GISCi

Gruppo Italiano Screening del Cervicocarcinoma

HTA E SCREENING CERVICALE

MARCO ZAPPA

27 • 28 ottobre, Verona

CONVEGNO NAZIONALE GISCi 2022

Il sottoscritto Marco Zappa
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

X□ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

□ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

- *……*
- *……*
- *……..*

IARC Handbook Vol 18: Cervical cancer screening

- A Working Group of international experts was convened by IARC to review and assess all available evidence for cervical cancer screening
- Conventional cytology, liquid-based cytology, and HPV nucleic acid testing were established to reduce cervical cancer incidence and mortality
- HPV DNA testing showed higher effectiveness and a better balance of benefits versus harms compared to other screening methods

https://publications.iarc.fr/604

International Agency for Research on Cancer

World Health Organization

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

The IARC Perspective on Cervical Cancer Screening

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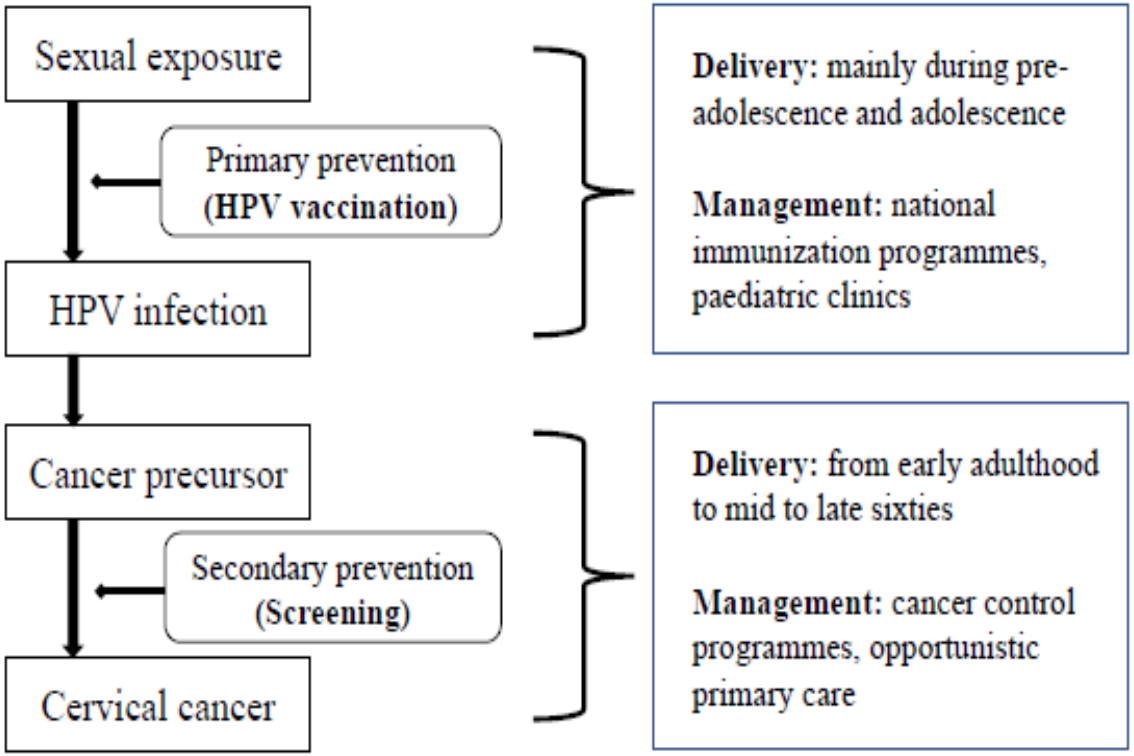
Table 3. Comparative Effectiveness of the Established Cervical Cancer Screening Methods.*

Methods Compared	Comparison of Benefit-to-Harm Balances
HPV DNA testing vs. VIA	HPV DNA testing >> VIA
HPV DNA testing vs. cytology	HPV DNA testing > cytology
HPV DNA testing vs. cotesting†	HPV DNA testing ≥ cotesting

2021 Nov 11;385(20):1908-1918

Fig. 5.2 Interplay between primary and secondary prevention strategies for cervical cancer



Created by the Working Group.

Cosa serve studiare/valutare in una situazione così favorevole?

- Azioni per migliorare l'efficacia sull'intera popolazione

  (aumento della copertura generale , aumento della copertura delle persone a maggior rischio); di minore importanza l'aumento della sensibilità delle procedure

- Azioni per migliorare il rapporto costo efficacia (migliore efficienza e migliore sostenibilità)

- Azioni per diminuire i rischi e il discomfort per la donna

- Azioni per rendere più agevole l'implementazione dei programmi di screening

supplemento 1
numero 3/4
anno 36
maggio
agosto
2012

EPIDEMIOLOGIA & PREVENZIONE

e&p

Rivista dell'Associazione italiana di epidemiologia

CON IL CONTRIBUTO DI:
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HTA REPORT

HEALTH TECHNOLOGY ASSESSMENT

RICERCA DEL DNA DI PAPILLOMAVIRUS UMANO (HPV) COME TEST PRIMARIO PER LO SCREENING DEI PRECURSORI DEL CANCRO DEL COLLO UTERINO

HPV DNA BASED PRIMARY SCREENING FOR CERVICAL CANCER PRECURSORS

EDIZIONI inferenze

OSSERVATORIO NAZIONALE SCREENING

GISCi

Gruppo Italiano Screening del Cervicocarcinoma

Consensus Conference

per la definizione del percorso di screening del cervicocarcinoma nelle donne vaccinate contro l'HPV

Alla stesura del documento hanno contribuito le principali società scientifiche del settore:

SITI - Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica;
SICPCV - Società Italiana di Colposcopia e Patologia Cervicovaginale;
AOGOI - Associazione Ostetrici Ginecologi Ospedalieri Italiani;
SIAPEC - Società Italiana di Anatomia Patologica e Citologia Diagnostica;
SIGO - Società Italiana di Ginecologia e Ostetricia;
SIV - Società Italiana di Virologia;
SICI - Società Italiana di Citologia.

Protocollo programmi organizzati in Italia

- Pap test fra 25 e 30-34 anni con intervallo triennale (triage HPV)
- HPV Dna HR da 30-34 fino a 65 aa con intervallo quinquennale (triage citologico ASCUS+)
- Primo invito spostato a 3° anni , per le vaccinate validamente prima dei 15 aa

OBIETTIVO PNP 2014-2018 prolungato al 2019

- *1.14* **Riorientare/ avviare** i programmi di screening della cervice uterina introducendo il test HPV / DNA

- Adozione di indirizzi regionali programmatori entro il 2016

- Completamento del passaggio entro il 2018 (2019)

% di donne tutte le età invitate con Test HPV su tutte le invitate allo screening ITALIA

2016 = 23,4%
2017 = 30,4%
2018 = 37,9%
2019 = 42,5%

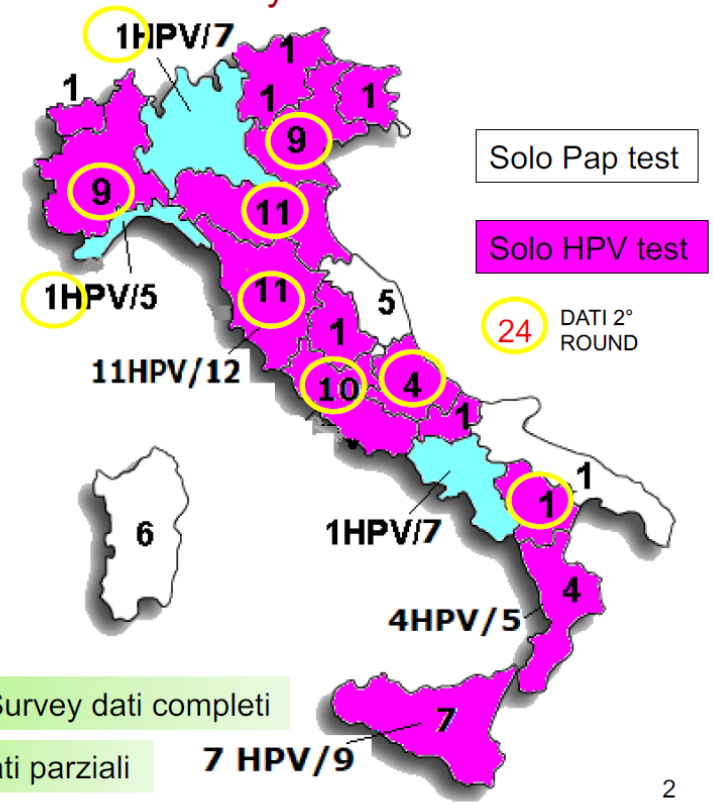
Anno	Regioni	Programm
2012	10	19
2013	10	21
2014	12	26
2015	**12**	**49**
2016	**16**	**61**
2017	**16***	**58**
2018	**17**	**65**
2019	**18**	**73**

Survey dati completi

dati parziali

* Il Veneto rispetto al 2016 è passato da 21 programmi a 9 perché sono stati accorpati

Programmi attivi con HPV test primario
Survey Coorte 2019



OBIETTIVO PNP 2020-2025

Linea n.10 :

.....

