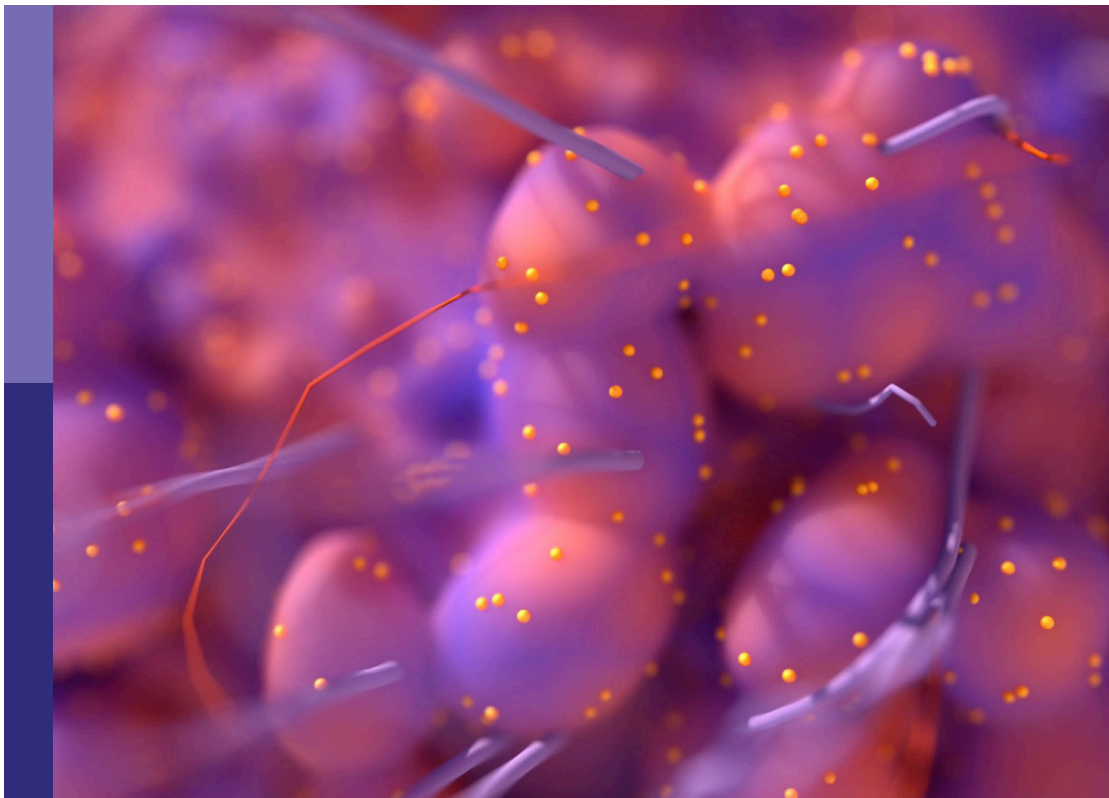
frontiers | Research Topics

# Cervical cancer control in Latin America and the Caribbean

**Edited by**
Angelica Nogueira-Rodrigues, Lucely Cetina-Pérez and Mauricio Maza

**Published in**
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-8325-5489-0
DOI 10.3389/978-2-8325-5489-0

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# Cervical cancer control in Latin America and the Caribbean

**Topic editors**

Angelica Nogueira-Rodrigues — Federal University of Minas Gerais, Brazil
Lucely Cetina-Pérez — National Institute of Cancerology (INCAN), Mexico
Mauricio Maza — Pan American Health Organization, United States

**Citation**

Nogueira-Rodrigues, A., Cetina-Pérez, L., Maza, M., eds. (2024). *Cervical cancer control in Latin America and the Caribbean*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-5489-0

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frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 08 May 2024
DOI 10.3389/fonc.2023.1226915



OPEN ACCESS

EDITED AND REVIEWED BY
Sophia George,
University of Miami, United States

*CORRESPONDENCE
Angélica Nogueira-Rodrigues
angelica.onco@uol.com.br

RECEIVED 22 May 2023
ACCEPTED 19 October 2023
PUBLISHED 08 May 2024

CITATION
Nogueira-Rodrigues A, Cetina Perez L and Maza M (2024) Editorial: Cervical cancer control in Latin America and the Caribbean. *Front. Oncol.* 13:1226915. doi: 10.3389/fonc.2023.1226915



# Editorial: Cervical cancer control in Latin America and the Caribbean

Angélica Nogueira-Rodrigues[1]*, Lucely Cetina Perez[2] and Mauricio Maza[3]

[1]Department of General Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil, [2]Department of Clinical Research, Instituto Nacional de Cancerologia, National Cancer Institute, Mexico City, Mexico, [3]Pan American Health Organization, Washington, DC, United States

KEYWORDS

**cervical cancer 1, Latin America, epidemiology, prevention, screening, treatment, elimination**

Editorial on the Research Topic:
Cervical cancer control in Latin America and the Caribbean

Worldwide, more than half a million women are diagnosed with cervical cancer (CC) annually, and over 300,000 die from the disease. Low-and middle-income countries (LMICs) account for around 85%, almost 10% of them in Latin America (LATAM) and the Caribbean, where mortality rates are almost five times higher than in high- income countries (HICs) (1, 2).

The long natural history of HPV-carcinogenesis provides a window of opportunity for secondary prevention with screening tests, which identify women infected with HPV or with cytologic abnormalities indicative of precancerous lesions. These lesions can be successfully controlled with early treatment (3). The existence of a primary infectious etiologic agent allows for primary prevention with prophylactic HPV vaccines capable of reducing the incidence of causative infections. Thus, cervical cancer is considered a preventable and treatable disease, despite the fact it continues to be the third highest cause of cancer in women in the region (3).

In May 2018, the World Health Organization (WHO) made a call to action for the global elimination of the disease as a public health problem. Elimination would occur when incidence rates scale down to less than 4 cases/100,000 women and would be possible through a strategy comprising three goals to be achieved by 2030: 90% HPV vaccination coverage of girls by 15 years of age, 70% screening coverage with high-performance tests of women by ages 35 and 45, and adequate management and treatment of 90% of precancerous lesions and invasive cancers (4). According to the WHO's predictions, in LMICs and in most countries of Latin America, CC elimination is possible in the long term but will depend heavily on achieving the target for vaccination coverage (5, 6).

The main objectives of this Research Topic, comprised of nine articles, are to outline the most recent strategies to control CC in the sovereign states of LATAM, to present obstacles to disease control in the region, and to discuss ideas to overcome them.

Starting from vaccination, the advent of HPV prophylactic vaccination offers a potential large step towards control of CC and other HPV-related cancers. Based on the high incidence of HPV-related cancers, the strong carcinogenic potential of certain HPV strains, and numerous trials proving the high efficacy of vaccines, immunization is considered one of the most important tools to alter the incidence of HPV-associated cancers in LMICs globally (7, 8). However, this Research Topic brings data to alert that HPV vaccine uptake in LATAM has been lower than expected. In the article from Nogueira-Rodrigues et al., a significant decline in its adhesion is reported, and several reasons are probably involved including limited knowledge of HPV and the HPV vaccine, misguided safety concerns, high cost, cultural barriers, and the COVID-19 pandemic. The authors present strategies to overcome the main barriers, such as adopting the one- dose schedule, delivering the vaccine to both health centers and schools, and advising health professionals to formally prescribe the vaccine.

Switching gears to screening strategies, in high-income countries, following the introduction of and adherence to Papanicolaou's smear test in the 1940s, CC incidence declined by more than 60%, confirming this test as the most effective cancer screening tool in the history of medicine. However, the PAP smear has achieved limited success in LMICs due to several reasons, mainly lack of organized screening programs within weak health systems, technique limitations, low population coverage and not sufficiently reaching the high-risk population group, poor quality control, and insufficient monitoring (7). Furthermore, this dismal scenario has been significantly impacted by the COVID-19 pandemic with further declines at all levels of CC prevention and increasing inequalities, as reported by Cruz-Valdez et al.

In concordance with the WHO's call for best practices to eliminate CC (4), the feasibility of self-collection of samples for high-risk HPV is currently being tested in several countries across the LATAM region, and a systematic review of the topic is presented in the Research Topic by Dartibale et al. HPV self-sampling is a promising strategy to overcome barriers to CC screening in areas with well-established screening programs, but may also reach those without organized screening and special populations such as indigenous, rural, and transgender women. Strategies to develop a concerted effort at local, regional, and national levels to support capacity building in reporting, monitoring, and surveilling, as well as strategies to comprehend and overcome cultural barriers for self-screening acceptance is shared by Mitchell et al., McFarlane et al., and Urrutia and Padilla.

Regarding treatment challenges, most CC patients in the region are diagnosed with locally advanced disease (9) and, since the late 1990s when a spate of US studies reported the benefit of cisplatin-based chemoradiation for CC, there has been a dearth of clinical advances in this setting and the cure rates of locally advanced disease have reached a plateau (10–13). Furthermore, efforts to increase disease control with additional chemotherapy have not been clearly positive so far (13–15). A systematic review and meta-analysis on concurrent chemoradiotherapy followed by adjuvant chemotherapy is presented in the Research Topic by Liu et al. Arango-Bravo et al. highlight a shortage in several aspects of CC treatment, including oncologists, chemotherapy units, and radiotherapy facilities, and that Mexico is a upper middle-income country country. To conclude, Maluf et al. make recommendations for the prevention, screening, diagnosis, staging, and management of CC in areas with limited resources based on an International Gynecological Cancer Society (IGCS) consensus meeting, defending that the development of guidelines by health care providers from LMI regions is more reflective of the reality on the ground.

Cervical cancer continues to be a public health challenge in LATAM and immediate coordinated efforts are urgently needed to best use the existing tools to control the disease. Given that HPV-associated tumors arise years, if not decades, after initial infection and that existing vaccines have no therapeutic efficacy on pre-existing CC (7), further delays to implement high- coverage HPV vaccination programs coupled with improvements in screening strategies will only mean continued loss of life from a preventable disease and undue financial burden on already constrained health systems.

## Author contributions

All authors contributed to conceptualization, data curation, formal analysis, validation, visualization; writing – original draft; writing – review & editing. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 18 August 2022
DOI 10.3389/fonc.2022.928560



OPEN ACCESS

EDITED BY
Anna Myriam Perrone,
Sant'Orsola-Malpighi Polyclinic, Italy

REVIEWED BY
Luisa Accardi,
National Institute of Health (ISS), Italy
Junzo Chino,
Duke University, United States
Gauravi Mishra,
Tata Memorial Hospital, India

*CORRESPONDENCE
Fernando Cotait Maluf
maluffc@uol.com.br

†Full list of attendees on Supplementary Files

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 25 April 2022
ACCEPTED 01 August 2022
PUBLISHED 18 August 2022

CITATION
Maluf FC, Dal Molin GZ, de Melo AC, Paulino E, Racy D, Ferrigno R, Uson Junior PLS, Ribeiro R, Moretti R, Sadalla JC, Nogueira-Rodrigues A, Carvalho FM, Baiocchi G, Callegaro-Filho D and Abu-Rustum NR (2022) Recommendations for the prevention, screening, diagnosis, staging, and management of cervical cancer in areas with limited resources: Report from the International Gynecological Cancer Society consensus meeting.
*Front. Oncol.* 12:928560.
doi: 10.3389/fonc.2022.928560



# Recommendations for the prevention, screening, diagnosis, staging, and management of cervical cancer in areas with limited resources: Report from the International Gynecological Cancer Society consensus meeting

Fernando Cotait Maluf[1,2*], Graziela Zibetti Dal Molin[1], Andreia Cristina de Melo[3], Eduardo Paulino[4], Douglas Racy[1], Robson Ferrigno[1], Pedro Luiz Serrano Uson Junior[2,5], Reitan Ribeiro[6], Renato Moretti[2], Jose Carlos Sadalla[7], Angelica Nogueira-Rodrigues[8], Filomena Marino Carvalho[9], Glauco Baiocchi[10], Donato Callegaro-Filho[2] and Nadeem R. Abu-Rustum[1†]

[1]Hospital Beneficiência Portuguesa (BP) Mirante, São Paulo, Brazil, [2]Hospital Israelita Albert Einstein, São Paulo, Brazil, [3]Instituto Nacional de Câncer-Inca, Rio de Janeiro, Brazil, [4]Oncomed, Rio de Janeiro, Brazil, [5]HCOR Oncologia, São Paulo, Brazil, [6]Instituto de Oncologia do Paraná, Paraná, Brazil, [7]Hospital Sírio Libanês, São Paulo, Brazil, [8]Universidade Federal de Minas Gerais, Minas Gerais, Brazil, [9]Faculdade de Medicina da USP, São Paulo, Brazil, [10]A.C. Camargo Cancer Center, São Paulo, Brazil, [11]Memorial Sloan Kettering Cancer Center, New York, NY, United States

**Introduction:** Nearly 85% of cervical cancer new cases are diagnosed in limited resources countries. Although several strategies have been proposed to reduce the disease burden, challenges remain to provide the best possible care. We report recommendations from an expert consensus meeting convened to address from prevention to management of cervical cancer in limited resources countries.

