

HPV Testing and Vaccination in Europe

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■ **Abstract:** Current cytology-based screening has a moderate sensitivity to detect cervical intraepithelial neoplasia grade 3 (CIN 3) and cervical cancer even in those states providing rigorous quality control of their cervical screening programs. The impact of vaccination against human papill-

omavirus (HPV) types 16 and 18 as well as the incorporation of HPV testing on the detection of CIN 3 and cancer is discussed. HPV testing used as a triage for atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions, test of cure after treatment, and HPV-based primary screening may improve current cervical screening programs.

HPV testing as a triage test for ASCUS seems to offer an improved sensitivity, with a similar specificity as compared to repeat cytology for diagnosing high-grade CIN and has been recommended throughout most EU states. HPV testing as a triage test for low-grade squamous intraepithelial lesions has a low specificity and is not recommended in most member states. HPV test of cure offers an improved sensitivity compared to cytology for women with persistent cervical precancer after treatment. HPV-based cervical cancer screening is more effective than screening with cytology. The effects of HPV-based screening depend on the organization of the program and on adherence to algorithms for screening triage. Otherwise, it is likely that HPV-based screening will increase the referral rate to colposcopy including more women with no detectable cervical lesion. HPV vaccination will require many years to evaluate any beneficial effects on cervical cancer incidence and mortality. ■

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In 2004, approximately 52,000 new cases of cervical cancer were diagnosed in Europe and 27,000 women died of their disease [1], yet there is a wide variation in the availability of cervical screening across Europe. Reasons for variation in incidence and death rates depend on the availability and effectiveness of cervical screening programs [1, 2]. In 2009, 16 of 35 European states provided opportunistic testing, whereas the other 19 states had organized screening. The age range for testing varied but was between 15 (Luxembourg) and 70 years (Latvia). Between 6 and 50 lifetime tests were offered in each program [3]. Where neither organized nor good-quality opportunistic screening is available, such as in several Eastern European and Baltic states, the effects on incidence and mortality are less marked, and in Estonia, Bulgaria, and Romania, both are increasing [2, 4]. The burden of cervical cancer is particularly high in new member states to the European Union (see Figure 1).

Increased exposure to human papillomavirus (HPV) may be inferred from at least some states, which is particularly problematic in the absence of organized cervical screening. In Western and Northern Europe, the burden of cervical cancer is smaller, with a possibility of a widening gulf in the future between states with and without organized screening. The landscape for cervical screening is changing as many Western European states have introduced HPV vaccination for adolescent girls. Screening programs are introducing HPV testing in a range of roles. This article seeks to explore current and future developments for cervical cancer screening and how this may affect management of cervical precancer throughout Europe.

HPV VACCINATION

Pooled data from 11 case-controlled studies revealed that the odds ratio of HPV-16 preceding squamous cancer of the cervix was 434.5 using GP 5+/6+ primer from 1,739 cases. HPV DNA was extracted from 96.6% of cases and 15.6% of controls [6]. HPV-16 was the commonest

