodine to the cervix, the test result is described as negative, positive, or suspicious for cancer. VIA positivity rates vary considerably, partly because of the intrinsic subjectivity of the method and partly because of variable participant characteristics. Visual examination only enables an assessment of the ectocervical epithelium, and is not appropriate for postmenopausal women or in younger women with a type 3 transformation zone. Visual inspection with Lugol's iodine has not been widely investigated as a primary screening test for cervical cancer, but it has been used as an adjunct to VIA and as an aid to precise treatment.

A quality assurance system, including training, supervision, evaluation of programme activities and long-term impact, and an effective information system, should be considered in any VIA-based screening programme. However, it is a challenge to ensure adequate training and quality assurance of naked-eye techniques in some settings.

(b) Beneficial effects of screening using VIA

VIA has been evaluated in cross-sectional studies in various settings in Africa, Asia, and Latin America for its sensitivity and specificity in detecting high-grade cervical precancerous lesions, compared with conventional cytology. The accuracy of VIA showed large heterogeneity: in meta-analyses, the pooled sensitivity to detect cervical intraepithelial neoplasia grade 2 or worse (CIN2+) lesions ranged from 48% to 83%, and the pooled specificity varied from 84% to 97%. The accuracy of VIA screening depends largely on provider training, menopausal status, and quality assurance. VIA performs poorly in perimenopausal and postmenopausal women, and its specificity may be lower in women living with HIV.

The effect of VIA screening in controlled settings on cervical cancer incidence and/or mortality compared with control populations receiving usual care (very low prevalence of screening) has been evaluated in three large

cluster-randomized trials in India. There was consistent reduction in cervical cancer mortality, ranging from a non-significant 14% reduction to a significant 35% reduction in the three trials, after a single round of screening in two studies (women aged 30–59 years in the Osmanabad District and Dindigul District studies) and after four rounds of biennial screening in one study (women aged 30–64 years in the Mumbai study). The reduction in mortality in the above-mentioned studies may have come from clinical stage shift and effective treatment of cervical cancer rather than from prevention of invasive cancer by detection and treatment of high-grade cervical precancerous lesions (CIN2, CIN3, and adenocarcinoma in situ). Given the low detection rate of such lesions, it is likely that the significant 31% reduction in cervical cancer mortality in the Mumbai study has come from a stage shift and effective treatment of early-stage invasive cervical cancers, whereas the significant 35% reduction in mortality observed in the Dindigul District study seems to be predominantly due to both detection and effective treatment of precancerous lesions and stage shift of invasive cancers. As a result of detection and treatment of cervical precancerous lesions, a significant 25% reduction in cervical cancer incidence was observed in the Dindigul District study. A smaller randomized controlled trial in South Africa showed a 37% reduction in CIN2+ lesions detected 6 months after a VIA screen-and-treat round compared with a control group.

To date, there is no evidence of reduction of cervical cancer incidence or mortality from routine population-based VIA screen-and-treat and conventional screening programmes implemented in some countries, including several in Africa and Asia.

(c) Harms of VIA

Harms of VIA have not been systematically studied or reported widely, either in research settings or in programmatic settings. The lack of reported evidence on harms suggests that visual screening tests for cervical neoplasia are considered safe. Mainly, physical harms due to VIA include harms related to unnecessary procedures and treatment after false-positive screening test results. Psychological harms include anxiety, fear, and stress due to the procedure and to a positive result.

6.4.2 Cytological methods

(a) Technical descriptions

Cervical cytology involves collecting exfoliated cells from the transformation zone and endocervical canal, because the precursors of cervical squamous cell cancers occur mainly in the transformation zone. For the microscopic examination of these cells, the collected material is applied to a glass slide for conventional cytology or placed into a vial for liquid-based cytology. Liquid-based cytology can reduce the proportion of unsatisfactory smears, and residual cellular material can be used for additional tests, including HPV testing and molecular biomarkers. Computer-assisted techniques for processing and reading of cytology samples have been adopted in some countries. Because of the high cost and the need for specific equipment, liquid-based cytology is difficult to introduce into resource-constrained settings. The Bethesda system was developed for reporting the results of cervical cytology using a unified terminology and has been used worldwide, but with variability in individual cytological categories. Because cytological examination depends on manual collection and microscopic evaluation is subjective, laboratory management and quality assurance systems are of pivotal importance in cervical cytology.

