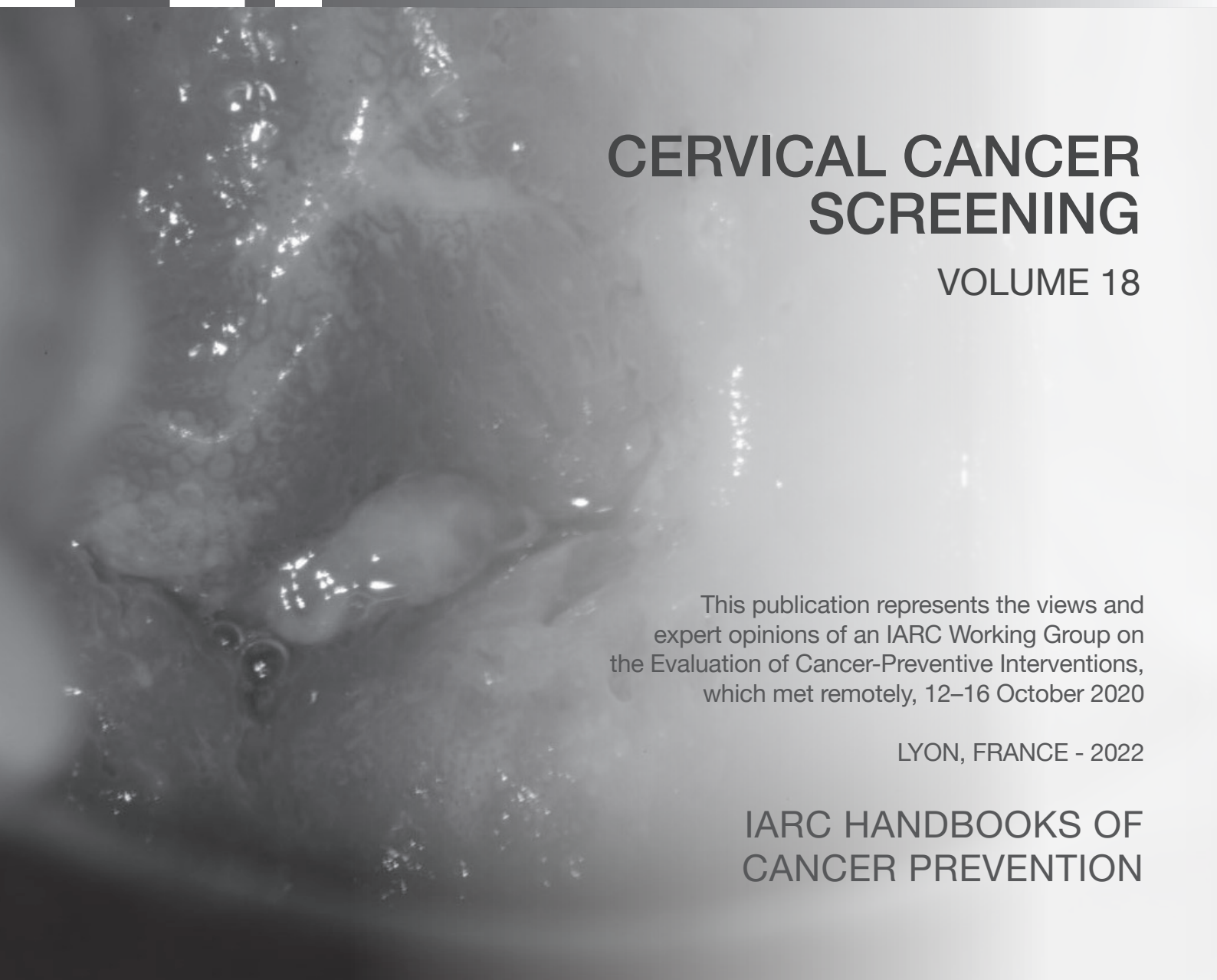
IARC HANDBOOKS



CERVICAL CANCER SCREENING

VOLUME 18

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IARC HANDBOOKS OF CANCER PREVENTION