**Methods:** The expert panel, composed by invited specialists from 38 developing countries in Africa, Asia, Eastern Europe, Latin America, and the Middle East, convened in Rio de Janeiro in September 2019, during the Global Meeting of the International Gynecological Cancer Society (IGCS). Panel members considered the published scientific evidence and their practical experience on the topics, as well as the perceived cost-effectiveness of, and access to, the available interventions. The focus of the recommendations was on geographic regions rather than entire countries because medical practice varies considerably in the countries represented. Resource limitation was qualified as limited access to qualified surgeons, contemporary imaging or

radiation-oncology techniques, antineoplastic drugs, or overall funding for provision of state-of-the-art care. Consensus was defined as at least 75% of the voting members selecting a particular answer of the multiple-choice questionnaire, whereas the majority vote was considered as 50% to 74.9%.

**Results:** Consensus was reached for 25 of the 121 (20.7%) questions, whereas for 54 (44.6%) questions there was one option garnering between 50% to 74.9% of votes (majority votes). For the remaining questions, considerable heterogeneity in responses was observed.

**Discussion:** The implementation of international guidelines is challenging in countries with resource limitations or unique health-care landscapes. The development of guidelines by the health care providers in those regions is more reflective of the reality on the ground and may improve medical practice and patient care. However, challenges remain toward achieving that goal at political, economic, social, and medical levels.

KEYWORDS

**cervical cancer, radiotherapy, chemotherapeutics, limited resource area, limited resource countries**

## Introduction

Cervical cancer is the fourth most common malignancy among females, both for incidence and mortality. It is estimated that nearly 570.000 new cases and 310.000 deaths worldwide each year (1). The burden of cervical cancer is disproportionately distributed between low-/middle-income countries (LMICs) and high-income countries (HICs). Whereas the incidence of cervical cancer and its mortality have decreased by nearly 75% over the past 50 years in most HICs, around 85% of new cases of this disease are diagnosed in LMICs (2, 3). Improvements in HICs have been ascribed mostly to the use of pap test screening and the ability to diagnose and treat patients with pre-invasive lesions, whereas low population coverage, poor-quality cytology, incomplete follow-up of screen-positive women, and barriers to effective treatment are potentially responsible for the low success of cervical-cancer prevention programs in LMICs (2, 4).

More than 80% of women followed over time will be exposed to at least one high-risk variance of Human Papilloma Virus (HPV). The HPV vaccination as a preventive strategy should target young people before initiation of sexual activity, focusing on girls and boys aged 10–14 years. Moreover, the availability of HPV vaccination has led to an even brighter future for women in HICs to reduce the burden of cervical neoplasia (5). HPV vaccination offers at the same time the potential to decrease the incidence and mortality of cervical neoplasia, but at the same time highlights the disparities in cervical cancer prevention if vaccines are not available due to socioeconomic factors, especially in low-income countries, depending on the coverage of its implementation (6–8). Although considerable progress has been made in Latin America, Africa, Asia, Eastern Europe and the Middle East, specific obstacles to widespread adoption of HPV vaccination have been highlighted and include limited awareness of HPV disease, the vaccine, safety, costs, and cultural barriers (9).

Although several strategies have been proposed aiming to reduce the burden of cervical cancer in LMICs (5, 7, 10), challenges remain for the practicing physician to provide the best possible care in areas with limited resources and with varying national health-care policies. This is the first article reporting the recommendations from an expert consensus meeting convened to address the challenges on prevention, screening, diagnosis, staging, and management of cervical cancer in areas with limited resources. The meeting was convened under the auspices of the International Gynecological Cancer Society.

**Abbreviations:** HSIL, high grade squamous intra-epithelial lesion; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone.

## Methods

### Panel organization, composition, and objectives

The questions addressed by the panel were proposed by a 15-member committee as the most relevant for decision-making in

areas facing resource limitations. The panel, composed of invited specialists in gynecological oncology from 38 developing countries in Africa, Asia, Eastern Europe, Latin America, and the Middle East, aimed to provide recommendations on salient issues that affect the management of cervical cancer in these areas (Supplementary Table 1). The panel was composed by physicians who are opinion leaders for the treatment of gynecological malignancies in gynecology, surgery, medical oncology, radiation oncology, radiology, and pathology in their respective countries. The panel provided the recommendations using an electronic voting system in sessions held on 19th and 20th September 2019, during the Global Meeting of the International Gynecological Cancer Society, convened in Rio de Janeiro, Brazil (Figure 1). To provide such recommendations, panel members considered the published scientific evidence and their practical experience on the topics, as well as the perceived cost-effectiveness of, and access to, the available interventions. One polling session with multiple-choice questions was scheduled for each of the main topics that constitute the subheadings described below. When answering each multiple-choice question, panel members were instructed to consider that their recommended intervention was approved and available, with no contraindications in the scenario described by the corresponding question. Moreover, recommendations were to be given for non-frail patients (defined as having an Eastern Cooperative Oncology Group [ECOG] performance status between 0 and 2) and for patients with squamous cell carcinoma or adenocarcinoma of the cervix. Finally, the staging classification used throughout was the latest version 2018 provided by the International Federation of Obstetrics and Gynecology (11).

## Definition of resource limitation

Despite the World Bank's classification of economies into four income groups (high, upper-middle, lower-middle, and low (12)), and notwithstanding the fact that the panel includes members from countries that may belong to different income groups, the socioeconomic framework used during the discussions and reported herein relates to the availability of ideal resources. This is particularly relevant in some of the countries represented, which have heterogeneous health-care systems. In Brazil, for example, significant disparities exist in health care; although this remains the responsibility of the federal government, care is in fact provided in two major systems (public and private) which display very diverse characteristics in terms of access to state-of-the art care. This is particularly evident in oncology, given the high costs associated with providing health care in the public system, the sole provider for nearly 75% of the Brazilian population (13). The same situation affects other countries represented by the panel, whereas some of the countries have a more uniform, albeit constrained, health-care system. Regardless of the situation in

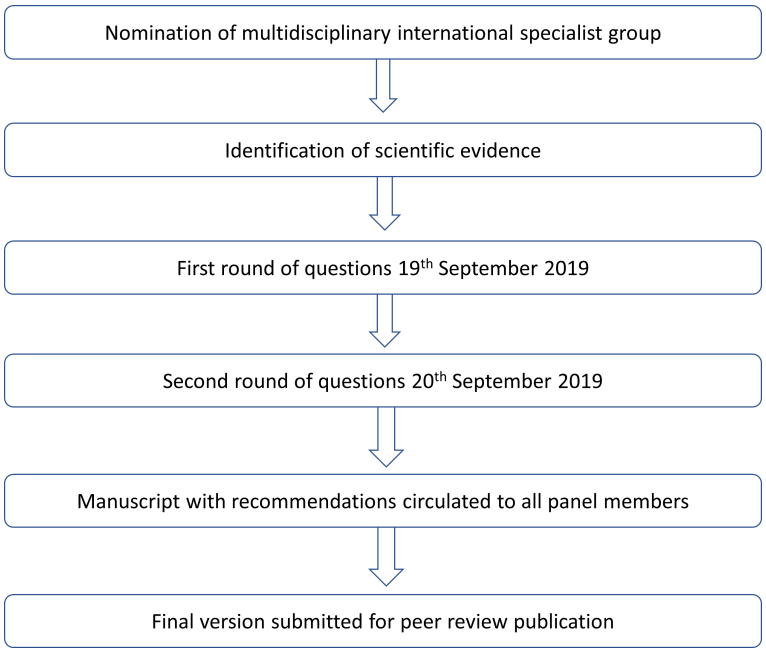


FIGURE 1
Development process.

individual countries, the focus of the current work and recommendations is on "area" rather than "country", under the assumption that medical practice may not be necessarily constrained in a whole country and still be subject to resource limitation in given areas or settings within a country. Finally, resource limitation was qualified as the limited access to qualified surgeons, contemporary imaging or radiation-oncology techniques, antineoplastic drugs, or overall funding for provision of state-of-the-art care.

## Statistical analysis

Results are presented descriptively for each of the questions addressed by the panel. Consensus was reached if at least 75% of the voting members selected a particular answer, not considering in the denominator of this proportion the response option "unqualified to answer" (Table 1). On the other hand, the response option "abstains" (used when a member felt impeded to provide a qualified response for reasons other than lack of knowledge, including the presence of conflicts of interest or absence of a reasonable response option) was considered in the denominator. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

# Results

## Section 1 - Prevention, screening, diagnosis, staging, and surveillance of cervical cancer

There was no consensus for any of the questions related to HPV vaccination and screening in areas with limited resources (Supplementary Table 2, 3). Regarding which HPV vaccine should be recommended, the quadrivalent vaccine was chosen by the largest percentage of panel members (42.1%), whereas 30.3% recommended any among the bivalent, quadrivalent and nonavalent vaccines. Despite the absence of consensus, 66.7% of panel members indicated a preference for two vaccine doses, separated by 6 months under the age of 15, with only 21.7% giving preference for three doses.

The Bethesda classification was the preferred classification for cervical cytology obtaining 72.2% of votes. In addition, at least 50% of voters recommended the following (1): an initial yearly cervical cytology followed by testing every 3 years after two consecutive normal exams (61.2% of voters) (2); stopping screening in women aged 65 years with evidence of two adequate negative prior screening results and no history of cervical intraepithelial neoplasia (CIN) of grade 2 or higher (59.3%); and (3) referral of patients with abnormal cytology to colposcopy followed by biopsy and treatment only if high grade squamous intraepithelial lesion (HSIL, i.e., CIN2/CIN3) or higher is confirmed on biopsy (52.6%). Nearly 40% of panel members believed HPV testing should be routinely available in areas with limited resources, whereas nearly a third recommended this practice only in selected cases, and 27.1% were against such testing. There was considerable variability in the opinion about the ideal age at which screening should begin for sexually active women.

Consensus was reached for two questions related to the diagnosis of cervical cancer in areas with limited resources (Supplementary Table 4): colposcopy is only indicated in cases with HSIL (CIN2/3) or higher cytological findings, and the histopathological report for surgical specimens should include information on margins, tumor size and grade, depth of invasion, lymph vascular and perineural invasion, mitotic index, necrosis, parametrium involvement, and lymph-node metastasis. Most of the votes was obtained for the need to have immunohistochemistry studies of suspected adenocarcinoma, neuroendocrine carcinoma, sarcoma, or rare tumors (72.0% of votes) and for considering that cervical cytology (positive for carcinoma) is insufficient for diagnosing clinically suspicious tumors (59.3%).

Regarding the diagnostic methods required for staging patients with cervical cancer, 80% of respondents recommended abdominal and pelvic computed tomography (CT) plus chest X-ray for those with early clinical stages (FIGO IB2 and 3). Likewise, 85.2% of panel members recommended these exams for patients with clinical stages II-IVA (Supplementary Table 5). For two questions, there was at least one recommendation made by at least 50% of voters (abdominal and pelvic CT plus chest X-ray for clinical stage IB1 or earlier cervical cancer, and abdominal and pelvic magnetic resonance imaging (MRI) plus chest X-ray for this same setting when trachelectomy is being considered.

Over 80% of panel members indicated their preference for follow-up every 3 months in the first 2 years, and every 6 months thereafter until 5 years from treatment. Slightly over 60% of voters were in favor of vaginal cytology in the follow-up of patients with early-stage disease undergoing radical hysterectomy, whereas 58.4% recommended follow-up every 3 months in the first 2 years, and every 6 months thereafter until 5 years from treatment in patients early-stage disease undergoing curative treatment. For the other questions, there was considerable heterogeneity in responses (Supplementary Table 6).

## Recommendations based on consensus:

* Colposcopy is only indicated in cases with HSIL (CIN2/3) or higher cytological findings.

