Azienda USL di Modena

in collaborazione con
Regione Emilia-Romagna
Assessorato politiche per la salute

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

La sorveglianza epidemiologica dello screening dei tumori del collo dell'utero nella Regione Emilia-Romagna

Seminario di studio

Bologna, 14 marzo 2016

**Sala 20 maggio 2012, Terza Torre,
Regione Emilia-Romagna
Viale della Fiera 8 – Bologna**

Aggiornamento delle linee- guida europee sullo screening cervicale

Francesca Carozzi
Responsabile Programma Regionale HPV in Toscana
Istituto per lo Studio e La prevenzione Oncologica (ISPO)
Firenze

Papillomavirus Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Papillomavirus Research

European guidelines f screening. Summary of the suppl ation

Lawrence von Karsa [a,*], Marc Dillner [e], Silvia Franceschi [f], Julietta Patnick [g], Guglielmo nberg [i], Ahti Anttila [j]

Il supplemento alla seconda edizione : linee guida europee settembre 2015

- developed in a time of transition when primary testing for oncogenic human papilloma virus (HPV) types and vaccination against infection with the HPV types have become complementary approaches to cervical cancer prevention in Europe.
- By focusing on the core topics of quality assurance:
  - in primary HPV testing,
  - organisation of HPV-based and cytology-based screening programmes,
  - implementation of HPV vaccination programmes
- the supplements lay the foundation for further development of the comprehensive European Guidelines in the coming years.

- The original volume of the second edition was published in 2008.

Executive Summary

- 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
  - Hungary ,Slovak Republic , Poland , Latvia , Bulgaria Lithuania
    - are five to seven times higher than in Finland (1.4) and Malta (1.2),
  - Romania
    - ten times higher

The current 10-fold gradient in the mortality rates of cervical cancer among the EU Member States

reflects the persistent absence, or inadequate implementation of cervical cancer screening programmes more than ten years after organized, population-based screening programmes following European quality assurance guidelines were unanimously recommended by the Health Ministers of the EU (Council of the European Union 2003).

Methodology

- To develop the evidence-based recommendations, the approach used for the European guidelines for quality assurance in colorectal cancer screening and diagnosis (Minozzi et al. 2012) was adopted and modified slightly to take into account the different subject matter and time period of the present project.

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

S1

Screening for cervical cancer with primary testing for human papillomavirus

Authors
G. Ronco
M. Arbyn
C.J.L.M. Meijer
P.J.F. Snijders
J. Cuzick

S2

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

Authors
A. Anttila
G. Ronco
F. Nicula
P. Nieminen
M. Primic Žakelj

S3

Implementation of vaccination against human papillomavirus in Europe

Authors
H. De Vuyst
R. Howell-Jones
D. Levy-Bruhl
P. Giorgi Rossi
S. Franceschi

Estratto da supplemento LLGG Europee Screening cervicale 15 settembre 2015

Table 1
Screening 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]

S1

Screening for cervical cancer with primary testing for human papillomavirus

Authors
G. Ronco
M. Arbyn
C.J.L.M. Meijer
P.J.F. Snijders
J. Cuzick

- to inform 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 main recommendations and conclusions dealing with the suitability of HPV primary testing for use in cervical cancer screening

