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European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination

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ABSTRACT

In a project coordinated by the International Agency for Research on Cancer (IARC) 31 experts from 11 European countries and IARC have developed supplements to the current European guidelines for quality assurance in cervical cancer screening. The supplements take into account the potential of primary testing for human papillomavirus (HPV) and vaccination against HPV infection to improve cervical cancer prevention and control and will be published by the European Commission in book format. They include 62 recommendations or conclusions for which the strength of the evidence and the respective recommendations is graded. While acknowledging the available evidence for more efficacious screening using HPV primary testing compared to screening based on cytology, the authors and editors of the supplements emphasize that appropriate policy and programme organization remain essential to achieve an acceptable balance between benefit and harm of any screening or vaccination programme. A summary of the supplements and all of the graded recommendations are presented here in journal format to make key aspects of the updated and expanded guidelines known to a wider professional and scientific community.

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Background

In the current 28 Member States of the European Union (EU), approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually [17]. Despite significant progress in Europe in recent decades in reducing the burden of cervical cancer, rates of death attributed to the disease are still high in many of the 'new' Member States that joined the EU after 2003: estimates of the annual age-standardized rates per 100,000 women in Hungary (6.9), the Slovak Republic (6.9), Poland (7.4), Latvia (8.2), Bulgaria (8.8) and Lithuania (9.8) are five to seven times higher, and in Romania (14.2) ten times higher than in Finland (1.4) and Malta (1.2), the EU Member States with the lowest rates in 2012. The age-standardized incidence rates of cervical cancer reveal a similar picture. The current 10-fold gradient in the mortality rates of cervical cancer among the EU Member States largely reflects the persistent absence, or inadequate implementation of cervical cancer screening programmes more than 10 years after organized, population-based screening programmes following European quality assurance guidelines were unanimously recommended by the Health Ministers of the EU [10].

Quality assurance aims to ensure that an endeavour leads to the outcome for which it is intended; this is particularly important for complex systems, such as screening programmes designed to lower the burden of cancer in the population [44]. The second edition of the European guidelines for quality assurance in cervical cancer screening [4,5] was published seven years ago. The continuing clear need to improve implementation of cervical cancer screening in the EU underlines the importance of re-emphasizing the European guidelines through the publication of the present supplements to the second edition. The supplements have been developed in a time of transition. Vaccination of girls and possibly also of boys in the future against the human papillomavirus (HPV) types that cause approximately 70% of cervical cancer has become an additional, complementary option of cervical cancer prevention, the main impact of which will emerge in a few decades when currently vaccinated girls are in their thirties and forties. In addition, cytology¹ is no longer the only test suitable for use in cervical cancer screening in the EU. The evidence presented in the first of the present supplements shows that primary testing for oncogenic HPV² fulfils the requirements for evidence-based screening tests laid down in the Council Recommendation [10],

provided that cervical cancer screening programmes follow the recommendations for quality assurance published in the second edition [4,5] and the present supplements of the European guidelines [2,11,34].

Of particular importance is the recent evidence from the second round of European randomized controlled trials showing a more pronounced effect of cervical screening using HPV primary testing compared to cytology-based screening [35,6]. Given the evidence for improved efficacy of HPV primary screening that is explained in the first supplement, decision-makers, advocates, professionals, and women in the EU are increasingly confronted with the question of whether or not, and if so, how these new developments should be integrated into more successful approaches to control cervical cancer in Europe, both for the individual women affected and for the population as a whole. By focusing on the core topics of primary HPV testing in the first supplement [34], organization of HPV-based and cytology-based screening programmes in the second supplement [2], and implementation of HPV vaccination programmes in the third supplement [11], the joint publication of these supplements aims to provide appropriate answers to these important questions and to lay the foundation for further development of the comprehensive European guidelines in the coming years.

Publication format

The supplements are presented in a joint volume including 62 main recommendations and conclusions for which the strength of the evidence and the respective recommendations is graded according to a defined format. These recommendations are presented at the beginning of each supplement and their annotation indicates the places in the subsequent text where the evidence and the rationale pertaining to each recommendation are explained, including cross-references to other supplements and recommendations. This enables the reader to rapidly review the key content of the supplements and to identify places in the volume likely to be of interest for further reading. In addition, some statements of advisory character are considered to be good practice but not sufficiently important to warrant formal grading are provided in each supplement.

Methodology

To develop the evidence-based recommendations, the approach used for the European guidelines for quality assurance in colorectal cancer screening and diagnosis [27] was adopted and modified slightly to take into account the different subject matter and time period of the present project. A multidisciplinary group of authors and editors experienced in quality assurance in cervical cancer screening, programme implementation and guideline development collaborated with a 'literature group' consisting of epidemiologists with special expertise in the field of cervical cancer screening and in systematic literature review. Experts in HPV vaccination were also

(footnote continued)

Oncogenic HPV also induces other cancers than those of the cervix uteri, such as vulvar, vaginal, anal and oropharyngeal cancers.