- implementazione di protocolli di screening cervicale differenziati per le donne vaccinate a 11-12 anni contro l'HPV", in concomitanza con l'arrivo all'età di screening delle prime ragazze vaccinate nel dodicesimo anno di età (coorte 1996)

Programmi con HPV Population based- Europa Occidentale

Paese	Età	Test	triage	Intervallo
Danimarca	23-64	Cit. 23-29 HPV+Cit. 30-59 HPV 60-64	HPV	3 aa (23-49) 5 aa (50-64)
Finlandia	30-64	HPV o Cit,		5 aa
Francia	25-65	Cit. 25-29 HPV 30-65	HPV Cit.	3 aa (25-29) 5 aa (30-65)
Irlanda	25-65	HPV		3 aa (25-29) 5 aa (30-65)
Norvegia	25-69	Cit. HPV	HPV Cit.	3 aa (25-33) 5 aa (34-65)
Olanda	30-60	HPV	Cit.	5 aa (30-40) 10 aa (40-60)
Portogallo	20- 59	Cit.+ HPV		3 aa
Svezia	23-64	Cit. 25-29 HPV 30-65		3 aa (25-49) 7 aa (50-64)
UK	25-64	HPV	Cit.	3 aa (25-49) 5 aa (50-64)

Modificato da IARC Handbook Vol 18

Table 2.4 Cervical cancer screening guidelines from cancer societies in the USA

Recommendation	Reference		
	American College of Obstetricians and Gynecologists (2016)	US Preventive Services Task Force (2018)	American Cancer Society (2020)
Age range			
Starting age (years)	21	21 Recommend against screening at younger ages	25
Stopping age (years)	65 if adequate negative screening within the past 10 yr[a]	65 if adequate negative screening within the past 10 yr[a]	65 if adequate negative screening within the past 20 yr[a]
Screening tests	HPV and cytology co-testing (ages 30–65) Cytology (ages 21–65)	Primary HPV testing (ages 30–65) HPV and cytology co-testing (ages 30–65) Cytology (ages 21–65)	HPV (preferred test) (ages 25–65) HPV and cytology co-testing (acceptable) (ages 25–65) Cytology (acceptable) (ages 25–65)
Screening interval for primary test			
HPV testing	Not more frequent than every 3 yr	Every 5 yr	Every 5 yr
Co-testing	Every 5 yr	Every 5 yr	Every 5 yr
Cytology	Every 3 yr	Every 3 yr	Every 3 yr
Screening for HPV-vaccinated women	As per the general guidelines	As per the general guidelines	As per the general guidelines
Screening for HIV-positive women	As per DHHS–CDC guidance	As per DHHS–CDC guidance	As recommended by CDC, NIH, and HIVMA

CDC, Centers for Disease Control and Prevention; DHHS, Department of Health and Human Services; HIVMA, HIV Medicine Association of the Infectious Diseases Society of America; HPV, human papillomavirus; NIH, National Institutes of Health; yr, year or years.

[a] Adequate negative screening could be either 3 consecutive Pap smears or 2 consecutive HPV tests. Guidance by the DHHS and the CDC for HIV-positive women comprises first screening 1 year after sexual onset and no later than age 21 years, or first screening on HIV diagnosis for women 21 years and older. Screening to be done with annual cytology or triennial HPV–cytology co-testing within the same age ranges as the general population.

Co-testing versus HPV DNA testing

Increased benefits

- Minimal increase in sensitivity for detecting CIN2+ and CIN3+
- Minimal difference in cumulative risks for CIN2+ and CIN3+ b/w co-test-negative women and HPV-negative women

Increased harms

- Lower specificity for detecting CIN2+ and CIN3+
- Increase in referrals to colposcopy, and possibly treatment
- Decrease in positive predictive value in referred women (increased detection of regressive lesions)

- The benefits of co-testing do not outweigh the harms.
- The impact of the cytological component of co-testing is very limited.
- The impact on cancer incidence is unclear.

Argomenti che verranno trattati

- Self sampling
- Triage / personalizzazione del rischio
- Arrivo delle corti vaccinali

Self Sampling /Auto prelievo

- Viene introdotto nell’Handbook al primo punto come mezzo per aumentare la partecipazione dei programmi con test HPV primario

Che cos'è il self sampling?

Il *self sampling*, in italiano 'autoprelievo', è il prelievo di cellule per il test HPV fatto direttamente dalla donna, in completa autonomia, senza la supervisione (in alcuni studi sì) di un operatore sanitario.

Potenzialità del self sampling

1)Favorire la partecipazione delle **donne che non rispondono all'invito tradizionale**

- a causa di **ostacoli organizzativi** (mancanza di tempo o la scarsa flessibilità degli orari ambulatoriali)
- per **motivazioni legate alla sfera personale**, quali per esempio l'imbarazzo o il fastidio associati alla modalità tradizionale di prelievo.

2) **Modalità alternativa o aggiuntiva per tutta la popolazione**

-nel caso in cui il programma di screening **non riesca a garantire un'accessibilità agli ambulatori che rispecchi le esigenze delle utenti** (limitatezza di punti prelievo, viabilità lenta e complicata, assenza di parcheggi, orari degli ambulatori non corrispondenti alle richieste della popolazione)

-**carenza di personale addetto al prelievo**, non riesca a garantire una buona estensione, e quindi non riesca a rispettare la periodicità di invito prevista dal protocollo per i richiami o nella

-**offrire comunque un miglior servizio per la popolazione**

Arbyn M. *et al* 2018

OPEN ACCESS

Check for updates

Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses

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Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2018;363:k4823
http://doi.org/10.1136/bmj.k4823

Accepted: 1 November 2018

ABSTRACT

OBJECTIVE
To evaluate the diagnostic accuracy of high-risk human papillomavirus (hrHPV) assays on self samples and the efficacy of self sampling strategies to reach underscreened women.

DESIGN
Updated meta-analysis.

DATA SOURCES
Medline (PubMed), Embase, and CENTRAL from 1 January 2013 to 15 April 2018 (accuracy review), and 1 January 2014 to 15 April 2018 (participation review).

REVIEW METHODS
Accuracy review: hrHPV assay on a vaginal self sample and a clinician sample; and verification of the presence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) by colposcopy and biopsy in all enrolled women or in women with positive tests. Participation review: study population included women who were irregularly or never screened; women in the self sampling arm (intervention arm) were invited to collect a self sample for hrHPV testing; women in the control arm were invited or reminded to undergo a screening test on a clinician sample; participation in both arms was documented; and a population minimum of 400 women.

RESULTS
56 accuracy studies and 25 participation trials were included. hrHPV assays based on polymerase chain reaction were as sensitive on self samples as on clinician samples to detect CIN2+ or CIN3+ (pooled ratio 0.99, 95% confidence interval 0.97 to 1.02). However, hrHPV assays based on signal amplification were less sensitive on self samples (pooled ratio 0.85, 95% confidence interval 0.80 to 0.89). The specificity to exclude CIN2+ was 2% or 4% lower on self samples than on clinician samples, for hrHPV assays based on polymerase chain reaction or signal amplification, respectively. Mailing self sample kits to the woman's home address generated higher response rates to have a sample taken by a clinician than invitation or reminder letters (pooled relative participation in intention-to-treat-analysis of 2.33, 95% confidence interval 1.86 to 2.91). Opt-in strategies where women had to request a self sampling kit were generally not more effective than invitation letters (relative participation of 1.22, 95% confidence interval 0.93 to 1.61). Direct offer of self sampling devices to women in communities that were underscreened generated high participation rates (>75%). Substantial interstudy heterogeneity was noted (I^2>95%).

CONCLUSIONS
When used with hrHPV assays based on polymerase chain reaction, testing on self samples was similarly accurate as on clinician samples. Offering self sampling kits generally is more effective in reaching underscreened women than sending invitations. However, since response rates are highly variable among settings, pilots should be set up before regional or national roll out of self sampling strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tests performed on self samples are less sensitive and less specific than tests performed on clinician samples when using a high-risk human papillomavirus (hrHPV) assay based on signal amplification

Response rates for hrHPV testing are higher for self sampling kits than for conventional invitations

WHAT THIS STUDY ADDS

Tests performed on self samples are similarly sensitive and slightly less specific than tests performed on clinician samples when using a hrHPV assay based on polymerase chain reaction

Response rates for hrHPV testing continue to be higher for self sampling kits than for conventional invitations

Introduction

Cervical cancer rates in western Europe, North America, Australia, and New Zealand are relatively low compared with rates in less developed countries.[1] However, demographic and social disparities in the burden of disease exist. In the United States, incidence is higher among Hispanic (8.9 per 100 000 women years in 2011-15, age adjusted using the 2000 US population as reference) and black (8.4) populations, versus the white population (7.4).[2] The contrasts can be explained by differences in access to screening. In western and northern Europe, both cervical cancer incidence and mortality have decreased after widespread screening.[3] In eastern Europe, where the coverage or quality, or both, of screening often is low to moderate, incidence has not dropped to the same extent and in some countries trends are even rising.[4-6] To be noted, 85% of cases of cervical cancers occur in less developed countries, with incidence rates reaching 35 per 100 000 women years in eastern Africa.[3]

Most cervical cancer cases occur in women who have never been screened for cervical cancer, or do not participate in routine screening.[7] However, recent trend analyses reveal an increasing burden of

BMJ: first published as 10.1136/bmj.k4823 on 5 December 2018. Downloaded from http://www.bmj.com/ on 30 October 2019 at Università di Torino. Protected by copyright.