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7. EVALUATIONS AND COMPARISON STATEMENTS

7.1 Visual inspection with acetic acid

Visual inspection with acetic acid (VIA) ***is established to reduce mortality from cervical cancer*** **(Group A).**

Visual inspection with acetic acid (VIA) ***may reduce the incidence of cervical cancer*** **(Group B).**

The evidence for a reduction in cervical cancer mortality after VIA screening comes from consistent and significant reduction in cervical cancer mortality after a single round (in the Dindigul District and Osmanabad District studies) or multiple rounds (in the Mumbai study) of VIA screening documented in three population-based cluster-randomized intervention trials. The significant reduction in cervical cancer mortality in the Mumbai study has come from clinical stage shift and effective treatment of early-stage invasive cervical cancers as suggested by the low detection rate of high-grade cervical intraepithelial neoplasia (CIN) despite four rounds of biennial screening, whereas both early detection and effective treatment of high-grade cervical precancerous lesions and stage shift of invasive cancers contributed to the significant reduction in cervical cancer mortality in the Dindigul District study and the non-significant reduction in cervical cancer mortality in the Osmanabad District study.

Reduction in cervical cancer incidence after VIA screening has been demonstrated in one of the three cluster-randomized trials (the Dindigul District study). About 44% of screen-positive women in the Dindigul District study received treatment for CIN (including CIN1, CIN2, and CIN3) lesions. The high frequency of treatment of screen-positive women with lesions might have led to the significant reduction in cervical cancer incidence in the Dindigul District study.

Screening regimen to which the evaluation applies. This evaluation applies to VIA screening provided by well-trained health-care workers and implemented with quality assurance and with appropriate follow-up and treatment. VIA is not indicated in women younger than 30 years or in postmenopausal women, and caution is needed in perimenopausal women and in women living with HIV.

Whether effectiveness has been established. Effectiveness to reduce cervical cancer incidence and mortality has not been documented in population-based screening programmes.

Magnitude of benefits and harms. The benefits in terms of reduction in cervical cancer incidence and mortality vary depending on the expertise and experience of the test providers, the adherence to treatment of lesions, the efficiency of the overall programme, and the characteristics (e.g. age, menopausal status) and risk of the underlying target population. A high

frequency of false-positive VIA tests is likely to increase the relative proportion of harms after VIA screening.

Balance of benefits and harms. The benefits may outweigh the harms, but only in VIA screening programmes implemented by well-trained providers, with quality assurance and with appropriate treatment of lesions and follow-up care.

Additional considerations. The harmful effects of VIA have not been systematically studied in visual screening studies or reported widely, either in research settings or in programmatic settings. Visual screening tests for cervical neoplasia are considered safe because few women report adverse events after VIA; however, the current lack of systematically collected and reported data should be addressed, and this should be an essential part of quality improvement activities where VIA is in use.

It is too early to consider the safety of new visual screening techniques such as visual inspection using digital cameras and automated visual evaluation of cervical images from contemporary digital cameras, because of a lack of data.

The main inherent risk of VIA remains its inability to precisely and reliably recognize endocervical disease, which means that it may falsely reassure women when no lesion is detected; this may eventually result in a screening programme being discredited.

Because of the high prevalence of human papillomavirus (HPV) infection and CIN grade 2 or worse (CIN2+) lesions in women living with HIV, VIA may lead to additional overtreatment compared with HIV-negative women.

VIA is not recommended for postmenopausal women, although ageing populations are becoming a major challenge for health-care services in many countries.

VIA has been implemented in resource-constrained settings or countries with low access to health care, because of its low cost, the low infrastructure requirements, and the possibilities to reduce losses to follow-up in screen-and-treat approaches. A wide range of health-care workers provided VIA in studies and continuing programmes, but proper training is needed and harmonized interpretation criteria for positivity still need to be defined.

7.2 Conventional cytology

Conventional cervical cytology *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* (Group A).