¹ Conventional cervical cytology with Papanicolaou staining (Pap smear) and validated liquid-based cervical cytology (LBC) are evidence-based screening tests that fulfil the requirements of the Council Recommendation on Cancer Screening of 2 December 2003 if performed in accordance with the European guidelines for quality assurance in cervical cancer screening. The applicable items in the Council Recommendation of 2 December 2003 are 1(a) for conventional cervical cytology with Papanicolaou staining (Pap smear) and 1(a) in combination with 6(e) for validated liquid-based cervical cytology (LBC) (see Annex 2 of the Supplements volume [10]). Primary testing for oncogenic HPV with validated assays also fulfils the requirements of the Council Recommendation of 2 December 2003 for evidence-based screening tests, provided the recommendations in Supplements 1 and 2 to the second edition of the European guidelines for quality assurance in cervical cancer screening are followed. The applicable items in the Council Recommendation are 6(c) and 6(e) (see Annex 2 of the Supplements volume [10]).

² Oncogenic HPV refers to the 13 high-risk HPV types (*hrHPV*): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. These include the 12 HPV types currently classified as *carcinogenic to humans* and one type (68) classified as *probably carcinogenic to humans* in the IARC monograph series [7,19]. Unless otherwise indicated, the terms *HPV primary testing* and *HPV primary screening* used in this supplement refer to HPV testing conducted with systems based on validated *hrHPV* DNA assays.

Table 1Screening for cervical cancer with primary testing for human papillomavirus^A. Recommendations and conclusions. Supplement 1^B.**Suitability of HPV primary testing for use in cervical cancer screening programmes**

1.1 Primary testing for oncogenic HPV^C can be used in an organized, population-based programme for cervical cancer screening (I-A) provided the other recommendations in this supplement are followed (VI-A). Primary testing for oncogenic HPV outside an organized population-based programme is not recommended (see also Suppl. 2, Rec. 2.1) (VI-E).^{Sect. 1.2.1.3; 1.2.3}

Avoidance of co-testing (HPV and cytology primary testing) at any given age

1.2 Only one primary test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3–1.7) (II-A).^{Sect. 1.3.1}

Age at which to start HPV primary testing in cervical cancer screening programmes

1.3 Routine HPV primary screening can begin at age 35 years or above (see also Rec. 1.1) (I-A).^{Sect. 1.3.2.1}

1.4 Routine HPV primary screening should not begin under age 30 years (I-E).^{Sect. 1.3.2.1}

1.5 The available evidence is insufficient to recommend for or against beginning routine HPV primary screening in the age range 30–34 years (VI).^{Sect. 1.3.2.1}

Age at which to stop HPV primary testing in cervical cancer screening programmes

1.6 In the absence of sufficient evidence on the optimal age at which to stop screening, HPV primary screening could stop at the upper age limit recommended for cytology primary screening (60 or 65 years), provided a woman has had a recent negative test (VI-B).^{Sect. 1.3.2.2}

Cervical screening using cytology primary testing outside the age range of HPV primary testing

1.7 Cervical screening based on cytology primary testing conducted outside the age range of HPV primary testing should follow the guidance provided for cytology-based screening in the second edition of the European guidelines for quality assurance in cervical cancer screening, and in Supplement 2 (see also Rec. 1.9, 1.10, 1.22 and 1.34) (VI-A).^{Sect. 1.3.2.1}

Screening interval after a negative HPV primary test

1.8 The screening interval for women with a negative HPV primary test result should be at least 5 years (I-A) and may be extended up to 10 years depending on the age and screening history (III-C).^{Sect. 1.3.3}

Management of women without an adequate HPV primary test result

1.9 Some women attending cervical cancer screening may prefer not to be tested for HPV. If a woman declines HPV primary testing, cytology can be performed (see also Rec. 1.7) (VI-C).^{Sect. 1.3.4}

1.10 Non-attenders and women with a technically inadequate HPV test result should be invited to have a new sample taken (VI-A); alternatively cytology testing without additional sample taking may be performed if technically feasible and preferred by the woman (see also Suppl. 2, Rec. 2.9–2.11) (VI-B).^{Sect. 1.3.4; 2.4}

Management of women after a positive HPV primary test

1.11 Cervical screening programmes using HPV primary testing must adopt specific policies on triage, referral and repeat testing of women with positive primary test results, taking into account the guidance in Rec. 1.12–1.31. The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening. (VI-A).^{Sect. 1.3.5}

1.12 Screening programmes should carefully monitor management of HPV-positive women. Monitoring should include compliance of individual women with further follow-up of positive primary test results, as well as results of triage, referral, colposcopies, biopsies, and treatment of precancers (VI-A).^{Sect. 1.3.5}

1.13 Triage, referral and repeat testing policies (see Rec. 1.11) should be regularly reviewed and, if necessary, revised taking into account the results of monitoring (see Rec. 1.12) and the available evidence (VI-A).^{Sect. 1.3.5}

Secondary testing**• Cytology triage**

1.14 Women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) (I-A).^{Sect. 1.4.1.1} The cytology test should preferably use the specimen collected during the HPV screening visit (VI-A).^{Sect. 1.4.1.1}

1.15 Direct referral to colposcopy of all HPV-positive women is not recommended (I-D).^{Sect. 1.4.1.1}

1.16 Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing, or to colposcopy (see Rec. 1.18–1.21) (I-A).^{Sect. 1.4.1.1}

1.17 Quality assurance of laboratories and professional practice in the provision of cytology, colposcopy and histopathology services used in cytology triage in HPV primary screening should comply with the recommendations in Chap. 3–6 of the European Guidelines second edition (see also Rec. 1.35) (VI-B).^{Sect. 1.4.1.1}