TABLE 1 Voting consensus.

| Session | Majority voting | Consensus |
|---|---|---|
| Session 1 Prevention, screening, diagnosis, staging, and surveillance of cervical cancer | * Two vaccine doses, separated by 6 months, under the age of 15 for boys and girls.<br>* Bethesda classification is the preferred classification for cervical cytology.<br>* Yearly cervical cytology followed by testing every 3 years after two consecutive normal exams.<br>* Stopping screening in women aged 65 years with evidence of two adequate negative prior screening results.<br>* IHC is necessary for suspected adenocarcinoma, sarcoma, neuroendocrine or rare tumors. | * Colposcopy is only indicated in cases with HSIL (CIN2/3) or higher cytological findings.<br>* Histopathological report for surgical specimens should include information on margins, tumor size and grade, depth of invasion, lymph vascular and perineural invasion, mitotic index, necrosis, parametrium involvement, and lymph-node metastasis.<br>* Recommended staging method is abdominal and pelvic computed tomography (CT) plus chest X-ray for those with clinical stages FIGO IB2 to IVA.<br>* Recommended follow-up is every 3 months in the first 2 years, and every 6 months thereafter until 5 years from treatment. |
| Session 2 Treatment of early-stage cervical cancer | * For stage IA2 cervical cancer is recommended radical hysterectomy when no fertility is desired, conization for similar diagnosis in women desiring to preserve fertility.<br>* For women with stage IB1-IB2 cervical cancer, surgery alone is recommended for areas in which RDT is not available. In areas where surgeons do not have a full training in gynecology oncology, chemoradiation should be recommended.<br>* For women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA, chemoradiation alone is recommended.<br>* Follow up is recommended after an incidental diagnosis of stage IA2 disease without lymph vascular invasion in a simple hysterectomy specimen in areas in which surgeons do not have full training in gynecology oncology.<br>* Conventional external RDT is the recommended technique as the minimum required treatment for women with early-stage cervical cancer who need adjuvant RDT.<br>* In institutions with only cobalt machines, patients with early-stage cervical cancer can be treated with external RDT.<br>* Vaginal vault brachytherapy after external radiotherapy, as a boost, for patients with early-stage cervical cancer and at least two intermediate-risk features. | * For women with stage IA2 cervical cancer wishing to preserve fertility, trachelectomy is the treatment recommendation indicated by panel members.<br>* Neoadjuvant chemotherapy followed by surgery is indicated for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which RDT is not available.<br>* Chemoradiation alone is recommended for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which surgeons do not have full training in gynecology oncology.<br>* Neoadjuvant chemotherapy followed by simple hysterectomy was recommended for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which surgeons do not have full training in gynecology oncology and RDT is not available.<br>* Open surgery was indicated as the recommended approach for patients with stage IB-IIA cervical cancer undergoing radical hysterectomy.<br>* For women with early-stage cervical cancer undergoing surgery and having at least one high-risk feature (positive surgical margins, pathologically involved pelvic nodes, or positive involvement of the parametria), adjuvant RDT and chemotherapy should be indicated.<br>* Both primary and adjuvant external RDT can be administered to women with early-stage cervical cancer in institutions where there are only conventional radiotherapy techniques. |
| Session 3 Locally advanced cervical cancer | * RDT alone can be indicated when chemotherapy is not available in a timely manner for patients with locally advanced disease.<br>* In terms of external RDT technique for stages IB3 through IVA disease, the minimal recommended option is conventional radiation. Cobalt machines is appropriate if it is the only external technique available.<br>* RDT with chemotherapy is appropriate if no brachytherapy is available for patients with stages IIB through IVA disease.<br>* When radiotherapy is not available, neoadjuvant chemotherapy followed by surgery in locally advanced disease is an option.<br>* For patients not eligible to cisplatin, the recommended radiosensitizing agent is carboplatin.<br>* Hysterectomy should not be recommended after chemoradiation for patients with bulky (>4 cm) tumors and no residual tumor after treatment. | * Primary concomitant chemoradiation is recommended for stages IIB to IVA cervical cancer.<br>* Chemoradiation alone is recommended for patients with locally advanced disease in areas where surgeons do not have full training in gynecologic oncology, and for patients with HIV/AIDS or other forms of immunosuppression.<br>* A two-dimensional conventional brachytherapy technique is recommended for eligible patients with stages IB3 through IVA disease after external radiation.<br>* For women with suspected or pathologically confirmed para-aortic node involvement, primary chemoradiation with extended-field radiotherapy is recommended.<br>* Weekly cisplatin is the preferred radiosensitizing agent for the general patient population and for patients with HIV/AIDS or other forms of immunosuppression. |
| Session 4 Treatment and clinical complications of metastatic or recurrent cervical cancer | * The recommended first-line treatment for patients with platinum-naïve metastatic or recurrent cervical cancer not amenable to salvage loco-regional treatment when all resources are available is a regimen of cisplatin, paclitaxel, and bevacizumab.<br>* When resources are limited, the recommended first-line treatment for such patients is cisplatin plus paclitaxel.<br>* The recommended first-line treatment for AIDS and other immunosuppressed patients not amenable to salvage loco-regional treatment in areas with limited resources is full-dose platinum-based chemotherapy doublet.<br>* When monotherapy is indicated as the first line with a non-platinum option, paclitaxel should be recommended.<br>* The best intervention to control vaginal bleeding secondary to tumor progression in a patient previously treated with | * For patients not amenable to salvage loco-regional treatment and not eligible to receive cisplatin, carboplatin plus paclitaxel should be the regimen of choice.<br>* The best intervention to treat fecal incontinence due to rectovaginal fistula is surgical management by a diverting colostomy.<br>* Sexual functioning appointments should be offered for cervical cancer survivors in the majority of patients.<br>* Either paclitaxel or gemcitabine can be considered as appropriate treatment options for women with metastatic cervical cancer at any point according to its availability and lower price. |

*(Continued)*

TABLE 1 Continued

| Session | Majority voting | Consensus |
|---|---|---|
| | radiotherapy is vaginal packing with or without tranexamic acid.<br>* Percutaneous nephrostomy is recommended as the best intervention to treat extrinsic ureteral compression secondary to tumor progression. | |

RDT, radiotherapy; IHC, Immunohistochemistry.

* Histopathological report for surgical specimens should include information on margins, tumor size and grade, depth of invasion, lymph vascular and perineural invasion, mitotic index, necrosis, parametrium involvement, and lymph-node metastasis.
* Recommended staging method is abdominal and pelvic computed tomography (CT) plus chest X-ray for those with clinical stages FIGO IB2 to IVA.
* Recommended follow-up is every 3 months in the first 2 years, and every 6 months thereafter until 5 years from treatment.

## Section 2 - Treatment of early-stage cervical cancer

There was consensus for seven (24.1%) of the 29 questions related to the treatment of early-stage cervical cancer in areas with limited resources (Supplementary Table 7). For women with stage IA2 cervical cancer wishing to preserve fertility, trachelectomy was the treatment recommendation indicated by 77.6% of panel members. For women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which radiotherapy is not available, 75.6% of panelists indicated neoadjuvant chemotherapy followed by surgery. For a similar patient in areas in which surgeons do not have full training in gynecology oncology, chemoradiation alone was recommended by 81.4% of panelists. If, conversely, neither radiotherapy is available nor do surgeons have full training in gynecology oncology in a given area, neoadjuvant chemotherapy followed by simple hysterectomy was recommended by 75.8% of panelists; in this case, however, 19.2% of panelists abstained from voting. Open surgery was indicated as the recommended approach by 95.2% of panel members in cases of patients with stage IB-IIA cervical cancer undergoing radical hysterectomy. For women with early-stage cervical cancer undergoing surgery and having at least one high-risk feature (positive surgical margins, pathologically involved pelvic nodes, or positive involvement of the parametria), adjuvant radiotherapy and chemotherapy was recommended by 80.0% of panelists. Finally, 94.0% of panel members indicated that both primary and adjuvant external radiotherapy can be administered to women with early-stage cervical cancer in institutions where there are only conventional radiotherapy techniques.

There was a majority vote for 11 (37.9%) questions related to the treatment of early-stage cervical cancer in areas with limited resources (Supplementary Table 7). For women with stage IA2 cervical cancer, 65.7% of voters recommended radical hysterectomy when no fertility is desired, whereas 67.5% recommended conization for similar diagnosis in women desiring to preserve fertility. For women with stage IB1-IB2 cervical cancer, surgery alone was recommended by 63.4% of panelists for areas in which radiotherapy is not available. For similar patients in areas where surgeons do not have a full training in gynecology oncology, 61.2% of panelists recommended chemoradiation, whereas 14.9% recommended radiation alone. For women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA, chemoradiation alone was recommended by 70.0% of panel members. After an incidental diagnosis of stage IA2 disease without lymph vascular invasion in a simple hysterectomy specimen, and absence of enlarged pelvic lymph nodes evaluated by computed tomography scan, the best course of action in an area without qualified surgeons in gynecologic oncology is strict follow-up in the opinion of 69.7% of voters. Conventional (2-dimension) external radiotherapy is the recommended technique as the minimum required treatment for women with early-stage cervical cancer who need adjuvant radiotherapy according to 64.0% of voters. In institutions with only cobalt machines, patients with early-stage cervical cancer can be treated with external radiotherapy in the opinion of 72.5% of panelists. On the other hand, 64.9% of panelists do not recommend adjuvant vaginal vault brachytherapy alone instead of external radiotherapy for patients with early-stage cervical cancer and at least two intermediate-risk features (lymph vascular invasion, cervical stromal invasion, or tumor size ≥4 cm). Conversely, 65.0% of panelists recommend vaginal vault brachytherapy after external radiotherapy, as a boost, for patients with early-stage cervical cancer and at least two intermediate-risk features. Finally, 59.0% of panelists always recommend vaginal vault brachytherapy after external radiotherapy, as boost, for patients with early-stage cervical cancer and at least one high-risk feature (positive surgical margins, pathologically involved pelvic nodes, or positive involvement of the parametria); it should be noted, however,

that an additional 34.4% of voters indicated they restrict this recommendation to patients with positive vaginal margins.

For the other 11 (37.9%) questions, there was considerable heterogeneity in responses from panel members. For some questions, there were two or more options sharing the vote in a relatively balanced manner. That was the case for questions related to the treatment of stage IB1-IB2 cervical cancer in general (with 40.8% of votes for surgery alone and 30.4% for surgery followed by radiation with or without chemotherapy); stage IB1-IIA disease in frail patients (41.5% of votes for chemoradiation and 32.1% for radiotherapy alone); early stages of cervical cancer after surgery with at least two intermediate-risk features (48.5% of votes for adjuvant radiotherapy alone and 43.3% for adjuvant radiotherapy and chemotherapy); for patients with cervical cancer scheduled for radical hysterectomy and pelvic lymphadenectomy in whom a suspicious lymph node is found at the beginning of the surgery (44.1% of votes for proceeding with surgery as planned and 42.3% for resecting the suspicious lymph node and performing lymphadenectomy and radical hysterectomy if it is confirmed positive by frozen section); and whether radical trachelectomy should be proposed in stage IB1 cervical cancer if trained surgeons are not available (49.6% of votes in favor, but with the patient referred to another service, and 41.2% of votes against radical trachelectomy). For some questions, there was a predominant answer achieving less than 50% of votes, with the remainder of votes distributed evenly among other options. Such was the case, for example, for neoadjuvant chemotherapy followed by surgery for stage IB1-IIA disease when radiotherapy is not available, and surgeons do not have adequate training in gynecological oncology.

## Recommendations based on consensus:

* For women with stage IA2 cervical cancer wishing to preserve fertility, trachelectomy is the treatment recommendation indicated by panel members.
* Neoadjuvant chemotherapy followed by surgery is indicated for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which radiotherapy is not available.
* Chemoradiation alone is recommended for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which surgeons do not have full training in gynecology oncology.
* Neoadjuvant chemotherapy followed by simple hysterectomy was recommended for women with cancer confined to the cervix with a clinically visible tumor >4 cm (stage IB3) to IIA in areas in which surgeons do not have full training in gynecology oncology and radiotherapy is not available.
* Open surgery was indicated as the recommended approach for patients with stage IB-IIA cervical cancer undergoing radical hysterectomy.
* For women with early-stage cervical cancer undergoing surgery and having at least one high-risk feature (positive surgical margins, pathologically involved pelvic nodes, or positive involvement of the parametria), adjuvant radiotherapy and chemotherapy should be indicated.
* Both primary and adjuvant external radiotherapy can be administered to women with early-stage cervical cancer in institutions where there are only conventional radiotherapy techniques.

## Section 3 - Locally advanced cervical cancer

There was consensus for eight (33.3%) of the 24 questions related to the treatment of locally advanced cervical cancer in areas with limited resources (Supplementary Table 8). Primary concomitant chemoradiation was recommended for stages IIB through IIIA (86.1% of votes), and IIIB, IIIC and IVA cervical cancer (90.4%), by most panel members. Chemoradiation alone was recommended by 86.5% of voters in patients with locally advanced disease in areas where surgeons do not have full training in gynecologic oncology, and by 79.6% of voters in the case of patients with HIV/AIDS or other forms of immunosuppression. In terms of the brachytherapy technique recommended for eligible patients with stages IB3 through IVA disease after external radiation, a two-dimensional conventional technique was indicated by 80.5% of voters. For women with suspected or pathologically confirmed para-aortic node involvement, primary chemoradiation with extended-field radiotherapy was recommended by 86.1% of voters. Finally, weekly cisplatin is the preferred radiosensitizing agent both in general (78.7%) and in patients with HIV/AIDS or other forms of immunosuppression (94.3%).

There was a majority vote for 11 (45.6%) questions posed to the panel (Supplementary Table 8). Radiotherapy alone was chosen by 72.1% of voters when chemotherapy is not available in a timely manner for patients with locally advanced disease. In terms of external radiotherapy technique for stages IB3 through IVA disease, the minimal recommended option was conventional radiation (64.1% of votes) compared with only 35.9% for conformal radiation. In institutions with only conventional radiotherapy, this was considered appropriate for all stages by 69.3% of panelists. Likewise, if cobalt machines were the only external technique available, it was considered

appropriate for all stages by 70.7% of voters. If no brachytherapy is available, external-beam radiotherapy with chemotherapy was considered appropriate by 67.0% of voters for patients with stages IIB through IVA disease. For women with stages IB3 through IVA disease treated with primary chemoradiation or radiotherapy alone, the maximal accepTable duration of radiotherapy (whole-pelvic irradiation plus brachytherapy or external-beam boost) was 7 weeks for 50.7% of voters. When radiotherapy is not available, 71.4% of voters recommended neoadjuvant chemotherapy followed by surgery in locally advanced disease. For patients not eligible to cisplatin, the recommended radiosensitizing agent was carboplatin for 73.8% of panelists. Hysterectomy should not be recommended after chemoradiation for patients with bulky (>4 cm) tumors and no residual tumor after treatment, according to 66.3% of voters. In patients with locally advanced disease and poor geriatric score and/or poor performance status, radiation alone was recommended by 50.9% of voters. If radiotherapy is not available for such patients, best-supportive care was recommended by 59.3% of panelists.