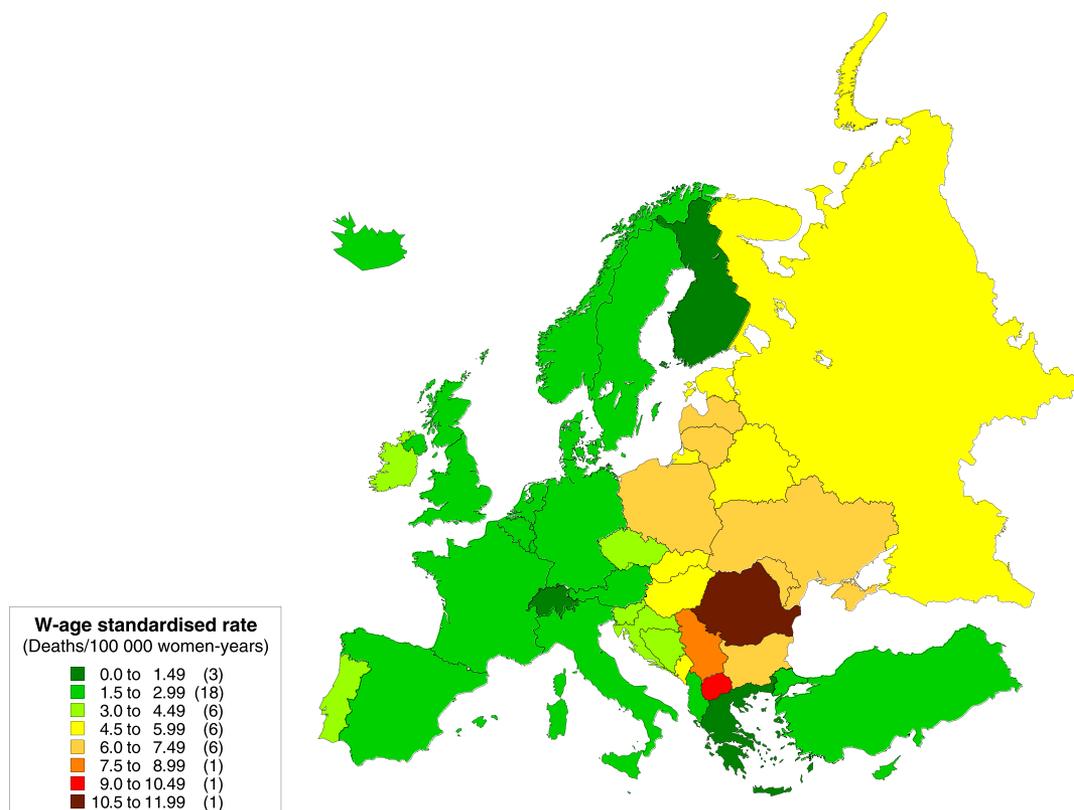


Figure 1. Geographic distribution of the age-standardized rate of mortality from cervical cancer, in 41 European countries, estimated for 2008 (per 100,000 women-years, standardized using the world reference population). The counts in brackets in the legend correspond to the number of countries in each range (reproduced with permission from Arbyn et al. [5]).

high-risk HPV type in cancer cases in all 4 continents from which cases were obtained. ARTISTIC data revealed that HPV-16 or -18 were present in 61% of cases with severe dyskaryosis but in 2.2% of normal cytology [7]. HPV-16 or -18 has also been detected in 63% of cervical intraepithelial neoplasia grade 3 (CIN 3) and 91% of cervical glandular intraepithelial neoplasia (cGIN) [8].

HPV vaccines protect HPV-naive women against approximately 50% to 90% of CIN 2+ [9, 10], more than 90% of CIN 3+ irrespective of the associated HPV type and almost 100% of CIN 3+ associated with HPV-16/18 [11] from vaccine trials involving young women. HPV-16 is responsible for proportionately more CIN 3 in young women, and so the vaccine trials may have overestimated the long-term protective vaccine effect. There was no significant protective effect for some oncogenic HPV types, such as with type 50, which is associated with cervical cancer in older women. Screening of vaccinated cohorts may be cost-effective if the frequency of testing is reduced [12] with sufficiently specific screening and triage methods, but the duration of vaccine protection and the need for boosters are unknown. There seems to be no reduction in efficacy at 8 years, and from computer simulation, protection will be maintained for more than 20 years [13]. The amount of high-grade CIN prevented also depends on the degree of cross protection offered to non-16/18 HPV types and the uptake within the target population. Given the emerging high efficacy of both current vaccines, then uptake preferably linked to school based or to a similar registry seems ideal. Women should not feel that screening is not required if they have received HPV vaccine.

A protective effect against cervical squamous cancer and cervical adenocarcinoma is expected with vaccination. Cytology has not been associated with a reduction in adenocarcinoma, although HPV testing as a primary screen is likely to reduce the incidence of both squamous and adenocarcinoma [14]. Overall, with an 80% vaccine uptake from a school-based vaccination program, Cuzick et al. [15] estimated a 63% reduction in cervical cancer for women younger than 30 years. This modeling study predicted that the relative protection and relative coverage seems better in girls vaccinated at 13 than for older girls.

HPV is also associated with most vaginal and anal cancers, around 50% of vulval cancer [16] and a minority of oropharyngeal cancer. There is a protective effect on the development of premalignant disease of the vagina, the vulva, and the anus [17]. The impact should be greatest in resource-poor countries, with a high incidence of cervical cancer without an existing cervical screening program.