• Referral of women with pre-invasive or more severe cytology at triage

1.18 Women with ASC-H (atypical squamous cells, high-grade squamous lesion cannot be excluded), HSIL (high grade squamous intraepithelial lesion), AIS (adenocarcinoma in situ) or a more severe finding at cytology triage should be referred to colposcopy without further observation or testing (III-A).^{Sect. 1.4.1.2}

• Referral of women with minor cytological abnormalities at initial triage

1.19 Women with ASC-US (atypical squamous cells of undetermined significance), AGC (atypical glandular cells), or LSIL (low grade squamous intraepithelial lesion) at triage after an initial HPV primary test in a screening episode may be followed up by retesting, preferably after 6–12 months, or referred directly to colposcopy (see Rec. 1.22–1.31) (VI-C).^{Sect. 1.4.1.2}

Referral of women with negative cytology at initial triage

1.20 Women who have negative cytology (negative for epithelial abnormality) at triage after a positive initial HPV primary test in a screening episode should be followed up by re-testing after an interval shorter than the regular screening interval, but after at least 6–12 months (see also Sect. 1.4.1 and Rec. 1.23 and 1.24) (VI-A).^{Sect. 1.4.1.2}

1.21 Direct referral to colposcopy of women with negative cytology at triage is not recommended (I-D).^{Sect. 1.4.1.2}

Management of women at repeat testing

1.22 The prevalence of HPV and the quality and organization of cytology screening affect the efficiency, effectiveness and appropriateness of management of women at repeat testing. These factors should be taken into account in the regular review of management protocols for repeat testing (see also rec. 1.13) (VI).^{Sect. 1.4.3}

• Type and interval of repeat testing

1.23 Cytology repeat testing after at least 6–12 months is an acceptable alternative to HPV repeat testing (see also Chap. 6, Sect. 6.3.1 in European Guidelines, second edition) (III-B).^{Sect. 1.5.1}

1.24 Women who were HPV-positive and cytology normal (negative for epithelial abnormality) in primary screening may be managed by HPV retesting with or without cytological triage, and after an interval of preferably at least 12 months (III-B).^{Sect. 1.5.1}

• Protocols using HPV testing with cytology triage in repeat testing

1.25 Women should be referred to colposcopy if cytology triage of a positive repeat HPV test yields ASC-US (VI-B) or more severe cytology (VI-A).^{Sect. 1.5.3}

1.26 Women who have negative cytology triage (negative for epithelial abnormality) of a positive (repeat HPV test) may be managed by one of the following options (see also Rec. 1.11–1.13) (VI-B).^{Sect. 1.5.3}

- Referral to second repeat testing after at least 12 months

- Referral to colposcopy

- Return to routine screening

1.27 Women who have a negative repeat HPV test should return to routine screening (III-A). Cytology triage is not needed for these women (III-E).^{Sect. 1.5.3}

• Protocols using cytology testing alone in repeat testing

1.28 Women with ASC-US or more severe cytology at repeat testing should be referred to colposcopy (VI-B).^{Sect. 1.5.3}

1.29 Women with normal cytology at repeat testing should return to routine screening (III-A).^{Sect. 1.5.3}

Table 1 (continued)

Suitability of HPV primary testing for use in cervical cancer screening programmes	
● Protocols using HPV testing alone in repeat testing	
1.30	Women who have a negative repeat HPV test should return to routine screening (II-A). ^{Sect. 1.5.3}
1.31	Women who have a positive repeat HPV test should be referred to colposcopy (II-C). ^{Sect. 1.5.3}
Self-sampling in screening programmes using HPV primary testing	
1.32	The clinical accuracy of HPV primary testing on self-collected samples taken for cervical screening is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec. 2.8–2.13) (III). ^{Sect. 1.7}
Selection of HPV tests suitable for primary cervical cancer screening	
1.33	Cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infections (VI-A). ^{Sect. 1.2.1.3; 1.6}
Implementation of HPV primary testing in cervical cancer screening programmes	
1.34	HPV primary screening programmes should follow the guidance in the European Guidelines, that is relevant to any cervical screening programme irrespective of the method of primary testing used. The relevant guidance includes the recommendations on programme organization, planning, monitoring and evaluation (see current Suppl. 2, and second edition, Chap. 2); communication; and quality assurance of the entire screening process including sampling, histopathologic interpretation and classification of cervical tissue; and management of detected lesions (see second edition, Appendix 1 and Chap. 3–6) (VI-A). ^{Sect. 1.2.3}
1.35	Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards. The laboratory should perform a minimum of 10,000 tests per year (see also Rec. 1.34) (VI-A). ^{Sect. 1.6}
1.36	Any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized (VI-B). ^{Sect. 1.2.1.3; 1.3.2.1}
	● Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening programmes.
	● Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols.
	● The feasibility and sustainability of the programme should be assured through adequate resourcing and coordination, including coordinated planning, feasibility and pilot studies, and quality-controlled rollout across a country or region (see Suppl. 2 and Annex 1).

^A Source: [34].

^B **Sect.** (superscript) after each recommendation in the list refers the reader to the section/s of the Supplements dealing with the respective recommendation. **Rec.** followed by a number refers to the number of the respective recommendation.