The evidence for a reduction in cervical cancer incidence and mortality after conventional cervical cytology screening comes from studies comparing cervical cancer incidence and mortality rates in women who were screened with those in women who were not screened, and from declining cervical cancer incidence and mortality rates from population-based registries in multiple countries and world regions.

Screening regimen to which the evaluation applies. The evaluation applies to conventional cervical cytology screening (Papanicolaou testing) performed within a quality-assured laboratory system with appropriate follow-up and treatment, recognizing the subjective nature of the test and the strong need for appropriate training and systems to ensure and maintain accuracy.

Whether effectiveness has been established. Conventional cervical cytology has been established to be effective in reducing cervical cancer incidence and mortality in population-based programmes.

Magnitude of benefits and harms. The benefits in terms of absolute reduction in cervical cancer incidence and mortality vary depending on the underlying population risk and the efficiency of the screening programme. Psychological benefits include a sense of reassurance after a negative test result. Psychological harms include anxiety related to the screening

procedure, receipt of results, and subsequent diagnostic and treatment pathways. A need to repeat the sample collection because of unsatisfactory specimens may be more frequent than with other methods of cervical screening. Physical harms of conventional cytology may include pain and discomfort during the screening procedure. The potential harms of any subsequent diagnostic procedures or treatment, such as risks of bleeding, infection, or adverse obstetric outcomes, are shared with other cervical screening methods.

Balance of benefits and harms. The benefits generally outweigh the harms. There is less certainty for women younger than 30 years, in whom effectiveness is less well demonstrated and the potential for obstetric harms is greater. Although studies demonstrate continuing effectiveness after age 65 years, the potential benefit in women with a history of regular normal screens may be small, and the physical discomfort associated with screening is likely to increase with age.

Additional considerations. The evidence supports significant benefits from well-organized programmes. The evidence suggests that protection from a single screen wanes over time, that consistent, regular screening lowers the risk more substantially than ad hoc or single-time screening does, that the risk of squamous cell carcinomas of the cervix is reduced by a greater magnitude than that of other cervical cancers, that screening of women younger than 30 years has less consistent evidence of effectiveness, and that screening of older women (e.g. older than 65 years) continues to be effective, with potentially greater benefits in those without a history of regular normal screens.

7.3 Liquid-based cytology

Liquid-based cytology *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* (Group A).

The evidence for a reduction in cervical cancer incidence and mortality after liquid-based cytology screening comes from randomized controlled trials and population-based nationwide observational studies comparing the accuracy, efficacy, and effectiveness of liquid-based cytology with those of conventional cytology, and considering that the techniques are sufficiently similar. A large body of evidence shows similar accuracy and effectiveness of liquid-based cytology compared with conventional cytology.

Screening regimen to which the evaluation applies. The efficacy has been tested in programmes adopting cytology as a stand-alone first-level test, with different strategies of referral for colposcopy, including repeating cytology for atypical squamous cells of undetermined significance (ASC-US) and low-grade lesions, HPV triage for ASC-US, and direct referral for colposcopy of all cytological abnormalities.

Whether effectiveness has been established. Liquid-based cytology proved to be as effective as conventional cytology in reducing cervical cancer incidence in nationwide population-based programmes. Despite some issues in implementation, liquid-based cytology had small or no negative impacts on screening programme performance.

Magnitude of benefits and harms. The benefits and harms of liquid-based cytology have been measured only in comparison with those of conventional cytology. The benefits in terms of reduction in cervical cancer incidence were shown to be very similar to those of conventional cytology. The reduction in the proportion of unsatisfactory specimens decreases the need to repeat the sample collection, which is associated with anxiety for women and resource

consumption. However, some studies of liquid-based cytology showed increased sensitivity for low-grade lesions, which results in a higher referral rate for further assessment.

Balance of benefits and harms. The benefits of screening with liquid-based cytology outweigh the harms.