For the other five (20.8%) questions, there was more heterogeneity in responses from panel members. In two cases, however, there was a predominant response approaching 50% of votes. In areas where no brachytherapy is available, external-beam radiotherapy with chemotherapy was recommended by 49.5% of panelists in the case of stages IB3 through IIA, whereas carboplatin plus paclitaxel was the choice of 49.4% of voters when neoadjuvant chemotherapy is indicated. For the other three questions, there was more heterogeneity in responses and a clear lack of a dominant option.

## Recommendations based on consensus:

* Primary concomitant chemoradiation is recommended for stages IIB to IVA cervical cancer.
* Chemoradiation alone is recommended for patients with locally advanced disease in areas where surgeons do not have full training in gynecologic oncology, and for patients with HIV/AIDS or other forms of immunosuppression.
* A two-dimensional conventional brachytherapy technique is recommended for eligible patients with stages IB3 through IVA disease after external radiation.
* For women with suspected or pathologically confirmed para-aortic node involvement, primary chemoradiation with extended-field radiotherapy is recommended.
* Weekly cisplatin is the preferred radiosensitizing agent for the general patient population and for patients with HIV/AIDS or other forms of immunosuppression.

## Section 4 – Treatment and clinical complications of metastatic or recurrent cervical cancer

There was consensus for only one (4.2%) of the 24 questions related to the treatment of metastatic or recurrent cervical cancer (Supplementary Table 9). This question related to the first-line treatment of patients not amenable to salvage loco-regional treatment and not eligible to receive cisplatin, for which 76.1% of voters recommended carboplatin plus paclitaxel. On the other hand, a majority vote was present for 13 (54.2%) questions posed to the panel. The recommended first-line treatment for patients with platinum-naïve metastatic or recurrent cervical cancer not amenable to salvage loco-regional treatment when all resources are available is a regimen of cisplatin, paclitaxel, and bevacizumab in the opinion of 69.2% of panelists. When resources are limited, the recommended first-line treatment for such patients is cisplatin plus paclitaxel according to 60.7% of voters. For patients with prior platinum (>6 months earlier) therapy, 57.4% indicated cisplatin plus paclitaxel when resources are limited. For patients with platinum therapy within the previous 6 months, 51.9% indicated carboplatin plus paclitaxel for areas with limited resources. The recommended first-line treatment for AIDS and other immunosuppressed patients not amenable to salvage loco-regional treatment in areas with limited resources is full-dose platinum-based chemotherapy doublet in the opinion of 66.7% of panelists. When monotherapy is indicated as the first line with a non-platinum option, paclitaxel was recommended by 71.6% of panelists. If there is no access to taxane or cost-limited resources for this drug, cisplatin plus fluorouracil was recommended by 61.8% of panelists. Salvage surgery alone was the recommended treatment option for a resecTable loco-regional recurrence without suspicion of lymph-node involvement in patients with comorbidities and/or contra-indication to cisplatin who were previously treated with radiation therapy in 54.7% of cases. If cisplatin is contra-indicated as a radiosensitizing agent, carboplatin is the recommended option for a resecTable loco-regional lymph-node recurrence in the opinion of 70.7% of panelists. For similar patients without comorbidities but treated initially only with surgery, chemoradiation with cisplatin was indicated by 59.1% of voters. Finally, the indication of best supportive care is the presence of an Eastern Cooperative Oncology Group performance status >2 in the opinion of 51.9% of voters, considering women with previously treated metastatic cervical cancer and with no access to a clinical trial. For the remaining 10 (41.7%) questions shown in Supplementary Table 9, there was more heterogeneity in responses, even if for some of these questions there was one predominant option garnering more votes (in some cases, close to half of the votes).

Eight of the questions presented to the panel were related to the management of clinical complications often seen in metastatic or recurrent cervical cancer. Consensus answers were given for two (25.0%) of those questions. Surgical management by diverting

colostomy and colostomy bags was considered by 92.6% of panelists as the best intervention to treat fecal incontinence due to rectovaginal fistula. Likewise, 78.8% of panelists indicated they would recommend sexual functioning appointments for cervical cancer survivors in the majority of patients. In addition, there were three (37.5%) questions with a majority vote. The best intervention to control vaginal bleeding secondary to tumor progression in a patient previously treated with radiotherapy was vaginal packing with or without tranexamic acid in the opinion of 74.7% of panelists. Best supportive care was the best intervention to control pelvic pain secondary to tumor progression in a patient previously treated with radiotherapy according to 59.7% of voters. Percutaneous nephrostomy was recommended by 74.3% of voters as the best intervention to treat extrinsic ureteral compression secondary to tumor progression. For the other three questions, there was more substantial heterogeneity in responses.

The third group of questions related to drugs used in cervical cancer included in the World Health Organization (WHO) essential medicines list that can be purchased at an affordable price from generic manufacturers. Among those seven drugs, only paclitaxel and gemcitabine were considered as appropriate treatment options for women with metastatic cervical cancer by at least 75% of panelists. Moreover, there was a majority vote that ifosfamide, methotrexate and vinorelbine are not appropriate in this setting, whereas fluorouracil and topotecan are appropriate.

### Recommendations based on consensus:

* For patients not amenable to salvage loco-regional treatment and not eligible to receive cisplatin, carboplatin plus paclitaxel should be the regimen of choice.
* The best intervention to treat fecal incontinence due to rectovaginal fistula is surgical management by a diverting colostomy.
* Sexual functioning appointments should be offered for cervical cancer survivors in the majority of patients.
* Either paclitaxel or gemcitabine can be considered as appropriate treatment options for women with metastatic cervical cancer at any point according to its availability and lower price.

## Discussion

To our knowledge, this is the first consensus meeting, and the first attempt to provide wide-ranging recommendations for cervical cancer, involving specialists from a large number of countries that face resource limitations to screen for and treat cervical neoplasia. Although the major goal of the current initiative was not to obtain consensus for each question addressed by the panel, consensus is a desirable feature that was defined a priori as at least 75% of valid responses. However, consensus was reached for only 25 (20.7%) of the 121 questions presented to the panel described here, whereas for 54 questions there was one option garnering between 50% and 74.9% of votes. Therefore, for nearly 45% of all questions presented to the panel, there was considerable heterogeneity in responses, and no consensus could be reached. On the other hand, the very low percentages of abstentions and of voters who considered themselves as "unqualified to answer" suggests that the topics chosen are relevant in current practice and that panel members indeed have specific and variable preferences for many of the clinical issues discussed. The extent to which lack of consensus for some of the questions was due to characteristics at the country level, such as specificities of the health-care system, has not been ascertained in the current work. Likewise, we cannot determine if some of the heterogeneity in responses reflects the varied professional background of the voting members.

It is well known that the implementation of international guidelines is challenging in countries with resource limitations or unique health-care landscapes, given that most of those guidelines come from North America and Western Europe (14, 15). One alternative for those countries is to follow guidelines adapted or stratified by resource availability from organizations, such as the National Comprehensive Cancer Network (NCCN) or the European Society of Gynecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (16, 17). For example, NCCN guidelines have been adapted to specific world regions, such as the Middle East and North Africa (18) or Asia (19), and usually within defined disease settings (18). Another option for individual countries facing resource limitation is to develop their own guidelines and consensus panels, a strategy that has been adopted, for example, in India (15, 20). In this current work, we have taken advantage of a large number of specialists from several countries gathering for an international meeting, in order to organize a panel that could provide consensus recommendations for topics previously identified as relevant in cervical and also in vulvar cancer (data not shown here). The topics addressed in this article pertain to prevention, screening, diagnosis, staging, surveillance and management of cervical cancer. Regardless of the preferred process to develop and implement disease-specific recommendations, both LMICs and HICs can benefit from recommendations by the World Health Organization, which often apply to specific issues in selected disease settings (21–23).

The results of this consensus have several limitations that are important to note. First, the definition of developing countries was determined by the real needs and restrictions of each country included in the consensus and faced by the experts in the field.

Limitation of access to surgically trained gynecological professional, high quality radiotherapy machines and systemic regimens. In this consensus the World Bank`s economies classification was not used solely to identify the countries included. Second, some questions related to concepts somewhat validated in the literature did not reached consensus, demonstrating that the difficulties faced by this countries included not only access but other adverse issues including socio-economic and cultural barriers. However, despite of these limitations, a fairly number of questions reached majority voting (65-70%) or consensus (>75%), making this consensus a valuable tool for countries with limitations of resources presented in this report. Finally, prospective intervention strategies will be necessary to eradicate cervical cancer in low- and middle-low-income countries and regular consensus including those countries can serve as a first step for this process.

## Author contributions

FM, GM, AM, EP, DR, RF, PU, RR, RM, JS, AN-R, FC, GB, DC-F, and AN-R have done substantial contributions to the conception of the work. All participated in the acquisition, analysis and interpretation of data for the work. All authors participated in the drafting of the work and revising it critically for important intellectual content All the authors approve the publication of the content and agree to be accounTable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.928560/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 08 September 2022
DOI 10.3389/fonc.2022.935704



OPEN ACCESS

EDITED BY
Lucely Cetina-Pérez,
National Institute of Cancerology (INCAN), Mexico

REVIEWED BY
Ruifang Wu,
Shenzhen Hospital, Peking University, China
Maria Hortlund,
Link Medical, Norway

*CORRESPONDENCE
Soroya Julian McFarlane
soroyajmcfarlane@uga.edu

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 04 May 2022
ACCEPTED 16 August 2022
PUBLISHED 08 September 2022

CITATION
McFarlane SJ, Morgan SE and Carcioppolo N (2022) Lessons learned from the "Goodie Box": A message design study developed and evaluated in community settings for cervical cancer prevention.
*Front. Oncol.* 12:935704.
doi: 10.3389/fonc.2022.935704



# Lessons learned from the "Goodie Box": A message design study developed and evaluated in community settings for cervical cancer prevention

Soroya Julian McFarlane[1]*, Susan E. Morgan[2] and Nick Carcioppolo[2]

[1]University of Georgia, Athens, GA, United States, [2]University of Miami, Coral Gables, FL, United States

Despite the availability of free pap testing services, Jamaican women have low human papillomavirus (HPV) screening rates; 16% of women in the Kingston Metropolitan Area have been screened within the prior 3 years. This paper discusses the testing of theory-based messages to increase HPV screening uptake in a low-resource setting, using HPV self-test kits designed for this intervention. A total of 163 Jamaican women, aged 30–65 years, who had not had a pap test in at least 3 years, from two low socioeconomic status communities in Kingston, were enrolled and assigned to one of two versions of an HPV self-test kit, either with or without culturally targeted fear appeal messages. The uptake of screening was high across conditions; 95.6% of participants used the HPV self-test and returned their kits. However, surprising variations were observed in self-test acceptability, explained by differing attitudes toward the message conditions. Based on the results, we recommend four key components to increase HPV screening in low-resource settings: 1) focus on perceived threat in message design, 2) avoid written materials due to literacy concerns, 3) use culturally appropriate interpersonal or community-based channels, and 4) consider alternative solutions (such as a self-test) available at no or low cost to address structural barriers.

KEYWORDS

**cervical cancer, screening, message design, self-test, low resource setting**

## The Goodie Box as follows: Lessons learned from a message design quasi experiment to increase cervical cancer screening in Kingston, Jamaica

The particularly high incidence and mortality of cervical cancer in Jamaica has been documented over decades of research (1–6), and cervical cancer continues to be a national public health priority. Jamaican women have been found to have higher prevalence of human papillomavirus (HPV), the virus that leads to cervical cancer, than found in earlier studies in Jamaica, in close-by English-speaking islands, and in certain countries in other regions (3). Cervical cancer mortality rates are also high—15.8 per 100,000 or approximately 185 deaths per year, representing almost half of those diagnosed annually (7). Ninety percent of these cervical cancer deaths in Jamaica happen because the women had never been screened (1). Despite this, routine screening is not practiced by most Jamaican women (8–11). Over one-third of Jamaican women have never had a pap smear test procedure (11). Only about 22% of Jamaican women have had a pap smear test within the prior year (12), with some parishes reflecting a screening coverage within the past year as low as 15% (11, 12).

Low screening has generally been associated with structural barriers, such as socioeconomic status, lack of access to screening, low education, and lack of knowledge in various contexts (see 13–19). However, the results of various studies in Jamaica hint at other factors at play. Free pap testing is generally available at nearby community clinics and public health facilities (11, 20), and although having insurance is correlated with increased screening, no differences in uptake of services was found across all socioeconomic groups (21). Additionally, while more formal education is associated with increased screening uptake, educated women still have low screening rates; less than 25% had been screened within the past year (21). Jamaican women do have low knowledge and awareness (9, 11). In one study, exposure to an educational session was associated with increased screening intentions from 82% to 96.2% (20). However, since screening intentions were already high at pretest, this begs the question of why actual screening behavior rates remain so low.

Addressing this question may warrant looking beyond individual and health system factors, to understanding the cultural conceptualizations of health and illness that impact screening behaviors. For example, fear of pain was found to be a significant concern for Jamaican women (20). Almost half the women (47%) who had never had a pap smear test report feelings of fear of the test, including fear of pain, compared to less than a third of women (31.7%) who had experienced a pap test (11). Fear of the pap test results was also noted as a barrier to uptake for Jamaican women with experience of the test as well as those without, although there was still a statistically significant higher fear among the latter group. (1, p. 9) explains that, "most women have heard of the pap smear but believe its purpose is to detect rather than prevent cervical cancer". Further, there is also a misconception among Jamaican women that the pap test itself causes cervical cancer (as cited in 22).

