Autoprelievo

Livia Giordano – CPO Piemonte – Torino

- Che cos'è?
- Razionale e scopi
- Tipi di dispositivi
- Efficacia su incremento di adesione
  - Per le non aderenti
  - Per lo screening routinario
- Sensibilità/specificità
- Gradimento delle donne
- Costi
- Futuri sviluppi

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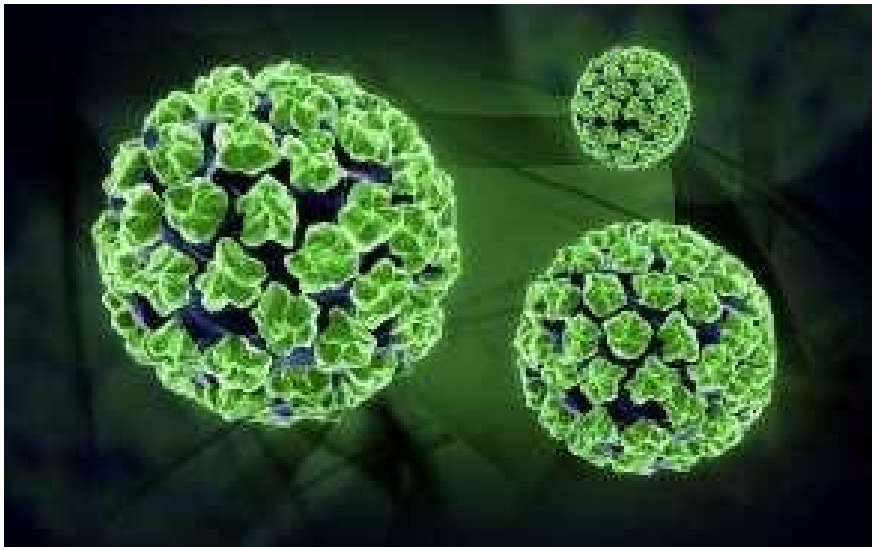
Che cos'è il self sampling?

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.



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Razionale

Il passaggio al test HPV come test di screening primario per il carcinoma della cervice uterina, in donne di età uguale o maggiore a 30 anni, offre la possibilità di effettuare la raccolta del materiale cervicale con sistemi di auto-prelievo.

High risk HPV testing can be performed on self-collected cervicovaginal samples because the virus spreads from the cervix down into the vagina and intact cervical cells are not needed to demonstrate the presence of the virus.

SCOPI

Questa modalità di raccolta può favorire, infatti, la partecipazione delle donne che non rispondono all'invito tradizionale a causa di **ostacoli organizzativi** per recarsi in ambulatorio per il test HPV, quali la mancanza di tempo o la scarsa flessibilità degli orari ambulatoriali, oppure per **motivazioni legate alla sfera personale**, quali per esempio l'imbarazzo o il fastidio associati alla modalità tradizionale di prelievo.

L'auto-prelievo potrebbe, inoltre, costituire una modalità alternativa rivolta a tutta la popolazione, anche quella già aderente, 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) oppure qualora, **per carenza di personale prelevatore 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.

punto di vista delle utenti, il test HPV con auto-prelievo presenta diversi vantaggi, tra i quali emergono:

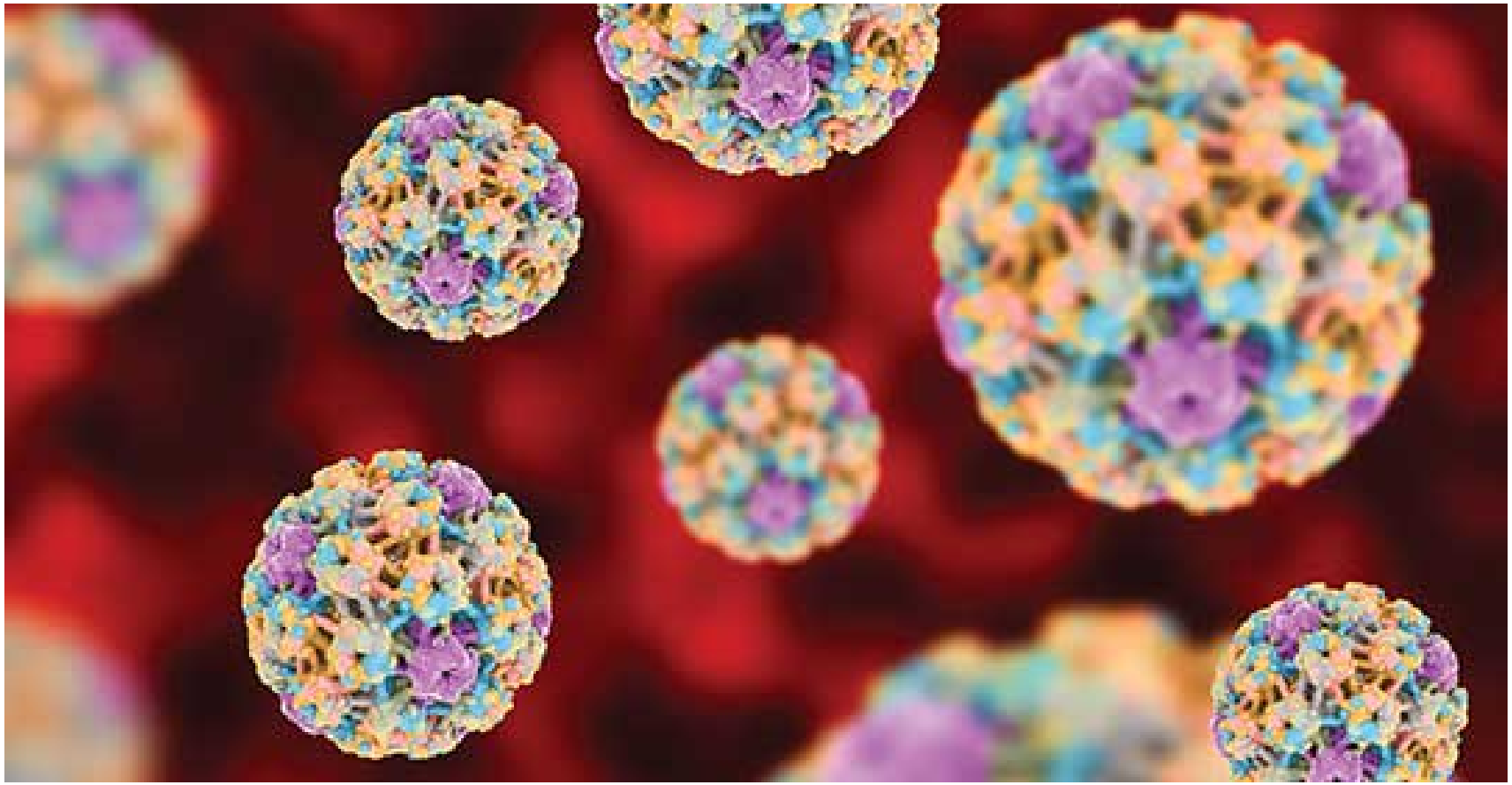
- la possibilità di eseguire il prelievo nella propria abitazione nel giorno e orario preferito, evitando spostamenti e senza dover richiedere permessi lavorativi;
- la rimozione dell'eventuale imbarazzo associato all'esame di tipo ginecologico;
- la riferita riduzione del dolore rispetto al test effettuato da personale sanitario.

Dal punto di vista dell'organizzazione sanitaria, il test HPV con auto-prelievo rappresenta:

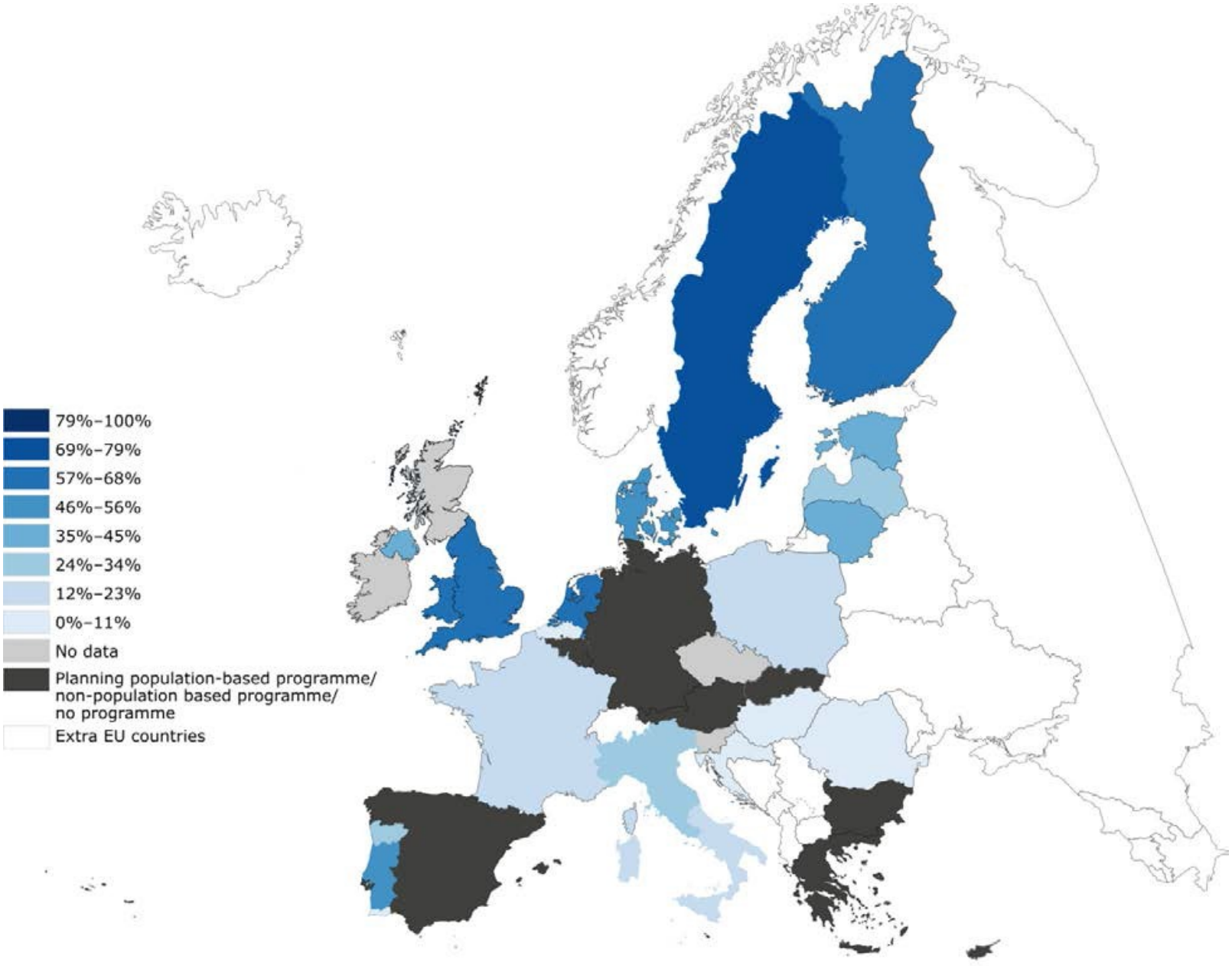
- uno strumento per incrementare l'adesione di particolari gruppi di donne (ad es: le donne non aderenti ai programmi organizzati di screening);