Additional considerations. In high-income countries, the introduction of liquid-based cytology into screening programmes has been driven mostly by the lower proportion of unsatisfactory specimens and by the opportunity to perform both molecular and cytology tests, in particular HPV tests, with a single sample. This opportunity has facilitated these two-step strategies, both when HPV testing is used as a triage test for ASC-US or low-grade squamous intraepithelial lesion (LSIL) cytology and when cytology is used to triage HPV-positive women. Some programmes have considered these advantages to overcome the barrier of higher costs.

7.4 HPV nucleic acid testing

HPV nucleic acid testing *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* (Group A).

The evidence for a reduction in cervical cancer incidence and mortality after screening with HPV nucleic acid testing comes from one randomized controlled trial showing that HPV testing reduces cervical cancer mortality, a pooled analysis of four randomized controlled trials showing that HPV testing leads to a greater reduction in cervical cancer incidence than cytology does, and screening cohorts and diagnostic studies comparing HPV testing with cytology and/or VIA.

Screening regimen to which the evaluation applies. The evaluation applies to HPV DNA testing and HPV messenger RNA (mRNA) testing.

Magnitude of benefits and harms. The bulk of the evidence is from studies of HPV DNA testing. HPV mRNA testing has been shown to have accuracy levels similar to those of HPV DNA testing for detection of CIN2+, and a negative HPV mRNA test has a lower 3-year risk of CIN2+ than negative cytology does. The first round of HPV testing, followed by triage testing of HPV-positive women, in regional, national, and pilot HPV screening programmes confirmed that HPV screening detects more precancerous lesions than cytology screening does. HPV screening also increased the proportion of positive screening results and colposcopy referrals and had an inconsistent effect on the proportion of CIN3+ in women referred for colposcopy (the positive predictive value for CIN3+). A positive HPV test result is associated with increased levels of anxiety and distress and may cause concerns about cancer and feelings of stigma and shame.

Balance of benefits and harms. The benefits outweigh the harms for women aged 30 years and older. There is less certainty for women younger than 30 years, especially when triage testing of HPV-positive women is not in place. The benefits–harms profile can be further improved by extending screening intervals to at least 5 years, because longitudinal HPV screening studies have shown very low risks of CIN3+ and cancer after a negative HPV DNA test.

Additional considerations. Testing should be performed with clinically validated tests. HPV testing can also be performed on a self-collected vaginal sample. Diagnostic studies have shown that similar accuracy for detection of CIN2+ can be achieved with HPV DNA testing on a self-collected sample and a provider-collected sample. On average, self-collection is better tolerated, both physically and psychologically, than provider-collected sampling.

7.5 Cytology based on Romanowsky–Giemsa staining

Cytology based on Romanowsky–Giemsa staining *is not classifiable as to its capacity to reduce the incidence of cervical cancer* or *to reduce mortality from cervical cancer* (Group C).

The literature search performed, which included a manual search for publications dating from before electronic literature databases, did not retrieve any comparative study on the accuracy, efficacy, or effectiveness of cytology based on Romanowsky–Giemsa staining in cervical cancer screening. Data on the performance of Romanowsky–Giemsa staining in screening programmes suggest low reproducibility and low specificity. The technique is adopted mainly for historical reasons and because of the lower costs of a single examination and the wider availability of materials compared with the Pap test. However, the high rate of unsatisfactory stains and the low specificity imply high induced costs for repeated tests. The absence of an international community for standardization of interpretation criteria makes quality improvement difficult.

7.6 HPV DNA testing versus VIA

HPV DNA testing has been compared with VIA in eight reviews and meta-analyses, two randomized controlled trials, six cross-sectional studies, and a pooled analysis of two cohorts.

Benefits. HPV DNA testing leads to a greater reduction in the incidence of stage II or higher cervical cancer and in cervical cancer mortality than VIA does. HPV DNA testing also detects more high-grade cervical lesions than VIA does.

Harms. Because of the high variability of VIA, the effect on rates of referral for colposcopy was inconsistent across studies. Therefore, the harms cannot be compared.

Balance of benefits and harms. Compared with VIA, HPV DNA testing shows higher benefits, which outweigh the potential increase in the rates of referral for colposcopy. VIA has substantial other limitations, such as subjectivity, heterogeneity, and potential outcome misclassification.