Additionally, low perceived susceptibility to cervical cancer and perceived severity of the disease is associated with a decreased likelihood to screen in Jamaica (11), where cultural beliefs mean that individuals only perceive an illness to be present if there are symptoms (as cited in 23). In a study on Jamaican women aged 15 to 49 years, 56.9% had never even had a pelvic examination, some offering the explanation that they were "healthy and have no sign of gynecological problems" (9, p. 480). There is also low confidence to screen, as women find the pap test embarrassing, even after an educational intervention (20; as cited in 22).

## The extended parallel process model

These findings above cumulatively suggest that a focus on messages that increase perceived susceptibility and perceived severity, including knowledge and awareness of the disease, and increase confidence to screen as an effective prevention measure, might encourage screening uptake. According to the Extended Parallel Processing Model (EPPM), an individual at risk can be influenced to adopt preventative strategies through exposure to messages that increase their perceived threat and perceived efficacy. Perceived threat includes susceptibility (personal risk) and severity (detrimental outcome) of the disease. Perceived efficacy includes self-efficacy (confidence in personal capacity) and response efficacy (confidence in treatment or intervention) to effect desired change (24, 25). These message features ideally lead the individual to 'danger control'—they feel fear, then process and accept the prescription for preventing the illness that is detailed in the messages. If the threat and efficacy messages are not balanced, it can lead individuals to 'fear control'—they process the message and reject it and as such do not conform to the recommended behavior change. Additionally, individual traits such as personality can lead an individual to perceive neither threat nor efficacy in the message, and therefore there is no impact that would lead to behavior change (24, 25). The development of the EPPM was informed by the fear as acquired drive model (26, 27); (27), the parallel process model (28), and protection motivation theory (29, 30).

Despite some debate about the effectiveness of this approach to message design, a meta-analysis by (31) showed that all the message characteristic manipulations (fear, severity, susceptibility, self-efficacy, and response efficacy) changed

behavior positively based on the strength of the appeal. The results of another meta-analysis revealed that not only were fear appeals effective but also they did not backfire and cause unintended consequences, based on the studies in the review (32).

## Cultural targeting

Although some studies have attempted to understand the EPPM's capacity to explain culture-specific reactions to fear and threat in minority populations in the United States, Asian, and African contexts (32–37), questions remain. One such question is how cultural differences may explain cognitive processing of threat and the related behavioral outcomes. In the current study, we consider how the implications of cultural manifestations of threat may have important potential in explaining variances in screening behaviors within a population.

"Cultural sensitivity is the extent to which ethnic/cultural characteristics, experiences, norms, values, behavioral patterns and beliefs of a target population as well as relevant historical environmental and social forces are incorporated in the design, delivery and evaluation of targeted health promotion materials and programs" (38, p. 11). A culturally targeted message design therefore attempts to account for cultural nuances in the approach to the development of material targeting a particular cultural context. Cultural targeting triggers cognitive mechanisms (such as attraction and comprehension) by appealing to an individual's preexisting communication preferences. This not only makes successful message processing more likely but can impact psychological antecedents of behavior that increases the chance for a positive message impact, including changing attitudes, outcome expectations, and improving self-efficacy (39). Further, research that explicitly tests culturally targeted compared with non-targeted communication material among diverse populations is needed to demonstrate its effectiveness and justify its deployment in health promotion interventions (38, 40, 41). In the modified model EPPM (23), Witte demonstrates including certain "universal" cultural variables; however, to the authors knowledge this model has not been further developed or tested.

## Methods

### The intervention—culturally targeted fear appeal messages

We therefore designed a culturally targeted fear appeal message for the Jamaican context, with a focus on culture-based 'contextualization', which involves framing "one's message in a context that is meaningful to the recipient" (39, p. 459) in order to encourage cognitive processing of the messages. To understand if this message would be effective, we developed two versions of an HPV self-test kit—with and without culturally targeted fear appeal messages—and tested them in a field experiment among Jamaican women aged 30 to 65 who had not had a pap smear test in at least 3 years.

The following hypotheses and research questions, based on the EPPM, were tested:

Hypothesis 1: Exposure to the culturally targeted fear appeal message will produce higher self-test acceptability, than those exposed to the no message (plain kit) condition.

Hypothesis 2: Women in the culturally targeted fear appeal condition will exhibit higher (a) perceived efficacy and (b) perceived threat when compared to those in the no message (plain kit) appeal condition.

Hypothesis 3: Message condition and self-test acceptability will be mediated by (a) perceived efficacy and (b) perceived threat.

Additionally, to understand if there was a relationship between culturally targeted fear appeal messages, attitudes, and behavior, we asked the following research questions:

RQ1: What is the relationship between message condition and kit attitudes?

RQ2: Is the indirect effect of message type on self-test acceptability conditional on kit attitudes?

The current study aimed to determine the efficacy of these culturally targeted fear appeal messages to increase screening uptake in this population using an experimental design in which one group received a self-test kit with no message appeals (control) and another group received a self-test kit with culturally targeted fear appeal messages embedded into the design of the kit (intervention). Before conducting the experimental study, a pilot test of the culturally targeted fear appeal messages was conducted with Jamaican women in focus groups. This step of the research was important to determine if the messages drafted by the researchers were, in fact, perceived as intended (manipulation check). Using the Extended Parallel Process Model (EPPM; 24, 25), we developed cervical cancer fear appeal messages that included threat (disease susceptibility and disease severity) and efficacy (self and response efficacy), at surface and deep levels of culture as outlined by Resnicow etal. (38). We integrated feedback on these initial messages from scientific experts on cervical cancer, a community partner organization, and focus groups with Jamaican women into the final messages to be used on a self-testing kit. This process of theory informed message design and the result of this evaluation is beyond the scope of the current manuscript and is described in much further detail elsewhere (see 42).

The culturally targeted fear appeal self-test kit was graphically designed to appeal to Jamaican women and featured illustrations, vibrant Jamaican colors, and a diagram explaining cancer progression. The control group received a plain white self-sampler kit with no message appeal; the only text was the words "Cervical Pre-Cancer/Cancer (bold); Self-sampler Screening Test (regular). The self-test kits in the two conditions included (1) a cotton swab, methanol-based solution, biobag, and hand sanitizer and (2) instructions for using and returning the kit. The instructions were also culturally targeted in the intervention condition, while the control condition received standard, non-targeted instructions (see 42 to view the designs). Beyond these differences, the experimental conditions were designed to be as similar as possible in terms of packaging and placement of text.[1]

## Site of experiment and participants

This study took place in two communities in Kingston, Jamaica, a developing country in the English-speaking Caribbean. No significant sociodemographic differences were found between the communities in income, education, marital status, and religiosity, although the control group was younger with higher employment rates (see Table 1 for comparison of communities). Across both communities, participants were aged 30 to 65; the mean age of participants was 42.87 (SD = 9.895). About 65.6% participants were employed, 83.3% earned less than $JA30,000 (USD$300), and 77.9% did not have health insurance. The majority of women who participated had at least a high school education (68.8%), and some had a technical diploma or college degree (21.9%); 9.4% had less than a high school education. More than half of the women (55.2%) were single and had never been married; 38.1% stated that they were either married or living with their significant other; and 4.7% of the women were separated or divorced. The majority (83.4%) shared that they considered themselves to be religious or that religion was important to them, and many (69.9%) spent between more than once a week to once a month participating in religious activities. The inclusion criteria targeted women who were not up to date on their routine pap smear examinations; the participating women had not been screened for at least 3 years. More than 50% (N = 83) of the women who participated had their last pap test between 3 and 6 years ago, 20% (N = 34) between 7 and 22 years ago, and 15% (N = 25) had never had a pap test in their lifetime.

[1] "Development Of Content, Format And Messages", which includes the text for the screening kits and how they were developed, is provided in a supplement.

## Procedure

Purposive and snowball sampling was used to recruit women in order to meet the requirements of the community-based study. The final sample for data analysis consisted of 163 women (89 in the control community; 74 in the intervention community) after eligibility screening and data cleaning in line with the inclusion criteria. (43) suggests that bootstrapping is sufficiently robust to support a sample size of less than 100 per condition for mediation analysis since it facilitates resampling with replacement of data, with correction for bias (44). A 'toss of the coin' method was used to randomly assign the standard-of-care, plain self-test kit to the control community and the culturally targeted fear appeal kit to the intervention community. The University of Miami Institutional Review Board and the Jamaican Panel on Ethics and Medico-legal Affairs, Ministry of Health, approved this study. This study was also registered on clinicaltrials.gov.

During data collection, outreach workers were hired to recruit participants from their own communities. They distributed promotional flyers and invited eligible women to enroll and participate in the study through door-to-door visits. The project team explained the goal of the research to potential participants as a study that aimed to understand if Jamaican women would use an HPV self-test to screen for cervical cancer. Data collection took place at a community church, a community center, and a basic school over the course of 2 weeks. Eligible women were encouraged to refer their female friends and family members from the same communities to the project. All participants were screened for eligibility, after which the PI obtained written informed consent.

Participants went through the following steps to complete the study: (1) completion of a baseline survey (demographic, sexual and reproductive background, knowledge and attitudes about HPV/cervical cancer); (2) a brief individual or small group sensitization session on the importance of cervical cancer screening conducted by the PI using a short intervention/educational script; (3) completion of a short survey on social proliferation and screening intentions; (4) using and returning of the self-test kit version they received at home or in the clinic bathroom; (5) completion of a posttest survey upon returning their samples. After completing all the steps, participants received a small incentive of $21USD ($2,500 Jamaican dollars). All returned HPV self-tests were sent to the Laboratory for Clinical and Biological Studies at the Sylvester Comprehensive Cancer Center at the University of Miami. The clinical results from the self-tests are beyond the scope of the current paper (45).

## Measurement

Seven-point Likert-type response scales were used to assess participants' responses (from strongly disagree to strongly agree), except where noted. Self-test acceptability was the dependent

TABLE 1 Participant socio-demographic characteristics by intervention condition.

| | Control Community N = 89 | Intervention Community N = 74 | p-value* |
|---|---|---|---|
| | | Mean (SD) | |
| Age, years | 41.09 (10.222) | 45.01 (9.099) | .01 |
| | | n (%) | |
| Income (monthly) | | | |
| Less than JA$15,000 | 34 (54.8%) | 25 (39.1%) | .13 |
| JA$15,001 - $30,000 | 21 (33.9%) | 25 (39.1%) | |
| More than JA $30,000 | 7 (11.3%) | 14 (21.9%) | |
| Employment | | | |
| Employed/self-employed | 51 (58%) | 56 (77.8%) | .03 |
| Retired/homemaker | 3 (4.2%) | 5 (5.7%) | |
| Unemployed | 13 (18.1%) | 32 (36.4%) | |
| Insurance | | | |
| Not insured | 76 (93.8%) | 51 (77.3%) | .00 |
| Insured | 5 (6.2%) | 15 (22.7%) | |
| Education | | | |
| <High School | 8 (9.2%) | 7 (9.6%) | .31 |
| High School | 56 (64.4%) | 54 (74.0%) | |
| >High School | 23 (26.4%) | 12 (16.4%) | |
| Marital Status | | | |
| Single/never married | 48 (57.5%) | 42 (62.7%) | .44 |
| Living with significant other/married | 37 (43.5%) | 25 (37.3%) | |
| Religious? | | | |
| Yes | 72 (82.8%) | 64 (88.9%) | .27 |
| No | 15 (17.2%) | 8 (11.1%) | |
| Religious Importance | | | |
| Very or somewhat unimportant/Unsure | 14 (13.5%) | 10 (15.9%) | .67 |
| Somewhat or very important | 74 (84.1%) | 64 (86.5%) | |
| Religious Involvemeny | | | |
| More than once a week/once a week/once a month | 61 (68.5%) | 53 (71.6) | .67 |
| Only special occasions/never | 28 (31.5%) | 21 (28.4%) | |

*Totals may not equal 163 due to missing values. Percentage totals exclude participants who omitted the question.

variable. Cognitive and affective variables from the fear appeal theory included perceived threat (susceptibility and severity) and perceived efficacy (self-efficacy and response efficacy). The authors also gathered data on participants' attitude toward the kit ('kit attitudes') as well as control (participant background and demographic) variables. These measures are described briefly below.

## Self-test acceptability

Acceptability of the self-test was measured using an 11-item scale ($\alpha$ = .86, M = 6.07, SD = .94); an example was "I would recommend using the self-test to my female family members and friends".

## Threat

Susceptibility was measured using three items including, "It is likely that I will develop cervical cancer" ($\alpha$ = .81, M = 4.35, SD = 1.77). Severity was measured with a two-item scale after removing a weaker item. The scale included "I believe that cervical cancer is a severe health problem" ($\alpha$ = .67, M = 5.76, SD = 1.28).

## Efficacy

Self-efficacy was measured and analyzed using three items ($\alpha$ = .68 M = 5.55, SD = 1.24). An example of an item was: "Doing a screening test like pap smear or HPV test is easy for me". Response efficacy was measured using three items, including "Screening tests like pap smears or HPV tests can save lives by catching cervical cancer early" ($\alpha$ = .83, M = 5.90, SD = 1.19).

## Kit attitudes

This six-item scale was created for the current research and included items such as "The instructions on the kit about how to

use the self- test were too complicated". The reliability was (α = .67, M = 6.08, SD = .79).