(b) Beneficial effects of screening using conventional cytology

There is a large body of observational evidence on the beneficial effects of screening using conventional cytology. The previous *IARC Handbook* on cervical cancer screening evaluated seven cohort studies and 20 case–control studies from multiple countries and concluded that cervical screening using conventional cytology can reduce the incidence of and mortality from cervical cancer. The present review identified five further cohort studies and 20 case–control studies, which continue to support the effectiveness of cytology screening in reducing cervical cancer incidence and mortality. The available studies are a mixture of population-based studies using administrative data sets, which avoid participation and recall biases, and studies based on recruitment invitations, which probably suffer from these biases but obtain detailed information to adjust for confounders. In the only randomized controlled trial to compare cytology screening with no screening, about 30 000 women in India participated in each of the cytology and control groups for a single round of screening. After 8 years of follow-up, the incidence of cervical cancer in the cytology group was higher than, although not statistically significantly different from, that in the control group (hazard ratio, 1.34; 95% confidence interval [CI], 0.99–1.82). Mortality from cervical cancer was lower, but not significantly lower, in the cytology group than in the control group (hazard ratio, 0.89; 95% CI, 0.62–1.27).

Two published meta-analyses were reviewed, with only one overlapping study. In 2007, the International Collaboration of Epidemiological Studies of Cervical Cancer published an analysis of almost 36 000 women from 12 observational studies to analyse risk factors for cervical cancer and included history of cytology screening. Cytology screening was associated with a reduced risk of cervical cancer for both squamous cell carcinoma (relative risk, 0.46; 95% CI, 0.42–0.50) and adenocarcinoma (relative risk, 0.68; 95% CI, 0.56–0.82). A 2013 systematic review undertook a meta-analysis of 12 studies with almost 4800 cases and 18 000 controls, and found lower odds of having undergone cytology screening in women with cervical cancer (odds ratio, 0.35; 95% CI, 0.30–0.41) but noted a large degree of heterogeneity.

National-level long-term ecological trend data from multiple countries also support the effectiveness of cytology-based cervical screening at a population level.

(c) Beneficial effects of screening using liquid-based cytology

Liquid-based cytology is based on the same sampling method, staining, and interpretation as conventional cytology; thus, both methods use the same process to identify precancerous lesions.

A large body of evidence shows similar accuracy of liquid-based cytology compared with conventional cytology. Several systematic reviews reported that when atypical squamous cells of undetermined significance (ASC-US) was used as the test threshold, the pooled sensitivity for detection of CIN2+ and for detection of CIN3+ was similar for conventional cytology and liquid-based cytology. However, in some reviews the pooled specificity was higher for conventional cytology than for liquid-based cytology. The eight large randomized controlled trials and several recent double-testing studies, mostly implemented in population-based programmes, reported similar or higher sensitivity, with similar or lower positive predictive value, for liquid-based cytology compared with conventional cytology. The proportion of unsatisfactory slides was consistently lower with liquid-based cytology compared with conventional cytology in all population-based studies.

Two observational studies and one randomized controlled trial reported a good correlation between baseline detection rate and subsequent incidence of CIN2, CIN3, and invasive cancers with liquid-based cytology.

