COURSE: Evidence-Based Approaches to HPV Screening implementation

Module 5. Use of self-sampling of cervico-vaginal cells

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CONTENTS

INTRODUCTION AND LEARNING OBJECTIVES

In previous modules we have shown that cervical cancer screening with an HPV test is more effective than screening with cytology. HPV testing can be performed on a sample taken by the woman herself which avoids the need for a gynaecological examination by a healthcare professional. The possibility of taking a self-sample may facilitate participation in cervical cancer screening. The fact that self-sampling can improve screening coverage is highly relevant given that most cervical cancer diagnoses occur in women who have never been screened or do not attend regular screening.

In this module, we will review the available evidence on the accuracy of HPV testing on a self-collected sample compared to HPV testing on a specimen collected by a healthcare provider during a gynaecological exam. We will also evaluate the conditions that determine the accuracy of HPV testing on self-samples. We will furthermore review examples of settings where self-sampling has been successfully implemented.

At the conclusion of this module, participants will be able to:

- Understand the role of self-sampling in cervical cancer screening.
- Interpret the accuracy of HPV tests on self-samples.
- Understand the acceptability of self-sampling by women in the target population.
- Understand key aspects affecting the implementation of self-sampling in a cervical cancer screening programme.
- Assess the overall implementation of self-sampling in screening programmes around the world.

UNIT 1. SELF-SAMPLING DEVICES

HPV infection is easily detectable in cervical cells shed in the vagina. Highly sensitive tests for detecting HPV DNA enable the use of samples taken by the woman from the vagina without the need for a gynecological examination. This process is called self-sampling.

A wide range of self-sample devices are available with or without a transport liquid that collect a sample from the vagina. **Figure 1** shows a few examples of vaginal self-sampling devices.

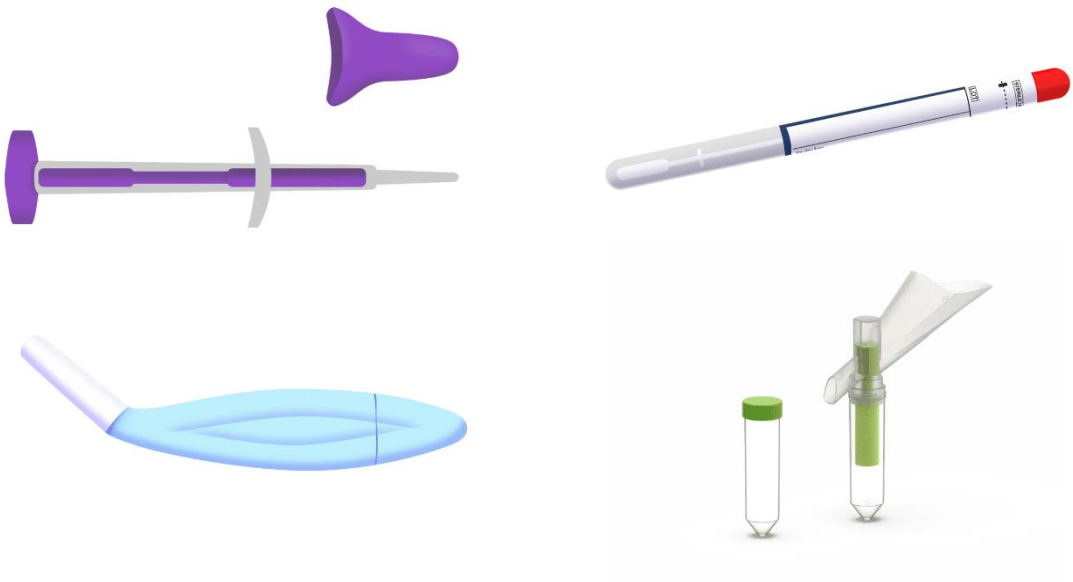


Figure 1. Self-sampling devices to take a vaginal specimen
(from top left to bottom right: brush, swab, lavage and urine)