## Control variables

Control variables included sociodemographic variables (age, sex, ethnicity/race, education level, household income), prior sexual activity (whether the participant had ever had sexual intercourse), and prior health behaviors (ever had ever had an abnormal pap test, had an HPV infection in the past, had genital warts, or been diagnosed with cervical, oral, or anal cancer). Prior sexual activity and prior health behaviors was measured with yes, no, don't know, or refuse response options.

## Data analysis

REDCap (Research Electronic Data Capture) (http://project-redcap.org/), a web-based tool for clinical researchers, was used to capture data from the field. Statistical Package for Social Sciences (SPSS) was used for data analysis.

# Results

The uptake of screening was high across conditions; 95.6% of participants used the HPV self-test and returned their kits. Since self-sampler uptake was so high, it was not statistically meaningful to pursue uptake as an outcome variable. Instead, self-sampler acceptability was used in any analyses as an outcome variable.

## Experimental hypotheses 1, 2, and 3

Hypothesis 1 predicted that exposure to the self-test kit with culturally targeted fear appeal messaging would produce self-test acceptability than those exposed to the self-test kit with no message appeal. Results from the ANCOVA indicated that there was no significant difference in self-test acceptability [F(1,147) = 2.97, p = 0.09] between the conditions.

Hypothesis 2 predicted that women in the culturally targeted fear appeal condition would exhibit higher (a) perceived efficacy and (b) perceived threat when compared to those in the no message appeal condition. To assess if there were differences between the groups on self-efficacy, response efficacy, perceived relevance, perceived susceptibility, and perceived severity, a statistical mediation analysis was conducted using SPSS PROCESS Model 4. Results demonstrated that there was no significant difference between conditions in perceived efficacy [F (1,148) = .12, p = .73] and a marginally significant difference between the groups in perceived threat [F(1,148) = 3.65, p = .06]. However, by examining perceived severity of the disease (a construct within perceived threat), there were significant differences between conditions [F(1,148) = 4.88, p = .02]. Comparing the estimated marginal means showed that respondents in the control/no message appeal condition reported higher perceived severity (M = 5.96) than respondents in the culturally targeted fear appeal condition (M = 5.47). As such, the opposite effect of what was hypothesized occurred; perceived severity was higher in the community that received the testing kit that did not have printed messages on the box, than women who received the culturally targeted fear appeal message.

Hypothesis 3 predicted that message condition and self-test acceptability would be mediated by (a) perceived efficacy and (b) perceived threat. Regression analyses were conducted revealing that message condition was not a significant predictor of perceived efficacy, b = -.08, SE = .17, p = .64, and that perceived efficacy was not a significant predictor of self-test acceptability, b = .12, SE = .07, p = 08. Additionally, message condition was not a significant predictor of perceived threat, b = .33, SE = .20, p = .10. Perceived threat was, however, a significant predictor of self-test acceptability b = .12, SE = .05, p = .03. Despite this relationship, the results did not support the overall mediational hypothesis.

## Research questions 1 and 2

RQ1 investigated the relationship between message condition and kit attitudes. A one-way ANCOVA was conducted to compare the impact of the message condition on kit attitudes, controlling for age and employment. Results from the ANCOVA indicated that there was a significant difference between conditions in kit attitudes [F(1,147) = 8.00, p = .01]. Comparing the estimated marginal means showed that the control (no message condition) had more positive kit attitudes (M = 6.24) than the culturally targeted fear appeal condition (M = 5.86). Therefore, culturally targeted fear appeal messages on the kit were not viewed as positively as no message appeal at all.

RQ2 investigated the indirect effect of message type on self-test acceptability conditional on kit attitudes. Regression analysis was used to investigate if kit attitudes mediated the effect of message condition on self-test acceptability, controlling for age and employment. Results indicated that message condition was a significant predictor of kit attitudes, b = .38, SE = .34, p = .01, and kit attitudes was a significant predictor of self-test acceptability, b = .81, SE = .07, p <.001. Message condition was no longer a significant predictor of self-test acceptability after controlling for the mediator, kit attitudes b = .28, SE = .17, p = .09, consistent with full mediation. Approximately 46% of the variance in self-test acceptability could be explained by the predictors ($R^2$ = .46). The indirect effect was tested using a

bootstrap estimation approach with 10,000 samples. These results indicated that the indirect coefficient was significant, SE = .09, 95% CI = .07,.61. Message condition was associated with approximately.3 points higher self-test acceptability scores as mediated by kit attitude (see Figure 1).

## Discussion

"Persuasion researchers have recognized for some time that it is easier to demonstrate attitude change in the laboratory than in the field" (46). Despite this, it is still incumbent on applied researchers to continue to utilize theory to understand real-world challenges through field experimentation (47). This research aimed to build on the EPPM to understand how culturally targeted fear appeal message characteristics are mediated by related cognitive processes, which ultimately influence attitudes, beliefs, and behavior. Despite the practical contributions of the study toward educating and screening 177 women who had not had a pap test in 3 to 40 years, or had never had a pap test at all, the current study was not able to explain what specific message features supported the success of the intervention. However, an indirect effect of message condition on self-test acceptability was observed, explained by differing attitudes toward the kit.

One might ask why attitudes toward the kit are important, if ultimately, the screening behavior was overwhelmingly positive. Women who received no message appeal had more positive kit attitudes and increased acceptability of the self-test than those who received the culturally targeted fear appeal message self-test kit. We believe that more positive attitudes toward the control kit and higher acceptability might be explained by literacy challenges among the participants—this, since the kit attitudes survey items measured the extent to which participants thought the self-test kit text was complicated, easy, or took too long to read. It would follow that participants therefore preferred the condition in which they did not have additional reading outside of the self-test instructions. Although not measured formally, there was anecdotal evidence of low functional literacy in this population, since an unusually high number of women claimed to have forgotten their glasses during data collection (a red flag of illiteracy in cancer prevention studies, see 48).

On the other hand, we believe self-test acceptability was still high across both conditions due to interpersonal communication support from the study team in reading the survey items and the kit to individuals, the brief oral education session by the PI, and the overall community-based project approach. Research has demonstrated the influence of message channels as a moderator of cultural targeting on persuasion, in that audio/video has stronger effects than print or mixed media (49). Prior research has also demonstrated the effectiveness of utilizing social networks (50) and social organizations like churches (51, 52) to disseminate messages and increase uptake of intervention, particularly in diverse communities. We therefore suggest that future studies should minimize the use of text (focus on audio/video formats) and adapt a community-based and interpersonal approach for health communication in this cultural context.

An additional significant finding was that women who received the 'no message appeal' self-test kit had higher perceived severity than the women who received the severity messages deliberately embedded in the culturally targeted fear appeal kits. Since both groups received a self-test kit, this can only be explained by the difference in presentation of the kit and its messages. We believe that the women may have instead perceived the control kit to have a more clinical appearance, which may have induced more perceived disease threat, compared to the colorful, culturally targeted design

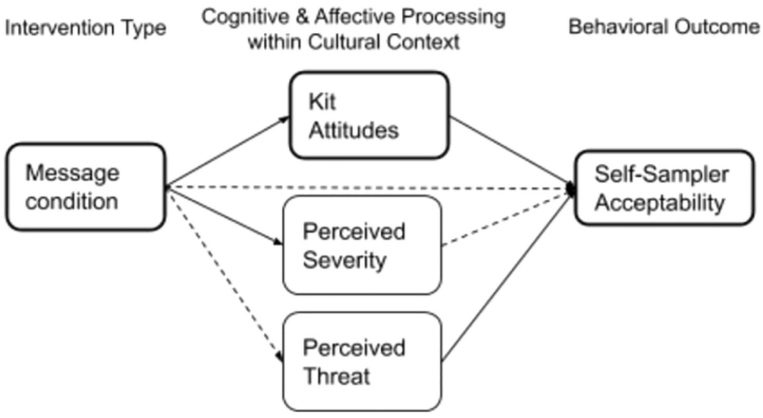


FIGURE 1
Mediations N-148. Mediation model (PROCESS Model 4) with message condition as the independent variable, and perceived threat, perceived severity and kit attitudes as mediators. Only mediators with one or more significant paths are depicted. Solid lines indicate significant paths (p< .05).

accompanied by fear appeal messages. While this result defies our original hypothesis, this evidence suggests that even a threat message that is not explicit can be considered in message design for cervical cancer prevention in this context. Additionally, cultural targeting may actually reduce the effectiveness of threat in fear appeals, and this needs further consideration and empirical testing.

Further, the provision of the self-test kit to all participants may have intrinsically influenced perceptions of threat and efficacy in participants because the immediate availability of the kit greatly reduced nearly all barriers Jamaican women experience when trying to obtain cervical screening (like identifying a provider, allocating financial resources for the test, and making an appointment, as well as fear of pain).

Therefore, multicomponent cancer communication interventions that consider addressing cultural and structural barriers may have the greatest potential to change behaviors in underscreened populations. Based on the results, the authors recommend four key components to increase HPV screening in low-resource settings: focus on perceived threat in message design; avoid written materials due to literacy concerns; use culturally appropriate interpersonal or community-based channels; and consider alternative solutions (such as a self-test) to be made available at no or low cost to address structural barriers.

### Limitations and future research

Noise in the data, often associated with field research, resulted in challenges controlling for all extraneous variables in order to effectively observe effects and explain the underlying mechanisms leading to those effects (47). The PI, a Jamaican woman who was heavily involved and visible in the project in both conditions, as well as outreach workers who were from each community to assist with recruitment of participants, may have enhanced attitudes and assessments of cultural acceptability across both conditions.

Additionally, the informed consent process, as well as the brief educational session about HPV and cervical cancer, which were administered to every woman across conditions, in retrospect could be seen to both contain threat and efficacy messages. For example, in the educational script, response efficacy could be evident in "Cervical cancer is the easiest gynecologic cancer to prevent with regular screening tests and follow up". With more controls between conditions, these limitations might be minimized, and a greater effect might have been observed. In addition, the study sample size is small; as such, in order to provide stronger support for the hypotheses presented, a larger range of studies is needed. Therefore, an important step for future research to understand the efficacy of culturally target fear appeals will be to test for each of these potential drivers of uptake (such as outreach workers, educational script, print message) compared with a true control condition (such as a government- or NGO-issued brochure), in a randomized control trial, to further refine a model of culturally targeted fear appeals and to determine the efficacy of specific messages to increase screening uptake.

## Conclusion

The current study has begun the process of examining how cultural and structural barriers can be addressed to positively influence cancer screening behavior. Culturally targeted fear appeal theory-based messages were embedded within an HPV self-test kit and tested in an underscreened, low-income community in a developing country. The results have practical and theoretical implications: first, HPV self-testing has incredible potential to increase efficacy and screening; second, high acceptability of screening may be encouraged by inducing perceived threat and utilizing an interpersonal and verbal (no text) message format to accommodate for literacy challenges. Ultimately, despite the inherent challenges in field research, the widening cancer health disparities affecting vulnerable communities create an imperative for continued work to refine theory-based communication interventions that potentially address the modifiable cognitive, affective, and behavioral factors that influence screening behavior in these contexts.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

This study was reviewed and approved by University of Miami Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

SJM conceptualized and led the data collection, analysis and write up. SEM contributed to conceptualization, editing

and review. NC provided support for methods and data analysis, and review. All authors contributed to the article and approved the submitted version.

## Funding

Funding This research project was funded by The Global Oncology Innovation Grant of the Sylvester Comprehensive Cancer Center at the University of Miami. The authors received no financial compensation for the research, authorship, and/or publication of this article.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 19 October 2022
DOI 10.3389/fonc.2022.948471



OPEN ACCESS

EDITED BY
Mauricio Maza,
Pan American Health Organization, United States

REVIEWED BY
Rachel Masch,
Mount Sinai Hospital, United States
Jacqueline Duncan,
University of the West Indies, Mona, Jamaica

*CORRESPONDENCE
Marcia E. L. Consolaro
melconsolaro@gmail.com

†The members of Group PREVENT YOURSELF is listed at the end of the article

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 19 May 2022
ACCEPTED 03 October 2022
PUBLISHED 19 October 2022

CITATION
Dartibale CB, Prado GdC, Carobeli LR, Meirelles LEdF, Damke GMZF, Damke E, Morelli F, Souza RP, Group PREVENT YOURSELF, da Silva VRS and Consolaro MEL (2022) Recent HPV self-sampling use for cervical cancer screening in Latin America and Caribbean: a systematic review. *Front. Oncol.* 12:948471. doi: 10.3389/fonc.2022.948471



# Recent HPV self-sampling use for cervical cancer screening in Latin America and Caribbean: a systematic review

Camila B. Dartibale, Gabriela de C. Prado, Lucimara R. Carobeli, Lyvia E. de F. Meirelles, Gabrielle M. Z. F. Damke, Edilson Damke, Fabrício Morelli, Raquel P. Souza, Group PREVENT YOURSELF†, Vânia R. S. da Silva† and Marcia E. L. Consolaro*†

Laboratory of Clinical Cytology and Infecções Sexualmente Transmissíveis (ISTs), Department of Clinical Analysis and Biomedicine, State University of Maringá, Maringá, Brazil

**Objective:** Cervical cancer is one of the deadliest cancers among women in Latin America and Caribbean (LAC), where most of the countries have not been successful in implementing population-level cytology-based screening programs. An increasing body of evidence supports the validity of self-sampling as an alternative to clinician collection for primary Human *papillomavirus* (HPV) screening. Therefore, this work aims to summarize recent HPV self-sampling approaches in LAC.