(d) Cytology based on Romanowsky–Giemsa staining

The term "Romanowsky staining" refers to several techniques used to stain cytological specimens, in which the Romanowsky effect is used to differentiate the cell components, i.e. chromatin is stained in purple and nuclei show shadows, enabling characterization of their morphology. Staining techniques based on the Romanowsky effect are known by several names, such as Romanowsky–Giemsa and May–Grünwald–Giemsa, and are used for different purposes in modern cytology. Currently, the technique is still used for cervical cancer screening in some countries of the former Soviet Union.

Despite a very extensive bibliographical search (including literature in Russian and/or predating electronic databases), the Working Group did not identify any study comparing the accuracy or efficacy of Romanowsky–Giemsa staining with that of conventional cytology in cervical cancer screening. The few reports on screening performance suggest a high variability in the proportion of unsatisfactory slides and detection of cervical lesions, and low specificity. No observational studies showed effectiveness in reducing the incidence of or mortality from cervical cancer of screening programmes implemented in countries where Romanowsky–Giemsa staining is used. The few informative population-based studies showed no effect. There are many possible explanations for not observing an effect in such studies, other than the accuracy of cytology.

(e) Harms of cytological techniques

Physical harms associated with pelvic examination and collection of cervical cytology samples include pain and, less commonly, vaginal bleeding, discharge, urinary problems, or feeling sick. Psychological harms such as anxiety can be experienced: (i) when samples are collected, (ii) as a result of waiting time to receive the results, (iii) from unsatisfactory smears, (iv) from abnormal results, and (v) upon follow-up because of abnormal results.

6.4.3 HPV testing

(a) Technical descriptions

HPV tests can be classified by the following parameters: the nucleic acid targeted (DNA or messenger RNA [mRNA]), the amplification method (signal amplification or target amplification), the method of identification of amplicons, the viral genes targeted, the level of genotyping detail (none, limited, extended, or full), the output result (qualitative or quantitative), and the inclusion of internal controls. HPV tests that separately identify the most carcinogenic HPV genotypes may enable fine-tuned risk-based management of women who are positive for carcinogenic HPV types. HPV tests are typically performed on cervical specimens taken by a health-care worker but can also be applied to self-collected vaginal samples or urine.

Various HPV assays have been validated for cervical cancer screening. Regulatory requirements for HPV assays differ around the world. Criteria have been developed for evaluating new HPV DNA assays in comparison with standard comparator tests. New HPV DNA tests may be accepted for screening if non-inferior sensitivity and specificity for CIN2+ compared with a standard comparator test and sufficient intra-laboratory and interlaboratory reproducibility can be demonstrated. New validation criteria are being developed that will expand the choice

of standard comparator tests, the validation of HPV tests other than DNA tests, and HPV testing on self-collected samples. Certain HPV tests require certified laboratories with trained staff and strict quality control, whereas others can be performed in field conditions or even as a point-of-care test. Availability, costs, logistic and regulatory aspects, throughput capacity, automation, user-friendliness, and the need for running water and electricity are important factors that influence the choice of an HPV screening test in a particular setting and situation.

(b) Comparison of HPV DNA testing versus cytology

The evidence comparing HPV DNA testing with cytology screening consists of 29 cross-sectional diagnostic studies, eight randomized controlled trials in routine cervical screening and one randomized trial in a previously unscreened population, 10 population-based studies using results from regional, national, and pilot HPV DNA screening programmes, six co-testing cohorts, and one pooled analysis of seven other co-testing cohorts. In a pooled analysis of the 29 diagnostic studies with paired HPV DNA and cytology test results, HPV DNA testing was 37% more sensitive than cytology at detecting CIN3+ and 35% more sensitive at detecting CIN2+, at the expense of 6% lower specificity. In seven of the eight randomized controlled trials in routine screening, HPV-based screening by HPV DNA alone or co-testing detected significantly more CIN2+ than cytology in the first screening round. Six randomized controlled trials performed two rounds of screening. In five of them, HPV-based screening detected significantly fewer CIN2+ than cytology in the second screening round, and in four of them, only a minimal change in cumulative detection of CIN2+ over two rounds was observed, reflecting no increase in overdiagnosis.