Generally better organized or high-quality opportunistic screening is associated with improved attendance at vaccination. What is seen in Europe is that the countries with population-based organized screening programs have also implemented school-based, opt-out (children are vaccinated unless their parents specifically request otherwise) vaccination programs that provide the highest vaccination coverage rates. This is probably because these countries have high-quality public health services that have the skills and experience to implement both public health programs. Meanwhile, the opposite is also true in that the countries that do not have good public health services have not implemented either effective cervical screening or HPV vaccination programs that have sufficient coverage to make any substantial impact on cervical cancer rates. As a result, the highest rates of HPV vaccination coverage are being realized in the populations that are already well protected by cervical screening.

In the youngest vaccinated cohort of women, the anticipated reduced incidence of cancer will take at least 10 years to be realized [15]. The full effect of the vaccinated cohort on cancer mortality may take many more years. More immediate changes to colposcopy involve the consequences of HPV triage of minor cytologic abnormalities, test of cure after treatment, and HPV-based screening.

TRIAGE OF ASCUS AND LSIL

For women with atypical squamous cells of undetermined significance (ASCUS), 10% have incident CIN 2+, and for low-grade squamous intraepithelial lesions (LSILs), 19% have incident CIN 2+ [18]. However, for ASCUS, the risk for CIN 2+ seems equivalent to that for LSIL in HPV-positive women from ASCUS-LSIL Triage Study (ALTS) data at 23% [19–21]. From a meta-analysis of 16 studies, Hybrid Capture II (HCII) seems more effective than cytology with ASCUS in detecting CIN 2+, with a 14% improved sensitivity over repeat cytology for similar specificity [22]. Cytology indicating LSIL does not benefit from HPV triage because of the high incidence of HPV positivity in this group. This has been disputed [23]. Many European states currently offer HPV testing for triage of low-grade cytologic abnormalities (see Figure 2). Identification of infection with HPV types 16 and 18 or multiple infections involving HPV-16 [24] may further refine HPV-based triage of minor cytologic abnormalities. Use of HPV-16/18 testing for ASCUS cytology improved detection of CIN 2+ in 1,923 women older than 21 years (24.4% vs 14.0% for other high-risk HPV vs 0.8% for HPV-negative women). The relative risk for CIN 2+ of HPV-16–positive versus non-HPV-16/18 was

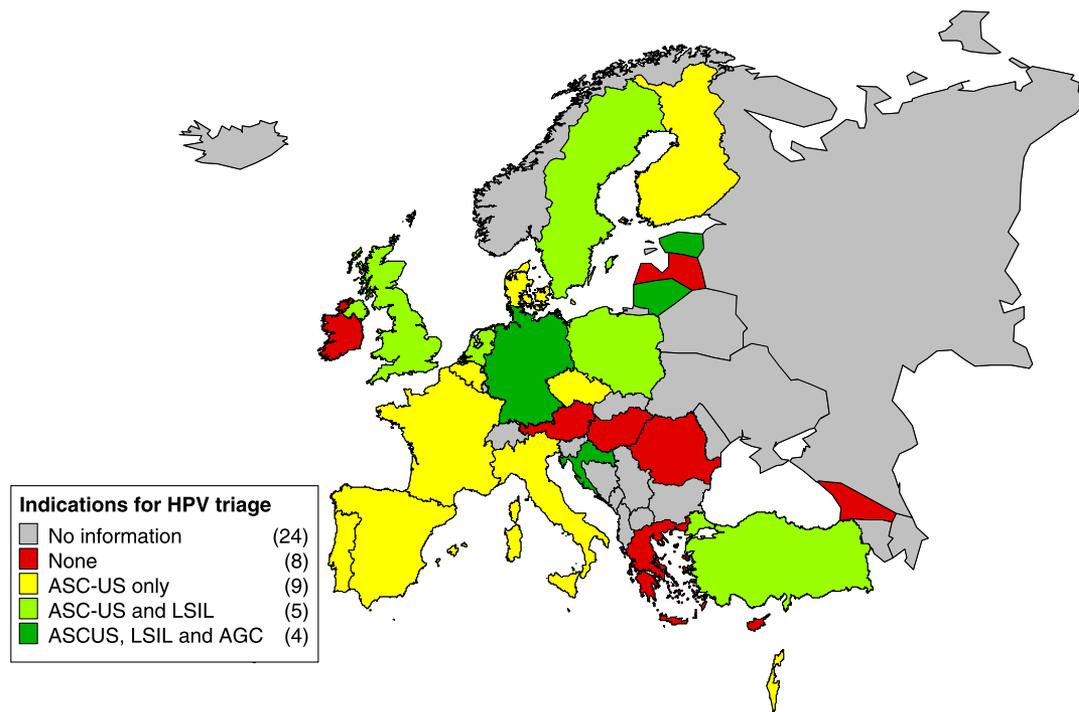


Figure 2. European states offering triage of ASCUS and LSIL (data from a European Federation for Colposcopy survey of practice, 2012).