To evaluate the diagnostic accuracy of high-risk human *papillomavirus* (hrHPV) assays on self samples and the efficacy of self sampling strategies to reach underscreened women.

Updated meta-analysis

Results

✓ The updated meta-analyses finally comprised 56 diagnostic test accuracy studies and 25 randomized trials.

✓ **hrHPV assays based on polymerase chain reaction were as sensitive on self samples as on clinician samples to detect CIN2+ or CIN3+ (pooled ratio 0.99, 95% confidence interval 0.97 to 1.02).**

✓**However, hrHPV assays based on signal amplification were less sensitive on self samples (pooled ratio 0.85, 95% confidence interval 0.80 to 0.89).**

The specificity to exclude CIN2+ was 2% or 4% lower on self samples than on clinician samples, for hrHPV assays based on polymerase chain reaction or signal amplification,respectively

Table 1 | Pooled relative sensitivity and specificity of high-risk human papillomavirus (hrHPV) assays based on signal amplification (SA) and polymerase chain reaction (PCR) on self samples versus clinician samples

			Ratio (95% CI)			
Assay	Outcome	No of studies	Sensitivity	Specificity	Test positivity	PPV
SA	CIN2+	23	0.85 (0.80 to 0.89)*	0.96 (0.93 to 0.98)*	1.14 (1.05 to 1.24)	0.71 (0.62 to 0.82)
	CIN3+	9	0.86 (0.76 to 0.98)*	0.97 (0.95 to 0.99)*		0.65 (0.57 to 0.78)
PCR	CIN2+	17	0.99 (0.97 to 1.02)	0.98 (0.97 to 0.99)*	1.00 (0.94 to 1.06)	0.97 (0.90 to 1.04)
	CIN3+	8	0.99 (0.96 to 1.02)	0.98 (0.97 to 0.99)*		0.90 (0.78 to 1.05)

PPV=positive predictive value; CIN2+=cervical intraepithelial neoplasia of grade 2 or worse; CIN3+=cervical intraepithelial neoplasia of grade 3 or worse.
*Statistically significantly different from unity.

BMJ Global Health

Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis

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To cite: Yeh PT, Kennedy CE, de Vuyst H, et al. Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. *BMJ Global Health* 2019;4:e001351. doi:10.1136/bmjgh-2018-001351

Handling editor Sanni Yaya

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2018-001351).

Received 6 December 2018
Revised 26 April 2019
Accepted 27 April 2019

Check for updates

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ABSTRACT

Introduction Human papillomavirus (HPV) self-sampling test kits may increase screening for and early detection of cervical cancer and reduce its burden globally. To inform WHO self-care guidelines, we conducted a systematic review and meta-analysis of HPV self-sampling among adult women on cervical (pre-)cancer screening uptake, screening frequency, social harms/adverse events and linkage to clinical assessment/treatment.

Methods The included studies compared women using cervical cancer screening services with HPV self-sampling with women using standard of care, measured at least one outcome, and were published in a peer-reviewed journal. We searched PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Health Sciences Literature (LILACS) and Embase through October 2018. Risk of bias was assessed using the Cochrane tool for randomised controlled trials (RCTs) and the Evidence Project tool for non-randomised studies. Meta-analysis was conducted using random-effects models to generate pooled estimates of relative risk (RR).

Results 33 studies in 34 articles with 369 017 total participants met the inclusion criteria: 29 RCTs and 4 observational studies. All studies examined HPV self-sampling; comparison groups were standard of care (eg, Pap smear, visual inspection with acetic acid, clinician-collected HPV testing). 93% of participants were from high-income countries. All 33 studies measured cervical cancer screening uptake. Meta-analysis found greater screening uptake among HPV self-sampling participants compared with control (RR: 2.13, 95% CI 1.89 to 2.40). Effect size varied by HPV test kit dissemination method, whether mailed directly to home (RR: 2.27, 95% CI 1.89 to 2.71), offered door-to-door (RR: 2.37, 95% CI 1.12 to 5.03) or requested on demand (RR: 1.28, 95% CI 0.90 to 1.82). Meta-analysis showed no statistically significant difference in linkage to clinical assessment/treatment between arms (RR: 1.12, 95% CI 0.80 to 1.57). No studies measured screening frequency or social harms/adverse events.

Conclusion A growing evidence base, mainly from high-income countries and with significant heterogeneity, suggests HPV self-sampling can increase cervical cancer screening uptake compared with standard of care, with a marginal effect on linkage to clinical assessment/treatment.

Systematic review registration number PROSPERO CRD42018114871.

Key questions

What is already known?
- ► Cervical cancer is one of the most common types of cancer among women globally and the leading cause of cancer deaths in women in low-income and middle-income countries, but early detection and treatment of precancerous lesions can prevent cervical cancer.
- ► High-risk human papillomavirus (HPV) testing is a relatively new, reasonably accurate method of secondary cervical cancer prevention.

What are the new findings?
- ► Meta-analysis shows that self-sampling for HPV testing may increase population uptake of cervical cancer screening, especially when HPV self-sampling kits were sent directly to women's homes or offered door-to-door by a health worker.
- ► However, linkage to follow-up testing and treatment after HPV self-sampling and after regular screening services alike is limited.

What do the new findings imply?
- ► A WHO recommendation on self-sampling for HPV may increase screening coverage (although strategies for improving linkage to treatment after positive test results are needed) and decrease the burden of cervical cancer.

INTRODUCTION

Cervical cancer is one of the most common types of cancer among women globally; in low-income and middle-income countries (LMICs), it is the leading cause of cancer deaths in women.[1 2] Cervical cancer develops from persistent high-risk human papillomavirus (HPV) infection.[3] Although vaccines exist that protect against infection and disease associated with specific types of HPV, many women in LMICs do not have access to HPV immunisation and die of this preventable cancer.[3] Secondary prevention measures include early detection and treatment of precancerous lesions. Cervical cancer screening has successfully reduced cervical cancer incidence and mortality, especially

- Systematic review and meta-analysis of HPV self-sampling among adult women on:

- cervical (pre-) cancer screening uptake,
- screening frequency,
- social harms/adverse events
- linkage to clinical assessment/treatment.

Comparing women using cervical cancer screening services with HPV self-sampling with women using standard of care.

Results

✓ 33 studies in 34 articles with 369.017 total participants met the inclusion criteria: 29 RCTs and 4 observational studies.

✓All studies examined HPV self-sampling; comparison groups were standard of care (eg, Pap smear, visual inspection with acetic acid, clinician collected HPV testing).

✓93% of participants were from high-income countries.

✓All 33 studies measured cervical cancer screening uptake.

Results

Meta-analysis found greater screening uptake among HPV self-sampling participants compared with control (RR: 2.13, 95% CI 1.89 to 2.40).

Study name	Statistics for each study				
	Lower limit	Risk ratio	Upper limit	Z-Value	p-Value
Arrossi et al., 2015	3.950	4.249	4.570	38.857	0.000
Bais et al., 2007	1.557	2.028	2.640	5.250	0.000
Broberg et al., 2014	1.996	2.322	2.702	10.903	0.000
Cadman et al., 2015	1.901	2.246	2.653	9.515	0.000
Carrasquillo et al., 2018	1.966	2.468	3.098	7.784	0.000
Darlin et al., 2013	2.244	3.500	5.459	5.525	0.000
Giorgi Rossi et al., 2011	0.750	0.946	1.195	-0.462	0.644
Giorgi Rossi et al., 2015	1.287	1.405	1.535	7.567	0.000
Gok et al., 2010	1.272	1.658	2.160	3.744	0.000
Gok et al., 2012	2.917	4.621	7.321	6.522	0.000
Gustavsson et al., 2018	1.177	1.206	1.237	14.719	0.000
Haguenoer et al., 2014	1.711	1.968	2.263	9.496	0.000
Ivanus et al., 2018	1.775	1.929	2.095	15.553	0.000
Kellen et al., 2018	2.575	2.777	2.995	26.466	0.000
Lazcano-Ponce et al., 2011	1.092	1.099	1.106	27.717	0.000
Modibbo et al., 2017	1.441	1.637	1.860	7.557	0.000
Moses et al., 2015	1.802	2.050	2.331	10.948	0.000
Murphy et al., 2016	0.517	0.902	1.574	-0.363	0.717
Piana et al., 2011	3.245	3.659	4.127	21.138	0.000
Racey et al., 2016	2.170	3.735	6.427	4.758	0.000
Sancho-Garnier et al., 2013	7.904	9.136	10.559	29.948	0.000
Sewali et al., 2015	1.584	3.391	7.258	3.145	0.002
Sultana et al., 2016	2.656	3.403	4.359	9.693	0.000
Szarewski et al., 2011	1.706	2.250	2.967	5.747	0.000
Tranberg et al., 2018	1.277	1.367	1.462	9.016	0.000
Virtanen et al., 2011	1.014	1.030	1.047	3.629	0.000
Viviano et al., 2017	0.937	0.985	1.035	-0.589	0.556
Wikstrom et al., 2011	3.646	4.224	4.893	19.201	0.000
Zehbe et al., 2016	1.364	2.032	3.027	3.486	0.000
	1.891	2.130	2.399	12.461	0.000