A pooled analysis of four randomized trials in routine screening, with a median follow-up of 6.5 years, yielded a 40% lower cumulative risk of cervical cancer in the HPV DNA-based screening arm compared with the cytology-based screening arm. In the randomized trial in a previously unscreened population, the cumulative cervical cancer mortality was 41% lower in the HPV-based screening arm than in the cytology-based screening arm after a follow-up of 8 years.

In eight of the 10 population-based HPV DNA screening studies, HPV-based screening detected significantly more CIN2+ than previous cytology screening. These studies also reported an increase in the proportion of positive HPV test results and colposcopy referrals, but the effect of HPV DNA screening on the proportion of CIN3+ detected in women referred for colposcopy was inconsistent across studies. Randomized controlled trials and co-testing cohorts reported a substantially lower 3–10-year risk of CIN3+ and an up to 70% lower risk of cancer after a negative HPV DNA test result than after negative cytology, which supports the use of longer intervals in HPV-based screening programmes.

(c) Comparison of HPV DNA testing versus VIA

Eight reviews and meta-analyses or pooled analyses, two randomized controlled trials, six cross-sectional studies, and a pooled analysis of two cohorts contributed to the comparison of HPV DNA testing and VIA on test accuracy, detection rate of high-grade cervical lesions, and cervical cancer incidence and mortality. The test accuracy of VIA was very heterogeneous across studies and prone to potential outcome misclassification. Overall, HPV DNA demonstrated higher pooled sensitivity than VIA, with a difference that was most pronounced in postmenopausal women.

A randomized controlled trial in South Africa showed a greater reduction in CIN2+ at 6 months after HPV DNA test-and-treat (77%) than after VIA-and-treat (37%) compared with no treatment, and a randomized controlled trial

in Osmanabad District, India, showed that, after 8 years of follow-up, greater reductions in the cumulative incidence of stage II or higher cervical cancer (> 2 times) and in cervical cancer mortality (> 1.6 times) were reached after a single round of screening with HPV DNA testing compared with VIA. For HPV DNA testing compared with VIA, the different studies did not consistently report a higher or lower proportion of colposcopy referrals or a larger number of colposcopies needed to detect one CIN2+ or CIN3+.

(d) Comparison of HPV DNA testing alone versus co-testing

HPV DNA testing alone versus co-testing (combined HPV DNA testing and cytology) has been evaluated in a meta-analysis, a joint analysis of cohort studies, four randomized controlled trials, seven prospective cohort studies, and retrospective analyses of a large laboratory database. The studies span nearly 15 years and differ in referral strategies, follow-up time, and outcomes examined (CIN2+, CIN3+, and invasive cancer). No evidence was found for the comparison of testing modalities regarding the outcome of mortality. Co-testing results in about 5% higher sensitivity but lower specificity than HPV DNA testing alone for outcomes of CIN2+ and CIN3+. The loss in specificity and the reduced positive predictive value of co-testing may lead to increased harms (namely, overdiagnosis of regressive lesions). Over longer follow-up, cumulative risks of CIN2+ and CIN3+ differ minimally between co-test-negative women and HPV-negative women.

(e) HPV testing on self-collected versus clinician-collected samples

Data on the comparison between self-collected vaginal samples and clinician-collected cervical samples are abundant for HPV DNA tests, with a key meta-analysis including 56 diagnostic test accuracy studies. In addition, three new accuracy studies and one study evaluating the longitudinal performance of HPV self-sampling were reviewed. The studies originate from all world regions except Oceania. The studies reviewed included different HPV DNA assays, all clinically validated, and different sampling devices and storage medium.

Similar sensitivity and specificity for the detection of CIN2+ or CIN3+ were observed when using polymerase chain reaction (PCR)-based HPV DNA tests on self-collected samples. Use of other types of HPV DNA assays for the detection of CIN2+, such as signal amplification, resulted in an average decrease of 15% in sensitivity and 4% in specificity. There was no indication that accuracy estimates for the detection of CIN2+ or CIN3+ were modified by sampling device or storage medium. Data on the long-term comparability were scanty.