^C Oncogenic HPV refers to the 13 high-risk HPV types (*hrHPV*): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. These include the 12 HPV types currently classified as *carcinogenic to humans* and one type (68) classified as *probably carcinogenic to humans* in the IARC monograph series [7,19]. Unless otherwise indicated, the terms *HPV primary testing* and *HPV primary screening* used in this supplement refer to HPV testing conducted with systems based on validated *hrHPV* DNA assays. Oncogenic HPV also induces other cancers than those of the cervix uteri, such as vulvar, vaginal, anal and oropharyngeal cancers.

recruited to participate in the project together with the other editors, authors and reviewers. The literature group systematically retrieved, evaluated and synthesized relevant publications dealing with cervical cancer screening according to clinical questions defined by the authors and editors. The clinical questions were subsequently elaborated according to the Patient-Intervention-Comparison-Outcome-Study (PICOS) method [18,30,31] that was modified slightly to take into account the aim of screening to lower the burden of the disease in the population.

Bibliographic searches for most clinical questions were limited to the time period January 2000 to March 2012 and were performed on Medline, and in many cases also on Embase and the Cochrane Library. Priority was given to recent comprehensive reviews. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant papers published before 2000. Where no observational data were available, outcomes simulated by mathematical models and expert opinion were accepted as the lowest level of evidence. Papers of adequate quality recommended by authors because of their clinical relevance were also included, especially in the time period after March 2012 and up to December 2014 prior to completion of final editing of the draft manuscripts that began in July 2014. Preliminary versions of the draft supplements were repeatedly reviewed and revised through multidisciplinary meetings and discussions in which authors, editors and members of the literature group participated. Prior to finalization and review by the complete group of editors, the draft manuscripts were intensively reviewed by selected editors and/or external experts.

The editorial board was responsible for the final formulation of the supplements and the grading of the evidence and strength of the recommendations. The level of evidence and the strength of each of the graded recommendations are indicated using the slightly modified scales adopted for the European guidelines for quality assurance in colorectal cancer screening [27,41]; see below:

Grading of recommendations and supporting evidence

For the level of evidence:

- I. Consistent multiple randomised controlled trials (RCTs) of adequate sample size, or systematic reviews (SRs) of RCTs, taking into account heterogeneity
- II. One RCT of adequate sample size, or one or more RCTs with small sample size
- III. Prospective cohort studies or SRs of cohort studies; for diagnostic accuracy questions, cross-sectional studies with verification by a reference standard
- IV. Retrospective case-control studies or SRs of case-control studies, trend analyses
- V. Case series; before/after studies without control group, cross-sectional surveys
- VI. Expert opinion

For the strength of the respective recommendation:

- A. Intervention strongly recommended for all patients or targeted individuals
- B. Intervention recommended
- C. Intervention to be considered but with uncertainty about its impact
- D. Intervention not recommended
- E. Intervention strongly not recommended

Screening for cervical cancer with primary testing for human papillomavirus

The first of the present supplements [34] aims to inform European policy makers and public health specialists, and any other interested parties about the critical issues that should be

considered in weighing the potential benefit and harm of cervical screening programmes based on HPV primary testing. It includes 36 graded recommendations dealing with the suitability of HPV primary testing for use in cervical cancer screening. Key messages and topics covered in the supplement include the lack of appropriate benefit from co-testing, and the appropriate target age group and interval for HPV primary testing. Management protocols for women with positive or technically inadequate HPV primary tests, the clinical accuracy of HPV testing using self-collected samples, and the selection of tests suitable for primary screening are also covered; and other policies and professional and scientific standards, such as consideration of health economic issues, are indicated that should be adhered to in the design and implementation of quality-assured cervical cancer screening programmes based on HPV primary testing. It is not the intention of the authors and editors to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. The supplement therefore focuses on the use of primary testing for HPV DNA in cervical cancer screening with cytology triage in the EU. As far as possible the authors and editors have attempted to achieve an equitable balance that is applicable across a wide spectrum of cultural and economic healthcare settings in

the EU. As with any standards and recommendations, these should be continuously reviewed in the light of future experience.

The scientific justification for the recommendations in the first supplement is provided by over 110 publications cited in the text, including published cross-sectional and longitudinal data from eight randomized clinical trials conducted in Canada, Finland, India, Italy, Sweden, The Netherlands and the United Kingdom [1,8,12,20–24,26,28,29,32,33,35–40]. It should be noted that the efficacy of HPV primary testing in cervical cancer screening has been demonstrated in studies using clinician-based samples. The authors and editors emphasize that currently the clinical accuracy of HPV primary testing on self-collected samples is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (Rec. 1.32 in Suppl. 1 [34], see also Table 1). Policy makers and professionals must be aware, however, that HPV testing on self-taken samples is less accurate than on clinician-taken samples. For this reason, self-sampling is not recommended for all women invited to screening (see Sect. 1.7 in [34] and Sect. 2.4.4 and Rec. 2.8–2.13 in Suppl. 2 [2], see also Table 2).

The authors and editors also emphasize that despite the convincing evidence for more efficacious screening using HPV primary testing,

Table 2

Organization of cytology-based and HPV-based cervical cancer screening^A. Recommendations and conclusions. Supplement 2^B.