**Method:** We performed a systematic review to identify studies focused on "Self-sampling", and "Human Papillomavirus DNA test" and "Latin America" in PubMed, Embase, Web of Science, Cochrane library and SCOPUS databases for publications dating between 01 January 2017 and 15 March 2022 based on the Preferred Reporting Items for systematic reviews and meta-analysis (PRISMA) statement. Additionally, the references of the articles were carefully reviewed.

**Results:** Of the 97 records selected, 20 studies including 163,787 participants, with sample sizes for individual studies ranging from 24 to 147,590 were included in this review. Studies were conducted in 10 LAC countries (18.5%), most with upper medium-income economies (70%). The range of age was 18 to ≥65 years. The vast majority of the studies (85%) addressed the HPV self-sampling strategy for primary cervical cancer screening with overall success for all women including under/never screened and those from special populations (rural, indigenous and gender minorities). Women generally found HPV self-sampling highly acceptable regardless of age, setting of collection, target population or country of residence.

**Conclusions:** HPV self-sampling is a promising strategy to overcome the multiple barriers to cervical cancer screening in LAC settings and increasing attendance in underscreened women in countries/territories with well-established screening programs. Furthermore, this strategy is useful even in

LAC countries/territories without organized cervical cancer screening and in special populations such as indigenous, rural and transgender women. Therefore, the information generated by the recent initiatives for HPV self-sampling approach in LAC can be beneficial for decision-making in both new and existing programs in the region.

KEYWORDS

cervical cancer, screening, self-sampling, HPV, Latin America, Caribbean

## 1 Introduction

Cervical cancer is a largely preventable disease but remains the fourth most common cancer (604,000 new diagnoses) and the fourth leading cause of cancer death (342,000) in women worldwide in 2020 (1). 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 (2, 3). Low-and-middle-income countries face the largest burden of this disease, with around 88% of the new global cervical cancer cases and more than 90% of the deaths (4).

Although most Latin America and the Caribbean (LAC) countries and territories today are middle-income economies, there are high heterogeneities across different development indicators (Supplementary Table 1). Therefore, recent reports ranked cervical cancer as the third most common cancer diagnosed in the LAC region (5), with considerable variations in incidence and mortality between countries/territories. Cervical cancer remains the leading cause of female cancer in 16.2% of the LAC countries/territories with estimated cancer data available (6). For 2020, it was estimated 56,439 new cervical cancer cases and 31,582 cancer deaths in LAC, with the incidence ranging from 7.2 cases/100,000 women in Martinique to 36.6 cases/100,000 women in Bolivia in (Supplementary Table 1). If current trends in incidence and mortality as well as in cervical cancer screening programs coverage in LAC continue, around 89% of the 51,500 cervical cancer deaths predicted for the Americas will occur in LAC in 2030 (7). Therefore, decades of Pap-based screening to detect pre-cancerous cervical lesions in a few countries in the region have not had a major impact in reducing cervical cancer incidence and mortality rates, which are still high across LAC (3, 5–9). There are several factors contributing to this lack of impact: suboptimal sensitivity of the Pap test; the need to perform a pelvic evaluation to collect the cervical sample for Pap test, which could be a significant limiting factor in populations that do not accept such pelvic examinations for cultural reasons; uneven allocation of resources; variable infrastructure and service availability; limited number of population-based cancer registries; scarce distribution of public health centers, which is even more evident in rural areas far from the large urban centers; and weakness of the programs and their inability to perform proper follow-up and treatment of women with positive screening results (3, 8, 9). Taken together, these difficulties result in a scenario of unequal care provided to cancer-affected individuals.

The limitations inherent to Pap tests prompted the development of new screening technologies: tests to detect the presence of Human *Papillomavirus* (HPV) DNA (8). HPV DNA tests have proven to be more sensitive, reproducible and to allow for safer extended screening intervals than conventional cytology or visual inspection with acetic acid (VIA) (10, 11). HPV testing is less dependent on operator expertise than Pap 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 (12). Self-sampling is highly acceptable in terms of easy use, convenience, privacy and physical and emotional comfort, in both high- and low and middle-income countries (13). In addition, comparable diagnostic accuracy has also been confirmed for cervical intraepithelial neoplasia grade two or worse of self-collected and clinician collected samples (14–16). 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 (12). The International Agency for Research on Cancer update of the efficacy and effectiveness of cervical cancer screening methods also supports this statement (17).

In recent years, more HPV DNA tests became available and the prices dropped significantly, making possible for eight LAC countries/territories to pilot the introduction of these technologies and more recently, twelve introduced these tests in population-based programs (Supplementary Table 1).

Therefore, the present systematic review was conducted to summarize the main recent experiences of the HPV self-sampling approach in LAC countries and territories in a context in which an increasing number of countries/territories are switching to virological testing.

# 2 Methods

We conducted this systematic review in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18, 19) focusing on the use of the self-sampling approach in LAC countries and territories with or without primary HPV-based screening.

## 2.1 Study definitions

We defined HPV self-sampling as a process in which a patient who wants to screen for HPV infection uses a kit to collect a vaginal sample and send it for analysis by a laboratory. We only included articles that focused on vaginal samples given our interest in cervical cancer. Collection devices include brush, swab and tampon and may occur in any setting (eg, home, community and clinic). We defined HPV clinician sampling as any sampling method where a clinician or other healthcare provider obtains the vaginal sample with speculum.

Additionally, we grouped LAC countries/territories based on the Human Development Index (HDI) using the 2021 World Bank's classification which economies are currently divided into low, lower-middle, upper-middle and high income economies. Income is measured using gross national income (GNI) per capita, in U.S. dollars, converted from local currency using the *World Bank Atlas* method. Estimates of GNI are obtained from economists in the World Bank country units and the size of the population is estimated by World Bank demographers from a variety of sources, including the UN's biennial *World Population Prospects*. For the current 2022 fiscal year, low-income economies are defined as those with a GNI per capita of $1,045 or less in 2020; lower middle-income economies are those with a GNI per capita between $1,046 and $4,095; upper middle-income economies are those with a GNI per capita between $4,096 and $12,695; high-income economies are those with a GNI per capita of $12,696 or more (20).

Finally, we classified the self-sampling studies in LAC into two modalities: 1) Pilot studies: those that were carried out as a government initiative in their local, regional or national programs or guidelines to cervical cancer screening; 2) Independent studies: research studies carried out independently of governmental initiatives.

## 2.2 Inclusion criteria

Studies were eligible for inclusion if they met the following criteria (1): included participants of LAC who performed or evaluated vaginal self-sampling for HPV DNA testing (2); original publications in English and Spanish languages and (3) published in a peer-reviewed journal in the last five years (01 January 2017 and 15 March 2022). Both qualitative and quantitative studies were included.

## 2.3 Search strategy and screening process

We performed a systematic review to identify studies focused on "Self-sampling", and "Human Papillomavirus DNA test", "Latin America" and "Caribbean" in PubMed, Embase, Web of Science, Cochrane library and SCOPUS databases for publications dating between 01 January 2017 and 15 March 2022 based on the 2020 PRISMA statement (19). To identify original publications in English and Spanish languages, researchers (Group PREVENT YOURSELF, CBD, GCP, LRC, LEFM, GMZFD, ED, FM, RPS) performed independent searches using various combinations of descriptors in PubMed/Embase or as a topic in WOK ("Self Care" OR "Self-Testing" OR "House Calls" AND "Self Care" OR "Self-Testing" OR "House Calls" AND "Papillomavirus Infections" OR "Papillomaviridae" OR "Alphapapillomavirus" OR "Human Papillomavirus DNA Tests" AND "Caribbean Region" OR "Central America" OR "South America" OR "Latin America").

Titles and abstracts were carefully selected to ensure publication originality and quantitative and qualitative consensus. The initially selected studies had to fit the following two criteria: the first criteria included original epidemiological and clinical studies involving HPV self-sampling for HPV DNA detection in LAC. The second criteria was to exclude duplicate studies, review studies, letters to editor and books. After consensus, the papers most closely related to the theme descriptors were selected. Then, the full-text articles were randomly distributed to all the investigators (Group PREVENT YOURSELF, CBD, GCP, LRC, LEFM, GMZFD, ED, FM, RPS, VRSS, MELC) who acted as independent evaluators in charge of the inclusion of articles in the final cohort, for data extraction. Any disagreement was resolved by discussing with the senior author (MELC). To increase the sensitivity of the search, the references of the original articles were carefully reviewed for recovery articles that could be additionally utilized in this review. To ensure that all relevant data from each paper were included in the review, a final consensus was achieved following an additional examination of the full texts by two individual experts (VRSS, MELC).

## 2.4 Data extraction and analysis

Two reviewers independently used a standardized data abstraction form to capture information on location of study, HDI, study characteristics and type, study population, sample size and results for HPV DNA self-sampling from each study. Differences in data abstraction were resolved through consensus by a third reviewer as needed.

Data was analyzed and then processed using Excel™ with the aim to display all relevant information in an organized manner.

# 3 Results

## 3.1 Selection of studies

We selected 85 records *via* electronic databases and references of papers, with 11 additional citations reviewed from references listed in prior reviews, including studies and hand-searches. Of the 96 records, 19 were excluded because they were duplicated and 17 because they were outside the period determined for the review. Following, 40 articles were omitted after reviewing the title and abstracts. Finally, 20 studies involving the use of vaginal self-sampling for HPV DNA detection in LAC in the last five years were included in this systematic review (Figure 1- PRISMA flow diagram).

## 3.2 Characteristics of the included studies

### 3.2.1 Overall characteristics

Table 1 presents summary characteristics of the 20 included studies. Details of the included studies are presented in Table 2. The 20 studies included at least 163,787 participants, the sample sizes for individual studies ranged from 24 to 147,590

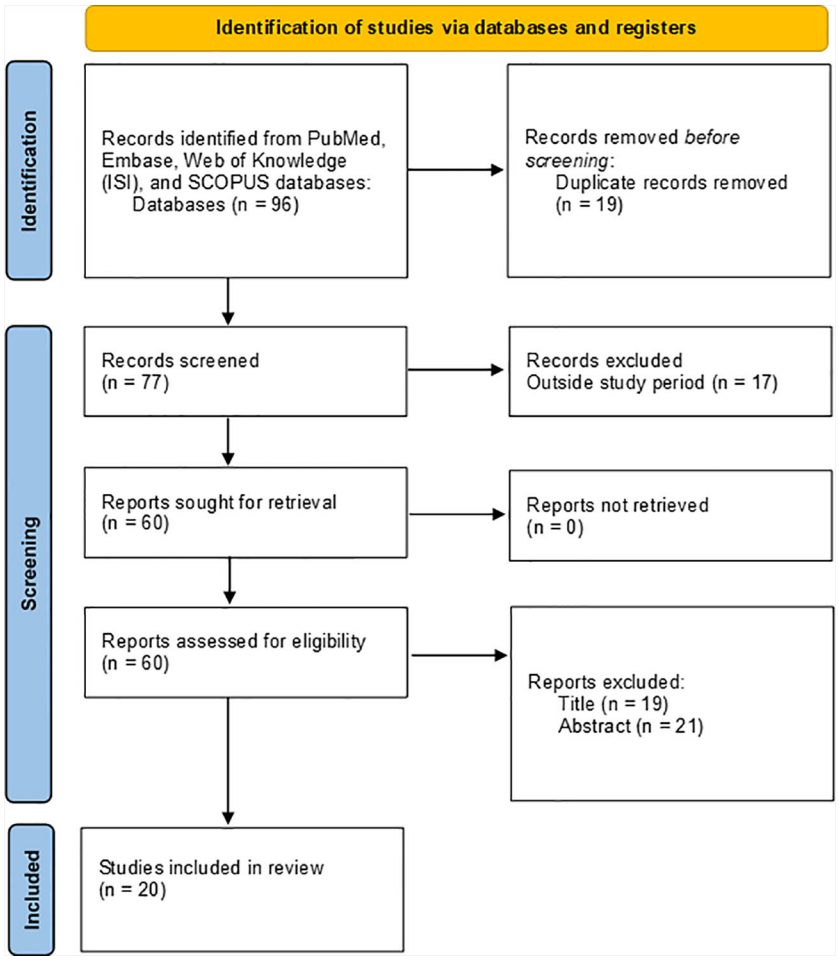


FIGURE 1
PRISMA flow diagram used in this systematic review.

participants and 45% were published in 2020. All included studies were conducted in 10 LAC countries/territories which in only two (Argentina and El Salvador) the national cervical cancer screening program recommended the HPV DNA test. These 10 LAC countries are in South America (50%) followed by Central America (40%) and North America (10%) (Table 2). No studies from the Caribbean region were included in this systematic literature review.

### 3.2.2 Participants characteristics

Participants ranged in age from 18+ with the 40% being 30+. However, many studies do not specify the maximum age of the participants included (21, 24–27, 32, 33, 40). Four studies specifically targeted women who were under/never screened for cervical cancer (24, 31, 32, 36). The remaining studies selected participants from specific subgroups or vulnerable populations, including women from rural areas (21, 33, 38), indigenous (21, 38, 39), gender minorities (transmales) (37), college students (35), others as HPV+ women by self-sampling (25–27) and with previous diagnosis of dysplasia (22).