The evidence for the detection of CIN2+ on specimens collected by self-sampling for HPV RNA tests based on three studies pointed to lower sensitivity and similar specificity compared with clinician-collected cervical samples.

Preliminary data on the introduction of self-sampling in nationwide programmes support its feasibility and effectiveness.

(f) Comparison of HPV RNA testing versus HPV DNA testing

Data on the accuracy of HPV RNA tests for the detection of CIN2+ were available for 11 studies on screening populations, four studies that reported on longitudinal outcomes, and 20 studies with triage of screen-positive cases, including one randomized trial. The studies were mainly from Europe, North America, and China.

Data on cross-sectional performance of RNA-based assays were consistent with higher specificity for CIN2+ compared with HPV DNA tests. This was achieved at the cost of a slight decrease in the sensitivity to detect CIN2+. Data on the accuracy to detect precancerous lesions in a primary screening setting with a follow-up of more than 4 years remain limited.

(g) Triage of women with a positive primary HPV screening test result

Appropriate triage testing, management, and follow-up of HPV-positive women is of critical importance to optimize the balance of benefits and harms of primary HPV screening. The general principle is to refer for diagnostic workup women who are at a higher risk of having a current or incipient precancer, to return to routine screening women who are at low risk, and to keep under surveillance women who are at intermediate risk. From a meta-analysis on the accuracy of tests used to triage HPV-positive women for detection of cervical precancer, including 93 studies, six commonly considered triage strategies were selected for assessment: (i) cytology at a threshold of ASC-US+, (ii) genotyping for HPV16/18; (iii) p16/Ki-67 immunocytochemistry (dual staining), (iv) VIA, (v) combined testing with HPV16/18 genotyping and cytology at a threshold of ASC-US+ (in which HPV16/18-positive women are referred directly for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology), and (vi) combined testing with HPV16/18 genotyping and VIA (similar to strategy (v) but using VIA to triage women who are positive only for other carcinogenic HPV types). In the first four (single-test) strategies, p16/Ki-67 dual staining was more sensitive for detection of underlying CIN3+ (85%), with an associated specificity for < CIN2 of 69%. The combinations of HPV16/18 genotyping and another triage test (cytology at a threshold of ASC-US+ or VIA) reached a similarly high level of sensitivity for CIN2+ and CIN3+ as dual staining. However, the cross-sectional specificity of these combinations for CIN2+ was lower (< 60% for < CIN2).

More complex algorithms than those assessed here can be considered to fine-tune management, particularly in relation to the management of an intermediate-risk group who are positive for carcinogenic HPV but have a negative triage test result at the index test, for whom surveillance is an option. The acceptability of any triage approach is ultimately context-specific and depends on a range of factors, including the underlying risk of CIN3+ and invasive cervical cancer in a population, the available technological options for triage testing, the cost–effectiveness, and the acceptability of the testing process to women.

(h) Harms of HPV testing

Psychosocial harms in screening have been measured by administering questionnaires in screening cohorts and through qualitative research. A positive HPV test result is associated with increased levels of anxiety and distress, but these levels decrease over time. A positive HPV test result may also cause concerns about cancer and evoke feelings of stigma and shame. The psychosocial impact of HPV testing depends on cultural factors and communication strategies and varies across health systems. A web-based survey and interview and questionnaire studies indicated that anxiety can be reduced by communicating that HPV infection is common. Two randomized controlled trials in European countries studied the psychosocial impact of HPV-based screening compared with cytology-based screening. These trials reported similar average levels of anxiety and distress in the two arms, but one of them reported a reduced level of sexual satisfaction in the HPV-based screening arm. The cervical sampling procedure also causes psychological and physical harms, which may be reduced by offering the option of self-collected vaginal sampling for HPV testing. Two meta-analyses together with recent studies of self-sampling showed that self-sampling lowers anxiety, discomfort, and pain and is less embarrassing than sampling by a clinician. Most women in these studies expressed a preference for self-sampling as a future sampling method, but some women were worried about the accuracy of the HPV self-sampling test and their capacity to collect the sample correctly.