7.7 HPV DNA testing versus cytology

HPV DNA testing has been compared with cytology in 29 diagnostic studies, eight randomized controlled trials in routine cervical screening and one randomized controlled trial in a previously unscreened population, 10 population-based studies using results from regional, national, and pilot primary HPV screening programmes, six co-testing cohorts, and one pooled analysis of seven other co-testing cohorts.

Benefits. HPV DNA testing leads to a greater reduction in cervical cancer incidence and mortality than cytology does. HPV DNA testing is more sensitive than cytology for detecting CIN2+ and leads to reduced detection of CIN2+ in the subsequent screening round. The 3–10-year risk of CIN3+ is lower after a negative HPV DNA test than after negative cytology.

Harms. HPV DNA testing leads to an increase in the proportion of screen-positive women and colposcopy referrals compared with cytology, which is attenuated by triage testing of HPV-positive women. Primary HPV DNA screening with triage testing can be implemented with only a minimal change in the rates of overdiagnosis of CIN2+.

Balance of benefits and harms. The benefits of a reduction in cervical cancer incidence and mortality outweigh the increase in the proportion of positive tests and colposcopy referrals and the potential increase in psychological harms. The balance will be even more favourable after multiple rounds of HPV-based screening because HPV DNA testing programmes enable longer screening intervals than cytology screening programmes do.

7.8 HPV DNA testing alone versus co-testing

HPV DNA testing alone has been compared with co-testing (combined HPV DNA testing and cytology) in a meta-analysis, a joint analysis of cohort studies, four randomized controlled trials, six prospective cohort studies, and retrospective analyses of a large laboratory database. The studies span nearly 15 years and differ with respect to referral strategies, follow-up time, and outcomes examined (CIN2+, CIN3+, and invasive cancer).

Benefits. Co-testing results in about 5% higher sensitivity for the outcomes of CIN2+ and CIN3+ compared with HPV testing alone. There is a lack of data from randomized controlled trials on the efficacy of HPV testing versus co-testing with regard to mortality, and limited data on the end-point of invasive cancer.

Harms. Compared with HPV testing alone, co-testing has a lower specificity for the detection of CIN2+ and CIN3+. Co-testing results in an increase in the rate of referrals for colposcopy and a decrease in the positive predictive value in referred women compared with HPV testing alone. The loss in specificity and the lower positive predictive value of co-testing may lead to increased detection of regressive lesions.

Balance of benefits and harms. The benefits of co-testing do not outweigh the harms. There is a minimal increase in sensitivity with co-testing; however, this gain is small and the impact on cancer incidence is unclear. Furthermore, this difference in sensitivity affects very few cases, suggesting that the relative contribution of the cytology component of co-testing is limited. Over longer follow-up, the cumulative risks of CIN2+ and CIN3+ for co-test-negative women differ minimally from those for HPV-negative women.

Additional considerations. Analysing all samples with cytology and HPV testing, rather than with HPV testing alone, requires far more resources.

7.9 Considerations on related issues

7.9.1 Triage

(a) Triage of HPV-positive women

Triage is used to optimize the balance of benefits and harms of cervical screening with HPV testing. Many triage approaches are feasible, including strategies that involve one-time (reflex) triage testing and two-time (follow-up or delayed) triage, and a range of combinations of technologies are feasible in both contexts. 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. All the triage options considered in the current review enable reaching a positive predictive value for CIN3+ of more than 10%. However, depending on the pre-test prevalence in HPV-positive women and the chosen triage approach, the number of women who must be referred for colposcopy to detect one case of CIN3+ varies from 3 to 9. For the strategies considered here, a negative triage test result was never associated with a risk of CIN3+ of lower than 1%; this might be a reason to keep the woman under further surveillance.

(b) Triage by HPV testing after an ASC-US or LSIL test result

The Working Group considered that HPV testing for women with ASC-US can substantially decrease the number of colposcopies, but that HPV testing for women with LSIL may not be effective in reducing harms in young women,

and that its impact in older women may vary across settings.