- 2.1 Irrespective of the method of primary testing (cytology or HPV assay) cervical cancer screening should always be performed in an organized, population-based screening programme with comprehensive quality assurance covering all steps in the screening process (see also Suppl. 1, Rec. 1.34, and Annex 1 and 2) (VI-A).^{Sect. 2.3}
- 2.2 If organized, population-based cervical screening programmes do not currently exist in a country or region, decision-makers should review the relevant policy on cervical cancer screening taking into account the Council Recommendation on Cancer Screening (Annex 2), the European Guidelines for quality assurance in cervical cancer screening, second edition, and the present Supplements (see also Annex 1) (VI-A).^{Sect. 2.3}
- 2.3 In countries or regions in which population-based cervical screening programmes using cytology primary testing are currently established, decision-makers should consider whether implementation of HPV primary testing in existing programmes would improve the balance between harm and benefit, and if so, integrate the change into the comprehensive cancer control programme (see also Suppl. 1, Rec. 1.1 and 1.36) (VI-A).^{Sect. 2.3}

Quality-assured process of screening programme implementation

- 2.4 If a decision is made to implement HPV primary testing in an existing population-based cervical screening programme, comprehensive planning, feasibility testing and pilot programmes should be conducted prior to routine implementation to ensure that an appropriate balance between harm and benefit is achieved in the transition to HPV primary screening, including effective and efficient use of resources (see also Annex 1) (VI-A).^{Sect. 2.3.1}
- 2.5 If a decision is made to implement a population-based cervical screening programme in a country or region previously lacking such a programme, special attention must be paid not only to selecting the method of primary testing (cytology or HPV testing), but also to testing and developing the capacity for a population-based approach to programme implementation including building up comprehensive quality assurance (see also Rec. 2.4 and Annex 1 and 2) (VI-A).^{Sect. 2.3.2}
- 2.6 The introduction of new population-based screening programmes should be coordinated by a unit with a comprehensive mandate and sufficient autonomy and resources to ensure that the European quality assurance guidelines are followed and that international experts familiar with the process and determinants of successful programme implementation can be consulted (see also Annex 1) (VI-A).^{Sect. 2.3.3}

Population based approach to cervical cancer screening

● Avoiding financial barriers to participating in screening

- 2.7 Screening should be free of charge or subject to only a limited charge for women who attend, regardless of whether cytological or HPV screening is offered (I-A).^{Sect. 2.4.1}

● Personal invitation letters

- 2.8 Personal invitation letters to participate in screening should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary (I-A).^{Sect. 2.4.2}

● Personal reminders

- 2.9 Women who do not attend screening should receive a personal reminder (I-A). The reminder should be sent by letter and should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary (II-A).^{Sect. 2.4.3}
- 2.10 A second personal invitation reminder should be sent if there is no response to an initial reminder (I-B).^{Sect. 2.4.3}
- 2.11 Personal invitation reminders may also be delivered by telephone call, provided women who are not reached by telephone are sent a reminder letter (I-B).^{Sect. 2.4.3}

● Self-sampling

- 2.12 Piloting self-sampling for women who did not participate in primary HPV screening despite a personal invitation and a personal reminder is recommended, provided it is conducted in an organized, population-based screening programme with careful monitoring and evaluation of the aimed performance and outcomes (see Rec. 2.8–2.11 and Suppl. 1, Rec. 1.32 and 1.36) (I-A).^{Sect. 2.4.4}
- 2.13 Prior to rollout towards national implementation, a self-sampling pilot project should demonstrate successful results compared to clinician-based sampling (positivity rate, positive predictive value of a positive test result, and cost-effectiveness). The pilot should also demonstrate that key organizational problems, such as the appropriate screening interval and compliance with invitation and management protocols for women with positive test results, have been adequately resolved (III-D).^{Sect. 2.4.4}

Monitoring cervical cancer screening performance

- 2.14 Monitoring of population-based cervical screening programmes should include the performance parameters defined in the European guidelines for quality assurance in cervical cancer screening (Suppl. 2, and Chap. 2 and 7 of the second edition 2) (VI-A).^{Sect. 2.6}
- 2.15 Programmes should achieve an invitation coverage of 95% (acceptable level) (III-A); > 95% is desirable (III-A).^{Sect. 2.6.1}
- 2.16 Programmes should achieve an examination coverage of 70% (acceptable level) (III-A); > 85% is desirable (VI-A).^{Sect. 2.6.1}
- 2.17 Programmes should achieve a participation rate of 70% (acceptable level) (III-A); > 85% is desirable (VI-A).^{Sect. 2.6.1}

^A Source: [2].

^B See footnote B of Table 1.

appropriate screening policy and programme organization are essential to achieving an acceptable balance between benefit and harm of any screening programme. These principles are particularly important in HPV primary screening, in order to avoid substantial increase in the number of women with positive test results and additional colposcopies and treatment of no additional benefit to participating women. Following the recommendations in the present supplement will enable programmes to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks (see Rec. 1.11 in [34], see also Table 1).

While most of the recommendations in the first supplement focus on the opportunities and the challenges of HPV primary screening that set it apart from cytology-based screening; decision-makers, programme managers and professionals should also be aware of the guidance in the previously published volume of the second Guidelines edition [4,5] that is relevant to any cervical screening programme irrespective of the method of primary testing used (see Rec. 1.34). Of prime importance in this regard are also the recommendations on programme organization, planning, monitoring and evaluation in the second supplement. The authors and editors also emphasize the importance of using reliable, validated HPV tests (see Rec. 1.33) in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see Rec. 1.35). In addition, any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in the supplement can be organized (see Rec. 1.36). The authors and editors also point out that sustainability is crucial to the success of any cervical screening programme, and in the first supplement they underline the importance of the respective recommendations in Supplement 2 and in Annex 1 of the Supplements volume.