6.4.4 Colposcopy

A colposcope is a low-magnification, stereoscopic, binocular field microscope with a powerful light source. It is used for visual examination of the lower genital tract, including the cervix, vagina, and vulva. Colposcopy is the cornerstone of management of screen-positive or symptomatic women. It facilitates the identification of the transformation zone and the characterization and localization of intraepithelial lesions to guide biopsies, where necessary.

Different classifications have been used to describe colposcopic findings. Expertise in performing colposcopy is attained and maintained by comprehensive training, experience with an adequate caseload, and continuing professional development. However, colposcopy training and assessment is neither uniform nor quality-assured worldwide.

In a cytology-based screening, colposcopy shows high sensitivity and low specificity for the diagnosis of high-grade squamous intraepithelial lesion (HSIL)/CIN2+ when used at a threshold of "any colposcopic abnormality" (biopsy taken after suspicion of SIL/CIN of any grade); at a threshold of "high-grade colposcopic impression" (biopsy taken after suspicion of HSIL), colposcopy shows medium sensitivity but high specificity for HSIL/CIN2+. In HPV-based screening, the central diagnostic role of colposcopy is maintained but the clinical characteristics of the patients and the number of women referred for colposcopy are profoundly different.

Recently, it has been suggested that the risk of underlying histological HSIL can be estimated before colposcopic evaluation by combining the screening test results (cytology and/or molecular test results such as HPV testing and genotyping). In this strategy, the practice of colposcopy and biopsy can be modified depending on the risk of precancer. Moreover, information provided by the colposcopic impression is taken into account to guide the number of biopsies needed.

6.4.5 Emerging technologies

(a) Emerging visual and cytological technologies

Established guidelines for diagnostic research (the Standards for Reporting of Diagnostic Accuracy Studies [STARD] statement) have been adapted for technology development for cervical cancer screening. The process from discovery and development to clinical implementation is complex and involves multiple stakeholders. As the understanding of the natural history of cervical cancer has improved and technology development has accelerated, the timeline from discovery to clinical practice has become much shorter. The most important criterion for a new test or tool is whether the test result will improve clinical management. Two promising emerging technologies are the use of artificial intelligence-based image recognition to improve visual evaluation of the cervix and cytological interpretation.

As image-capture technology, Internet bandwidth, electronic storage capacity, and computing power have improved exponentially, it has become possible to develop complex systems for image capture, recognition, and interpretation. Using large annotated image banks, these systems use either the Internet cloud or small, powerful, cloud-independent computer devices to store and interpret the incoming images. A variety of approaches have been used to both screen and triage women by examining the cervix in the VIA or colposcopy setting. Most commonly, these systems discriminate between normal or low-grade squamous intraepithelial lesion (LSIL) and HSIL. No convincing real-life studies of sufficient power have been undertaken so far.

Early results from automated cytology systems have shown potentially valuable results for both morphological interpretation and quantitative assessment of p16/Ki-67 dual-stained slides. Some studies reported improved sensitivity and

specificity compared with manual evaluation of morphology and dual-stain assessment. This has the capacity to reduce unnecessary referral for colposcopy.