Brushes or swabs-used for vaginal self-sampling

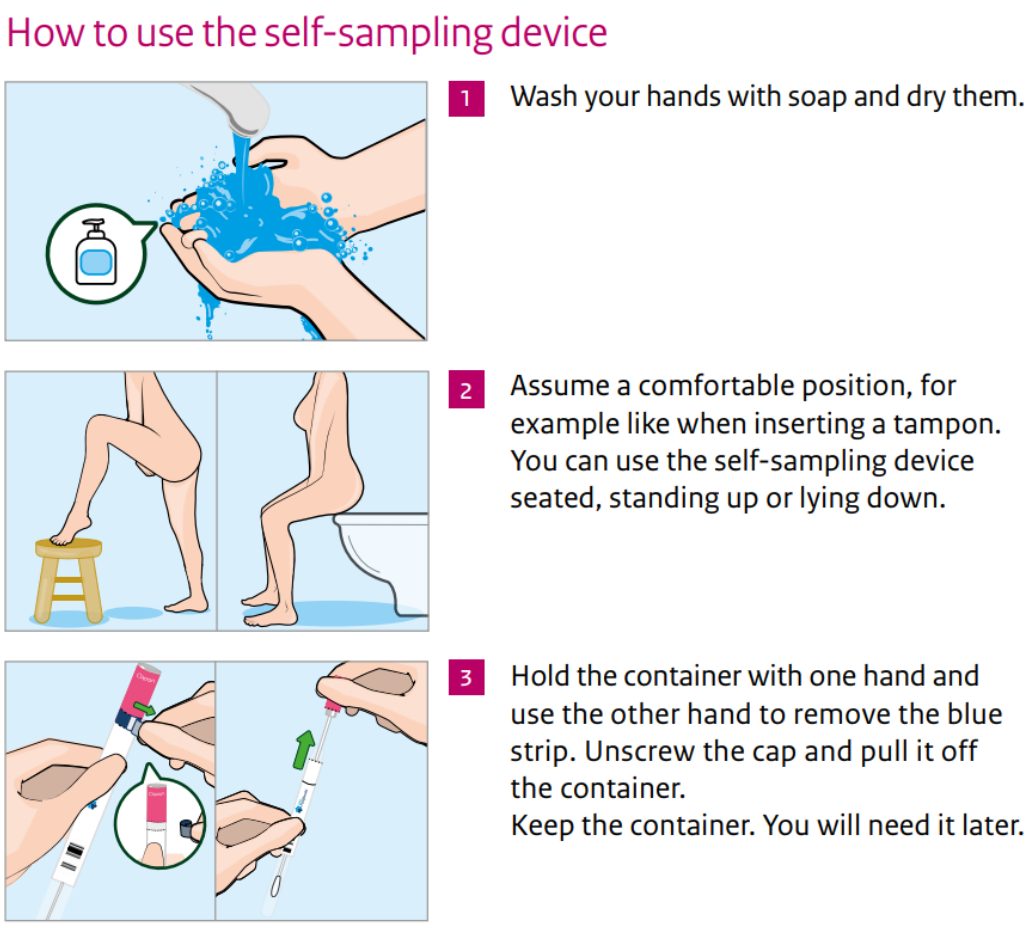
Despite the different designs in brushes or swabs, the process of collecting the sample involves similar steps for most of them:

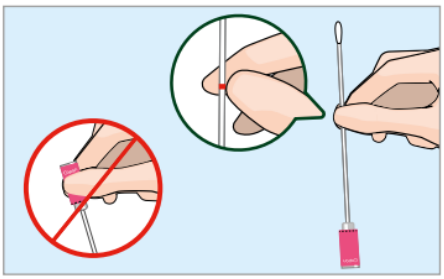
- 1) Insert the swab/brush into the vagina and gently rotate as described in the instructions
- 2) Remove the swab/brush and transfer it into a tube which may contain a preservative liquid or not
- 3) Snap off the swab/brush shaft and cap the collection tube

- 4) Discard shaft and
- 5) Label the collection tube and send it to the laboratory

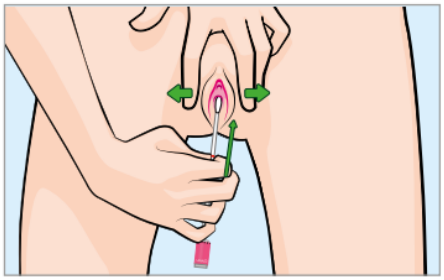
The steps above refer to the collection process itself, but the specific instructions of each device provide more details on the different steps and are accompanied by drawings. In **Figure 2**, you can find an example of the self-sampling instructions used in the Netherlands.

Figure 2. Example instructions for how to collect a vaginal self-sample using a swab in cervical cancer screening of The Netherlands (Roeske, n.d.).



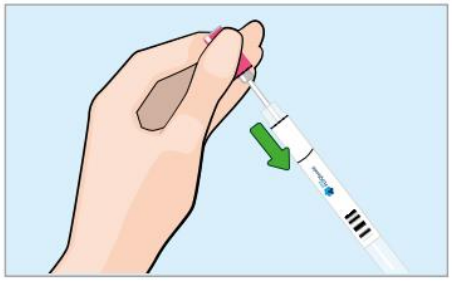


4 Hold the swab stick with two fingers by placing them on the **red** mark.



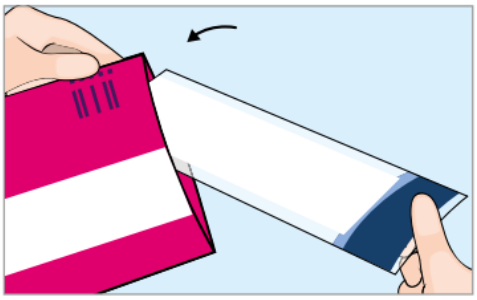
5 Spread your labia with one hand.
Use the other hand to insert the swab stick until your fingers touch your vagina.
This is far enough to take a good sample.

6 Rotate the swab stick inside your vagina for 20 seconds. The swab stick does not need to touch the vagina walls or cervix.
After rotating for 20 seconds, there is sufficient material on the swab stick.



7 Remove the swab stick from your vagina, taking care not to touch the tip with your hands. Put the swab stick back inside the container.
Push the cap onto the container until you feel it click.

8 Put the closed container in the plastic holder. The holder is in the transparent plastic bag with a blue edge. The white absorption cloth must remain in the plastic bag. Seal the bag properly.



9 Put the bag with the container in the return envelope.

10 Return the self-sampling device in the return envelope within one week. In the meantime, you can keep it at room temperature at home. It does not need to be refrigerated. You do not need a stamp.

Once the sample is in the collection tube, the specimen is stable at room temperature for several days to weeks depending on the device. Yet, it is important to respect the instructions regarding the timing and conditions for transport to the laboratory.

Lavage sampling devices

In this case, instead of scraping, the device inserts a liquid through the vagina where the shed cervical cells will get suspended. The device then collects the liquid with the cells on it. It has been reported that lavage sampling may yield more DNA than a dried sample (Verhoef et al., 2013).