-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

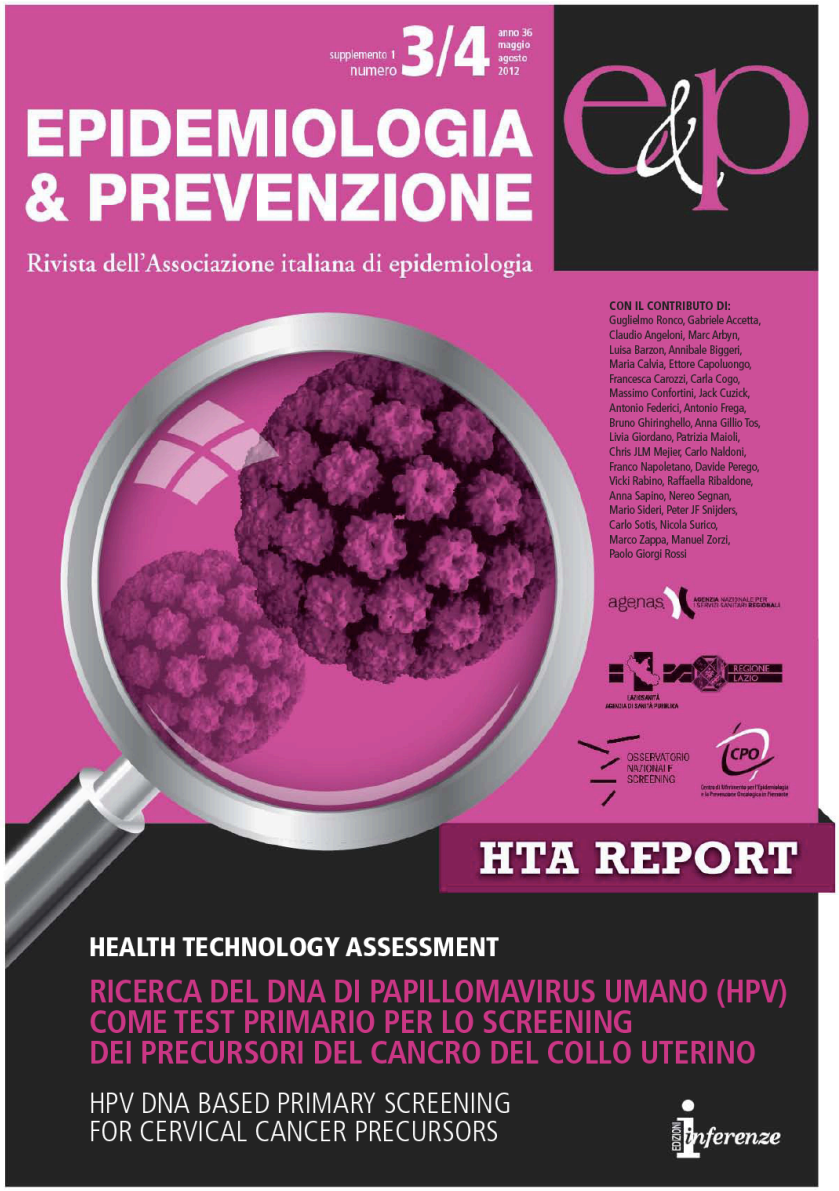
-in order to avoid substantial increase in the number of women with positive test results and additional colposcopies and treatment of no additional benefit to participating women. Following the recommendations in the present supplement will enable programmes to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks (Rec. 1.1).

HTA report italiano: Luglio 2012.
Contiene un'anticipazione ufficiale delle LLGG EU
www.epiprev.it

Gennaio 2013 documento Ministero della Salute di supporto alla programmazione regionale.

Piano Nazionale della Prevenzione 2014-2018

Linee Guida Europee 2015



Il test HPV anticipa la diagnosi di CIN3 e ha una maggiore efficacia nel prevenire i Ca invasivi