Organization of cytology-based or HPV-based cervical cancer screening

The second supplement [2] addresses the persisting gap in the EU between knowledge of the potential of population-based cervical screening to reduce the burden of the disease in the population, on the one hand, and the extent to which this knowledge has been translated into effective national programmes to control cervical cancer, on the other hand. As pointed out in the Council Recommendation on cancer screening (Annex 2 of the Supplements volume, see also [10]), the most effective and appropriate way for screening to reduce cervical cancer incidence and mortality is through implementation of population-based programmes according to the European quality assurance guidelines. Despite this knowledge, many old and new Member States of the European Union do not have population-based screening programmes in place or have programmes that are underperforming. The supplement provides 17 recommendations on the policy and organizational issues that are inherent to the use of cytology and HPV testing in screening programmes. First and foremost is recognition of the need to implement HPV primary screening only in organized, population-based programmes (see Rec. 2.1 in Suppl. 2 [2], see also Table 2). This is an important prerequisite for effective quality assurance of any cancer screening programme (see Annex 1 [25,43] and of the Supplements volume) and one that applies particularly to HPV primary screening.

The scientific justification for the recommendations in the second supplement is provided by over 90 publications cited in the text. In light of the evidence that HPV primary screening of appropriate quality can yield better results than cytology-based screening, policy-makers in EU countries or regions with cytology-based population programmes are advised to review current policies and consider whether transition to HPV primary screening would improve the balance between harm

and benefit in their programmes. Policy makers in EU countries or regions lacking any population-based cervical screening programme are advised to review current policies and consider implementation of organized population-based cervical screening programmes taking into account the current European guidelines [4,5], including the supplements [2,11,34], and the Council Recommendation [10] (see Rec. 2.2 and 2.3). In addition to these general aspects, problems are discussed that are commonly encountered in implementing cervical cancer screening programmes in EU Member States with population-based programme policies, in those with opportunistic programmes, or in Member States in Central and Eastern Europe, and solutions are suggested that have proven to be effective in successful European screening programmes. The recommendations in the supplement are focussed on strategies to optimize screening attendance, including invitations, reminders and self-sampling. For evaluation and monitoring, the supplement also provides key performance indicators specifically related to HPV primary screening; and for the first time, European quality standards are introduced for key performance indicators (coverage by invitation, coverage by examination; and rate of participation or uptake) (see Rec. 2.15–2.17).

In the text more detailed advice is provided on the steps that programme management should take in navigating the protracted process of establishing an organized, population-based screening programme, including a checklist for planning, feasibility testing, piloting, monitoring and evaluation (see Sect. 2.7). This guidance illustrates and supplements the recommendations in Annex 1 dealing with the determinants of successful implementation of cancer screening programmes [25,43]; see also [3,45].

Implementation of vaccination against human papillomavirus in Europe

The third of the present supplements [11] summarizes the evidence base for HPV vaccination using the currently licensed bivalent and quadrivalent vaccines in the EU.³ Over 90 publications are cited and nine graded recommendations are provided to promote effective implementation of this tool for cervical cancer control in the EU. Clinical trials have shown the current prophylactic HPV vaccines to be safe and highly effective against persistent vaccine-related HPV infections and anogenital precancerous lesions among women who were not infected by these types at the time of vaccination [13,46,48]; see also [15,16]. The use of HPV vaccines in pre-adolescent girls and young women for the primary prevention of cervical cancer and some other HPV-related diseases has been endorsed by the European Medicines Agency (EMA) in 2006 (quadrivalent HPV 6/11/16/18 vaccine)⁴ and 2007 (bivalent HPV 16/18 vaccine),⁵ and in a position paper by the World Health Organization (WHO) in 2009 and 2014 [47,49]. Since then, 21 of the 28 Member States of the European Union plus Norway and Iceland have introduced national HPV vaccination programmes. Recently, WHO updated its HPV vaccines position paper to recommend a two-dose regimen with increased flexibility in the interval between doses [49]. EMA has also granted marketing authorizations for bivalent and quadrivalent vaccines in the EU for a two-

³ The 9-valent vaccine that was recommended by the European Medicines Agency (EMA) in March 2015 for the prevention of diseases caused by nine types of human papillomavirus (HPV) was not considered in the preparation of the present supplement because at the time of writing and editing the Supplements it was not licensed for use in the EU. See accessed 28/05/2015: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/03/WC500184898.pdf.

⁴ See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf.

⁵ See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf.

Table 3
Organization of HPV vaccination^A. Recommendations and conclusions. Supplement 3^B.