3.7, and the relative risk for CIN 3+ was 4.5 [25]. From the ALTS data, the 2-year cumulative risk for CIN 2+ of HPV-16 with ASCUS/LSIL cytology was 50.6%, whereas the risk of women infected with high-risk HPV non-16 was 4.7% to 29.5% depending on HPV type [26]. All high-risk HPV cases in this setting require colposcopy, but those with HPV-16 and normal satisfactory colposcopy should not be considered for return to normal recall. A further publication from Kelly et al. [27] revealed that the cumulative incidence of CIN 2+ of 4.4% at 3 years after a normal and satisfactory colposcopy was low enough, with those women with preceding borderline (equivalent to ASCUS) or mild dyskaryosis (equivalent to LSIL) to be returned to normal recall. However, HPV typing was not performed in Kelly et al's paper.

The availability of a marker that provides a similar sensitivity as HPV testing, but with a significantly higher specificity, would be desirable to improve current triage testing of ASCUS cytology results and to allow for reducing the colposcopy referral rates after LSIL on cytology. Various studies have been performed to evaluate the potential utility of applying p16 immunocytochemical staining protocols especially for the triage of equivocal or mildly abnormal cytology results. Most have shown a similar sensitivity to HPV testing, but at a substantially higher specificity with p16 cytology when used for triage of Pap

cytology results categorized as either ASCUS or LSIL or atypical glandular cells. This effect was even higher in women younger than 30 years because of the high prevalence rates of HPV infections in the younger age groups [28]. The clinical performance of the simultaneous detection of p16 and Ki-67 expression within the same cervical epithelial cell as a morphology-independent marker of cell cycle deregulation has also been evaluated in the triage of ASCUS and LSIL Pap cytology results. p16/Ki-67 dual-stained cytology provided an initial high sensitivity level for detecting underlying CIN 2+, whereas the specificity was substantially further improved over the specificity rates that are observed when morphology interpretation algorithms are applied on cervical cells showing single immunoreactivity for p16 [29]. Codetection is not seen in the normal cell.

Overall, the effect of HPV triage, typing, and biomarkers aims to increase the proportion of CIN 2+ in cases presenting with minor abnormal cytology. The expectation is that the positive predictive value (PPV) for the colposcopic prediction of CIN 2+ would improve in this group.

HPV TEST OF CURE

In a meta-analysis of 5 studies including 1,032 women treated by excision, the sensitivity for HCII to detect CIN 2+ was 90.7% versus 76.6% for cytology (threshold of ASCUS),

with a specificity of 74.6% versus 89.7% [30]. The time of testing was between 3 and 6 months. The incidence of recurrent CIN 2+ was 6.6%. However, HPV testing represented a 2-fold increase in the rate of referral back to colposcopy compared to cytology-based follow-up but with an approximate 15% increase in the detection of recurrent high-grade CIN. If combined HPV testing and cytology (using a cutoff of ASCUS) was used at follow-up then the sensitivity increased from 91.4% to 93.1% and the specificity decreased from 79.0% to 75.7%. Both these changes were not significant. Two meta-analyses [18, 22] showed heterogeneity, but HPV DNA testing provided a significantly improved sensitivity for a non-significantly reduced specificity compared to cytology. In a prospective study of 917 women treated for CIN and tested for HPV in addition to cervical cytology at 6 and 12 months, Kitchener et al. [31] noted that the recurrence rate of CIN 2+ for HPV/cytology-negative women was 2.9% at 3 years and suggested that these women could be returned to routine screening after a double-negative HPV/cytology at 6 months. Long-term follow-up in a multicohort study of 435 women after excision for CIN 2+ [32] had a recurrence rate for CIN 2+ of 16.5% at 5 years and 18.3% at 10 years. Women with 3 consecutive negative cytology samples or 2 negative HPV tests at 6 and 24 months had a population at risk for CIN 3 and could be returned to routine screening.

The ideal time of testing seems to be around 18 to 24 months [33], but 2 HPV tests after treatment may be preferred to one. The specificity of HPV testing seems worse after treatment than in a triage and in a screening setting. Women older than 50 years with incomplete excision of CIN 3 at the lateral or deep excision margins represent a high-risk group and would benefit from repeat excision rather than HPV testing [34].