The acceptability by women of vaginal lavage is comparable with that of brush-based self-sampling devices (Karjalainen et al., 2016).

Urine self-sampling devices

HPV can also be detected in the first fraction of urine. Urine contains cells and debris accumulated around the meatus of the urethra. However, it is recommended to use the first-void urine as it contains higher concentrations of HPV DNA if present. Due to the instability of DNA in urine, it is important to mix the urine immediately with a preservative liquid in the collection device.

Women participating in urine-sampling studies consider it an acceptable screening method and feel more confident they collected the sample correctly and therefore more confident in the HPV test result (De Pauw et al., 2021 **RISCC**).

A meta-analysis of published studies involving 11,159 women who collected a urine sample and 10,774 women with clinician-collected sample (Cho et al., 2022), showed that polymerase chain reaction (PCR) -based HPV testing has similar clinical accuracy in urine and clinician-collected specimens for detecting CIN2+. However, the authors do not recommend urinary HPV testing based on signal amplification or mRNA testing. The accuracy of urine screening compared to clinician collected samples and the feasibility of different devices for adequate urine collection minimizing the volume to be collected, are still being evaluated (Daponte et al., 2021; Ørnskov et al., 2021; Téblick et al., 2021).

Its use in cervical cancer screening is not yet recommended by any society or organization. Therefore, the rest of this module focuses on vaginal self-sampling.

Self-sampling is an approach allowing, and potentially improving, access to screening.

The self-collection process is acceptable to most women as they can collect the sample at home (or any place of convenience allowing privacy) or in a medical centre without the need for a gynaecological exam by a healthcare provider. In fact, women that have self-collected a sample perceive it as discreet, private, female-friendly, painless and time-saving. (World Health Organization & UNITAID, 2019)

The fact that self-sampling can improve screening coverage is highly relevant given that most cervical cancer diagnoses occur in women who have never been screened or do not attend regular screening. In fact, the World Health Organization (WHO) considers screening using self-sampling as a key tool in accelerating the global fight against cervical cancer (World Health Organization, 2021b, 2021a). The return of self-sampling results to the screening participant is key to guarantee a follow-up of those with a positive result.

Importantly, the implementation of self-sampling should be preceded by an education campaign directed to participants and healthcare providers to inform about the approach. Quality must also be ensured throughout the process, from sample collection, assay test to detect HPV, to adequate communication of results to participating women and the need for follow-up.

ACTIVITY

Read the following statements and decide if they are TRUE or FALSE.

1. Self-sampling for cervical cancer screening can only be done using a vaginal sample.
2. A cervico-vaginal self-sample can be collected using a brush, a swab or a lavage device.
3. Self-collected samples need to be delivered to the laboratory on the same day or the day after sample collection.

The correct answers are:

1 False, 2 True, 3 False.

UNIT 2. EFFICACY AND PERFORMANCE

2.1. Accuracy of HPV testing in self-samples

The use of self-sampling in cervical cancer screening programs relies on a high concordance of results with those obtained by a professional through a gynecological exam.

HPV DNA testing on self-samples

A meta-analysis of published studies carried out in paired samples of underscreened women (Arbyn et al., 2018) estimated the relative sensitivity and specificity for CIN2+ and CIN3+ of HPV testing (on self- versus clinician-collected samples taking into account the HPV detection assay used). The sensitivity for the detection of CIN2+ by HPV testing as primary screening test on self- versus clinician-collected samples was similar, provided HPV DNA assays were based on the PCR technique (**Table 1**).

Table 1. Relative sensitivity and specificity of HPV testing on self- versus clinician-collected samples, by laboratory technique (Arbyn et al., 2018).

HPV detection technology	Outcome	No. studies	Relative sensitivity (95%CI)	Relative specificity (95%CI)
Signal amplification	**CIN2+**	23	0.85 (0.80 to 0.89)*	0.96 (0.93 to 0.98)*
	CIN3+	9	0.86 (0.76 to 0.98)*	0.97 (0.95 to 0.99)*
PCR	**CIN2+**	17	0.99 (0.97 to 1.02)	0.98 (0.97 to 0.99)*
	CIN3+	8	0.99 (0.96 to 1.02)	0.98 (0.97 to 0.99)*

**Statistically significant (i.e. confidence interval excludes unity).*

NOTE: *Confidence intervals that include unity (for example: 0.96 to 1.02) of a relative sensitivity on a self- versus a clinician-collected sample indicate that the sensitivity of HPV testing on self-sample is not different from the sensitivity of HPV testing on a clinician-collected sample.*

The meta-analysis showed the following findings:

- **When the HPV test is based on a PCR approach**: the sensitivity of HPV testing in self-samples for the outcome CIN2+ or CIN3+ is **similar** compared to clinician samples.
- **When HPV testing is done with a signal amplification technique**: the sensitivity of HPV testing, particularly for CIN2+, is lower in self-samples than in clinician-collected samples
- **For both techniques** (signal amplification or PCR), the specificity of HPV testing in self-samples is slightly lower than that of clinician-collected samples.

Similar results and conclusions have been obtained in an updated meta-analysis in which the relative accuracy of HPV testing in self-samples versus clinician-collected samples has been estimated through test agreement/concordance data (Arbyn et al., 2022 **RISCC**).