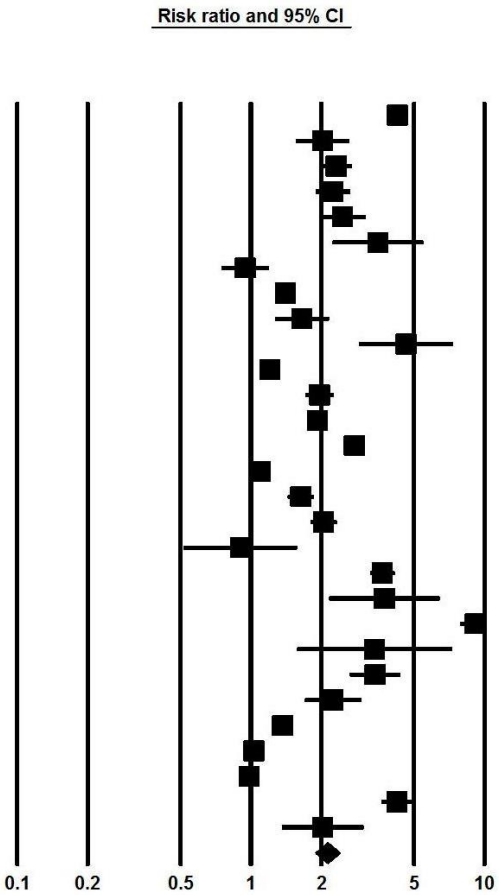


Figure 2. Meta-analysis showing relative risk of uptake of cervical cancer screening, overall.

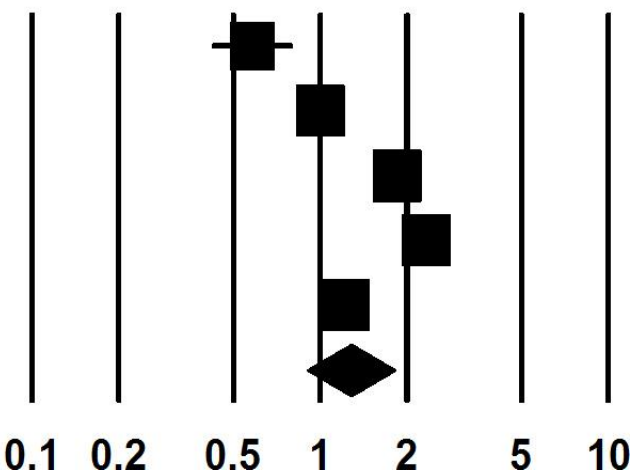
Yeh P.T. *et al* 2019

Results

✓Effect size varied by HPV test kit dissemination method, whether mailed directly to home (RR: 2.27, 95% CI 1.89 to 2.71), offered door-to-door (RR: 2.37, 95% CI 1.12 to 5.03) or requested on demand (RR: 1.28, 95% CI 0.90 to 1.82)

Figure 5. Meta-analysis showing relative risk of uptake of cervical cancer screening, opt-in (self-sampling kit on demand) versus control.

Study name	Statistics for each study				
	Lower limit	Risk ratio	Upper limit	Z-Value	p-Value
Giorgi Rossi et al., 2011	0.423	0.581	0.798	-3.354	0.001
Giorgi Rossi et al., 2015	0.899	1.003	1.119	0.051	0.959
Ivanus et al., 2018	1.700	1.849	2.012	14.325	0.000
Kellen et al., 2018	2.149	2.333	2.534	20.110	0.000
Tranberg et al., 2018	1.133	1.225	1.325	5.089	0.000
	0.902	1.280	1.817	1.382	0.167



Yeh P.T. *et al* 2019

Gradimento delle donne

2 revisioni della letteratura hanno confrontato l'accettabilità dell'autoprelievo da parte delle donne rispetto al prelievo eseguito da un operatore sanitario, concludendo che il primo è ampiamente preferito rispetto al secondo

Motivazioni espresse:

- Desiderio di privacy
- Imbarazzo di fronte ad un operatore
- Possibilità di farlo da sole e nei tempi compatibili con l'attività lavorativa e la gestione della famiglia

Percezioni negative.

- Incertezza di aver raccolto il prelievo correttamente
- Disagio

Desiderio di un insieme dei due (participatory medicine)

Conclusion

hrHPV testing with an appropriate assay offers a promising new strategy that could increase population coverage substantially. When used with hrHPV assays based on polymerase chain reaction, testing on self samples was similarly accurate as on clinician samples.

Offering self sampling kits generally is more effective in reaching underscreened women than sending invitations.

However, since response rates are highly variable among settings, pilots should be set up before regional or national roll out of self sampling strategies.

- **IARC Handbook Vol 18**

BJC

British Journal of Cancer (2015) 112, 667–675 | doi: 10.1038/bjc.2015.11

Keywords: HPV test; self-sampling; randomised controlled trial; cervical cancer; screening

Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter

P Giorgi Rossi*[,1,2], C Fortunato[3], P Barbarino[4], S Boveri[5], S Caroli[1,2], A Del Mistro[6], A Ferro[7], C Giammaria[8], M Manfredi[9], T Moretto[10], A Pasquini[9], M Sideri*[,5], M C Tufi[4], C Cogo[11] and E Altobelli*[,3] the HPV Self-sampling Italian Working Group[12]

[1]Servizio Interaziendale di Epidemiologia, Azienda Unità Sanitaria Locale, via Amendola 2, Reggio Emilia 42122, Italy; [2]IRCCS—Arcispedale S. Maria Nuova, 42122 Reggio Emilia, Italy; [3]Department of Life, Health and Environmental Sciences, University of L'Aquila, Viale San Salvatore, Edificio Delta 6, 67100 L'Aquila, Italy; [4]UOC Screening e prevenzione ASL Roma G, 00019 Tivoli (Rome), Italy; [5]Preventive Gynaecology Unit, European Institute of Oncology, 20141 Milano, Italy; [6]Istituto Oncologico Veneto IOV-IRCCS, 35128 Padova, Italy; [7]Dipartimento di Prevenzione Azienda ULSS 17, 35042 Este-Monselice (PD), Italy; [8]UOC Ginecologia e Ostetricia, Screening Oncologici Regionali Ospedale Cardarelli, 86100 Campobasso (CB), Italy; [9]Programma Screening Oncologici AUSL di Bologna, 40068 San Lazzaro di Savena (BO), Italy; [10]Dipartimento di Prevenzione Azienda ULSS 7 Pieve di Soligo – Conegliano, 31053 Pieve di Soligo (TV), Italy and [11]Registro tumori del Veneto, 35131 Padova, Italy

Background: We performed a multicentre randomised controlled trial to evaluate the effect on participation in organised screening programmes of a self-sampling device mailed home or picked up at a pharmacy compared with the standard recall letter.

Methods: Women aged 30–64 non-responding to screening invitation were eligible. Response rate to first invitation ranged from 30% to 60% between centres. The control was the standard reminder letter to undergo the test used by the programme (Pap test in three centres and HPV DNA test in three other centres). Home mailing of the self-sampler was preceded by a letter with a leaflet about HPV. The analysis was intention-to-treat.

Results: In all, 14 041 women were randomised and recruited: 5012 in the control arm, 4516 to receive the self-sampler at home, and 4513 to pick up the self-sampler at a pharmacy. Participation was 11.9% in the control, 21.6% (relative participation: 1.75; 95% CI 1.60–1.93) in home, and 12.0% (relative participation: 0.96; 95% CI 0.86–1.07) in the pharmacy arms, respectively. The heterogeneity between centres was high (excess heterogeneity of that expected due to chance, i.e., I^2, 94.9% and 94.1% for home and pharmacy arm, respectively). The estimated impact on the overall coverage was +4.3% for home mail self-sampling compared with +2.2% for standard reminder.

Conclusions: Home mailing of self-sampler proved to be an effective way to increase participation in screening programmes, even in those with HPV as primary testing. Picking up at pharmacies showed effects varying from centre to centre.

