Worldwide use of HPV self-sampling for cervical cancer screening

B. Serrano a,b,*, R. Ibáñez a,b, C. Robles a, P. Peremiquel-Trillas a,b, S. de Sanjose c,d, L. Bruni a,b

A R T I C L E   I N F O

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self-sampling

A B S T R A C T

An increasing body of evidence supports the validity of self-sampling as an alternative to clinician collection for primary Human Papillomavirus (HPV) screening. Self-sampling effectively reaches underscreened women and can be a powerful strategy in low- and high-resource settings for all target ages. This work aims to summarize the current use of HPV self-sampling worldwide. It is part of a larger project that describes cervical cancer screening programmes and produces standardized coverage estimates worldwide. A systematic review of the literature and official documents supplemented with a formal World Health Organisation country consultation was conducted. Findings show that the global use of HPV self-sampling is still limited. Only 17 (12%) of countries with identified screening programs recommend its use, nine as the primary collection method, and eight to reach underscreened populations. We identified 10 pilots evaluating the switch to self-sampling in well-established screening programs. The global use of self-sampling is likely to increase in the coming years. COVID-19’s pandemic has prompted efforts to accelerate HPV self-sampling introduction globally, and it is now considered a key element in scaling up screening coverage. The information generated by the early experiences can be beneficial for decision-making in both new and existing programs.

1. Introduction

Cervical cancer is a largely preventable disease but remains the fourth most common cancer and the fourth leading cause of cancer death in women worldwide (Ferlay et al., 2020). Most of these cases occur in countries where women are not routinely screened or whose programs do not reach quality standards. In well-established successful programs, cases mainly result from women who do not participate in screening (Benard et al., 2021; Ibáñez et al., 2015).

Given the highly effective and cost-effective cervical cancer prevention strategies available, in 2020, the World Health Organisation (WHO) launched a global initiative to eliminate cervical cancer as a public health problem during the 21st century (Global strategy to accelerate the elimination of cervical cancer as a public health problem, 2020). Human Papillomavirus (HPV) tests have proven more sensitive, reproducible and to allow for safer extended screening intervals than conventional cytology or visual inspection with acetic acid (VIA) (Ronco et al., 2014; Arbyn et al., 2012). HPV testing is less dependent on operator expertise than cytology or VIA, making it more suitable for resource-constrained settings. Furthermore, HPV testing can be performed on vaginal samples collected by the woman herself, known as self-sampling. Self-sampling is a safe and easy approach increasing the opportunities of reaching women that otherwise would not participate in a clinician-based screening or facilitate their access to a screening test (WHO Guideline on self-care interventions for health and well-being, 2021). Systematic reviews and meta-analysis confirm that self-sampling is a highly acceptable method for cervical cancer screening in terms of ease of use, convenience, privacy, and physical and emotional comfort, in both high- and low-middle-income countries (LMIC). In addition, comparable diagnostic accuracy has also been confirmed for cervical intraepithelial neoplasia grade two or worse (CIN2+) of self-collected and clinician collected samples if amplification approaches such as polymerase chain reaction (PCR) based tests are used (Nishimura et al., 2021; Arbyn et al., 2018; Kamath Mulki and Withers, 2021).

Despite its potential benefits, the implementation of vaginal self-sampling has challenges, including healthcare workers training to explain the self-sampling procedure adequately to participating women, transportation of the collected specimens, laboratory technical

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differences between cervical and vaginal samples processing, and finally, skilled clinicians to manage and follow-up positive women (Hawkes et al., 2020). It is important to include clinical management algorithms and follow-up systems for HPV positive women, as well as to confirm the long-term protection afforded by an HPV negative self-sampling result. Though more evidence on this point is needed, it seems that the current 5-year interval for women with an HPV negative clinician collected result could also be feasible with a negative self-sample (Zhang et al., 2018).

Consequently, the WHO now recommends primary HPV based screening and includes self-sampling among the recently published guidelines on self-intervention for health and as part of the cervical cancer screening guidelines (WHO Guideline on self-care interventions for health and well-being, 2021), and the International Agency for Research on Cancer update of the efficacy and effectiveness of cervical cancer screening methods also supports this statement (Bouvard et al., 2021). Furthermore, the COVID-19 pandemic has accelerated the introduction of HPV self-sampling because it reduces the risk of exposure to the virus and expands health services, helping to address delays in screening. We aim to summarize for the first time the global use of the self-sampling approach in countries recommending primary HPV-based screening.