Most accuracy studies on self-sampling approaches involved women who did not attend regular screening or had never been screened. Few studies have been conducted in regularly screened women (Polman et al., 2019) but because of the COVID-19 pandemic, self-sampling has been introduced in many countries allowing to evaluate its performance in population-based screening programs such as in the Netherlands, Sweden and Australia (Bavor et al., 2023; Elfström et al., 2023 **RISCC**; Inturrisi et al., 2021 **RISCC**).

In the cervical cancer screening program from the Netherlands, women could choose between a clinician- or a self-collected sample. The comparison of the HPV testing performance in non- paired samples (Inturrisi et al., 2021 **RISCC**) showed that self-sampling had slightly lower sensitivity to detect CIN2+. This lower accuracy was associated to a delayed time to turn test-positive (**Figure 3**). These differences have not been observed in diagnostic settings so selection bias cannot be discarded (i.e different characteristics between women using self-sampling and those with clinician-collected samples). Additionally, regular attenders may have smaller lesions more difficult to detect, thus, populations need to be comparable.

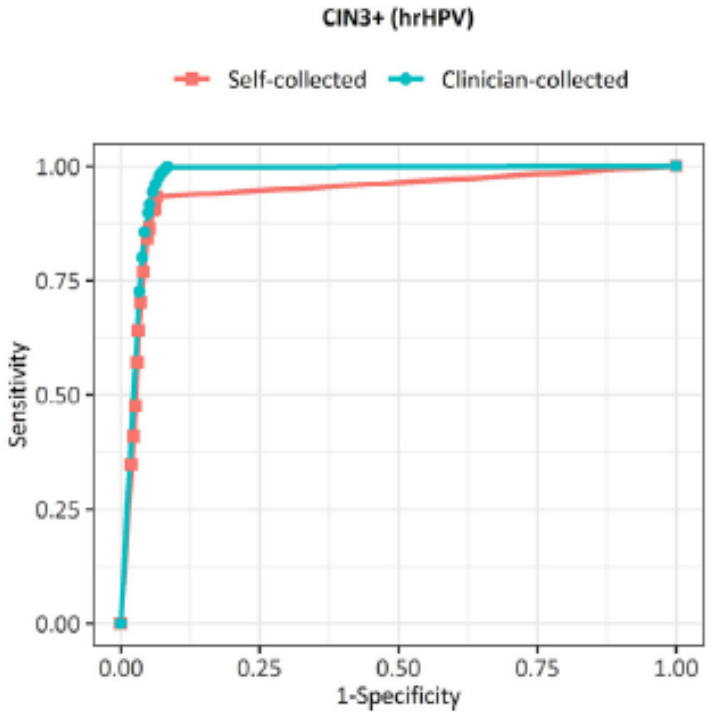


Figure 3. Receiving operating curve (ROC) of overall HPV Ct values on self-collected (red) and clinician-collected (blue) samples for clinical endpoints CIN3+ (Inturrisi et al., 2021 **RISCC**).

The ROC curves of the HPV tests in both sampling techniques (self-sampling and clinician-collected) were similar up to the HPV test's predefined cutoff point for positivity. This could suggest that self-sampling for HPV DNA detection may require a cutoff adjustment to compensate for slightly lower sensitivities in detecting CIN3+. In agreement with the need to potentially adjust the cutoff to maintain HPV testing accuracy, some studies show higher Ct values for HPV tests applied to vaginal self-samples compared to paired clinician-collected cervical samples of the same women (Latsuzbaia et al., 2022 **RISCC**, 2024 **RISCC**).

This potential need for cutoff adjustment has not hindered the offering of self-sampling as an option in cervical cancer screening programs.

Did you know?

Before implementing self-sampling, several aspects need to be assessed to ensure, among others, the proper performance of the HPV test. It is clear that the accuracy of HPV testing may be influenced by multiple factors such as the collection by the subject, the self-collection device, transport medium and transport conditions, procedures to handle self-

samples in the laboratory or the HPV-assay used (Arbyn et al., 2023 **RISCC**; Arbyn et al., 2022 **RISCC**). Therefore, it is important that the type of device used to collect the sample and the HPV test used have been validated against clinician-collected smears.

For more information, please see Unit 4.4 within this module.

NOTE:
For more information on the parameters to measure the accuracy of tests, please see ***MODULE 2.*** *For more information on the validation of HPV tests, please see* ***MODULE 3.***

HPV mRNA testing on self-samples

A systematic review (Arbyn et al., 2022 **RISCC**) estimated the relative sensitivity and specificity for CIN2+ and CIN3+ of HPV mRNA testing on self- versus clinician-collected samples (**Table 2**).

Table 2. Relative sensitivity and specificity of HPV mRNA testing on self- versus clinician-collected samples (Arbyn et al., 2022 **RISCC**)

HPV detection technology	Outcome	No. studies	Relative Sensitivity (95%CI)	Relative specificity (95%CI)
mRNA (Aptima®)	**CIN2+**	5	0.84 (0.74 to 0.96)*	0.96 (0.91 to 1.01)
	CIN3+	5	0.64 (0.43 to 0.93)*	

** Statistically significant (confidence interval excludes unity).*

This study showed that Aptima®, the only commercial clinically validated test with comparison data between the two sampling methods, is less sensitive for CIN2+ and CIN3+ in self-collected-samples but similarly specific compared with clinician-collected samples.

The lower sensitivity for CIN2+ of mRNA tests in self-collected samples provided the basis for WHO screening guidelines not to recommend mRNA tests in primary screening on self-samples.