(b) Emerging molecular technologies

DNA methylation of some human genes and coding regions of the HPV viral genome is associated with CIN and cervical cancer. Methylation patterns are different in CIN2+ compared with normal cervical tissue or moderate cervical lesions, and an increase in methylation is associated with severity. DNA methylation assays show promise for the detection of CIN2+ in triage of HPV-positive women, because they enable automation and self-sampling. Compared with cytology, molecular testing of DNA methylation is objective and decreases the risk of interpretation errors. Methylation of the following human genes has often been reported as providing promising biomarkers: *CADM1*, *EPB41L3*, *FAM19A4*, *MAL*, *miR-124-2*, *PAX-1*, and *SOX-1*; however, none of these biomarkers alone can detect cervical cancer. Increasing methylation is also observed in the E2, L1, and L2 viral coding regions as characteristic patterns, especially for HPV types 16, 18, 31, 33, and 45. A combined multi-type methylation assay might be preferable for triage of HPV-positive women.

A detection assay for the E6 oncoprotein from HPV16/18/45 has shown promising test performance when assessed as a primary screening method for cervical cancer or as a triage test for HPV-positive women in both clinician-collected and self-collected samples.

6.5 Screen-and-treat approach and women at differential risk

6.5.1 Screen-and-treat approach

Multistep cervical cancer screening programmes involving colposcopy and histology require considerable investment in infrastructure, training of a skilled workforce, and quality control efforts. Furthermore, multistep cervical cancer screening strategies require multiple visits with patient–provider interactions and have a substantial risk of loss to follow-up, particularly in resource-constrained settings. Screen-and-treat approaches are designed to require fewer resources compared with multistep programmes, and to decrease the need for repeat visits. Although different screen-and-treat strategies exist, the unifying feature is that treatment is performed without a colposcopy-directed biopsy and histological confirmation of precancer.

Current screening modalities used in screen-and-treat programmes include VIA and HPV testing. Although VIA is simple and widely available, it is also highly subjective and its performance is inconsistent. Point-of-care HPV testing can provide a similar turnaround time to that of VIA, with substantially improved accuracy. Typically, in screen-and-treat programmes more women need to undergo treatment than in multistep screening programmes; this increases the risk of overtreatment. Because of the high prevalence of HPV infections and CIN2+ lesions in women living with HIV, VIA may lead to additional overtreatment compared with HIV-negative women.

Treatment approaches include ablative treatment, such as cryotherapy and thermal ablation, and excisional treatment. Only a subset of women are eligible for ablative treatment, and therefore colposcopy and excisional treatment capacity is required in all programmes. Few studies have assessed the feasibility of full screen-and-treat programmes. A large randomized

trial in South Africa demonstrated a greater reduction in the prevalence of precancer with an HPV screen-and-treat protocol than with a VIA screen-and-treat protocol, compared with delayed evaluation. Novel approaches for screen-and-treat programmes or screen–triage–treat programmes that are undergoing evaluation include self-sampling with partial HPV genotyping, and automated visual evaluation.

6.5.2 Screening of women at differential risk

(a) Screening of women living with HIV

The burden of cervical cancer remains significantly higher in women living with HIV than in HIV-negative women. Incidence rates vary widely by world region and are highest in eastern and southern Africa. Systematic reviews and meta-analyses have reported that women living with HIV have a 2–5-fold higher incidence of HSIL and a 4-fold higher risk of invasive cervical cancer compared with HIV-negative women. HIV infection can cause rapid progression from HPV infection to cancer.

A recent systematic review and meta-analysis reported that women living with HIV taking antiretroviral therapy had a lower prevalence of carcinogenic HPV infections, a lower incidence of HSIL, and a lower incidence of invasive cervical cancer compared with those not taking antiretroviral therapy. The greatest reductions were observed in women with sustained HIV viral suppression and in women initiating antiretroviral therapy at a high CD4+ cell count.

The screening tests for precancerous lesions in women living with HIV are the same as in HIV-negative women, but the performance is affected by the high prevalence of HPV infection. Treatment of HSIL in women living with HIV can be ablative or excisional, and several studies have observed a higher risk of recurrence after treatment in women living with HIV than in HIV-negative women.