(c) Triage with HPV DNA tests versus HPV mRNA tests

The Working Group considered that there was no evidence that using HPV RNA testing as a triage test could increase specificity for CIN2+ compared with HPV DNA testing; there was no indication that the sensitivity of HPV RNA tests for CIN2+ was different than that of HPV DNA tests.

7.9.2 Self-sampling

The Working Group considered that the use of self-sampling approaches for HPV DNA detection provided high values of sensitivity and specificity compared with the use of clinician-collected samples. The higher sensitivity of HPV DNA detection through polymerase chain reaction (PCR) assays may enable the detection of cervical infections as well as vaginal infections, resulting in an improved predictive value compared with less-sensitive tests. The accuracy of self-sampling for the detection of HPV DNA was not device-dependent. The use of self-sampling approaches for HPV RNA detection showed a significantly reduced sensitivity when compared with the use of clinician-collected samples.

The evidence on whether self-collected samples could be used for genotype comparison or other molecular tests remains limited, particularly for the detection of adenocarcinoma and adenocarcinoma in situ. The self-sampling studies had some limitations; in some instances, the diagnostic protocols and workflow were not well documented, because the use of self-sampling was off-label. Thus, the currently available data do not enable quality assessment of self-sampling protocols in scaling up the use of self-sampling. The trade-offs in coverage or participation when self-sampling is being implemented at a large scale will need to be explored further.

7.9.3 Screen-and-treat strategies

The Working Group noted that the observational screen-and-treat studies are very heterogeneous in the design and methodology used, and more data are needed, particularly for HPV screen-and-treat strategies. Self-sampling with rapid on-site HPV testing would enable the development of single-visit screen-and-treat programmes; these would benefit from the high accuracy and reproducibility of HPV testing. The role of extended genotyping to discriminate between the highest-risk and the lowest-risk HPV types needs to be evaluated further in this context, because it would enable treatment to be avoided for women infected with HPV genotypes that very rarely cause cancer but are very common in the population. Other triage strategies that can be conducted on self-collected specimens, such as testing for DNA methylation, could decrease unnecessary treatment, but more evidence is needed.

Automated visual examination is a novel strategy that can provide visual screening or triage with high accuracy and limited investment in infrastructure. HPV self-sampling followed by automated visual examination could provide rapid, high-quality screening and triage with integrated assessment of eligibility for treatment, enabling the introduction of effective cervical cancer prevention programmes in resource-constrained settings.

7.9.4 Interventions to increase participation in screening

Among all strategies reviewed by the Working Group, invitation letters appear to increase participation in screening, although most studies have been carried out in high-income countries. In low- and middle-income

countries, mail systems are often unreliable and specific postal addresses are often lacking, which can limit the effectiveness of invitation letters. Evidence also indicates that educational interventions are effective in increasing screening participation. HPV self-sampling has the potential to increase participation, especially when an opt-out strategy is used. In high-income settings, self-sampling is offered mainly through the mail system, but this method is not feasible in many low- and middle-income countries, as with invitation letters. Outreach and navigation strategies have been demonstrated to be highly effective in increasing screening participation, especially if coupled with HPV self-sampling offered during home visits by community health workers, but implementation of this strategy at a large scale will be dependent on the availability of primary health workers or an equivalent outreach infrastructure. The offer of HPV self-sampling kits to women routinely attending health centres has been shown to be effective in high-income settings. This strategy is much less dependent on human resources than community outreach and takes advantage of the fact that, in many populations, women are the main health caregivers in households. Although the introduction of HPV testing may help to improve the organization of health systems and programmes (e.g. through laboratory centralization, reduced overscreening, and better adherence to recommendations for screening ages), if HPV testing is not coupled with self-sampling it may face barriers similar to those observed for cytology-based screening. Combination and adaptation of effective strategies to address specific contexts, levels of resources, and socioeconomic groups are needed to increase participation in screening.