2.2. Follow-up of women with a positive HPV result on a self-sample

When implementing self-sampling in a screening programme, it is important to include clinical management algorithms for women with positive results and to implement efficient alert and appointment system to ensure that as many women as possible receive triage and treatment.

NOTE: *For more information on the triage options for clinician-collected cervical samples, please see* ***MODULE 4A****.*

Triage with cytology

Self-sampling cannot guarantee *a sufficient number of intact ectocervical and/or endocervical cells* in the sample for a correct cytological evaluation. Therefore, cytology on self-samples is unreliable.

Several studies comparing self-collected samples with those collected by healthcare professionals found a deficiency of endocervical cells in 66% of self-samples compared with 14% of clinician-based samples (Budge et al., 2005; Nobbenhuis et al., 2002). The sensitivity of cytology for detecting high-grade cervical lesions in self-samples was 23% to 77% lower than that of clinician samples.

Reflex cytological triage of self-samples is not recommended.

Cytology triage on women with an HPV positive test on a self-sample should therefore be carried out on new cervical samples taken by a healthcare professional in a follow-up visit. This follow-up visit could mean that the possible increase in coverage by self-sampling could not result in an increased detection rate of lesions due to the loss of follow-up of those positive women who do not attend subsequent visits.

EXAMPLE

In the Netherlands, a higher loss to follow-up has been observed among women screened using self-sampling compared to those with clinician-based sampling (Olthof et al., 2024). Specifically, 7% of women with a positive HPV self-sample did not attend subsequent cytology triage. Furthermore, among women with normal cytology triage, the proportion who did not attend repeat cytology was 3.6% for those with clinician-collected samples versus 13.6% for those with self-collected samples.

The lower adherence to follow-up suggests that the lack of contact with a professional does not facilitate adequate follow-up of a positive test result and therefore, a clear communication with the screening participant is key to ensuring compliance with any required follow-up. Where this drop-out is important, more sensitive reflex triage scenarios could be favoured.

Other triage options

Genotyping and other reflex molecular tests such as **DNA methylation** can be performed to triage HPV positive women using the originally taken self-specimen enabling management according to the risk of CIN2+ associated with the triage result. Therefore, they can bypass a potential drop-out of women requiring a follow-up visit for a clinician-collected sample.

However, evidence on the performance of other triage strategies in self-samples is scarce and show some aspects to be considered for its implementation (Rebolj et al., 2023):

Limited genotyping for HPV16/18

- ADVANTAGE: Available in many countries together with the results of the primary HPV assay.
- CAVEAT: Women with a non HPV16/18 positive result will require a cytology triage to further stratify the risk of CIN3+ and decide the most appropriate clinical management. Extended genotyping could bypass this issue if HPV positive results are provided in risk tiers.

Methylation

- ADVANTAGE: High sensitivity for CIN3+. Commercially available host-methylation tests show high reassurance against cancer
- CAVEAT: Multiple protocols and various methylation targets (viral, host or both) described. Scalability and automation. Costs may be high.

2.3. Longitudinal evaluation of self-sampling

It is important to consider the long-term protection conferred by an HPV negative self-sample, providing a safe screening interval for women with a negative self-sample to return to screening. Publications are forthcoming from many settings worldwide exploring the response to and the acceptability of self-sampling and strategies to introduce the approach. However, data on the longitudinal impact of self-sampling are scanty (Aasbø et al., 2022; Auvinen et al., 2022; Drysdale et al., 2022; Hermansson et al., 2022; Kraut et al., 2022; Sultana et al., 2022).

EXAMPLE

Data from the PaVDaG study which includes 4,617 women with follow-up data up to the second round of screening (6 years) found that the 5-year risk of CIN2+ and CIN3+ following an HPV negative self-sample was 0.6% and 0.2%, respectively (Stanczuk et al., 2021 RISCC).

Though more evidence is needed, the low risk of CIN2+ in women with negative HPV self-samples suggests that the current interval of 5 years established for women with a negative HPV result in a clinician-collected sample could also be feasible for women with a negative self-sample.

Did you know?

Brentnall et al. (2023 RISCC) provides a review on potential paired study designs that can be used to assess the performance of self-sampling versus clinician-collected samples

ACTIVITY

Connect the concepts to their corresponding characteristics

EXERCISE 1:

1. The detection of CIN2+ on self-samples is similar to that of clinician samples
2. The detection of CIN2+ on self-samples is less sensitive than that on a clinician sample

A. when using PCR techniques to detect HPV DNA in self-samples

B. when testing for HPV mRNA in self-samples

EXERCISE 2:

1. Cytology
2. Limited or extended genotyping and methylation markers

A. Can be done in the same self-sample but is not yet optimal for implementation

B. Requires an additional clinician-collected sample and therefore can result in loss of follow-up of women with a positive result at self-sampling. Moreover, its accuracy on a self-sample is poor

The correct answers are:

Exercise 1: 1A, 2B

Exercise 2: 1B, 2A

UNIT 3. ACCEPTABILITY OF SELF-SAMPLING

The acceptability of self-sampling by the user may vary depending on the target population. Although there is generally a high acceptance of the approach, local pilot studies or clinical trials are recommended to assess the acceptability prior to its implementation in regional or national screening programmes.

The acceptability of self-sampling usually measures the participation in screening among women offered self-sampling (i.e. whether or not the woman returns the device) or via a questionnaire seeking the woman's opinion on self-sampling.