+ 2,1% copertura sull'intera popolazione

USLUmbria1
SERVIZIO SANITARIO REGIONALE

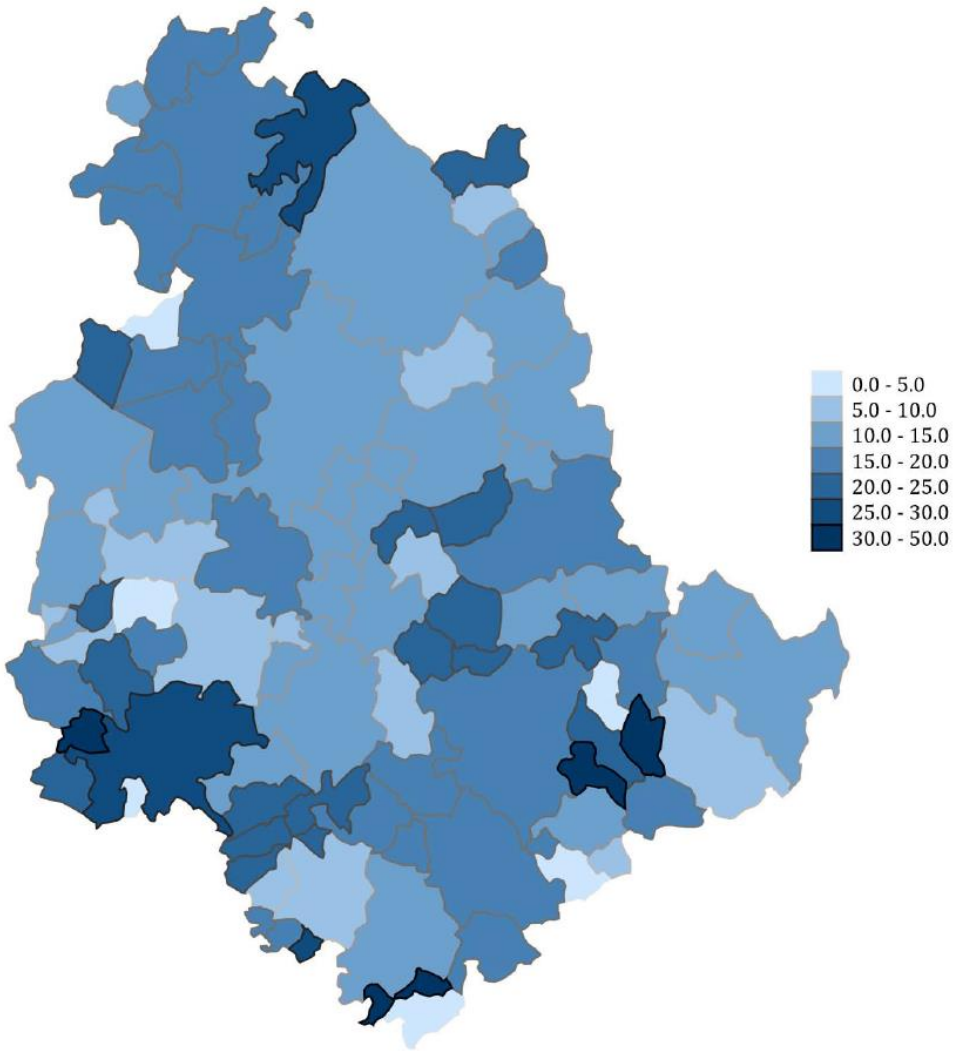
Autoprelievo : l'esperienza dell'Umbria

Riccione, 30.05.2019

Maria Donata Giaimo

Adesione grezza auto-prelievo screening HPV 2014-2016 per comuni

14,4%



Il progetto «Self-Sampling»

Progetto di ricerca ISPO "Self Sampling"

8000 women from 3 different area of Tuscany Region
Age_ 34-64 years
Not responders to the previuos screening round

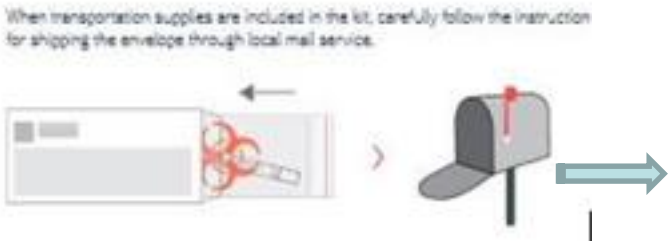
4000 Control Arm (BR 1)
Regular recall by letter for HPV screening
(with pre-fixed appointment)

2000 Active Arm (BR 2)
'DRY' self sampling device
Sent at home by mail

2000 Active Arm (BR 3)
'WET' self sampling device
Sent at home by mail

Tube with transport medium 'WET'

- Lettera d'invito
- Informativa
- Consenso informato
- Istruzioni di prelievo
- Questionario di gradimento



LAB

HPV PRIMARY SCREENING ON SELF-COLLECTION SAMPLES: compliance to invitation and HPV prevalence

Methods

The hr-HPV test was carried out on Cobas4800® (Roche).

Compliance:

Control Arm (BR1): 17,1 Self sampling arms= 19.0 p= 0.135

DRY Arm :19,1

WET ARM : 18,9

(p= 0.892 between 2 sperimental arm ;

HPV Prevalence in self sampling arms compared to control arm

Control Arm (BR1): 9,2 Self samplig arms =11,3 p= 0.145

DRY Arm :10,9

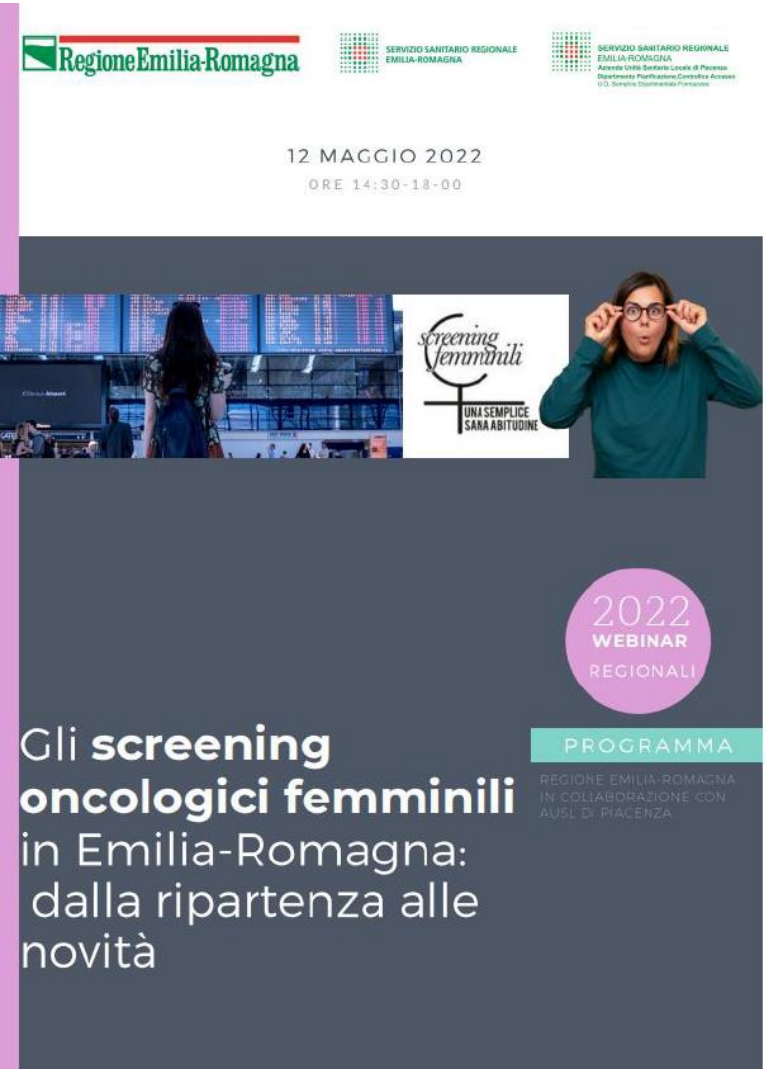
WET ARM : 11,6

(p=0.792 between 2 sperimental arm ;

Compliance to colposcopy:

Control arm: 81% women attended colposcopy

Self sampling : 79% women attended colposcopy



L'autoprelievo nello screening della cervice uterina: Esperienza del Programma di Bologna

Carmen Bazzani
UA Centro Screening
UOC Governo dei Percorsi di Screening
Azienda USL di Bologna

Centro Coordinamento Screening
Via Montebello, 6 - 40121 Bologna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna

Istituto delle Scienze Neurologiche
Istituto di Ricovero e Cura a Carattere Scientifico

Screening femminili
UNA SEMPLICE SANA ABITUDINE

INVITO TEST HPV CON AUTO-PRELIEVO

Test HPV
QUANDO
VUOI TU

Data di nascita,
Bologna,

Gentile Signora,
Le proponiamo una nuova modalità, semplice e innovativa, per eseguire il test HPV a casa, nell'ambito del programma di screening per la prevenzione dei tumori del collo dell'utero. L'esame è gratuito, così come gli eventuali accertamenti successivi.

Usufruisca di questa opportunità che Le raccomandiamo per prendersi cura oggi della sua salute di domani.