- un'opzione per incrementare l'offerta del test, soprattutto se ostacolata da aspetti organizzativi quali la ridotta disponibilità di personale prelevatore.

Quante donne sono coperte da un test di screening????



Cervical cancer screening programmes in the EU: examination coverage by programme specific age-range (table 4.9, all ages)*



*The estimates do not take into account opportunistic screening and only include women invited and screened

Table 4.11. Cervical cancer screening programmes in the EU

Participation rate (%)

Numerator (N) = Individuals screened of invited in the year

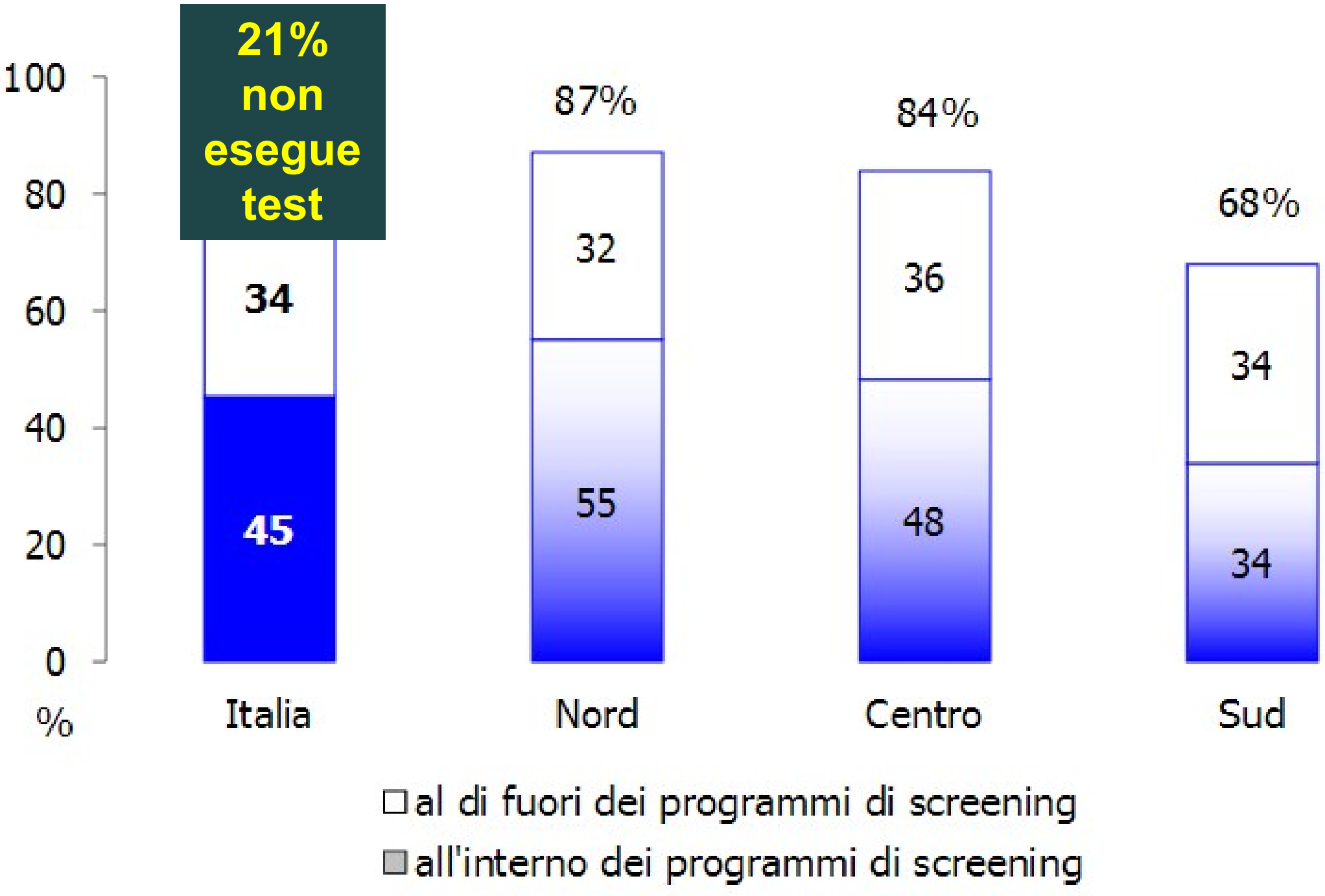
Denominator (D) = Individuals personally invited in the year

	30-59 years			All ages			Notes
	N	D	%	N	D	%	
Belgium Flemish region	29,752	257,259	11.6%	41,805	365,843	11.4%	
Croatia				42,694	414,018	10.3%	
Denmark	168,973	249,531	67.7%	232,674	361,284	64.4%	
Estonia	24,423	42,442	57.5%	24,423	42,442	57.5%	
Finland	135,213	205,531	65.8%	164,878	244,587	67.4%	
France 13 depts.	69,844	319,635	21.9%	92,921	439,887	21.1%	
Hungary	33,154	110,100	30.1%	43,442	146,570	29.6%	
Italy	1,187,186	2,840,670	41.8%	1,533,615	3,693,399	41.5%	
Italy North	664,354	1,288,734	51.6%	836,571	1,645,064	50.9%	
Italy Centre	281,720	704,228	40.0%	362,365	907,714	39.9%	
Italy South	241,112	847,708	28.4%	334,679	1,140,621	29.3%	
Latvia	49,328	134,375	36.7%	70,163	199,747	35.1%	
Lithuania	77,666	161,170	48.2%	91,905	191,912	47.9%	
Netherlands	442,080	670,275	66.0%	504,338	760,228	66.3%	
Poland				586,291	3,220,572	18.2%	
Romania				103,886	733,010	14.2%	
Sweden	373,422	694,844	53.7%	508,670	964,664	52.7%	
UK England	1,970,233	3,299,317	59.7%	2,491,095	4,244,755	58.7%	
UK Northern Ireland	48,826	100,588	48.5%	61,102	126,724	[illegible]	
Europe	**4,610,100**	**9,085,737**	**50.7%**	**6,593,902**	**16,149,642**	**40.8%**	*1*

Notes

1) If programme covers only some regions, just these areas are considered.