Most studies conducted in Europe evaluated the acceptability of self-sampling primarily among underscreened women (Arbyn et al., 2023; Costa et al., 2022; Morgan et al., 2019) and few have evaluated it among regular screening users (Ibáñez et al., 2023; Polman et al., 2019). In both populations, self-sampling has generally shown very good acceptability, serving as an alternative to a visit with a healthcare professional for those women who prefer it. In contrast, in low-resource settings self-sampling has been shown highly acceptable in the general population, rather than used as an alternative to regular screening, it is sometimes the unique approach to reach high coverage (de Sanjose & Holme, 2019; Holme et al., 2020).

There are various means of delivering self-sampling devices to women:

- **Mail-to-all:** The self-sampling device is sent directly to the woman (also called opt-out) so that she chooses to participate or not after receiving it.
- **Opt-in:** Women receive an invitation containing information on how a self-sampling kit can be requested for home delivery or, alternatively, can be collected at their local clinic/pharmacy. This option is the most interesting from an economic and environmental point of view.
- **Community mobilization & outreach:** Women are offered a self-sampling kit either at a cervical cancer screening awareness event or at home/work upon a visit by a community healthcare worker. It has been applied in resource-constrained settings with a very high incidence of cancer and where women have difficulties in travelling to health centres (Arrossi et al., 2019; Lazcano-Ponce et al., 2011).

- **Offer at healthcare services:** The self-sampling device is offered when women attend the healthcare services for whatever reason. Some evidence suggests that face-to-face interactions with a trained healthcare practitioner are most likely to generate the largest increases in participation (Franco, 2018; Ibáñez et al., 2023; Peeters et al., 2020).

Systematic reviews and meta-analyses of thirty-three randomized controlled trials in underscreened women (Arbyn et al., 2018; Costa et al., 2022 **RISCC**) assessed the efficacy (in terms of response rate) of offering self-sampling kits for HPV testing compared to conventional invitations using different invitation strategies (**Table 3**).

Table 3. Absolute participation in self-sampling and control arm and participation difference between them in the intention-to-treat population (Costa et al., 2022 **RISCC**).

	Self-sampling %	Control %	Relative participation % (95%CI)	Participation difference % (95%CI)
Mail-to-all	24.3	10.4	2.5 (2.1, 3.0)	13.2 (11.0, 15.3)
Opt-in	16.7	11.3	1.5 (1.2, 1.8)	4.4 (1.2, 7.6)
Community mobilisation & outreach	92.9	52.7	1.9 (0.9, 4.3)	39.1 (8.4, 69.9)
Offer at healthcare services	49.7	21.6	2.3 (2.0, 2.7)	28.1 (23.5, 32.7)

In the intention-to-treat analysis (i.e, it considers as self-sampling participants those women with a clinician-collected sample after receiving the self-sampling invitation), all self-sampling invitation scenarios were more effective in reaching under-screened women compared to sending screening invitations or reminders, especially when a *mail-to-all* strategy was used. Face-to-face distribution of self-sampling kits, whether through community outreach or healthcare services, was a very effective approach for reaching under-screened populations. Mailing kits to all also improved participation rates in high-income countries, while opt-in invitations showed the lowest increase and were only significant in the intention-to-treat analysis (Costa et al 2022 **RISCC**).

In summary, HPV self-collection has shown to increase participation in countries with high resources such as Denmark or Sweden and has the potential to increase

participation in settings with limited resources. However, the combination and adaptation of effective self-sampling strategies to specific contexts, levels of resources and socioeconomic groups is needed to achieve high levels of coverage and optimal follow-up for women with positive results. For example, in high-income settings, self-collection is mainly offered via the mail system but this method is unfeasible in most resource-constrained settings for the same reasons that apply to delivery of invitation letters (i.e. poor mailing system or the lack of updated residents census).

KEY IDEA

Good acceptability of self-sampling by women fosters participation, particularly among women who are infrequent users of screening services.

ACTIVITY

Read the following statements and decide if they are TRUE or FALSE.

1. Self-sampling can be used to reach women who are not regularly engaged in preventive interventions.
2. Opt-in for self-sampling is the most effective self-sampling invitation strategy to increase participation.
3. Face-to-face distribution of self-sampling kits, whether through community outreach or healthcare services for self-sampling, is the most effective invitation to increase participation.
4. There is no need to provide additional information about self-sampling, as women are aware of its benefits.
5. Any HPV test is good as a primary screening test for self-sampling.
6. When a self-sampling kit is offered to women after a cervical cancer screening awareness event, or at home/work during a visit by a community healthcare worker, it is called an "opt-in" strategy.
7. Self-sampling is not relevant to increasing screening coverage.
8. Low participation can only be reduced by making screening mandatory.

9. The "offer at healthcare services" strategy is when the self-sampling device is offered to women who attend healthcare services for any reason.
10. Local clinical trials are recommended to assess the acceptability prior to self-sampling implementation in regional or national screening programmes.

The correct answers are:

1 True, 2 False, 3 True, 4 False, 5 False, 6 False, 7 False, 8 False, 9 True, 10 True

UNIT 4. IMPLEMENTATION OF SELF-SAMPLING

Several technical aspects need to be considered before a self-sampling modality is to be implemented at large scale (Arbyn et al., 2023 **RISCC**; Hawkes et al., 2020; Rebolj et al., 2023):

The HPV assay

As with clinician-collected samples, having information on the presence of human cellular material (e.g., beta-globin) is valuable. It provides assurance that there are enough human cells available for HPV testing. Clear instructions to women on how to properly collect the sample will help to minimize invalid specimens (likely due to a lack of sufficient material) in self-collected samples.