*Attraverso questo invito può **eseguire il prelievo di materiale cervicale in piena autonomia**, senza la necessità di recarsi in orari e giorni prestabiliti presso il Consultorio familiare.*

✓ **SI PRESENTI CON QUESTA LETTERA, LA TESSERA SANITARIA E UN DOCUMENTO DI IDENTITÀ** presso una farmacia aderente al progetto dove potrà ritirare il tampone;

- ✓ raccolga il campione seguendo le **ISTRUZIONI** che Le forniranno in farmacia;
- ✓ consegni il campione **IN FARMACIA entro 48 ore** (conservi il tampone in frigorifero fino alla sua riconsegna);

Si ricordi di:

- ✓ fare l'esame almeno 3 giorni dopo la fine delle mestruazioni, in assenza di perdite di sangue e di dolori pelvici;
- ✓ non usare lavande, creme ed ovuli nei 3 giorni precedenti l'esame;
- ✓ non avere rapporti sessuali, né effettuare ecografie transvaginali o visite ginecologiche nei 2 giorni precedenti l'esame.

La lista delle farmacie aderenti al percorso di screening è disponibile al link tinyurl.com/FarmacieScreeningHPV o tramite il QR code riportato qui a fianco.
L'informativa sul trattamento dei dati personali è disponibile sul sito www.ausl.bologna.it nella sezione Screening e sul Fascicolo Sanitario Elettronico.

Qualora avesse recentemente subito un intervento ginecologico, fosse in gravidanza o avesse partorito da meno di 3 mesi, NON proceda con l'auto-prelievo, ma prenda un appuntamento presso un Consultorio familiare.

In caso preferisca aderire al percorso tradizionale, con esecuzione del prelievo da parte di un'ostetrica, potrà prendere un appuntamento:

- in autonomia, utilizzando il Portale Web **https://screening.ausl.bologna.it**
- scrivendo all'indirizzo mail **centro.screening@ausl.bologna.it** indicando nome, cognome, data di nascita e telefono
- chiamando il numero verde **800-314858** dal lunedì al giovedì ore 10-14; il venerdì ore 10-12.

Il risultato dell'esame Le sarà comunicato con lettera a casa e su Fascicolo Sanitario Elettronico. Qualora invece fossero necessari approfondimenti, riceverà una telefonata dal personale sanitario del Centro Screening.

Cordiali saluti.

Il Direttore Sanitario AUSL Bologna
Dott. Lorenzo Roti

Centro screening
Via Montebello, 6 - 40121 Bologna
NUMERO VERDE 800 31 48 58
centro.screening@ausl.bologna.it

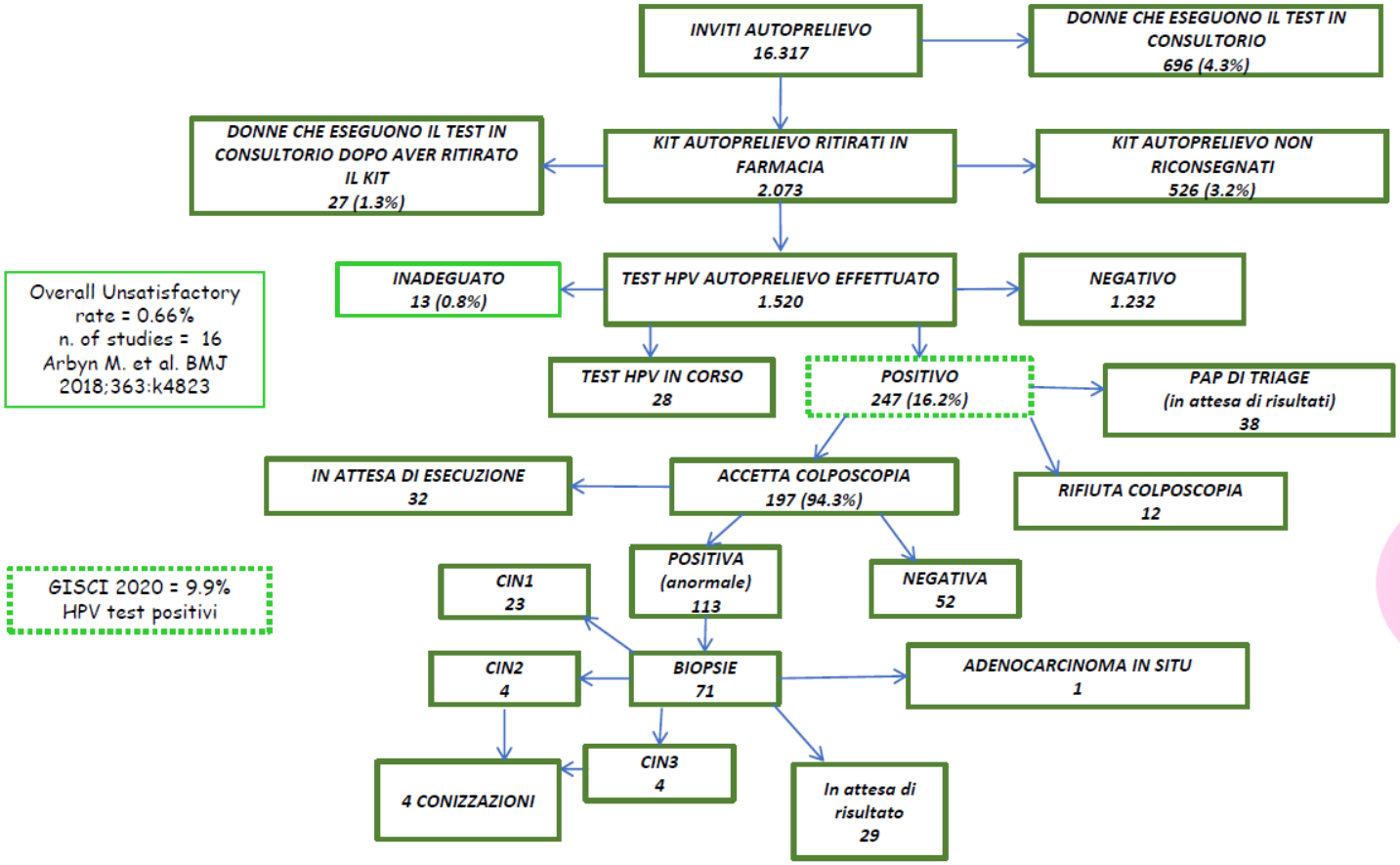
Azienda USL di Bologna
Sede Legale: Via Castiglione, 29 - 40124 Bologna
Tel. +39.051.6225111 fax +39.051.6584923
Codice fiscale e Partita Iva 02406911202

Farmacie Federfarma Bologna LloydsFarmacia

- Da novembre 2021
- Donne tra i 30 e i 64 anni di età:

bassa/nulla adesione storica allo screening → ritardo di chiamata 2020 e 2021, circa 17.000 donne

HPV AUTOPRELIEVO INVITI ED ESAMI ESEGUITI DAL 15/11/2021 AL 26/04/2022



Adesione totale delle invitate ad HPV auto-prelievo = 13.6%

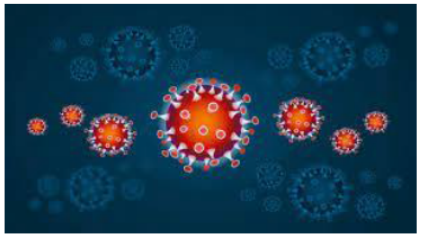
Work in progress….

Esperienza nel covid

DGR 1100 del 30.07.2019

DELIBERAZIONE DELLA GIUNTA REGIONALE n. 1100 / DGR del 30/07/2019

OGGETTO:
Modifica del Calendario Regionale Vaccinale, di cui alla D.G.R. n. 1564 del 26/08/2014, approvazione del Progetto "Utilizzo dell'auto-prelievo nel programma di screening per la prevenzione del carcinoma della cervice uterina con test per Papilloma Virus (HPV) nell'AULSS 9 Scaligera" e contestuale autorizzazione del finanziamento per la sua realizzazione.