2. Methodology

This work is part of a larger project that describes cervical cancer screening programmes worldwide and produces standardized cervical cancer screening coverage estimates (Bruni, Serrano et al. Submitted). In brief, the project methodology included a systematic review of the scientific literature and official documents, conducted up to October 2020, to identify all available data on official national recommendations and cervical cancer screening coverage worldwide for the 194 WHO member states and eight associated countries and territories (American Samoa, Bermuda, China-Hong Kong special administrative region, French Polynesia, Greenland, Palestine, Puerto Rico, and Tokelau). The search algorithm included an initial search in official websites (e.g., health departments and national epidemiological institutions), followed by a global review with internet search engines. A systematic search in PubMed was also performed, using a combination of terms relevant to "cervical cancer", "screening", and "coverage" for each specific country. Reference lists of included documents were also reviewed for additional information. Professional translators assisted investigators in searching for information and interpreting the data in countries with official languages such as Arabic, Russian, or Chinese. All retrieved information on official national recommendations was cross-checked and supplemented with official responses to the WHO Non-Communicable Diseases Country Capacity Survey 2019. The global data search was finally supplemented with a formal WHO country consultation, conducted from Nov 27th, 2020, to Feb 12th, 2021. Countries were grouped into five geographical regions using the United Nations classification system, and by income level using the 2019 World Bank’s classification. The data produced through this work represents the first edition of the WHO cervical cancer screening estimates (Bruni, Serrano et al. Submitted). Future updates of these WHO indicators to monitor the worldwide uptake of self-sampling over time is planned.

3. Results

Official recommendations for cervical cancer screening were identified in 139 (69%) countries and territories. Up to February 2021, 48 (24%) countries recommended primary HPV-based screening. HPV testing was recommended alone or in combination with other screening tests. Most countries recommending primary HPV screening are transitioning from cytology. Six countries (Canada, New Zealand, Belgium, Belarus, Japan and Trinidad & Tobago) reported plans in 2020 for HPV-based screening introduction in the coming one or two years (Fig. 1). Among the 140 LMIC, 17% had introduced such screening (three low-,

Fig. 1. Self-sampling approach in countries officially recommending HPV-based screening.
The solid pattern indicates that the country recommends HPV-based screening (either alone or combined with cytology and/or VIA), the stripped pattern indicates that the country plans the introduction of primary HPV screening in the coming years. The boundaries shown and the designations used on this map do not imply the expression of any opinion whatsoever concerning the legal status of any country, territory, city or area or its authorities, or concerning the delimitation of its frontiers or boundaries.
Table 1
Self-sampling approach in countries officially recommending HPV-based screening.