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

Lancet. 2014 Feb 8;383(9916):524-32

Identificazione cumulativa di carcinoma cervicale invasivo

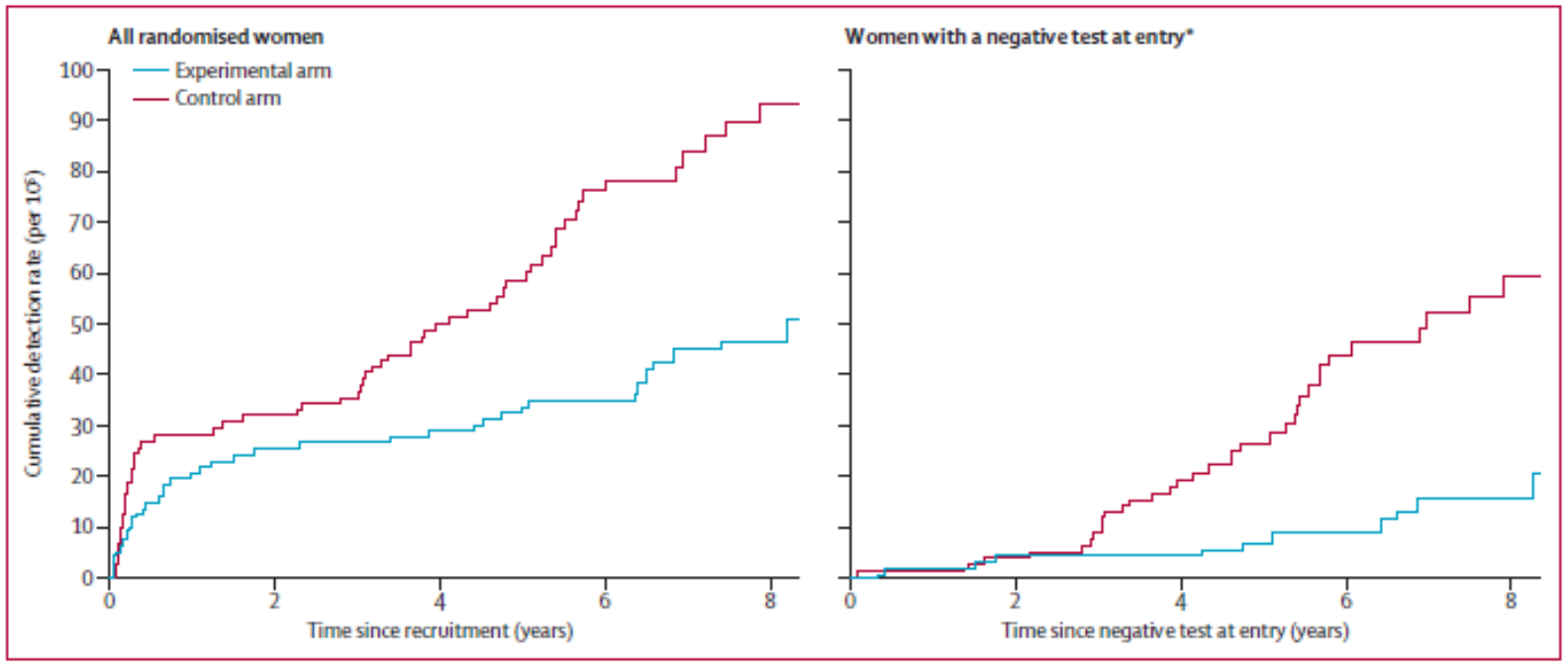


Figure 2: **Cumulative detection of invasive cervical carcinoma**
*Observations are censored 2-5 years after CIN2 or CIN3 detection, if any.

Overall pooled rate ratio 0.60 (0.40-0.89)

Pooled rate ratio > 2-5 years from enrolment 0.45 (0.25-0.81)

Ronco et al, 2014

Tasso di identificazione relativo pooled di carcinoma cervicale invasivo, per morfologia, stadio ed età all'arruolamento

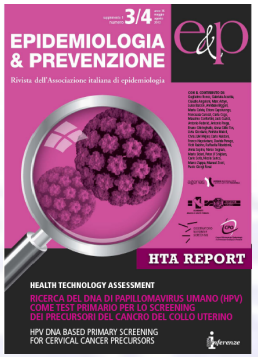
	Pooled rate ratio* (95% CI)	I^2 (p for heterogeneity between studies)
Morphology		
Squamous-cell carcinoma	0·78 (0·49–1·25)	0·0% (0·84)
Adenocarcinoma	0·31 (0·14–0·69)	0·0% (0·59)
Adenocarcinoma *vs* squamous-cell carcinoma	0·34 (0·12–0·90)	..
Stage		
1A	0·58 (0·34–1·01)	0·0% (0·82)
>1A	0·56 (0·31–1·00)	31·8% (0·22)
>1A *vs* 1A	0·86 (0·35–2·13)	..
Age at enrolment (years)		
<30†	0·98 (0·19–5·20)	0·0% (0·34)
30–34	0·36 (0·14–0·94)	7·2% (0·36)
35–49	0·64 (0·37–1·10)	0·0% (0·55)
≥50	0·68 (0·30–1·52)	36·5% (0·21)

All randomised women are included, for the overall study period. *Estimates (experimental *vs* control arm) obtained by a study-adjusted fixed effects model.[35] †Women from Swedescreen and POBASCAM excluded.