Follow-up for cGIN is not included in the test of cure algorithm because of a lack of data on outcome. However, a prospective study of 42 Finnish and Italian women suggested that HPV testing with cytology or HPV testing alone 6 months after excisional treatment of cGIN had an improved sensitivity for predicting recurrent cGIN than cytology alone. Because of the study size, no conclusions could be drawn from subsequent visits [35].

HPV testing after treatment would allow most women to not require colposcopy as part of follow-up and the colposcopist would see a higher number of posttreatment cases with CIN. The effect of the PPV of the colposcopic prediction of CIN 2+ is difficult to predict in this group and depends on the extent to which colposcopy is used in current follow-up protocols.

HPV-BASED PRIMARY SCREENING

An audit of 6,321 cervical cancers in England between 2007 and 2010 revealed that the largest group of cancers in the screened population accounting for almost one half had a smear at some time in the past but had missed their latest invite to attend. The highest incidence of cancer was seen in women between 30 and 39 years [36, 37]. Priorities for successful cervical cancer screening are improved coverage and the improved sensitivity expected with HPV-based screening. Primary HPV screening for cervical cancer is superior to cytology-based screening in detecting CIN 2+ lesions [38], in reducing the incidence of CIN 3+ [38–40] and of cervical cancer [14, 22, 41] in longitudinal studies irrespective if HPV testing is used alone or as cotesting with cytology. Studies across Europe and North America have shown a consistent increased detection of CIN 3 in the first round but then a reduction in CIN 3 rates with at least 2 rounds of HPV-based screening compared to cytology [14, 40, 42–44]. Earlier detection of CIN 3 with HPV-based screening means that detection of self-limiting abnormalities is not occurring. Moreover, HPV testing is reproducible, objective, and can be easily automated. The inherent low sensitivity of cytology means that several tests are required to reach a cumulative sensitivity, which, because of the generally slow natural history of cervical precancer, still has a considerable impact on the prevention of invasive cancer. This leads to a delayed diagnosis of high-grade CIN and cancer in some cases. Most randomized controlled trials and pilot projects used either cotesting or HPV testing alone with cytology triage. In both concepts, women who were tested positive for high-risk HPV and had abnormal cervical cytology as well as women who showed HPV persistency were referred for colposcopy. Koliopoulos et al. [45], in a meta-analysis of 25 studies, reported a combined sensitivity of HCII HPV testing of 90.0% in detecting CIN 2+ compared to cytology (threshold of ASCUS; 72.7%). The sensitivity for HPV testing of women older than 30 years increased to 94.8%. All but 1 study was cross sectional. However, the specificity for CIN 2+ was poorer for HPV testing against that for cytology (86.5% vs 91.9%; threshold of ASCUS). The sensitivity of cytology also varies considerably between countries with a poor sensitivity for cytology (e.g., in Germany), inflating the benefit of HPV-based screening. In another meta-analysis, Arbyn et al. [18] found a sensitivity for HCII of 97.9%, with a pooled specificity of 91.3%. Similar results were reported by Cuzick et al. [46], by Dillner et al. [47], and, in a more recent meta-analysis, by

Arbyn et al. [22]. Combined HPV and cytology testing in the screening setting does not improve the detection rate of CIN 3+ [40, 47] compared to HPV testing alone and would increase the false-positive rate. Furthermore, the test-positive rate for cytology varied considerably in a prospective multicenter trial by Dillner et al. [47] in different European countries not explained by the prevalence of HPV.

The low cumulative risk for CIN 3+ with a negative HPV test means that the 5-year disease-free rate approaches the 2-year disease-free rate for negative cytology [48] or, alternatively, is 40% to 50% better than that for cytology [39, 42, 43, 49, 50]. This provides a basis to lengthening the screening interval with HPV-based screening [40], permitting a greater opportunity for equitable screening within a limited financial resource. In women younger than 30 years, the specificity of HPV testing is unacceptable because of the high prevalence of transient HPV infections [14, 39, 46, 47, 51, 52] of which many are of no clinical concern. The specificity for cytology improves with older age. Overall, the consensus is to start HPV-based screening at 30 years, but it is best to pilot for each state and consider cytology for younger women. Any changes to existing screening programs should respect national health strategies. Organized and monitored systems are needed whatever modality of screening is chosen. Currently, some Italian regions are the only places in Europe offering HPV-based screening.