<table>
<thead>
<tr>
<th>Country</th>
<th>Income</th>
<th>Recommended*</th>
<th>Year intro HPV-based screening / Self-sampling</th>
<th>Target population</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUROPE</strong></td>
<td></td>
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<tr>
<td>Albania</td>
<td>Upper middle-</td>
<td>In national program</td>
<td>2019/2019</td>
<td>All women</td>
<td>Before the implementation of the national HPV-based screening programme with self-sampling, a pilot study was conducted in the Fier region in southern Albania (year 2017). The national program started in 2019, in Tirana district and gradually expands over 3 years through the country.</td>
</tr>
<tr>
<td>Denmark</td>
<td>High</td>
<td>In national program</td>
<td>2012/2018</td>
<td>Underscreened women</td>
<td>HPV-based screening with the option of self-sampling is implemented in some municipalities while other municipalities use cytology as primary test</td>
</tr>
<tr>
<td>Finland</td>
<td>High</td>
<td>In national guidelines</td>
<td>2017/2017</td>
<td>Underscreened women</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>High</td>
<td>In national guidelines</td>
<td>2020/2020</td>
<td>Underscreened women</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>High</td>
<td>In national program</td>
<td>2017/2017</td>
<td>All women</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>High</td>
<td>In national program</td>
<td>2015/2015</td>
<td>Underscreened women</td>
<td>By Nov 2020, HPV-based screening was introduced by 16/21 regions. Seven regions had fully introduced self-sampling for underscreened women, and one additional region had partially introduced self-sampling.</td>
</tr>
<tr>
<td>Greece</td>
<td>High</td>
<td>Pilot study</td>
<td></td>
<td>Underscreened women</td>
<td>Pilot study in women residing in underserved rural areas of Northern Greece (year 2015).</td>
</tr>
<tr>
<td>Italy</td>
<td>High</td>
<td>Pilot study</td>
<td></td>
<td>All women</td>
<td>Pilot study in women residing in a specific area in Verona (Veneto region) (year 2019).</td>
</tr>
<tr>
<td>Portugal</td>
<td>High</td>
<td>Pilot study</td>
<td></td>
<td>Underscreened women</td>
<td>Pilot study in underscreened women living in Regional Health Administration of Portugal Centro (year 2018).</td>
</tr>
<tr>
<td>Spain</td>
<td>High</td>
<td>Pilot study</td>
<td></td>
<td>All women</td>
<td>Pilot study in women living in Galicia (year 2019), and in Cataluña (year 2021).</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>High</td>
<td>Pilot study</td>
<td></td>
<td>Underscreened women</td>
<td>Pilot study in underscreened women living in selected areas in London (year 2017).</td>
</tr>
<tr>
<td><strong>AFRICA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kenya</td>
<td>Lower middle-</td>
<td>In national guidelines</td>
<td>2018/2018</td>
<td>All women</td>
<td>HPV-test (with self-sampling) is not generally available in the country. Most facilities use VIA/VILI, followed by cytology.</td>
</tr>
<tr>
<td>Rwanda</td>
<td>Lower middle-</td>
<td>In national program</td>
<td>2013/2021</td>
<td>All women</td>
<td>HPV-based screening (with self-sampling) is being used at different hospitals in three districts of the country with a goal of scaling it up countrywide.</td>
</tr>
<tr>
<td>Uganda</td>
<td>Lower</td>
<td>In the strategic plan</td>
<td>2020/2020</td>
<td>All women</td>
<td>Before the implementation of the national HPV-based screening programme with self-sampling, a pilot study was conducted (year 2019) in women living with HIV at 16 selected health facilities in the country. The pilot results were used to generate recommendations for effective implementation of HPV testing for cervical cancer screening with the aim of increasing uptake of cervical cancer screening in women living with HIV and other groups in Uganda. The Pilot recommendations were considered to scale up the screen-triage- and-treat using HPV and VIA to 640 health facilities with HIV clinics across Uganda from October 2020–2025 with support from partners.</td>
</tr>
<tr>
<td><strong>AMERICA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>Upper middle-</td>
<td>In national guidelines</td>
<td>2014/2014</td>
<td>Underscreened women</td>
<td>Before the implementation of the national HPV-based screening programme with self-sampling, a pilot study was conducted (year 2011). Progressive implementation of the HPV test nationwide. Self-sampling started in Jujuy and Tucumán provinces. For population with socio-cultural &amp; geographic barriers.</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Upper middle-</td>
<td>In national cancer strategy</td>
<td>2017/2017</td>
<td>Special populations</td>
<td>Progressive implementation of the HPV test nationwide. Self-sampling started in Jujuy and Tucumán provinces. For population with socio-cultural &amp; geographic barriers.</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Lower middle-</td>
<td>In national guidelines</td>
<td>2020/2020</td>
<td>All women</td>
<td>Before the implementation of the national HPV-based screening programme with self-sampling, a pilot study was conducted in Chimaltenango, Guatemala y Sacatepéquez (year 2014) Proressive implementation of the HPV test nationwide. HPV-based screening started in Tumbes, Loreti and Junín</td>
</tr>
<tr>
<td>Perú</td>
<td>Lower middle-</td>
<td>In national guidelines</td>
<td>2017/2017</td>
<td>All women</td>
<td>Proressive implementation of the HPV test nationwide. HPV-based screening started in Tumbes, Loreti and Junín.</td>
</tr>
<tr>
<td>Honduras</td>
<td>In national guidelines</td>
<td>2015/2015</td>
<td>Special populations/All women Women with difficulties to access health services or all women who asks for (regions Francisco Morazán, El Paraíso y Copan).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Country</th>
<th>Income</th>
<th>Recommended* Year intro HPV-based screening/ Self-sampling</th>
<th>Target population</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>Lower-middle</td>
<td>Pilot study</td>
<td>Special populations/All women Pilot study in women living in high-risk and marginalized areas in Veracruz (year 2010) and in all women living in Morelos State (year 2007).</td>
<td></td>
</tr>
<tr>
<td>OCEANIA</td>
<td>Australia</td>
<td>High- In national program 2018/2018</td>
<td>Underscreened women</td>
<td>Should be done in a health care setting and at a health professional’s request.</td>
</tr>
<tr>
<td>Asia</td>
<td>Malaysia</td>
<td>Upper-middle Into national program 2019/2019</td>
<td>All women</td>
<td>The country is currently in transition towards a generalized use of HPV test as the primary screening test. The rollout of the HPV screening test started in 2019 and will be nationwide by 2024. Malaysia adopts the Australia cervical screening guidelines.</td>
</tr>
<tr>
<td></td>
<td>Myanmar</td>
<td>Lower-middle Into national program 2018/2018</td>
<td>Special populations</td>
<td>HPV-based screening for women living in rural areas</td>
</tr>
<tr>
<td></td>
<td>Brunei</td>
<td>High- Pilot</td>
<td></td>
<td>In 2019, Brunei has embarked on research study to look at acceptability of self-sampling HPV test. The Ministry of Health is considering the implementation of the HPV test.</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>High- Pilot study</td>
<td>Underscreened/All women/ Special populations Pilot studies in some regions: in Manitoba in underscreened women, in Newfoundland and Labrador in rural and urban settings, and in Ontario in aboriginal First Nation community in Northwest Ontario.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Zealand</td>
<td>High- Public consultation + pilot studies</td>
<td>Underscreened</td>
<td>Planned introduction HPV test in national program. The Parliamentary Review Committee strongly recommends the introduction of self-sampling, starting with a pilot study. Public consultation for the introduction of self-sampling. There are currently two pilot studies in progress in Maori women.</td>
</tr>
</tbody>
</table>