DGR 1423 del 21.10.2020

(Codice interno: 431848)

DELIBERAZIONE DELLA GIUNTA REGIONALE n. 1423 del 21 ottobre 2020
Approvazione della rimodulazione del Progetto "Utilizzo dell'auto-prelievo nel programma di screening per la prevenzione del carcinoma della cervice uterina con test per papilloma Virus (HPV) nell'AULSS 9 Scaligera", di cui alla D.G.R. n. 1100 del 30/07/2019, e proroga delle attività progettuali.
[Sanità e igiene pubblica]

Caratteristiche del progetto

- Non disegnato come un progetto di studio
- Adattato alle esigenze del programma di screening (inviti secondo proposta del software regionale)
- Stravolto dall'emergenza COVID-19, che si è presentata anche come possibile elemento di spinta
- Rivisto radicalmente nella fase di consegna dei dispositivi (hanno seguito il modello SOF)

- Circa 10.000 donne dell'AULSS 9 Scaligera (Verona e Provincia) invitate a screening con auto-prelievo
- Offerta dello screening con auto-prelievo a popolazione generale : donne mai invitate, aderenti, non aderenti
- Bacino territoriale ampio con diversità di estensione, adesione, modalità di consegna del SOF
- Grande motivazione da parte dei referenti locali del progetto (pure in periodo COVID-19!)
- Periodo spedizione inviti : 10 gennaio 2021- 31 luglio 2021

Alcuni dati

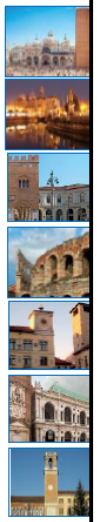
	Test Eseguito	test non eseguito per PAP test recente	test non eseguito-motivo non specificato	test non eseguito per gravidanza o motivi clinici	dato non disponibile	Invito inesitato	TOTALE	adesione corretta (%)	inesitati (%)
Distretto 1	1145	202	48	35	3999	593	6022	21,9	9,8%
Distretto 3	420	75	15	13	497	21	1041	44,4	2,0%
Distretto 4	834	177	59	17	1487	201	2775	34,8	7,2%
ULSS 9	**2399**	**454**	**122**	**65**	**5983**	**815**	**9838**	**28,0**	**8,3%**

Inesitati 2019
ULSS 9: 3%

Adesione corretta 2019-
Distretto 1: 39,5%
Distretto 3: 64,6%
Distretto 4: 43,4%
ULSS 9 tot: 43,9%

Per ULSS 9:
Suddivisione inviti:
45% primi esami, (o non invitate, % rilevante per distretto 3, o non aderenti)
55% esami successivi.

adesione primi esami (sia non aderenti, che non invitate):16%,
adesione esami successivi: 40%



AZIENDA ZERO

REGIONE DEL VENETO
AZIENDA ZERO

… da Eurogin 2022

- Molti paesi europei si stanno preparando ad introdurre il self sampling nei loro programmi di screening organizzato
- La maggior parte di questi interventi è offerto alle non aderenti
- Olanda e Svezia partiti con self-sampling come modalità di prelievo per le donne invitate a screening HPV

Olanda: Invitation letter ‘ Personalized sampling methods’

….*’if you don’t want to partecipate because you feel unconfortable about a smear test, then you can do a self-test at home.*

The self test can be requested via …..»

Domande su possibili applicazioni nel nostro contesto

- E’ capace di raggiungere i gruppi più svantaggiati ?
- Rimane il problema di come trasmettere il kit: troppi kit inutilizzati!
- Può esserci un’alternativa al consegna diretta, alla spedizione?
- Ruolo dei MMG
- Ruolo delle Farmacie (vedi screening CRC)
- Importanza della informazione
- Manca ancora una valutazione economica…

Necessità in Italia

- condurre un HTA specifico corroborato da studi pilota.
- Approccio stratificato anche nelle modalità di coinvolgimento delle donne
- Lo screening cervicale può divenire personalizzato anche nelle modalità di esecuzione del test

Triage

- For this *Handbook*, the Working Group updated a previous meta-analysis on the accuracy of six tests or combinations of tests used to triage hrHPV-positive women identified at screening for the detection of underlying cervical precancer (HAS, 2019). Literature retrieval was extended up to 31 January 2020.

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Test di triage valutati

1) cytology at a threshold of ASC-US+
2) genotyping for HPV16/18
3) p16/Ki-67 immunocytochemistry (dual staining),
4) VIA,
5) combined testing with HPV16/18 genotyping and cytology at a threshold of ASC-US+ (in which HPV16/18-positive women are referred directly for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology)
6) combined testing with HPV16/18 genotyping and VIA

- **IARC Handbook Vol 18**

- p16/Ki-67 dual staining was more sensitive for detection of underlying CIN3+ (85%), with an associated specificity for < CIN2 of 69%.
- The combinations of HPV16/18 genotyping and another triage test (cytology at a threshold of ASC-US+ or VIA) reached a similarly high level of sensitivity for CIN2+ and CIN3+ as dual staining. However, the cross-sectional specificity of these combinations for CIN2+ was lower (< 60% for < CIN2).

- **IARC Handbook Vol 18:**

- The acceptability of any triage approach is ultimately context-specific and depends on a range of factors, including the underlying risk of CIN3+ and invasive cervical cancer in a population, the available technological options for triage testing, the cost–effectiveness, and the acceptability of the testing process to women.

- **IARC Handbook Vol 18:**

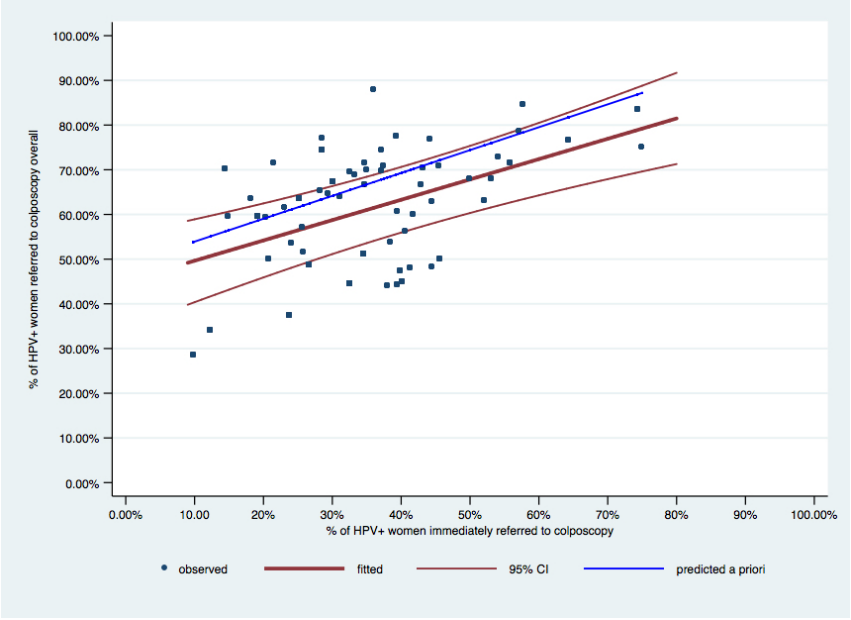
- Un test di triage va valutato longitudinalmente sia per quanto concerne la sua accuratezza sia per quanto riguarda il consumo di risorse

Basandosi su i dati dei programmi Italiani Ronco et al trovarono che

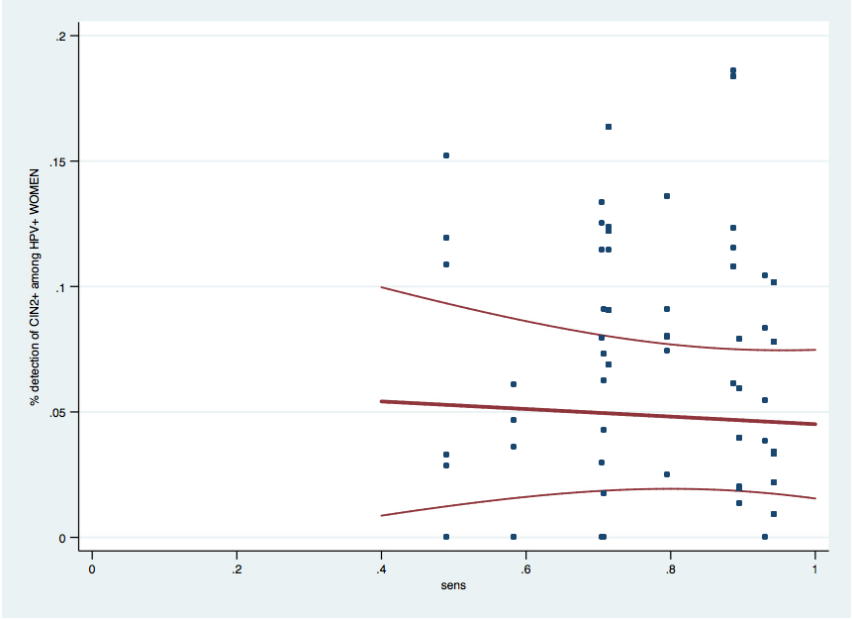
A 10% increase in cytology triage (ex. 30% -> 40%) implies only a 4.5% increase in overall referral HPV+ women.

Overall CIN2+ detection is almost independent from CIN2+ from triage positivity

Overall colposcopy referral (in HPV+) by triage positivity

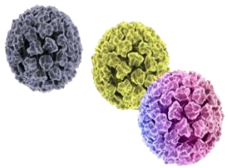


CIN2+ DR (in HPV+) by triage positivity



Ronco et al, Eur J Cancer 2016

HPV GENOTYPING : RISK BANDS FOR CIN3 +

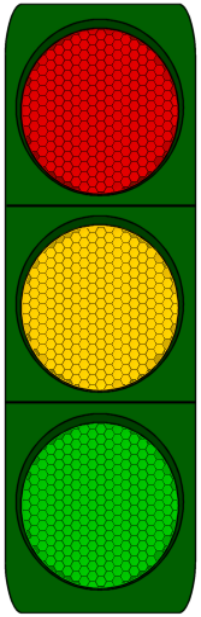


NILM – Immediate Risk for ≥CIN3*
Stratified by genotype (hierarchical)

Genotype	≥CIN3
Any	3.1%
16	8.1%
31	7.5%
18	2.9%
33/58	2.8%
52	1.7%
45	0.8%

Genotype	≥CIN3
35/39/68	0.7%
51	1.1%
56/59/66	0.3%
Neg	0.2%

*women ≥25 yrs
Stoler et al. Gyn Oncol, 2019 153:26-33.