- 3.1 HPV vaccination is best implemented through organized, population-based programmes (III-A).^{Sect. 3.6}
- A population-based programme is likely to achieve higher coverage, less social inequalities in vaccine uptake, and lower vaccination costs per vaccine (III).^{Sect. 3.6}
 - If a country has started implementation with the opportunistic approach, transition to an organized, preferably school-based (or other public-service-based) programme is recommended (III-A).^{Sect. 3.6}
- Target age for HPV vaccination**
- 3.2 The primary target group to consider for routine population-based vaccination is girls at an age before the onset of sexual activity, usually between 10 and 13 years (I-A).^{Sect. 3.2.1}
- Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme (I).^{Sect. 3.2.2}
- Monitoring and evaluation of HPV vaccination programmes**
- 3.3 Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (VI-A).^{Sect. 3.3}
- Coordination between vaccine evaluation and cancer control programmes is recommended. It will be critical to assess the impact of the vaccine and its synergies with screening and health education (VI-A).^{Sect. 3.3}
 - Long-term evaluation based on systematic registration of HPV vaccination and linkage studies using relevant healthcare registries should be used to assess vaccine effectiveness and safety in various settings. If a country has the capacity, it is desirable that assessment of vaccine impact include: surveillance for vaccine-related and other oncogenic HPV infections, precancerous lesions, and HPV-related cancers (VI-A).^{Sect. 3.3}
 - The minimum set of information for monitoring HPV vaccination should include data on vaccine coverage, monitoring of adverse events following immunization and, if possible, a sentinel surveillance of impact on precancerous lesions (VI-A).^{Sect. 3.3}
- 3.4 Standard definitions and parameters for coverage of vaccination should be developed and used in vaccination monitoring (VI-A).^{Sect. 3.5}
- Age at primary vaccination, age at catch-up vaccination, number of doses by single year of age and time between doses, and duration of follow-up since offering primary vaccination should be included in the definitions and performance parameters (VI-A).^{Sect. 3.5}
- Planning, piloting, and modifying HPV vaccination programmes**
- 3.5 Planning and modification of vaccination programmes and policies should take into account local conditions, including vaccine and vaccination costs and resources required in monitoring, provision of information, and communication. Pilot studies are recommended to assess how to improve coverage and public awareness (VI-A).^{Sect. 3.6}
- Procurement**
- 3.6 Decision-makers should be aware of the wide range of prices for HPV vaccines in the EU and the potential to reduce the overall costs of HPV vaccination programmes by negotiating vaccine prices that are comparable to the low prices obtained in some EU Member States (VI-A).^{Sect. 3.6}
- Coverage target for HPV vaccination programmes**
- 3.7 HPV vaccination programmes should aim for a minimum coverage of 70% and preferably > 80% (III-A).^{Sect. 3.5}
- The reported 3-dose coverage of primary vaccination in a population-based vaccination programme should reach 70% within the first 12 months (III-A). The same coverage target applies for programmes using a 2-dose schedule (VI-A).^{Sect. 3.5}
- HPV screening and HPV vaccination**
- 3.8 Vaccination status should be known to screening and vaccination registries for women reaching the target screening age (VI-A).^{Sect. 3.3}
- 3.9 Planning and research on synergies between HPV vaccination and HPV screening is recommended to improve the effectiveness and cost-effectiveness of prevention of HPV-related disease (VI-A).^{Sect. 3.2}

^A Source: [11].

^B See footnote B of Table 1.

dose schedule administered by injection at a 6-month interval for girls aged 9–14 and 9–13 years, respectively. If the respective vaccines are administered at an older age, the three-dose schedule should be used [15,16]. Some EU countries, such as Belgium, France, Italy and the UK, have already implemented a 2-dose HPV vaccination schedule.

The primary target group for routine vaccination is girls at an age before debut of sexual activity, usually 12–13 years. Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme, as clinical trials have shown satisfactory immune response and efficacy against infection in women aged 15–26 years being HPV 16 and 18 DNA negative. The question whether boys should also be included in the HPV vaccination target population is currently under debate and is the subject of ongoing research. Vaccination of boys could contribute to herd immunity and offer protection against other HPV-related cancers and genital warts in the vaccinated subjects. Moreover, mathematical modelling studies indicate that vaccinating boys would be cost-effective if vaccine coverage in girls is lower than 30–50%, as is the case in a number of EU Member States, or if vaccine cost is substantially diminished, i.e., is halved.

Clinical trials and post-licensure studies have shown that the current vaccines are safe, and efforts are still on-going to monitor rare events like auto-immune diseases, or possible adverse effects in special groups such as women who have been inadvertently vaccinated while being pregnant. An important measure in process-monitoring of HPV vaccination is the assessment of vaccine coverage data by year of birth and number of administered doses. In addition, individual vaccination records should be retained, to permit linkage of

HPV-related disease incidence with individual vaccination status in the future.

A measurable early indicator of the impact of vaccination will be the prevalence of HPV infections in young vaccinated women. Indirect evidence of population level impact of the HPV vaccines has already been provided through the demonstration of a decrease in the prevalence of HPV, the incidence of high-grade cervical abnormalities, and the incidence of genital warts soon after the introduction of vaccination programmes. However, long-term monitoring of endpoint indicators is essential to assure that programmes attain their expected impact. This will require careful assessment of changes in the epidemiology of severe precancerous lesions and cancers over decades through linkage between screening and cancer registries irrespective of early indicator studies.

As of early 2014, seven EU countries had not yet initiated HPV vaccination campaigns, all of them new Member States (Estonia, Hungary, Lithuania, Poland, Slovakia, Cyprus and Croatia). HPV vaccination is perceived as being too expensive by many new Member States, but vaccine prices for vaccination campaigns have decreased considerably in recent years, and modelling studies have shown that cost-effectiveness of HPV vaccination tends to be largest in countries with the highest cervical cancer burden, as is the case in most of these countries.