**Sources:**


Denmark: Danish Health Authority. Recommendations for cervical cancer screening - 2018 [Screening for livmoderhalskræft - anbefalinger 2018]. Available at: https://www.sst.dk/da

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do colo do útero em casa. 23/10/2018]. Available at: https://www.rtp.pt/noticias/


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Myanmar: WHO country consultation


* Source from which the information was retrieved (national guidelines, screening program website, strategic plan…)
five lower-middle- and 16 upper-middle-income countries), compared to 39% countries among the 62 high-income countries (Bruni, Serrano et al. Submitted).

Among the 48 countries with HPV-based programs, 17 (35%) report having introduced self-sampling in their national programs or guidelines, either for underscreened populations in eight countries (Argentina, Australia, Denmark, Ecuador, Finland, France, Myanmar and Sweden) or as the primary screening option for all women in nine countries (Albania, Kenya, Guatemala, Honduras, Malaysia, Netherlands, Peru, Rwanda and Uganda). Most of these countries have simultaneously introduced the use of HPV-based screening and the self-sampling approach (Fig. 1, Table 1). Among the 17 countries recommending HPV self-sampling, two (12%) are low-, five (29%) are lower-middle-, four (24%) are upper-middle- and six (35%) are high-income countries. Eight additional countries are also piloting self-sampling to decide whether to include this option in their screening guidelines, either targeting all women (Brunei, Mexico, Italy, Spain) or targeting underscreened populations (El Salvador, Greece, Mexico, Portugal and United Kingdom). Most countries recommending HPV-based screening are located in Europe and America, 17 and 16 countries respectively, and among them, one in three countries have also introduced self-sampling in their screening recommendations, and seven more countries are piloting this approach. Among the six countries planning to introduce HPV-based screening, New Zealand and Canada are also piloting self-sampling (Fig. 1, Table 1).