OTHER INDICATIONS FOR HPV TESTING

Management of cases after hysterectomy for CIN or cGIN may benefit from HPV testing compared to vault cytology. Another group is women with persistent low-grade cytology in the absence of colposcopic findings on the cervix or vagina and without estrogen deficiency. A current management option is to review the latter group of women with colposcopy and cytology annually until the cytology returns to normal or an abnormality is detected. The value of HPV testing in these scenarios is currently under evaluation in the United Kingdom. A list of indications for resolution of uncertainty is presented (see Table 1).

HPV testing is unlikely to help women with cervical atresia as collection of HPV DNA would not be from the upper endocervical canal and may be falsely reassuring. Such testing would be from the ectocervix only and hence will be unrepresentative of the entire transformation zone.

HPV self-testing may improve coverage of the screened population as an acceptable alternative to cervical sampling from a medical or nursing practitioner. More than

Table 1. Suggested Management for Resolution of Uncertainty

For cytology-based screening
Further scenarios for possible HPV testing ± typing
• Posthysterectomy for CIN/cGIN or preoperatively if patient not on normal recall
• Low-grade abnormality when colposcopy of the cervix and vagina is normal
–If postmenopausal (not taking HRT) – initially consider 6 wk of vaginal estrogen
–If premenopausal but taking progestogens – consider stopping progestogens or consider 6 wk of vaginal estrogen
–If breastfeeding – consider 6 wk of vaginal estrogen
If HPV-positive – continue within colposcopy service

HRT indicates hormone replacement therapy.

20% of the invited population fails to attend for routine cervical cytology, and attendance rates for colposcopy vary from 70% for new referrals to 50% for review patients in England. In a study of 28,073 women declining 2 invites to regular screening, self-collected HPV cervicovaginal samples had a similar sensitivity compared to conventional cervical samples, but a 26.6% compliance compared to 16.4% compliance for a group offered a further invite for conventional testing [53]. This study seems to offer hope for improved compliance for those who default initial invites within the cervical screening program.

PRACTICALITIES OF SCREENING IN RESOURCE-POOR STATES

Screening has the potential for both generating benefit and causing harm, and so, it needs to be done correctly. The European guidelines for quality assurance [54, 55] published by the European Union detail the requirements for effective screening.

A database of the target population allows a screening program to directly invite women to screening, which has been shown to increase recruitment in countries where women are predisposed to accept the invitations. This database also allows the screening program to identify poor or nonattenders so supplementary efforts can be implemented to increase recruitment in these groups and it is required for quality assurance of screening. However, a population database is only one of many elements that comprise organized screening.

The first organized cervical screening program was launched in the province of British Columbia in Canada in 1949 and was followed by Finland in 1964. Since then, a group of Western European countries have implemented national organized programs with high coverage, including Denmark, Iceland, Ireland, Italy, the Netherlands, Norway,

Portugal, Slovenia, Sweden, and the United Kingdom. State-reimbursed opportunistic screening is available in Austria and Germany. France has, for many years, relied on opportunistic screening, which has been very effective in reducing cervical cancer rates, but this is largely due to a widespread availability of high-quality health services and cultural traditions that have led to acceptable coverage in the absence of invitation. In Eastern Europe, Slovenia has successfully implemented an effective, organized cervical screening program that closely follows the European Guidelines and has achieved high coverage. In contrast, Estonia and Poland have followed the same path but have not been able to raise coverage rates to a level that will make any substantial impact on cancer rates. More recently, the Czech Republic, Serbia, and Latvia have been working to implement organized programs, but it is too early in the process to assess their coverage or effectiveness. Self-sampling by women may need to be considered.

OUTLOOK AND CONCLUSIONS

Strategies are being introduced into various European screening programs to improve the detection of CIN 3 and cervical cancer. HPV vaccination has been ongoing for several years, and the older members of the catch-up population are beginning to enter screening. We can exploit the known improved sensitivity to detect CIN 2+ with HPV testing in various formats, and several states have introduced HPV triage for minor abnormal cytology as well as test of cure after treatment. There are unanswered questions including the use of HPV testing after treatment of cGIN, after hysterectomy for CIN, and the use of any additional triage tests such as HPV typing or using biomarkers. The referral threshold for colposcopy must be refined. It is likely that HPV-based cervical screening will be introduced to several European states over the next decade. All these interventions must be supported by appropriate expertise and staffing to enable population screening.

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