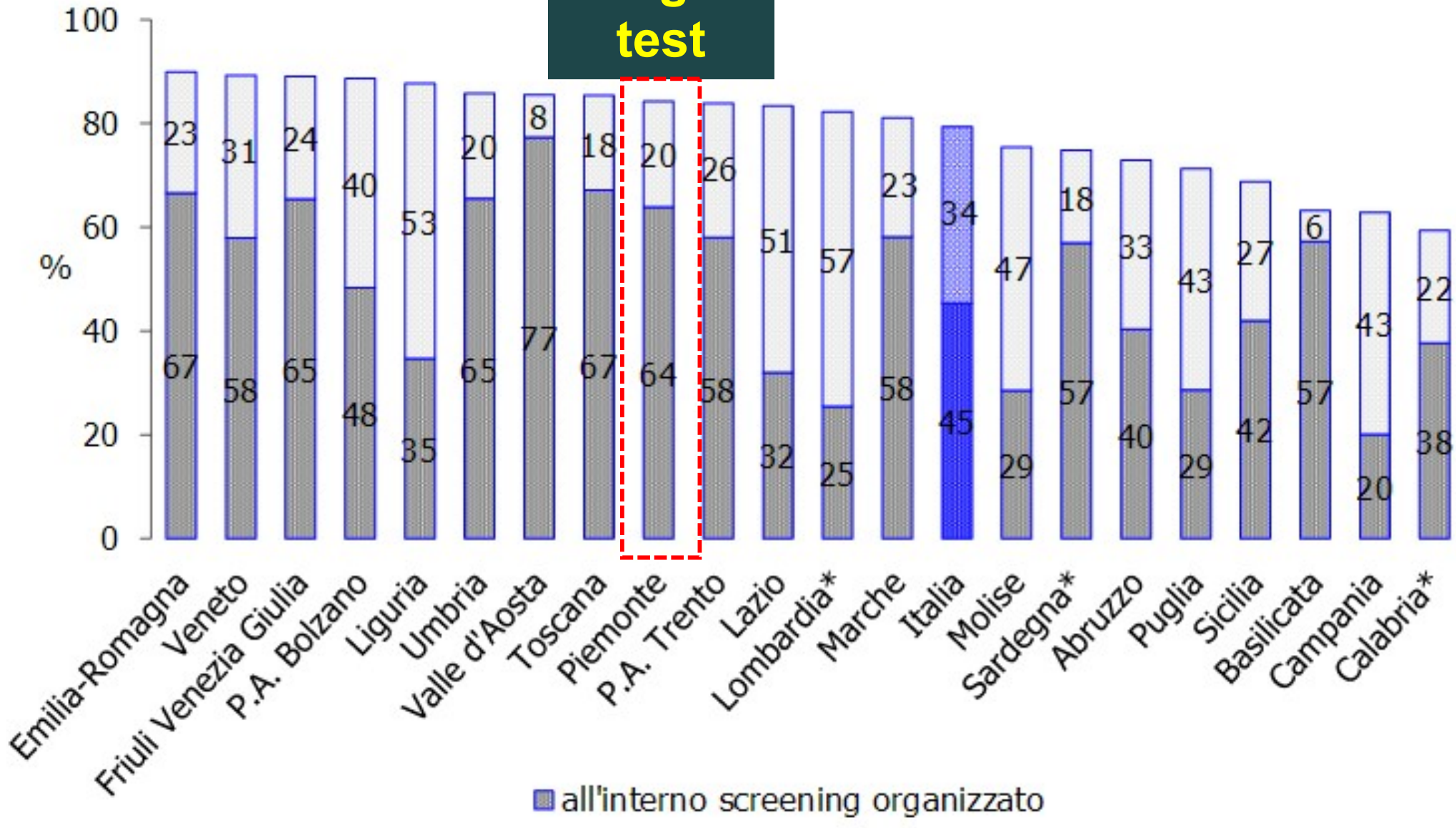
Copertura con test preventivo entro i tempi raccomandati. Donne 25-64enni. Passi 2014-2017



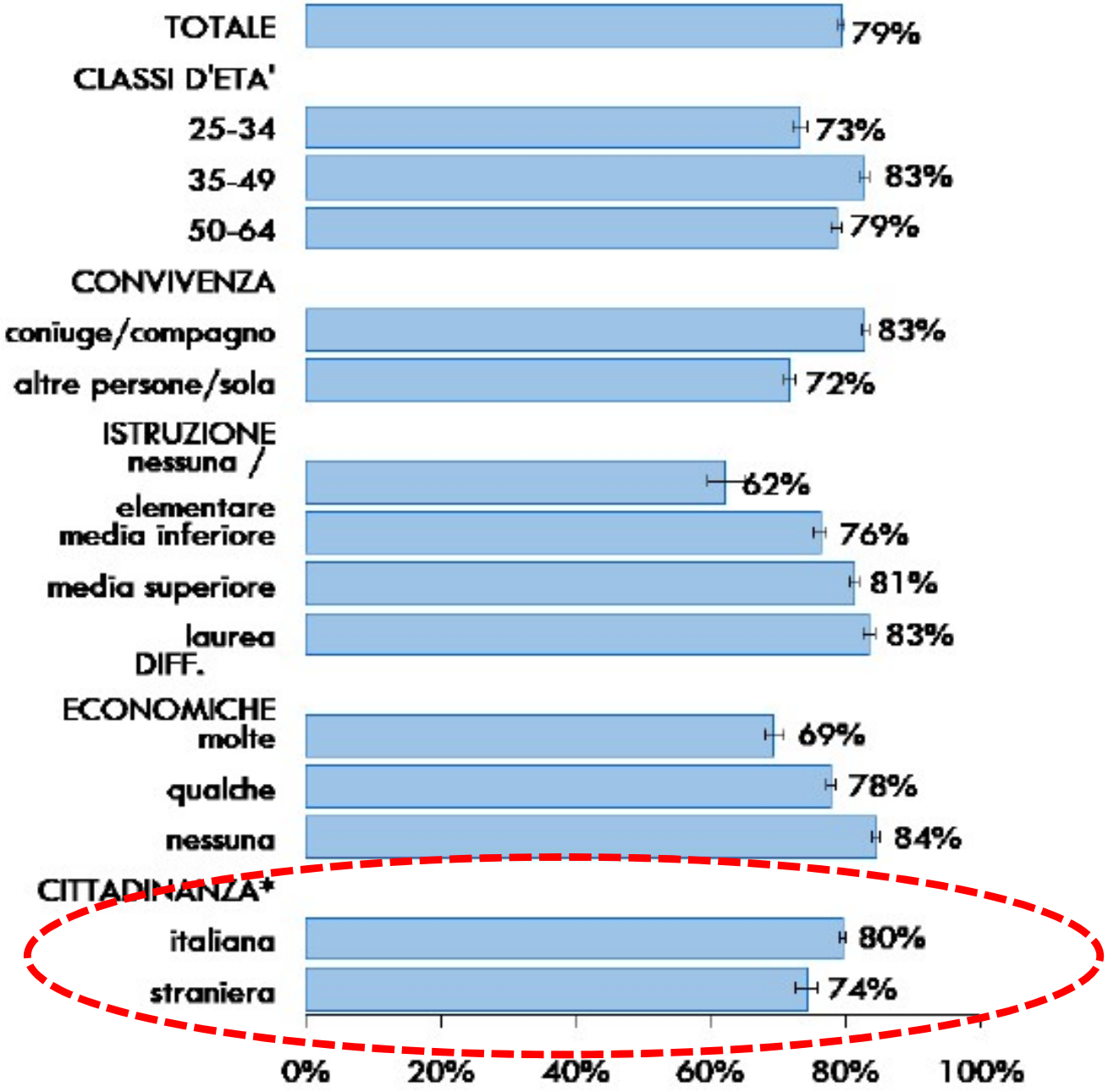
Copertura entro i tempi raccomandati, per Regione. Donne 25- 64enni. Passi 2014-2017

16% non esegue test

** Regioni che non hanno aderito con un campi … to della Lombardia si riferisce al periodo 2014-2016.*



Copertura al test preventivo entro i tempi raccomandati per caratteristiche socio-demografiche - Donne 25-64enni (%) Passi 2014-2017



Recupero donne non aderenti (1992-2018)

Lettera di sollecito postale

Adesione cumulativa Regione Piemonte 1992- 2018: **48.0%**

Donne aderenti al primo invito: 45.4%

Incremento dovuto al sollecito: **2.6%**

Donne sollecitate nel periodo: 16.2% (0,6%-47,5%)

Donne aderenti tra le sollecitate: **16.1%**

The reasons that women do not attend for screening are complex, but include:

- Emotional/personal barriers, e.g. embarrassment, fear of discomfort or pain, fear of the result, preference for a female nurse/doctor.
- Practical and organisational barriers, e.g. travel difficulties, childcare issues, work commitments.
- Knowledge/awareness barriers, e.g. lack of understanding about the causes of cervical cancer and the purpose of screening.
- Demographic factors, e.g. being from a specific ethnic minority group or a deprived background.

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- Esistono in commercio diversi sistemi di autoprelievo che differiscono per il mezzo di trasporto (liquido o secco), per la forma del dispositivo, per la modalità di prelievo (lavaggio, spazzola o tampone).

Devices for sample collection come in four basic types:

- *1. Brush (spazzola)*
- *2. Swab (tampone)*
- *3. Lavage (lavaggio)*
- *4. Tampon. (assorbenti)*

Designs vary from the simple 'stick-style' cytobrush or cervical swab (a stick with a specially designed sampling brush or swab head on one end), to more complicated devices comprised of a plunger-based 'applicator' (insertion device) with a brush, swab or lavage of liquid inside.

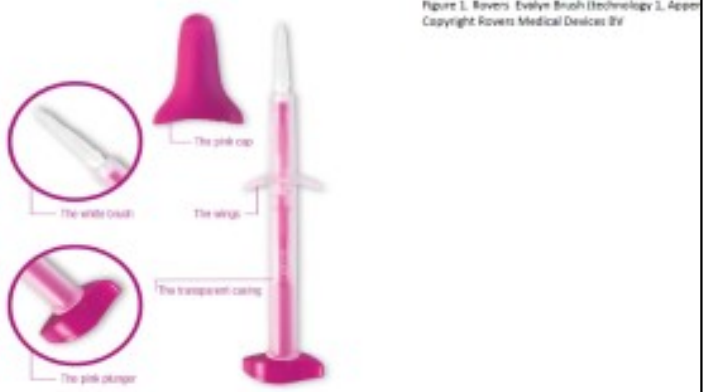

Figure 1. Rovers Evalve Brush (technology 1, Appen
Copyright Rovers Medical Devices BV

ure 3. HerSwab (technology 3, Appendix 2). Copyright Eve Medical Inc

gure 2. Delphi Screener (technology 2, Appendix 2).
Copyright Delphi Bioscience BV

Figure 5. Just For Me (technologies 5 [kit] and 12 [brush component], Appendix 2). Copyright Preventive Oncology International Inc

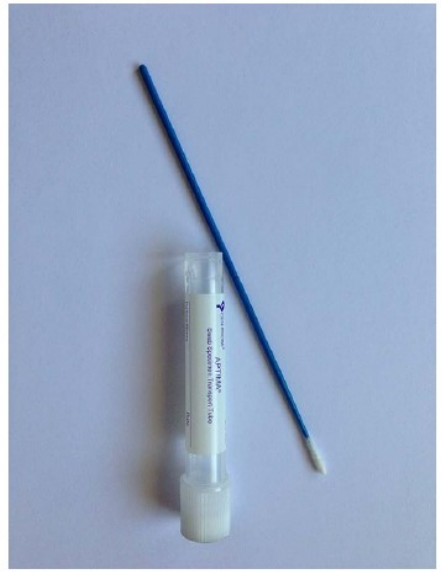

Figure 7. UDoHPVTest (technology 7, Appendix 2). Copyright UDoTest

Transportation

- The sample can be transported in a ‘dry’ state or in a ‘liquid’ state.
- Some transportation containers are generic in type, while others are specially designed to fit directly with laboratory equipment (to reduce handling and improve workflow).