4. Discussion

The present work summarizes for the first time the current implementation of screening with HPV self-sampling worldwide, in a context in which an increasing number of countries are switching to virological testing. Currently, 35% of the 139 countries with identified official screening recommendations promote the use of primary HPV-based screening. The use of HPV self-sampling is only recommended in 17 countries at the time of this review, 35% among countries recommending HPV-based screening. In eight of them, it is recommended for reaching underscreened populations and in nine as the primary collection method. In ten more countries, self-sampling is in a piloting phase.

A minimum screening coverage of 70% among screening targeted women has long been recommended to observe an impact in mortality from the disease. The WHO’s elimination initiative is reinforcing this 70% target of women aged 35–45 years screened at least twice with a high-performance test and 90% treatment of women with identified lesions (Global strategy to accelerate the elimination of cervical cancer as a public health problem, 2020). Currently, screening and treating identified cervical lesions is the main strategy to reduce cervical cancer in the short-term. However, recent estimates confirm that program performance is suboptimal in most countries. Two out of three women aged 30–49 years have never been screened, with significant disparities between high- and LMICs (83% vs 27% ever coverage, respectively). In addition, 55 (39%) LMIC still lack cervical cancer screening programmes, most of them from Africa and Asia (Bruni, Serrano et al. Submitted).

The use of self-sampling for HPV primary screening provides a key opportunity to increase coverage, particularly in low-resource settings, where infrastructure and specialized workforce is very limited. Although only eleven LMIC have introduced such screening in their official recommendations at the time of this review, it is essential to emphasize that the increased awareness aiming to eliminate cervical cancer may facilitate its introduction in the coming years. However, economic factors and varying healthcare priorities can limit the implementation of HPV-based screening. The cost of HPV testing is perceived as a significant barrier to primary HPV testing, but modeling studies have already demonstrated the benefits of even a single high-precision screen over lifetime (Canfell et al., 2020). Importantly, several new, more affordable assays designed explicitly for LMIC, allowing point-of-care HPV testing are currently under development (Arbyn et al., 2020). HPV-based screening with self-sampling is a highly cost-effective approach. It overcomes the human constraints faced by many LMICs, as only women that screen positive will require gynecological exams, and therefore reducing the specialized workforce (de Sanjose and Holme, 2019).

Another advantage of self-sampling devices is that they do not require a cold chain and are stable after collection, minimizing the infrastructure and logistics required for transport to a central HPV testing facility (Cho et al., 2021). However, it is critical to ensure an adequate follow-up and management of screen positives. If not, gains on increased participation are of no use (Zhang et al., 2018; Verdoold et al., 2015; Paolino et al., 2020). Further, the increased risk of cervical cancer in women living with human immunodeficiency virus (HIV) and the limited data on the use of self-sampling in this population may require additional accuracy studies in settings where HIV prevalence is high (Wong et al., 2018).

Our findings show that HPV self-sampling is mainly used to reach underscreened populations. In many countries, the COVID-19 disease has disrupted cervical cancer screening programs, changing the perspectives of self-sampling as a primary screening method for all women. Recently, a thorough evaluation of the impact of the pandemic and the key learnings to strengthen cancer screening activities worldwide have been reported. Wentzensen et al. discuss the opportunity to renew and make cervical cancer screening more resilient, highlighting the advantages of risk-based management, HPV-based screening, and in particular, the use of HPV-self sampling (Wentzensen et al., 2021).

HPV self-sampling is a promising strategy to overcome the multiple barriers to cervical cancer screening in low-resource settings and increasing attendance in underscreened women in countries with well-established screening programs. The HPV self-sampling approach may be the only way to improve access to and uptake of screening, especially in those regions of the world with the highest burden of disease, and is now considered a key pillar to reach the WHO elimination target (WHO Guideline on self-care interventions for health and well-being, 2021; de Sanjose and Holme, 2019). The information generated by the early experiences can be beneficial for decision-making in both new and existing programs.

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CRediT author statement

Laia Bruni conceptualized the project. Beatriz Serrano designed the data-extraction form, did the literature search, and collected the data. Beatriz Serrano prepared the tables and figures and wrote the
manuscript. All authors contributed to data interpretation, critically revised subsequent drafts, and read and approved the submitted version.

References