(b) Screening of older women

After menopause, there are marked physiological changes of the cervix, which can sometimes result in discomfort during speculum insertion, unsatisfactory specimen collection, lower-accuracy results, and potential harm from overtreatment. Therefore, it is imperative to determine the balance of benefits and harms of cervical cancer screening in older women.

In well-screened populations, most published national guidelines are based on the natural history of HPV infections, surveillance trends, expert opinion, and modelling; most guidelines recommend stopping screening at age 65 years in women with prior adequate negative screening history. However, empirical data are scant on when to stop screening in women aged 65 years and older, in previously unscreened women, in women with an inadequate screening history, and in women with continuing risk factors for the development of cervical cancer, such as women living with HIV.

Both cytology and primary HPV testing can be used to screen postmenopausal women to identify test-positive cases that require treatment with effective available modalities. In most guidelines, primary HPV testing every 5 years is the preferred method of screening in older women, and as data accumulate this interval may be lengthened to 7 years. Several published studies have reported that the protection offered by a negative cytology test result at age 60–65 years is not lifelong, so extending screening beyond age 65 years will offer longer protection against cervical cancer even in well-screened populations, with potential harms of treating women with false-positive results at colposcopy.

(c) Screening of women with a personal history of precancerous lesions

Women who have been treated for known or suspected HSIL/CIN2+ or adenocarcinoma in situ are at higher risk of subsequent disease.

Although most women who have undergone treatment for precancerous cervical lesions do not experience a recurrence of disease, they should undergo post-treatment management and surveillance for test of cure before returning to routine screening. Most current guidelines are based on the pre-treatment diagnosis and the post-treatment histology, including the margin status. Initial testing protocols include cytology and/or HPV-based testing, with a range of surveillance intervals (i.e. 6 months or 12 months) for 1–5 years; some guidelines lengthen surveillance intervals after successive normal test results to support test of cure. After accumulating a history of normal test results, women may return to routine screening intervals or may continue with a less-intensive surveillance protocol. The most recent guidelines emphasize follow-up with HPV-based testing to determine test of cure and return to routine screening. Newer risk-based surveillance protocols take into account current screening test results and previous screening test results and biopsy results.

(d) Screening of HPV vaccinated populations

In late 2006, HPV vaccination became a primary prevention front in cervical cancer control, complementing screening, a secondary prevention activity. In 2018, WHO established as a priority the elimination of cervical cancer as a public health problem, based on the proven effectiveness of both strategies and the expectation of their joint impact in reducing the incidence of cervical cancer to below the target of 4 new cases per 100 000 women per year.

Although vaccination and screening are complementary, they are managed very differently because they apply to different periods in a woman's lifetime and are managed by different parts of the health-care system. However, they can both be viewed as preventive steps in the same continuum in the natural history of cervical cancer. Vaccination prevents the acquisition of HPV infection, the intermediate precursor to precancer development.

As successive birth cohorts of vaccinated women reach the age of screening, the prevalence of precancer decreases, and as a result the efficiency of screening falls via a gradual decrease in the positive predictive value of screening. Although this effect happens with any screening technology, it is expected that cytology will be more severely affected. Because of its performance characteristics, reproducibility, and reliance on objective criteria for defining positivity, primary HPV testing is a more rational approach to the screening of women after vaccination. However, even with the adoption of HPV testing, questions arise regarding the benefits and potential harms of maintaining the same screening frequency in vaccinated and unvaccinated women. A related question is whether populations with high vaccination coverage should adopt less-intensive screening by starting screening later in life and being screened less frequently.

Many jurisdictions and professional bodies have considered the appropriateness of screening policies based on vaccination history. To date, only Italy has proposed screening algorithms that depend on vaccination status and lesion prevalence; all other proposals specify screening policies irrespective of HPV vaccination status.

The integration of vaccination and screening as public health processes that share information, data, resources, and expertise can provide a unified surveillance mechanism to monitor the long-term impact of both prevention fronts and provide an empirical basis for future changes in screening policies.