SCELTA DEL SISTEMA DI TRASPORTO

La scelta è stata quella del Qvintip (Aprovix AB, Uppsala, Svezia) che utilizza un "bastoncino" che si trasporta in modo asciutto **è stabile per 4 (quattro) settimane fino a temperatura di 30°C, ed addirittura per 2 (due) settimane con una temperatura esterna di 40°C**;
tale kit è stato studiato presso il Department of Obstretics and Gynecology, Uppsala University Hospital (Professor Matts Olofsson, Uppsala University Hospital; 75185 Uppsala, Svezia), ed è stato dimostrato che tutti i campioni raccolti in auto-prelievo contenevano **una quantità di HPV-DNA >= 2000 copie**;
i test molecolari di Laboratorio necessitano di **500-770 copie di HPV-DNA.**

Table 2 | Variation in relative sensitivity and specificity of high-risk human papillomavirus (hrHPV) assays on self samples versus clinician samples, by self sampling device and storage medium

Covariate	No of studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)
Self sampling device			
hrHPV assay based on signal amplification			
Brush	13	0.84 (0.78 to 0.90)*	0.93 (0.91 to 0.96)*
Swab	7	0.85 (0.78 to 0.91)*	0.93 (0.90 to 0.95)*
Lavage†	2	0.84 (0.69 to 1.04)	0.74 (0.55 to 0.98)*
Tampon	1	0.86 (0.78 to 0.96)*	1.02 (1.00 to 1.03)
hrHPV assay based on polymerase chain reaction			
Brush	12	0.98 (0.95 to 1.02)	0.95 (0.91 to 0.99)*
Swab	4	0.98 (0.93 to 1.03)	0.93 (0.89 to 0.98)*
Lavage†	4	0.95 (0.87 to 1.04)	1.09 (0.91 to 1.30)
Tampon	0	NA	NA
Storage medium			
hrHPV assay based on signal amplification			
Cell preserving†	3	0.84 (0.78 to 0.90)*	0.93 (0.91 to 0.96)*
Virological†	15	0.86 (0.81 to 0.91)*	0.95 (0.92 to 0.98)*
Dry samples	0	NA	NA
Other	1	0.90 (0.71 to 1.13)	0.92 (0.71 to 1.21)
hrHPV assay based on polymerase chain reaction			
Cell preserving	6	1.00 (0.96 to 1.04)	0.92 (0.88 to 0.97)*
Virological†	3	0.97 (0.91 to 1.04)	0.94 (0.89 to 0.99)*
Dry samples†	7	0.96 (0.90 to 1.02)	1.01 (0.94 to 1.10)
Other	1	0.95 (0.80 to 1.13)	1.05 (0.69 to 1.58)

Relative values were computed by using a bivariate normal model, separating studies using a hrHPV assay based on signal amplification or a hrHPV assay based on polymerase chain reaction. Pooling was performed using a bivariate normal model.
NA=not available.
*Relative accuracy statistically significantly different from unity.
†When the bivariate model containing covariates did not fit or when the number of studies <4, a separate pooling of the relative sensitivity and relative specificity using a model for ratios of proportions was run.

M. Arbyn, BMJ, 2018

l'abbinamento tra il dispositivo ed il test è decisivo nella valutazione dell'adozione dell'autoprelievo

Il self sampling

Il self sampling non può essere utilizzato per fare il Pap test, per cui in caso di test HPV positivo la donna viene invitata a fare il Pap test di triage o direttamente la colposcopia, nel corso della quale viene contestualmente effettuato il prelievo per il Pap test.

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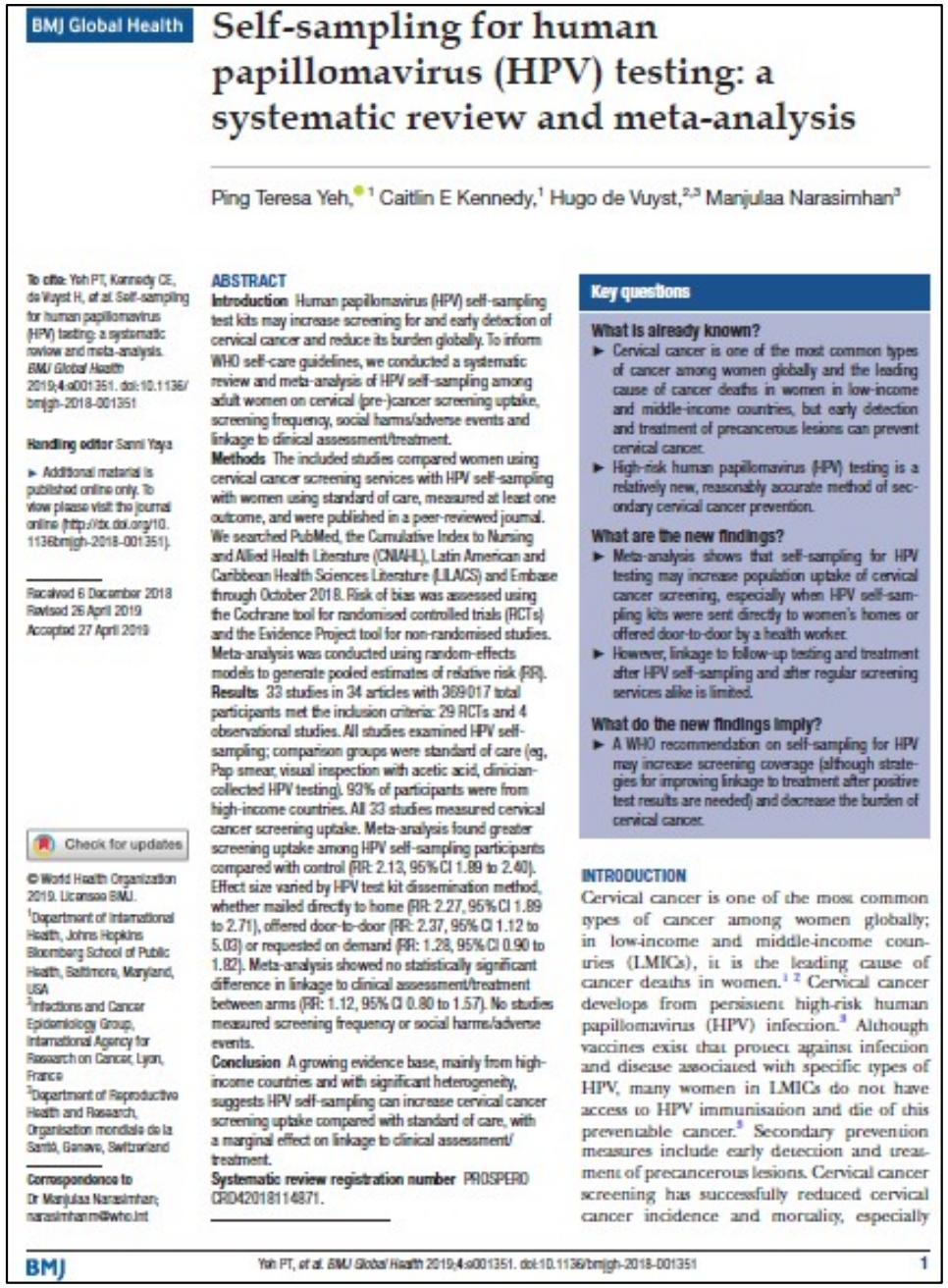

BMJ Global Health

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

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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 (1)

✓ 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 (2)

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	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