Table 4: **Study-adjusted pooled relative detection rate of invasive cervical carcinoma, by morphology, stage, and age at enrolment**

Ronco et al, 2014

Executive summary del report HTA italiano



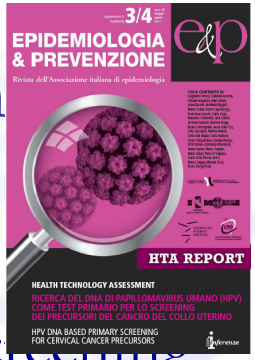
Chiara evidenza scientifica che uno screening con test clinicamente validati per il DNA di HPV oncogeni come test di screening primario e con un protocollo appropriato, è più efficace dello screening basato sulla citologia nel prevenire i tumori invasivi del collo

Executive summary del report HTA italiano

ELEMENTI ESSENZIALI DI UN PROTOCOLLO APPROPRIATO

- **Lo screening basato sul test HPV non deve iniziare prima dei 30-35 anni.**
- **L'intervallo di screening** nell'ambito di programmi organizzati di popolazione dopo un test HPV primario negativo **deve essere di almeno 5 anni**.
- **Le donne positive ad HPV non devono essere inviate direttamente a colposcopia,** ma è necessario utilizzare sistemi di **triage.** Il metodo attualmente raccomandabile è basato sull'esecuzione della citologia (Pap test) nelle donne HPV positive.
- **I test per il DNA di HPV oncogeni utilizzati devono essere validati** quanto a sensibilità e specificità per lesioni di alto grado, secondo ciò che è riportato nelle Linee guida europee.
- **Non esistono prove che il doppio test con citologia e HPV sia più protettivo** del solo test HPV come test primario,

Executive summary del report HTA italian
RACCOMANDAZIONI FINALI



- il requisito fondamentale per introdurre programmi di screening basati sul test HPV come test primario è la capacità di **garantire l'applicazione di protocolli di screening appropriati.**
- Protocolli di screening che non rispettino le indicazioni sopra formulate possono causare aumenti considerevoli degli effetti indesiderati e dei costi rispetto allo screening citologico e devono quindi essere evitati,
- A tale scopo è essenziale una corretta **formazione e informazione** della componente sanitaria e della popolazione.

Recommendations and conclusions[17]

Suitability of HPV primary testing for use in cervical cancer screening programmes

1.1 Primary testing for oncogenic HPV[18] 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 pre-cancers **(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-A).** [Sect 1.5.3]

- **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 the 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]

- **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]

Table 1.5. Detection of CIN2+ in self-taken and clinician-taken samples. Absolute sensitivity and specificity for the detection of CIN2+ by HPV testing on self-samples, and HPV and cytology testing on clinician-taken samples in primary screening

Test and sample type	Test cut-off	Number of studies	Sensitivity in % (95% CI)	Specificity in % (95% CI)
HPV self-taken	defined by manufacturer	14	76 (69–82)	86 (84–90)
HPV clinician-taken	defined by manufacturer	14	91 (87-94)	88 (85-91)
cytology clinician-taken	ASC-US or more severe	12	83 (75–89)	91 (87–94)
	LSIL or more severe	8	71 (66–76)	97 (97–98)

Source: (Arbyn et al. 2014)

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).

S2

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

Authors
A. Anttila
G. Ronco
F. Nicula
P. Nieminen
M. Primic Žakelj

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,

the extent to which this knowledge has been translated into effective national programmes to control cervical cancer

the most effective and appropriate way for screening to reduce cervical cancer incidence and mortality is through implementation of population-based programmes following 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 **seventeen recommendations** on the policy and organizational issues that are inherent to the use of cytology and HPV testing in screening programmes.

Recommendations[22]

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

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) **(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]

S3

Implementation of vaccination against human papillomavirus in Europe

Authors
H. De Vuyst
R. Howell-Jones
D. Levy-Bruhl
P. Giorgi Rossi
S. Franceschi

F. Carozzi 14 Marzo 2016 RER

Recommendations and conclusions[24]

Organization of HPV vaccination

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 immunisation 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 3.3]

Grazie per l'attenzione !!

f.carozzi@ispo.toscana.it