- ✓ ***Risk band 1***
  HPV 16, 31, 18
- ✓ ***Risk band 2***
  HPV 33/58 52 45
- ✓ ***Risk band 3***
  HPV 35/39/68 51 56/59/66

(Stoler et al., Gyn . Onc. 2019, 153:26)

Karolinska Protocol (Dillner Eurogin 2022)

According to new clinical guidelines, follow-up of HPV positivity will be determined by age and type

- 5 year screening intervals 23-49 or 7 years 50-70 after HPV negativity
- HPV 16,18,45 (high oncogenicity, vaccine types)- reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - Cytology negative to repeat testing after 18 months
- HPV 31,33,52,58 (medium oncogenicity, vaccine types)-reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - Cytology negative
    - Age <28 new sample after 5 years
    - Age >28 – new sample after 3 years
- HPV 35,39,51,56,66,68 (low oncogenicity, non vaccine types)- reflex testing with cytology from age 33
  - Cytology positive to colposcopy
  - Cytology negative to repeat testing after 5 years

Stratificazione del rischio dopo l’esame

- Genotipizzare può portare a una stratificazione del rischio basata sul risultato del test

- Può portare a maggior efficienza (valutazione contesto specifica)
- Può portare a un alleggerimento del carico dello screening per la donna
- Complessità organizzativa e comunicativa

Quale screening nelle vaccinate

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

- Handbook 18 IARC

Perché negli USA non si cambia politica di screening nelle vaccinate

to guide management. This decision was influenced by the low coverage of HPV vaccination in young women, as well as the lack of vaccination registries that would enable clinicians to link primary care records with vaccination histories. Similarly, the 2020 ACS guideline for cervical cancer screening issued recommendations that were independent of vaccination status (Fontham et al., 2020).

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Uniche eccezioni

- Canada , inizio screening spostato a 25 aa (Popadiuk CMAJ 2019) per alto livello di copertura vaccinazione in giovani età

- Irlanda test aggiuntivo per le non vaccinate a 28 anni (HIQA)

ISPRO
Istituto per lo studio, la prevenzione e la rete oncologica

SST Servizio Sanitario della Toscana

Progetto "*Integrazione dei programmi di vaccinazione e di screening per la prevenzione del cervicocarcinoma: interventi per ridefinire e implementare nuovi protocolli di screening per le donne vaccinate prima dell'età d'inizio dello screening*"

Versione: n. 2 del 06.08.2018
Promotore dello studio: Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO)
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Progetto CCM multicentrico nazionale
Coinvolgimento Toscana, Piemonte , Basilicata e Liguria Veneto e Emilia -Romagna

Protocollo dello studio

- Linkare le invitate a 25 anni con archivi di screening
- Invitare (con firma del consenso informato) le donne di 25 anni che hanno avuto l'opportunità di essere vaccinate a 16 anni a sottoporsi a test HPV con eventuale genotipizzazione se positive
- Costruire una coorte di donne HPV negative vaccinate da invitare 5 anni dopo

Indicazioni studio Consensus

1) Adottare politiche attive di recupero per le donne non vaccinate e non aderenti allo screening.
2) Valutare a livello di ogni regione la qualità dell'incrocio con l'archivio vaccinale e i possibili problemi connessi.
3) Confermare innalzamento a 30 anni per l'invito allo screening delle vaccinate a 12 anni, così come già raccomandato dalla conferenza di Consenso del 2015. Questa indicazione trova conferma anche dalla revisione di letteratura sugli studi di costo-efficacia.
4) Proseguire nell'arruolamento della coorte vaccinata e HPV negativa a 25 anni su cui valutare l'allungamento dell'intervallo di screening dopo HPV negativo.
5) Valutare attentamente la possibilità di estendere a tutte le donne giovani non vaccinate il protocollo di screening utilizzato nel presente progetto ovverosia test HPV con triage citologico; in caso di negatività del Pap test di triage ripetizione del Pap test dopo tre anni.
6) Valutare con ricerche ad hoc il tipo migliore di test HPV da utilizzare nelle vaccinate (per es. utilizzare test HPV che permettono qualche stratificazione dei tipi di HPV) e i cut off da utilizzare nella citologia di triage.

Quale intervallo per le vaccinate

Modelling studies have shown that the combination of vaccination and screening is cost-effective and is good value for money, with screening starting later in life – for example at age 30 years for the bivalent or quadrivalent vaccines and at age 35 years for the nonavalent vaccine – and with longer screening intervals (Kim et al., 2017; Pedersen et al., 2018). A related point is that

Pedersen et al Eur J cancer 2018

- The most cost-effective screening strategy for 9vHPV- and 2/4vHPV-vaccinated women involved HPV testing once and twice per lifetime, respectively.

- ➔ In Italia in genere non ci si muove sul criterio della massima CE. Si accettano anche livelli di minore CE se garantiscono sensibili guadagni di salute.

Cambiamenti delle performance far primo e secondo round HPV anno 2019– Italia

- DR CIN2+ primo round HPV = 6,0/1000
- DR CIN2+ al secondo round = 2,5/1000

- VPP primo round = 13,9%
- VPP secondo round =7,9 %

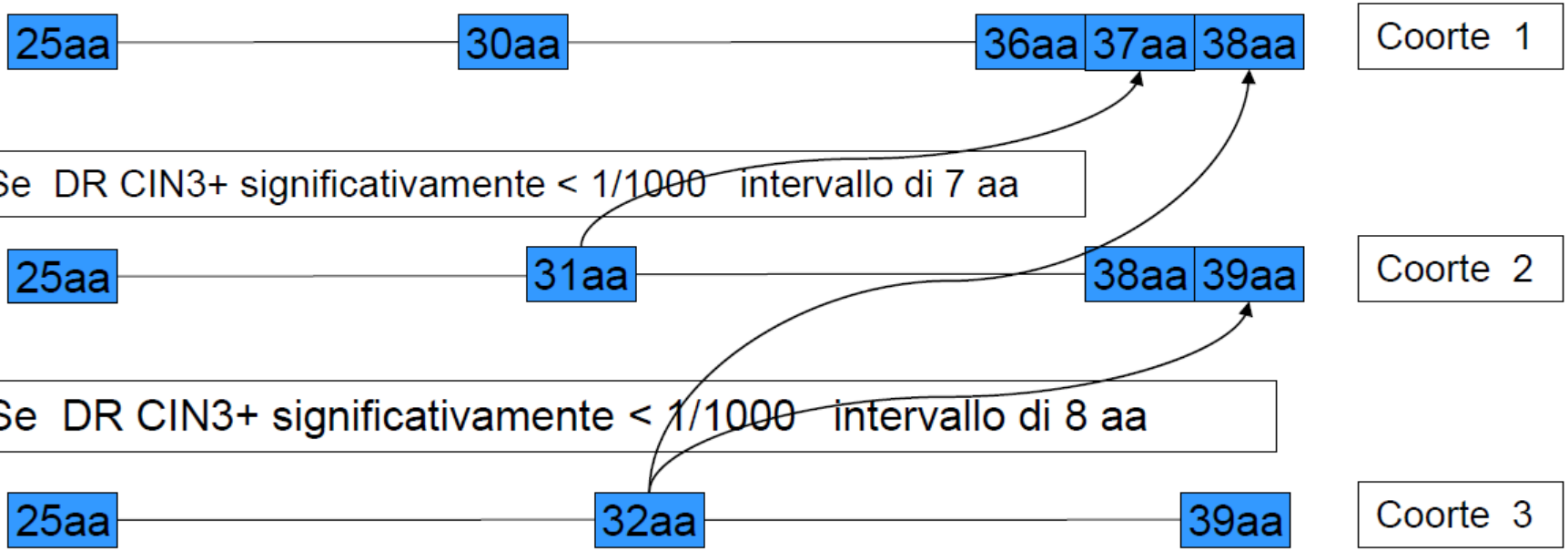
Screenate con HPV

Screenate con HPV e negative round precedente.

Calcolo DR CIN3+

donne vaccinate a 16 aa

Se DR CIN3+ significativamente < 1/1000 intervallo di 6 aa



Possibile anche confronto con coorte 00 di donne non vaccinate screenate con HPV a 25 aa

- Necessità di avere un monitoraggio tempestivo e una valutazione continua dei cambiamenti che avvengono.

Consensus Study: Vaccinazione e screening nella popolazione delle donne di 25-26 aa dopo il primo invito Vaccinazione a 16 anni

	vaccinate	Non Vaccinate
Screenate	23.6%	18.0%
Non Screenate	23.3%	35.2%

Visioli et al, Submitted.

grazie per la pazienza

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