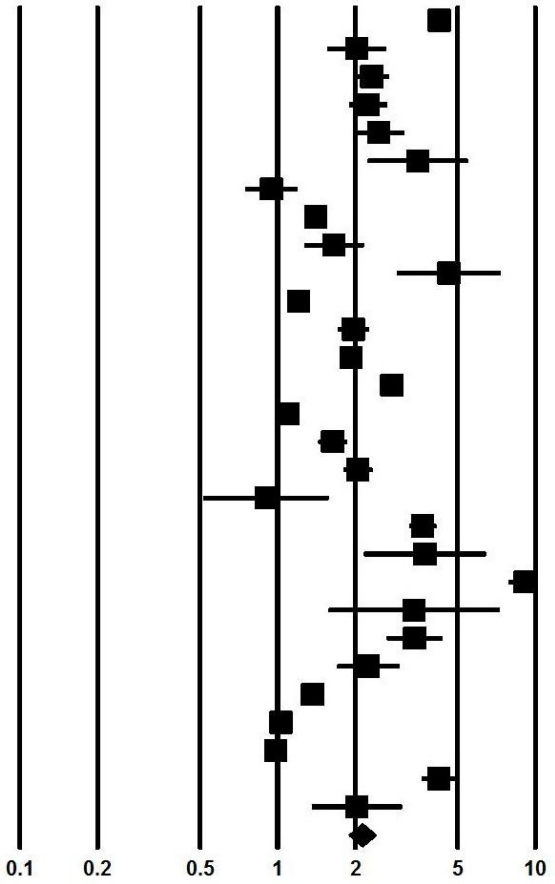


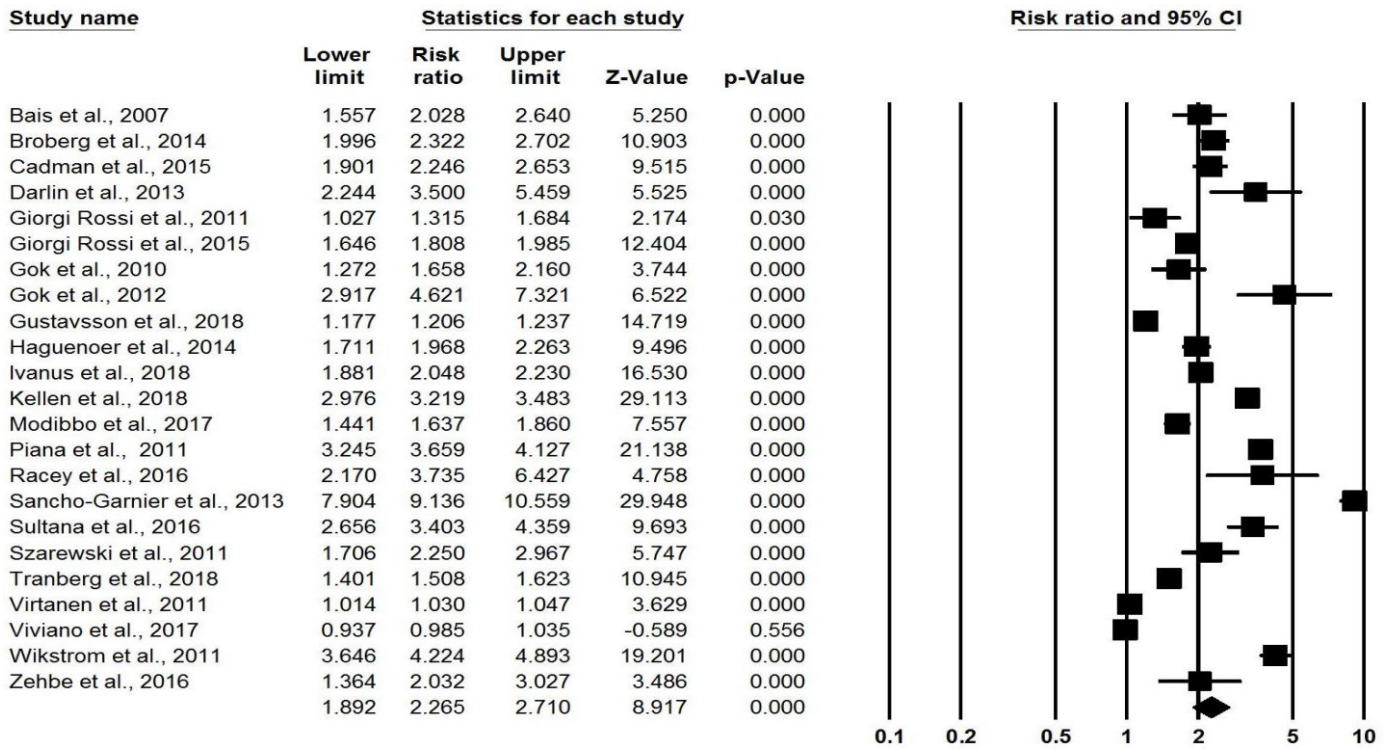
Figure 2. Meta-analysis showing relative risk of uptake of cervical cancer screening, overall.

Yeh P.T. *et al* 2019

Results (3)

✓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 3. Meta-analysis showing relative risk of uptake of cervical cancer screening, pt-out (self-sampling kit directly mailed to home) versus control.



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Giorgi Rossi et al., 2011	1.027	1.315	1.684	2.174	0.030
Giorgi Rossi et al., 2015	1.646	1.808	1.985	12.404	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	1.881	2.048	2.230	16.530	0.000
Kellen et al., 2018	2.976	3.219	3.483	29.113	0.000
Modibbo et al., 2017	1.441	1.637	1.860	7.557	0.000
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
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	1.401	1.508	1.623	10.945	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
	1.892	2.265	2.710	8.917	0.000

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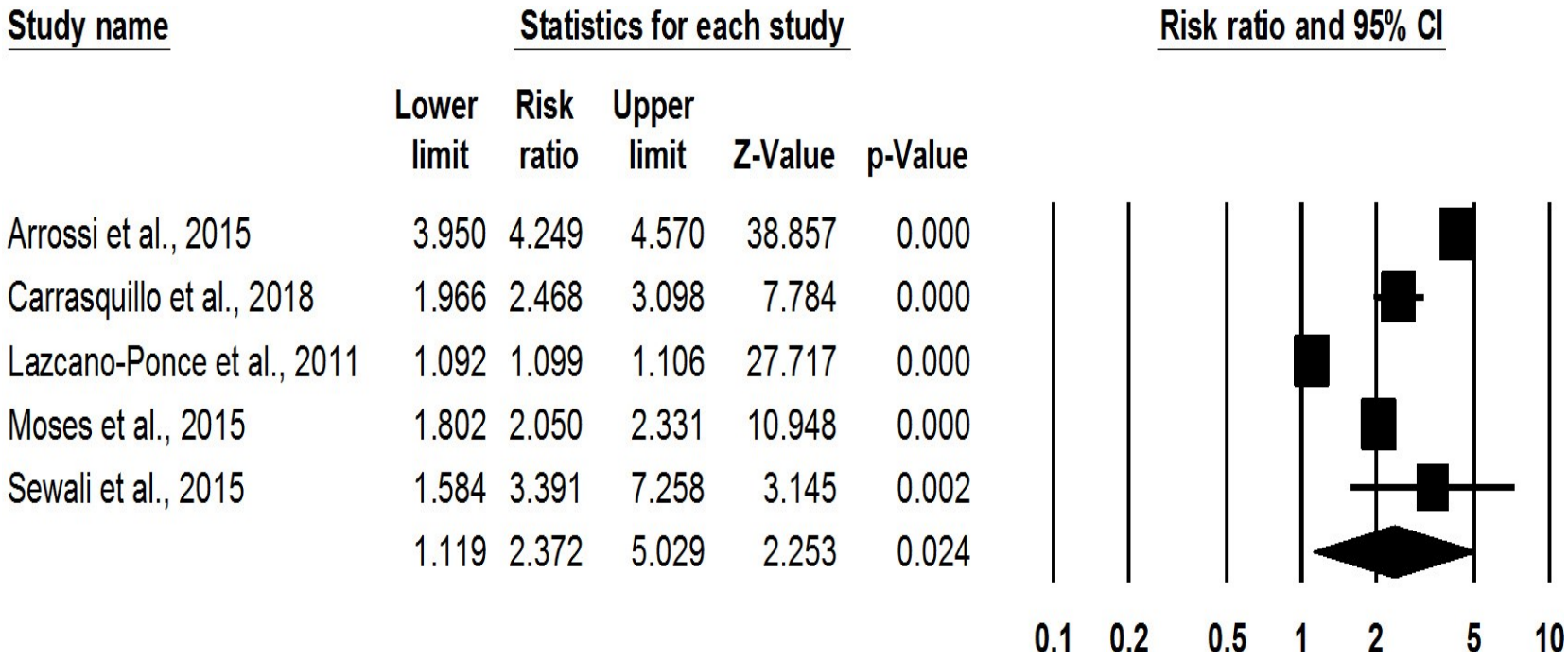
Results (4)

✓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 4. Meta-analysis showing relative risk of uptake of cervical cancer screening, opt-out (self-sampling kit offered door-to-door by health worker) versus control.



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Results (5)

✓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	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

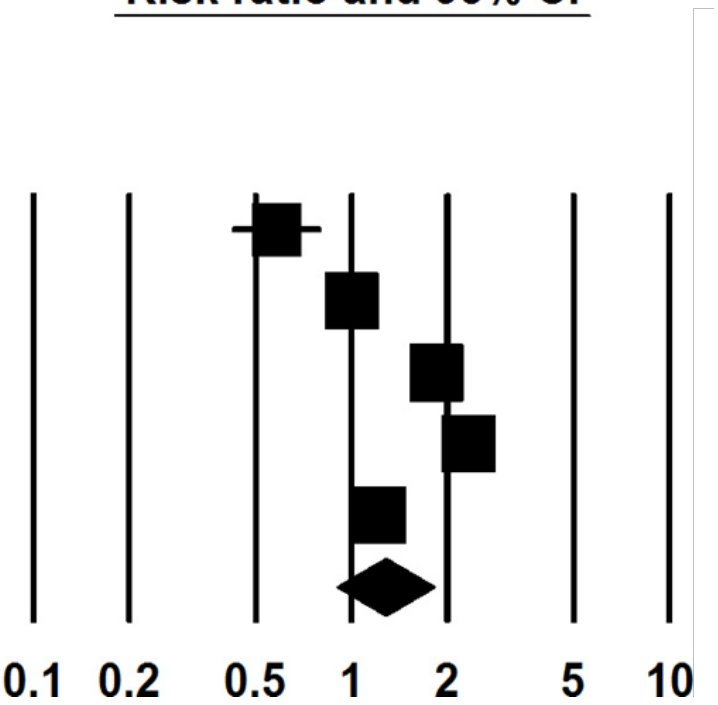

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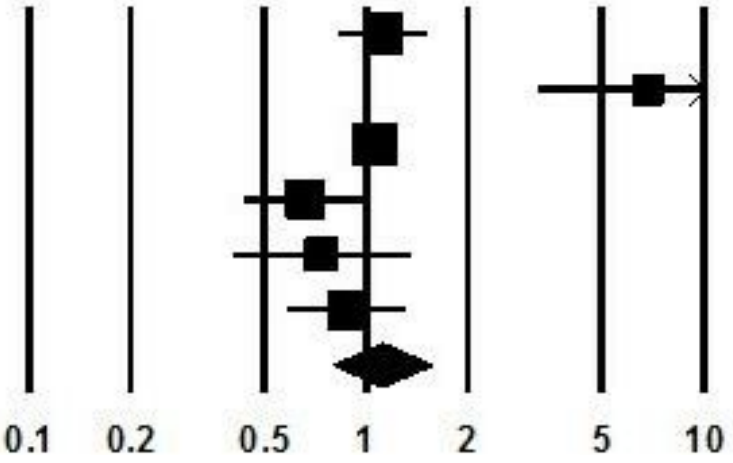
Figure 6. Meta-analysis showing relative risk of linkage to clinical assessment or treatment, self-sampling versus control.