In most of the EU Member States with HPV vaccination campaigns, the vaccine is offered free of charge, predominantly through organized, population-based programmes distributing the vaccine at schools or public health centres. The success in terms of coverage of the target groups has been highly variable, ranging from < 30% to 80% and over. At the lower end of the range, in France and Luxembourg, the

programmes rely on opportunistic vaccination. The highest rates of 80% and above are in countries or regions with population-based vaccination programmes (Denmark, Malta, Portugal, Sweden and the UK and Flemish community in Belgium). Most of the countries choose routine target groups that include ages in the range 11–13 years. Organized school-based programmes usually provide the best coverage and more equitable access to HPV vaccines, followed by organized programmes through health-care centres and through general practitioners. Opportunistic programmes usually achieve low or ill-defined levels of coverage. Vaccination campaigns targeting adolescents pose specific challenges, compared to those targeting younger children aged 10–13 years.

Given the current variation in HPV vaccination coverage in the EU, the importance of an organized, population-based approach to vaccine delivery and the need for adaptation of existing vaccine delivery infrastructure to the special requirements of HPV vaccination are common to all EU countries (see Rec. 3.1 in Suppl. 3 [11], see also Table 3). Higher vaccination coverage is a reasonable goal in many EU Member States. HPV vaccination programmes should aim at a minimum coverage of 70% and preferably > 80% (see Rec. 3.6). Effective monitoring and evaluation will be key to improving the coverage and effectiveness of vaccination programmes across the EU. Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (see Rec. 3.3). Every effort should be made to record individual vaccination status to ensure that it will be known for future cohorts reaching the target age for screening (see Rec. 3.8).

Discussion and conclusions

In an evidence-based process, supplements have been developed that expand the current second edition of the European guidelines for quality assurance in cervical cancer screening [4,5] to cover topics essential to successful implementation of population-based programmes for HPV primary screening and vaccination. In addition to a large package of recommendations graded according to the strength of the recommendations and the supporting evidence, numerous recommendations considered to be good practice by the authors and editors but not of sufficient importance to warrant formal grading are provided in the 200-page Supplements volume that will be published by the European Commission. Neither the Supplements volume nor the previously published volume of the second Guidelines edition should be regarded as a text book or in any way a substitute for practical clinical training and experience, but together they provide important European reference documents that decision makers in EU Member States and other countries should consult to determine whether current policies and programmes for cervical cancer prevention and control can be improved before a new and fully revised third edition of the European guidelines becomes available.

The need for further improvement in cervical cancer prevention and control in Europe, particularly in many of the newer EU Member States is the rationale for focusing the present supplements on topics relevant to HPV primary screening and vaccination. The completion of the supplements by a multidisciplinary group of experts in cervical screening, HPV vaccination and quality assurance and their publication by the European Commission has the potential to become a watershed in improvement of cervical cancer prevention and control in Europe. Based on robust evidence the editors of the supplements explain that cytology primary testing is no longer the only method for population-based cervical

cancer screening that fulfils the requirements of the Council Recommendation on Cancer Screening of 2 December 2003. HPV primary testing is also an appropriate, evidence-based screening method, provided the recommendations in the supplements are followed in programme implementation.

Recognition of the conformity of cervical cancer screening based on HPV primary testing with the Council Recommendation on Cancer Screening is of prime importance because the first report on cancer screening in the EU documented considerable interest in the EU members states in following through on the Council Recommendation by establishing and improving cancer screening programmes in accordance with European Guidelines for quality assurance [9,42]. Raising awareness for the supplements through publication of the present summary should encourage responsible authorities and programme managers to review current policies to determine whether further improvement in cervical cancer prevention and control may be achieved through modification of existing screening programmes or implementation of new, HPV-based programmes where cervical screening programmes are lacking; and through optimized implementation of HPV vaccination.

The choice of content of the present summary is to some extent arbitrary and cannot in any way be regarded as an alternative to the requirement for reading each supplement as a whole and within the context of the complete second edition of the European quality assurance guidelines [4]. This will be possible when the full Supplements volume is available. It should be kept in mind however, that despite encouraging progress, the availability of the extensive supplements will not provide answers to all of the questions that are relevant to future improvement in cervical cancer prevention and control in Europe. Additional points, such as the potential role of methods other than cytology in triaging women with positive HPV test results and evaluation of new primary tests and vaccines require further attention.

It has recently been pointed out that the variation in Europe in the implementation of cancer screening offers a unique opportunity to learn from best practices in collaboration between cancer registries and screening programmes [3] and in quality assurance [14]. In order to accelerate improvements in cancer control, cancer registries should take co-responsibility with screening and vaccination programmes and registries in promoting continuous improvement of primary and secondary cancer prevention in Europe. Additional sustainable investments are vital to further development of infrastructures and activities for quality assurance, including organization training, evaluation and monitoring in the national settings and also at the pan-European level. This is an important point that is also emphasized in Annex 1 [43] of the Supplements volume and that not only applies to cervical cancer screening but also HPV vaccination [3,14].

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The authors of the present manuscript are the members of the editorial board of the current supplements to the second edition of the European guidelines for quality assurance in cervical cancer screening. J. Dillner served on the editorial board only for issues related to screening, not vaccination.

Competing interests

J. Dillner has received research grants to his university with significant funding from Merck/SPMSD, a manufacturer of HPV

vaccines, for monitoring studies on HPV vaccines. He declares no personal remuneration.

L. Dillner is the spouse of J. Dillner who has reported the competing interest listed above.

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