NOTE: *An invalid specimen implies that the woman may miss the chance of being screened as she either needs to collect a new self-sample or return to the clinic for repeat sample collection.*

PCR-based assays for detecting HPV DNA have higher accuracy compared with signal amplification or RNA tests.

Technologies need to be clinically validated for the entire process involving self-sampling. Clinical validation for clinician collected samples is not enough.

Did you know?

Similarly to the VALGENT protocol to validate genotyping tests, the VALHUDES protocol is a diagnostic test accuracy study aimed to compare the clinical sensitivity and specificity of HPV tests based on PCR that have already been validated according to the international criteria on vaginal self-samples and first-void-urine, collected in agreement with standardized protocols, with matched clinician-collected samples (Arbyn et al., 2018).

The 2021 WHO guidelines (World Health Organization, 2021b) recommend the use of self-sampling using a high accuracy HPV test. Both a validated PCR-based HPV test and a validated device should be used on self-sampling screening approach. Preferably, this recommendation should take place as part of a population screening programme with careful monitoring and assessment of the strategy and its results.

The collection device

The relevance of the sampling devices to be used in a screening programme cannot be minimized.

Use a device that is safe, non-invasive and specifically designed to enable women to collect an adequate amount of vaginal material by themselves.

The device needs to comply with the current legislation from the setting where it will be used (I e., CE marking, IVDR regulations, etc.).

Devices should be adequate for the strategy being used. Devices may be given directly to the women, may be mailed or the woman may pick it up at a determined place such as a pharmacy or a health centre.

EXAMPLE

Sampling kits that do not use transport medium (dry samples) are more suitable when kits are delivered at home via mail as it avoids leakage and reduces the chances of contamination. On the other hand, a swab is likely to be more convenient than a brush as it is of a smaller size, participating women perceive it as less invasive, and it is easier to fit in mailboxes.

The sample quality

Degradation of the collected sample can impact on the HPV test accuracy and therefore, the full workflow from sample collection to HPV detection needs to be assessed to estimate the sample stability time.

Verify the conditions of transportation and storage of the collection device. Compliance with standards and an efficient workflow helps prevent sample degradation and reduces errors.

Provide clear and detailed instructions to women on how to perform self-sampling correctly, including storage and shipping of the collected sample. Effective communication is key to building trust and ensuring that individuals understand and perform the collect sample correctly. Educating participants about the benefits and limitations of self-sampling additionally facilitates informed decision-making, which increases acceptance and participation in the screening program.

Train all professionals involved in the screening process in the use of self-sampling. This is crucial for ensuring that devices are used correctly, samples are collected accurately, and any issues are effectively resolved. Training also ensures quality control, proper management of samples, and adherence to the latest guidelines and regulatory standards (IARC & Department of Health and Health Service Executive of Ireland, 2023; Rebolj et al., 2023; World Health Organization, 2021b).

Use clinically validated collection devices, transport mediums and DNA extraction procedures (i.e, validate the workflow) as they can affect the sample integrity. Previous meta-analyses comparing the accuracy of HPV testing on diverse self-sampling devices with clinician-collected samples did not reveal accuracy differences (Arbyn et al., 2018; El-Zein et al., 2018; Sechi et al., 2022). However, more recent trials directly comparing multiple self-sampling devices among each other demonstrated inferior performance of certain devices (Cadman et al., 2021; Latsuzbaia et al., 2022 **RISCC**). The HPV assay should be validated for screening purposes.

Quality control is essential to optimize performance and ensure the validity of the screening program at every stage.

This includes both the pre-analytical phase of self-sampling specimens (such as transport medium, storage, and resuspension if collected in a dry medium) and the analytical phase, where HPV detection is carried out (control of women with negative

HPV results) to ensure good program validity across all its intervention methods. It allows to detect and resolve issues, optimize performance, ensure compliance with standards, and ultimately improve patient outcomes.

NOTE: *For more information on the general implementation aspects of a new screening test or modification to the screening program, please see* ***MODULE 8****.*

ACTIVITY

Read the following statements and decide if they are TRUE or FALSE.

1. Any HPV assay can be used in self-collected samples if it is validated for clinician-collected samples.
2. It is recommended to use a device that is safe and specifically designed to collect an adequate amount of vaginal material.
3. The whole process from sample collection to result needs to be validated.
4. The choice of the self-sampling devices needs to be adequate for the invitation and screening strategy planned.

The correct answers are:

1 False, 2 True, 3 True, 4 True

UNIT 5. OVERVIEW OF SELF-SAMPLING IMPLEMENTATION PROGRAMMES

Self-sampling is now considered a key pillar in accelerating cervical cancer prevention (de Sanjose & Holme, 2019). Countries are now introducing self-sampling as the priority screening approach, especially after the COVID-19 pandemic, either as an opt-in programme, by mailing the test with the option to opt out, via self-collection at the health centre or through outreach strategies (Arbyn et al., 2020).

Through an extensive review of the global literature on the use of self-sampling approaches based on government recommendations up to 2021 (Serrano et al., 2022 **RISCC**), **Figure 3** shows countries where self-sampling has been implemented for all women (**orange**), only for underscreened women (**yellow**) and countries that are piloting and planning to introduce HPV self-sampling (with an asterisk *****). Many sites not depicted in the figure are testing the use of self-sampling approaches.