Study name	Lower limit	Risk ratio	Upper limit	Z-Value	p-Value
Cadman et al., 2015	0.831	1.118	1.504	0.735	0.462
Giorgi Rossi et al., 2015	3.245	6.823	14.347	5.064	0.000
Gustavsson et al., 2018	1.004	1.068	1.136	2.071	0.038
Moses et al., 2015	0.434	0.658	0.997	-1.976	0.048
Sancho-Garnier et al., 2013	0.405	0.738	1.346	-0.992	0.321
Viviano et al., 2017	0.589	0.880	1.314	-0.625	0.532
	0.797	1.118	1.569	0.644	0.519

Statistics for each study

Risk ratio and 95% CI



✓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.

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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.

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

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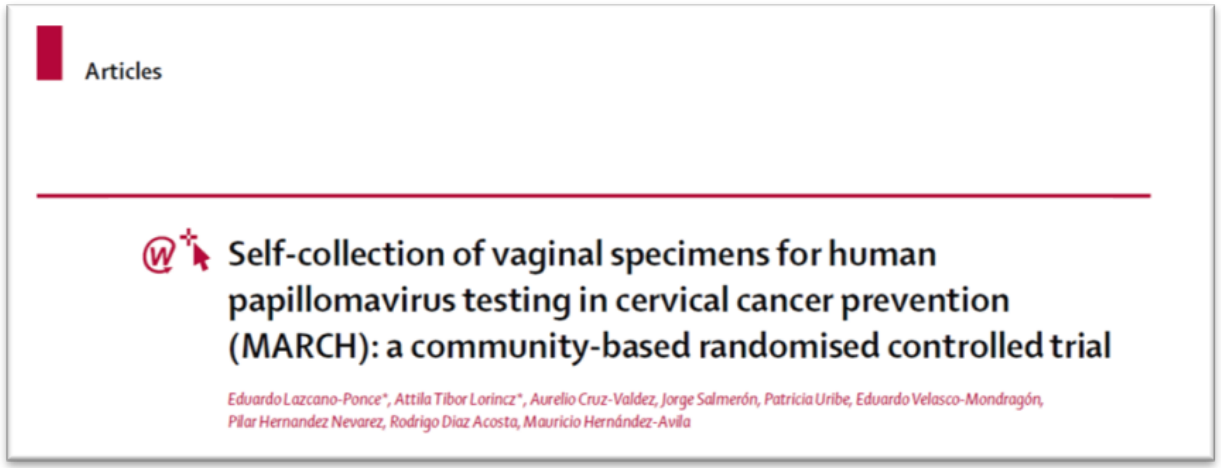
Background: We performed a multicentre randomised controlled trial to evaluate the effect on participation in organised screening programmes of a self-sampling device mailed home or picked up at a pharmacy compared with the standard recall letter.

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.

- Che cos'è?
- Razionale e scopi
- Tipi di dispositivi ed il sistema di trasporto
- Efficacia su incremento di adesione
  - Per le non aderenti
  - Per lo screening routinario
- Sensibilità/specificità
- Gradimento delle donne
- Costi
- Futuri sviluppi



Lancet - 2011 Nov 26;378(9806):1868-73.

A community-based, randomised equivalence trial in Mexican women of low socioeconomic status aged 25–65 years.

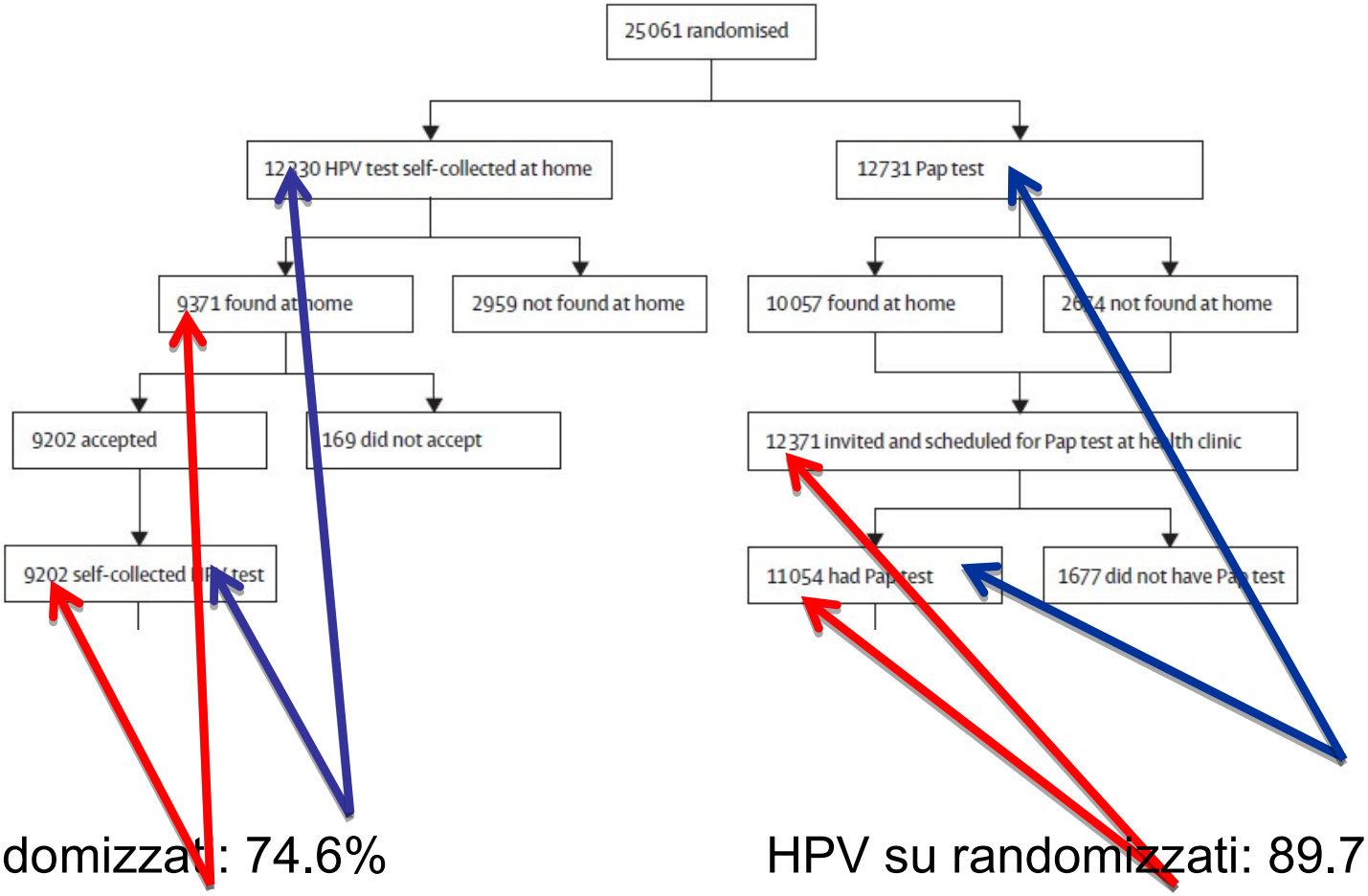
Participants came from 540 medically underserved, predominantly rural communities in Morelos, Guerrero, and the state of Mexico.

12 330 women were randomly allocated to HPV screening and 12 731 to cervical cytology; 9202 women in the HPV screening group adhered to the protocol, as did 11 054 in the cervical cytology group.

Study primary endpoint was CIN 2 or worse, detected by colposcopy

Self sampling

Control



HPV su randomizzati: 74.6%
HPV su elegibili: **98-2%**

HPV su randomizzati: 89.7%
HPV su elegibili: **89.4%**

Self collection of vaginal samples was not associated with any adverse events.

Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial

Nicole J Polman, Renée M F Ebisch, Daniëlle A M Heideman, Willem J G Melchers, Ruud L M Bekkers, Anco C Molijn, Chris J L M Meijer, Wim G V Quint, Peter J F Snijders*, Leon F A G Massuger, Folkert J van Kemenade, Johannes Berkhof

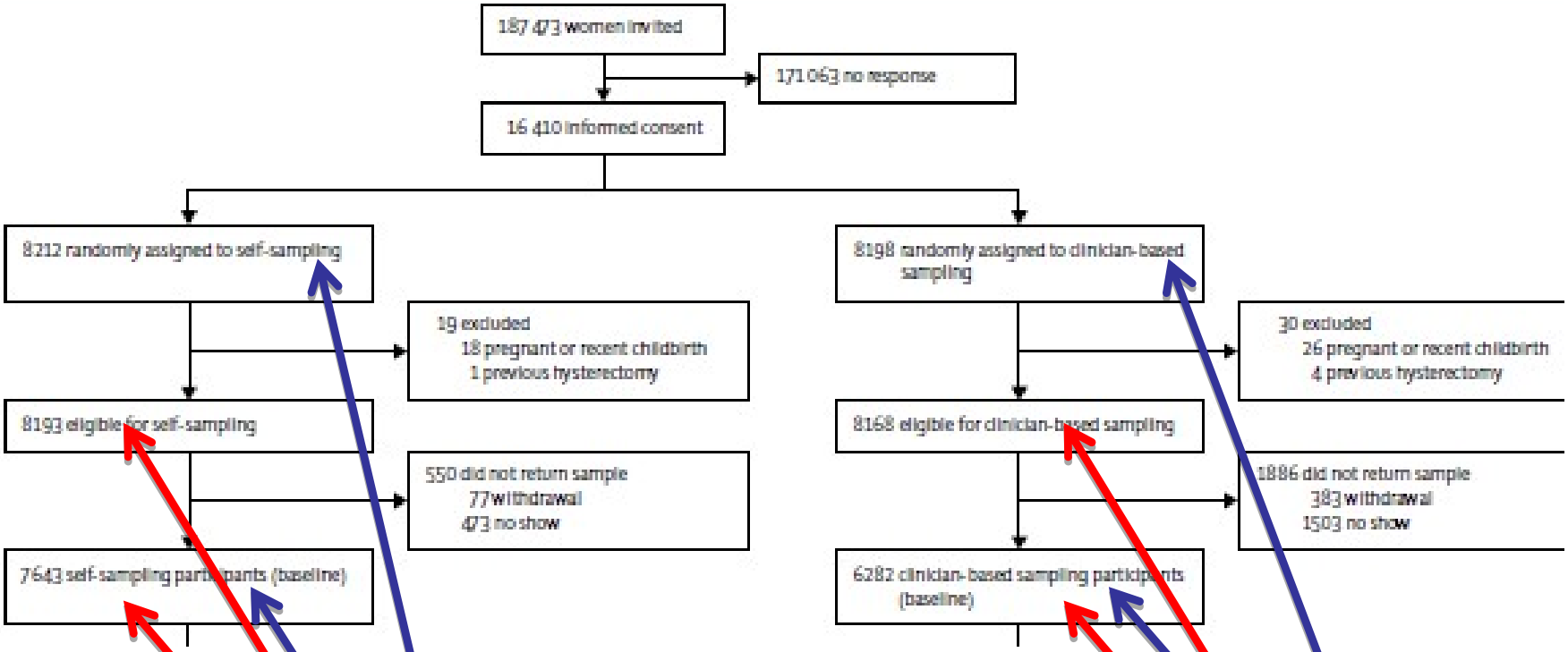
Lancet Oncol 2019; 20: 229–38

The IMPROVE study

- Within an organised screening setting
- Brush based self-sampling device in combination with a clinically validated, PCR-based HPV assay.
- **Aim:** to assess whether HPV testing on self-collected samples is non-inferior to clinician-collected samples in terms of the detection of cervical intraepithelial neoplasia (CIN) of grade 2 or worse (CIN2+) and grade 3 or worse (CIN3+).

Self sampling

Control



Self-sampling

HPV su randomizzati: 93,1%

HPV su elegibili: **93,3%**

Clinician-based sampling

HPV su randomizzati: 76,6%

HPV su elegibili: **76,9%**

- Che cos'è?
- Razionale e scopi
- Tipi di dispositivi ed il sistema di trasporto
- Efficacia su incremento di adesione
  - Per le non aderenti
  - Per lo screening routinario
- Sensibilità/specificità
- Gradimento delle donne
- Costi
- Futuri sviluppi

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.

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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.[1]

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

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

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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.

Table 4 | Absolute proportion in self sampling arm and contrasts between self sampling and control arms

Parameter	No of studies*	Absolute proportion self sampling % (95% CI)	No of studies†	Relative proportion (95% CI)	Proportion difference % (95% CI)
Unsatisfactory sample	16	0.7 (0.4 to 1.0)	NA	NA	NA
Test positivity‡	22	11.1 (9.8 to 12.4)	NA	NA	NA
Adherence to follow-up	20	80.6 (67.0 to 91.5)	10	0.91 (0.80 to 1.04)	−4.8 (−13.1 to 3.5)
CIN2+ detection per thousand invited §¶	18	2.6 (1.4 to 4.1)	14	2.28 (1.44 to 3.61)	1.6 (0.1 to 3.1)
CIN2+ detection per thousand screened**¶	18	9.8 (7.1 to 13.0)	14	1.13 (0.63 to 2.04)	2.9 (−1.7 to 7.5)

NA=Not available; CIN2+=cervical intraepithelial neoplasia grade 2 or worse.
*Reporting the parameter in both the self sampling and control arms.
†Reporting the parameter in the self sampling arm.
‡Of high-risk human papillomavirus (hrHPV) assay in the self sampling arm (per protocol).
§Depends on participation, adherence to follow-up, prevalence of disease among participants, and sensitivity of tests (screening and follow-up).
¶Restricted to data where a Pap smear was taken in the control arm.
**Depends on adherence to follow-up, prevalence of disease among participants and sensitivity of tests (screening and follow-up).

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.

The IMPROVE study

	Unadjusted data		Adjusted data*	
	n/N (% [95% CI])	Relative accuracy (95% CI)	% (95% CI)	Relative accuracy (95% CI)
CIN2 or worse				
Sensitivity				
Self-sampling	78/84 (92·9% [87·3–98·4])	0·96 (0·90–1·03)	93·1% (88·1–98·0)	0·97 (0·91–1·03)
Clinician-based sampling	106/110 (96·4% [92·9–99·9])		96·3% (93·0–99·7)	
Specificity				
Self-sampling	7074/7532 (93·9% [93·4–94·5])	1·00 (0·99–1·01)	94·0% (93·5–94·6)	1·00 (0·99–1·01)
Clinician-based sampling	5831/6190 (94·2% [93·6–94·8])		94·3% (93·7–94·9)	
Sensitivity (no under-screened)				
Self-sampling	72/78 (92·3% [86·4–98·2])	0·97 (0·89–1·04)	92·7% (87·4–98·1)	0·97 (0·90–1·04)
Clinician-based sampling	87/91 (95·6% [91·4–99·8])		95·4% (91·3–99·5)	
CIN3 or worse				
Sensitivity				
Self-sampling	39/41 (95·1% [88·5–100])	0·99 (0·91–1·08)	95·2% (89·1–100)	0·99 (0·92–1·07)
Clinician-based sampling	69/72 (95·8% [91·2–100])		95·8% (91·3–100)	
Specificity				
Self-sampling	7074/7570 (93·4% [92·9–94·0])	1·00 (0·99–1·01)	93·5% (93·0–94·1)	1·00 (0·99–1·01)
Clinician-based sampling	5831/6237 (93·5% [92·9–94·1])		93·5% (93·0–94·2)	
Sensitivity (no under-screened)				
Self-sampling	36/38 (94·7% [87·6–100])	1·00 (0·91–1·10)	95·0% (88·4–100)	1·00 (0·92–1·10)
Clinician-based sampling	54/57 (94·7% [88·9–100])		94·5% (88·8–100)	

CIN=cervical intraepithelial neoplasia. *Adjusted for HPV-positive women without histology or two times normal cytology.

Table 5: Clinical performance of self-sampling compared with clinician-based sampling

www.thelancet.com/oncology Vol 20 February 2019

The crude sensitivity of HPV testing on self-collected samples for the detection of **CIN2+** was similar to that of clinician-collected HPV testing (relative sensitivity 0·96 [95% CI 0·90–1·03]; table 5). The crude specificity of self sampling was also similar to that of clinician-based sampling (relative specificity 1·00 [0·99–1·01]).

For endpoint **CIN3+**, the sensitivity and specificity of HPV testing on self-collected samples were similar to those of clinician-collected HPV testing (relative sensitivity 0·99 [0·91–1·08]; relative specificity 1·00 [0·99–1·01]). Results were similar for the adjusted data.

- Che cos'è?
- Razionale e scopi
- Tipi di dispositivi ed il sistema di trasporto
- Efficacia su incremento di adesione
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  - Per lo screening routinario
- Sensibilità/specificità
- Gradimento delle donne
- Costi
- Futuri sviluppi

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)

Preventive Medicine 125 (2019) 5–11

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in the Netherlands

Nicole J. Polman[a,*], Yanne de Haan[a], Nienke J. Veldhuijzen[b], Daniëlle A.M. Heideman[a], Henrica C.W. de Vet[b], Chris J.L.M. Meijer[a], Leon F.A.G. Massuger[c], Folkert J. van Kemenade[d], Johannes Berkhof[b]

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[b] Department of Epidemiology and Biostatistics, Amsterdam UMC, location Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[c] Department of Obstetrics and Gynaecology, Radboud University Medical Center, Nijmegen, the Netherlands
[d] Department of Pathology, Erasmus University Medical Center, Rotterdam, the Netherlands

- **Q1) HPV-positive women from both study groups were asked about their experiences with self-sampling and clinician-based sampling (n = 497);**
- **Q2) HPV-negative women from the self-sampling group were asked about their experiences with self-sampling (n = 2366); and**
- **Q3) HPV-negative women in the clinician-collection group were asked about their experiences with clinician-based sampling (n = 2092).**

- Women reported significantly lower levels of shame, nervousness, discomfort and pain during self-sampling compared to clinician-based sampling.
- However, trust in correct sampling was significantly higher during clinician-based sampling.
- The majority of women in group Q1 preferred self-sampling (76.5%) to clinician-based sampling (11.9%) in future screening, while 11.6% of women reported to have no preference for either method.

- **To conclude, women from a regular screening population have a positive attitude towards self-sampling but express some concerns with respect to accuracy. The majority prefers self-sampling to clinician-based sampling in future screening. Based on these results, a screening approach where women can choose for either self-sampling or clinician-based sampling seems highly justifiable**

RESEARCH ARTICLE Open Access

Age-related acceptability of vaginal self-sampling in cervical cancer screening at two university hospitals: a pilot cross-sectional study

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Abstract

Background: To determine whether age is a barrier against acceptability of cervicovaginal self-sampling in screening for cervical cancer at two gynecology outpatient clinics.

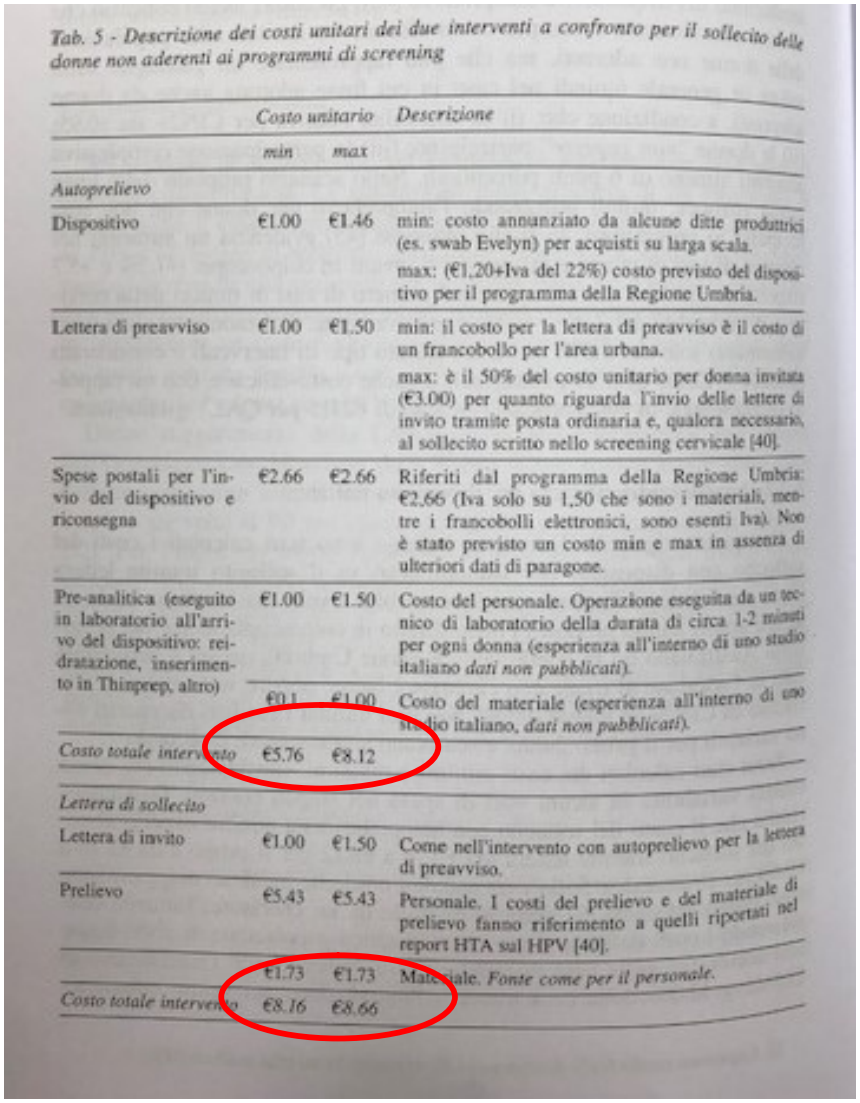
Methods: This is a cross-sectional study involving 116 women over 21 years of age with an abnormal Pap smear. Clinical and laboratorial data were recorded in electronic files. Women received detailed self-collection instructions. After the self-sampling procedure (Evalyn Brush®), women were instructed to answer a questionnaire about vaginal self-sampling acceptability that consisted of seven multiple-choice items. The participants were divided into three age brackets: 21 to 29 years, 30 to 49 years, and 50 years and over. Chi-square, Fischer exact, Kolmogorov-Smirnov and Kruskal-Wallis tests were used.

Results: The analysis of the participants' perception of the procedure stratified according to age groups showed a decline in the fear of hurting oneself during the procedure as age increased. Most participants reported that it was very easy to understand how to use the self-sampling brush and that it was easy to use it. Most of them were neither embarrassed nor afraid of getting hurt during the procedure. The majority preferred self-sampling to collection by a healthcare professional. The main reason was practicality: the possibility of choosing the place and time for sampling.

Conclusions: The participating women found self-collection simple to understand and easy to accept regardless of age. The younger women indicated more fear and discomfort in self-sampling, which points to the need for attraction strategies that are more appealing to the younger generations.

Keywords: Vaginal self-sampling, Cervical cancer screening, Human papillomavirus

- Che cos'è?
- Razionale e scopi
- Tipi di dispositivi ed il sistema di trasporto
- Efficacia su incremento di adesione
  - Per le non aderenti
  - Per lo screening routinario
- Sensibilità/specificità
- Gradimento delle donne
- Costi
- Futuri sviluppi



Tab. 5 - Descrizione dei costi unitari dei due interventi a confronto per il sollecito delle donne non aderenti ai programmi di screening

	Costo unitario		Descrizione
	min	*max*	
Autoprelievo			
Dispositivo	€1.00	€1.46	min: costo annunziato da alcune ditte produttrici (es. swab Evelyn) per acquisti su larga scala. max: (€1,20+Iva del 22%) costo previsto del dispositivo per il programma della Regione Umbria.
Lettera di preavviso	€1.00	€1.50	min: il costo per la lettera di preavviso è il costo di un francobollo per l'area urbana. max: è il 50% del costo unitario per donna invitata (€3.00) per quanto riguarda l'invio delle lettere di invito tramite posta ordinaria e, qualora necessario, al sollecito scritto nello screening cervicale [40].
Spese postali per l'invio del dispositivo e riconsegna	€2.66	€2.66	Riferiti dal programma della Regione Umbria: €2,66 (Iva solo su 1,50 che sono i materiali, mentre i francobolli elettronici, sono esenti Iva). Non è stato previsto un costo min e max in assenza di ulteriori dati di paragone.
Pre-analitica (eseguito in laboratorio all'arrivo del dispositivo: reidratazione, inserimento in Thinprep, altro)	€1.00	€1.50	Costo del personale. Operazione eseguita da un tecnico di laboratorio della durata di circa 1-2 minuti per ogni donna (esperienza all'interno di uno studio italiano *dati non pubblicati*).
	€0.1	€1.00	Costo del materiale (esperienza all'interno di uno studio italiano, *dati non pubblicati*).
Costo totale intervento	€5.76	€8.12	
Lettera di sollecito			
Lettera di invito	€1.00	€1.50	Come nell'intervento con autoprelievo per la lettera di preavviso.
Prelievo	€5.43	€5.43	Personale. I costi del prelievo e del materiale di prelievo fanno riferimento a quelli riportati nel report HTA sul HPV [40].
	€1.73	€1.73	Materiale. *Fonte come per il personale.*
Costo totale intervento	€8.16	€8.66	

Jaramillo L, et al. L'autoprelievo per il test HPV per la prevenzione del cervicarcinoma in donne non aderenti allo screening: un intervento di prevenzione Efficace, Sostenibile e Trasferibile

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Futuri sviluppi e possibili applicazioni nel nostro contesto

- Molti paesi europei si stanno preparando ad introdurre il self sampling nei loro programmi di screening organizzato (UK, Francia, Norvegia, Svizzera, Danimarca, Svezia, Olanda, Romania, ecc.)
- La maggior parte di questi interventi è offerto alle non aderenti (**hard to reach subgroups**)
- **E nello screening routinario**?
  - 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)
  - Manca ancora una valutazione economica…

Despite the advantages, self-sampling may also presents new challenges for patient care…

- Self-sampling could conceivably decrease the opportunities for direct contact between the patient and the clinician, contributing to the possibility of decreased follow-up, as well as the potential for over-testing.
- In addition, women will need clear instructions to prevent feelings of insecurity during sampling and fear of hurting themselves .
- Self-sampling without appropriate follow-up or clear instructions on how to interpret a positive result also has the potential to increase patient anxiety, especially given the likelihood of many HPV infections to clear spontaneously .
- In all of these cases, HPV education is important to ensure appropriate patient engagement .
- Moving forward, additional infrastructure and guidelines will be needed to support the use of HPV self-sampling

From: Gupta et al. Self-Sampling for Human Papillomavirus Testing: increased Cervical Cancer Screening Participation and incorporation in international Screening Programs , Frontiers in Public Health, 2018

The role of vaginal microbiome analysis in HPV diagnosis and monitoring

The vaginal microbiome is an emerging treatment area;

An emerging area related to HPV screening is the role of vaginal microbiome analysis in detecting the presence of commensal and pathogenic bacteria that are positively or negatively associated with HPV infection;

- Recent developments in vaginal microbiome testing have now made detection of HPV and associated microorganisms readily accessible, providing additional information with the potential to complement and improve the diagnosis and control of HPV infection and cervical cancer.

Grazie per l'attenzione