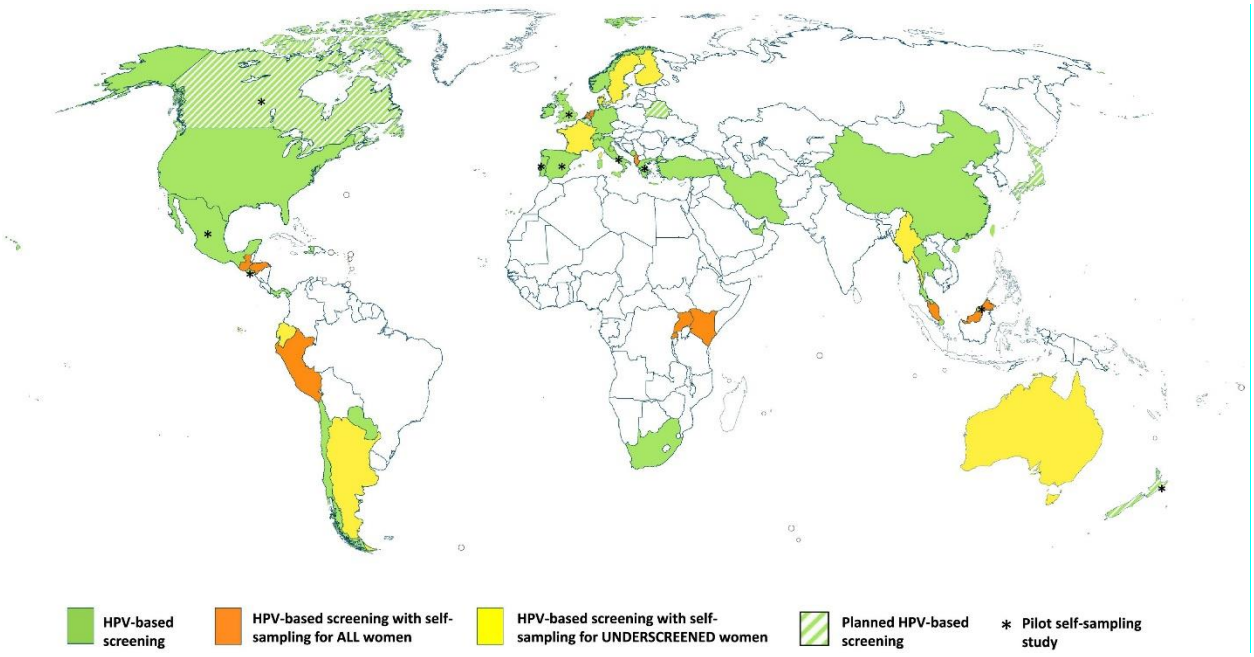


Figure 3. Worldwide implementation of HPV testing and self-sampling in 2021 (Serrano et al., 2022 **RISCC**)

The map provides an insight on the ongoing advances on self-sampling although the list of countries is likely to be changing continuously.

Countries such as Sweden, Australia and the Netherlands already offer self-sampling for HPV testing to all women in the screening-eligible population (i.e those aged over 23, 25 and 30 years, respectively) (Cancer Council Australia, n.d.; National Institute for Public Health and the Environment, n.d.; NKCx, n.d.). On the other hand, regions in Central and South Denmark have conducted or are currently conducting several self-sampling pilot studies for non-attenders (Maver & Poljak, 2020) and several regions in Spain are offering self-sampling as primary screening approach in women over 30 years of age (Torne et al., 2025).

Pioneering work in Argentina (Arrossi et al., 2017), Central America (Holme et al., 2020) and Nigeria (Modibbo et al., 2017) has shown the feasibility of the approach and that HPV testing using self-sampling approaches *'as part of organized cervical screening programs will likely be a fast evolving one, with the continued development of new HPV assays, pre-analytic devices, and hopefully, manufacturer-validated claims for the use of self-collection'* (Hawkes et al., 2020).

All the systematic reviews on self-sampling indicate a higher participation to cervical cancer screening programs compared to standard of care by almost doubling participation. However, many of the evaluations are based on a specific research project and are not measuring programmatic changes in coverage (Di Gennaro et al., 2022). Moreover, the magnitude of the effect by introducing a strategy of self-sampling varies strongly by setting, highlighting the need of pilot studies before rolling-out scenarios over the whole region or country (Arbyn et al., 2018).

KEY IDEA

Self-sampling can be a game changer in secondary prevention of cervical cancer

SUMMARY

Implementation of self-sampling in screening requires:

- clinically validated HPV detection technologies based on PCR.
- to include clinical management algorithms for women with positive results and to implement a good alert and appointment system to ensure that these women are triaged.
- a triage test for the HPV positive women. Reflex cytological triage of self-samples is not recommended, so a visit with a health professional is required for collecting a sample for cytology.
- more evidence for establishing the optimal screening interval, but the low risk of CIN2+ in women with a history of negative HPV self-samples suggests that a 5-year screening interval, currently used for clinician-collected samples, could also be appropriate for self-samples. A safe interval for women with a previous HPV positive test is yet to be stablished.
- a high level of acceptability among the target population (local trials are recommended prior to implementation).
- combining and adapting effective self-sampling strategies to specific contexts, resource levels, and socioeconomic groups to achieve high coverage and ensure optimal follow-up for women with positive results, and an HPV assay with a control for the presence of human cellular material.
- using a device that is safe and specifically designed to collect an adequate amount of vaginal material.
- training of the professionals involved and education of the target population.
- quality controls for all processes, and periodic evaluation of the strategy.

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