### 3.2.3 Studies design

Most included studies were quantitative (23, 24, 26–40). These studies examined a wide range of end users, including under/never screened (24, 31, 32, 36) and vulnerable subpopulations such as indigenous women (21, 38, 39), women from rural areas (21, 33, 38) and transgender men (37). Of these studies, 50% included women above the age 30 followed by 37.5% of women above 25. Most quantitative studies (75%) focused on end users in upper-middle-income countries, while only 25% were conducted in lower middle-income countries.

In general, in these quantitative studies, self-sampling has great acceptability for all women (23, 28, 29, 33, 34, 40), for women from special populations (21, 37–39) and in never/under screened women (24, 31, 32, 36). Furthermore, the self-sampling strategy was ratified as an important tool for increased coverage to cervical cancer screening in several of these studies (23, 24, 26, 28, 30–34, 36–40). In studies evaluating women's preference for the method of collection, most preferred self-sampling over clinician-sampling for cervical cancer screening (28, 31, 33, 34).

TABLE 1 Summary description of included studies.

| Characteristic | Articles* |
|---|---|
| Region | |
| North America: Mexico (21–23). | 3 |
| South America: Argentina (24–27), Bolívia (28–30), Brazil (31–33), Colombia (34), Peru (35). | 12 |
| Central America: El Salvador (36, 37), Guatemala (38, 39), Guatemala, Nicaragua and Honduras (40). | 5 |
| Populations (not mutually exclusive) | |
| Women from the general population (23, 28–30, 34, 40). | 6 |
| Women from the rural areas (21, 33, 38). | 3 |
| Neverscreened or underscreened (24, 31, 32, 36) | 4 |
| Indigenous women (21, 38, 39) | 3 |
| Women HPV+ by self-sampling (25–27) | 3 |
| College students (35) | 1 |
| Sexual and gender minorities (37) | 1 |
| Women with previous diagnosis of dysplasia (22) | 1 |
| Study design | |
| Qualitative (21, 22, 25) | 3 |
| Quantitative (23, 24, 26–40) | 17 |
| Specimen collection devices | |
| Swab (21, 29, 30, 38, 39) | 5 |
| Brush (22–24, 26, 31–37, 40) | 12 |
| Multiple devices (28) | 1 |
| Unspecified/Not used (25, 27) | 2 |
| Setting for self-sampling | |
| Clinic (22, 23, 30, 35, 37) | 5 |
| Home (24, 25, 31, 32, 36, 38, 39) | 7 |
| Community setting (28) | 1 |
| Multiple Settings (21, 26, 27, 29, 33, 34, 40) | 7 |

*The number of studies within each category is not mutually exclusive.
HPV, Human papillomavirus.
HPV+, Positive HPV test.

TABLE 2 Characteristics of included studies.

| First author, year | Country/ Territory | Location | Income | HPV test | Self-sampling use* | Self-sampling device | Setting | Target population | Age (years) | Sampling size | Study design | Main findings of the study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arrossi, 2017 (24) | Argentina | South America | Upper middle- | In national program | Pilot study | Brush | Home | Underscreened women | 30+ | 2983 | Quantitative: databases analysis based on Health System Framwork | HPV self-sampling offered by CHWs at home visits can be adequately scaled-up in programmatic conditions to increase screening of hard-to-reach women. |
| Arrossi, 2019 (26) | Argentina | South America | Upper middle- | In national program | Pilot study | Brush | Multiple settings | Special population (HPV+) | 30+ | 4865 | Quantitative: multi-component mobile health (mHealth) intervention to increase adherence to triage | Expected to improve follow-up results for women with HPV+ self-sampling testing. |
| Antelo, 2020 (25) | Argentina | South America | Upper middle- | In national program | Pilot study | NU | Home | Special population (HPV+) | 30+ | 48 | Qualitative: use of SMS to be tested in the trial. | HPV+ women by self-sampling preferred not receive negative results *via* SMS because they believed that the communication between them and the health professionals during the delivery of the results should be prioritized. |
| Paolino, 2020 (27) | Argentina | South America | Upper middle- | In national program | Pilot study | NU | Multiple settings | Special population (HPV+) | 30+ | 2389 | Quantitative: databases analysis based on Public Health System | The adherence of HPV+ women who performed self-sampling to triage test (cytology) at 18 months was low (42.9%). |
| Surriabre, 2017 (28) | Bolivia | South America | Lower middle- | Pilot study | Research | Multiple devices | Community | All women | 25-59 | 222 | Quantitative: study evaluating the possibility of introducing self-sampling | Most women preferred self-sampling over clinician-sampling for cervical cancer screening. |
| Allende, 2019 (29) | Bolivia | South America | Lower middle- | Pilot study | Research | Swab | Multiple settings | All women | 25-64 | 1123 | Quantitative: cross sectional study | Despite greater acceptance of the HPV self-sampling, women kept greater confidence in the screening performed by the gynecologist. |
| Allende, 2020 (30) | Bolivia | South America | Lower middle- | Pilot study | Pilot study | Swab | Clinic | All women | 25-64 | 362 | Quantitative: cross sectional study | Self-sampling could overcome sociocultural barriers to cervical cancer screening. |
| Torres, 2018 (33) | Brazil | South America | Upper middle- | Pilot study | Pilot study | Brush | Multiple settings | Special population (Rural) | 18+ | 412 | Quantitative: cross sectional study | Self-sampling had a high level of acceptance with 80% of women preferring this mode of collection than by a health professional. |
| Castle, 2019 (31) | Brazil | South America | Upper middle- | Pilot study | Pilot study | Brush | Home | Never/ Underscreened women | 25-65 | 483 | Quantitative: study evaluating the preference and adherence to self-sampling | Self-sampling is a promising strategy for un/under-screened women who are recalcitrant or unable to undergo clinic-based cervical screening. |

*(Continued)*





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TABLE 2 Continued

| First author, year | Country/ Territory | Location | Income | HPV test | Self-sampling use* | Self-sampling device | Setting | Target population | Age (years) | Sampling size | Study design | Main findings of the study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pantano, 2021 (32) | Brazil | South America | Upper middle- | Pilot study | Pilot study | Brush | Home | Never/ Underscreened women | 30+ | 355 | Quantitative: study evaluating the acceptabilityto self-sampling | Self-sampling is an adequate strategy to improve the effectiveness of the cervical cancer program by increasing screening in a high-risk group. |
| Torrado-García, 2020 (34) | Colombia | South America | Upper middle- | In national program | Pilot study | Brush | Multiple settings | All women | 35-65 | 423 | Quantitative: cross sectional study | Women living in low-income households preferred the self-sampling procedure (98% of acceptability). |
| Manrique-Hinojosa, 2018 (35) | Peru | South America | Upper middle- | In national program | Research | Brush | Clinic | Special population (College students) | 18-30 | 221 | Quantitative: transversal study | The frequency of high- risk HPV was greater in the group through the self-sampling in comparison with previous national investigations. |
| Laskow, 2017 (36) | El Salvador | Central America | Lower middle- | In national program | Pilot study | Brush | Home | Underscreened women | 30-59 | 60 | Quantitative: self-sampling feasibility and acceptability | For a majority of non-attenders women, CHWs-based self-sampling was an acceptable way to participate in a cervical cancer screening program. |
| Maza, 2020 (37) | El Salvador | Central America | Lower middle- | In national program | Pilot study | Brush | Clinic | Special population (Transgender men) | 19-55 | 24 | Quantitative: feasibility of using self-sampling | HPV self-sampling was accepted by the majority of participants. |
| Gottschlich, 2017 (39) | Guatemala. | Central America | Upper middle- | Pilot study | Pilot study | Swab | Home | Special population (indigenous) | 25-54 | 202 | Quantitative: cross sectional study | HPV self-sampling samples were well accepted by indigenous communities. |
| Murchland, 2019 (38) | Guatemala. | Central America | Upper middle- | Pilot study | Pilot study | Swab | Home | Special population (Indigenous and rural) | 18-60 | 956 | Quantitative: self-sampling acceptability | HPV self-sampling was highly acceptable in rural and indigenous communities. |
| Holme, 2020 (40) | Guatemala, Honduras, and Nicaragua | Central America | Upper middle-, Lower middle- and Lower middle- | Pilot study | Pilot study | Brush | Multiple settings | All women | 30+ | 147590 | Quantitative: self-sampling introduction in public health centers | HPV testing, including self-sampling, was acceptable and feasible to implement for a large volume of women across the three countries and achieved a high coverage between screened women. |
| Allen-Leigh, 2017 (21) | Mexico | North America | Upper middle- | In national program | Pilot study | Swab | Multiple settings | Special population (Indigenous and rural) | 20+ | 503 | Qualitative: self-sampling barriers | Low-income, indigenous women residing in rural, underserved areas found a number of advantages of HPV self-sampled tests. |
| Flores, 2021 (23) | Mexico | North America | Upper middle- | In national program | Research | Brush | Clinic | All women | 30-65 | 505 | Quantitative: performance and acceptability of self-sampling | Self-sampling was well accepted among study participants. |

*(Continued)*





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TABLE 2 Continued

| First author, year | Country/ Territory | Location | Income | HPV test | Self-sampling use* | Self-sampling device | Setting | Target population | Age (years) | Sampling size | Study design | Main findings of the study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rodriguez, 2021 (22) | Mexico | North America | Upper middle- | In national program | Research | Brush | Clinic | Special population (previous dysplasia) | NI | 61 | Qualitative: attitudes and acceptability of self-sampling | Women reported high acceptability for self-sampling and positive attitudes toward HPV diagnostic procedures. |

NI, Not informed; NU, Not used.
*, Pilot study- those that were linked to a government initiative in their local, regional or national programs or guidelines; Research studies- those that were not linked to a governmental initiative.
CHWs, community health workers.
HPV, Human papillomavirus.
HPV+, Positive HPV test.
SMS, Short Message Service.

Three studies employed a qualitative design method that included in-depth interviews and focus group discussions, to explore women's acceptability and preferences related to HPV self-sampling (21, 22, 25). Of these, two studies were conducted in North America (21, 22) and 1 in South America (25), all in upper middle-income countries; all focused on special populations such as indigenous and rural women (21), HPV+ women by self-sampling (25) and women with a previous diagnosis of dysplasia (22). Specifically, Antelo et al. (25) analised the content of the SMS in the trial among women with HPV+ self-sampling tests. The data showed that SMS is accepted when notifying these women, but it should not replace the delivery of results in doctor-patient encounters. Allen-Leigh et al. (21) studied the barriers to use of self-sampled HPV testing and cytology among low-income, indigenous women residing in rural areas. They showed that these women found a number of advantages of HPV self-sampled tests. Finally, Rodriguez et al. (22) assessed attitudes and acceptability of self-sampling among women with a previous diagnosis of cervical dysplasia and showed high acceptability.

### 3.2.4 Self-sampling strategy for cervical cancer screening

The vast majority of studies (85%) addressed the HPV self-sampling strategy for primary cervical cancer screening. Overall, in these studies, the strategy of self-sampling as a primary screening for cervical cancer was successful for both all women and those from special populations.

On the other hand, 15% of the studies evaluated interventions to increase triage adherence among women with HPV+ self-sampled tests (25–27). However, the results were varied, not allowing to conclude the real impact on the follow-up of these women.

### 3.2.5 Settings and devices for self-sampling

End users self-sampled from their homes (35%) (24, 25, 31, 32, 36, 38, 39), in multiple settings (35%) (21, 26, 27, 29, 33, 34, 40), in clinics (25%) (22, 23, 30, 35, 37) and in the community (28). In general, the self-sampling strategy was well accepted in the different settings in which it was offered.

Among the studies that used one type of device for self-sampling, the brush was the most used (70.6%) (22–24, 26, 31–37, 40), followed by swab (29.4%) (21, 29, 30, 38, 39) and both were well accepted.

### 3.2.6 Geographic region and income

The vast majority of the studies were conducted in South America (60%), followed by Central America (25%) and North America (15%). No studies from the Caribbean region were found that met our inclusion criteria.

Specifically in South America, the country with more studies was Argentina, in Central America was Guatemala and in North America was Mexico. Among the 20 studies, 15 (75%)

introduced self-sampling as a pilot in their local, regional or national programs or guidelines to cervical cancer screening including Argentina (n = 4), Bolivia (n = 1), Brazil (n =3), Colombia (n = 1), El Salvador (n = 2), Guatemala (n = 2), Honduras, Guatemala and Nicaragua (n = 1), and Mexico (n = 1). Five additional studies were not linked to programs or guidelines. These studies were carried out in Bolivia (n = 2), Peru (n =1) and Mexico (n = 2) (Figure 2). Despite being the result of independent research, these studies can support the decision whether to include self-sampling in their countries' screening guidelines for all women (Bolivia and Mexico) and for special populations (Peru and Mexico).

Furthermore, among the 20 studies included, 14 were performed in upper-middle, 5 in low-middle and 1 in both upper-middle and low-middle income. Of the included participants, around 91% were from low-middle-income countries.

### 3.2.7 Sexual and gender minorities

Only one study conducted in El Salvador examined preferences among sexual and gender minorities (37). The results showed that among transmales who had undergone self-sampling for HPV, 95.6% expressed a preference for self-sampling and willingness to self-sample in the future.

## 4 Discussion

The present work summarizes the current approaches to cervical cancer screening by HPV self-sampling in LAC, in a context in which an increasing number of countries/territories are switching to HPV testing. Overall, this systematic review contains twenty eligible studies involving at least 163,787 participants. The data from these studies are summarized in Tables 1 , 2. The vast majority of studies (85%) addressed the HPV self-sampling strategy for primary cervical cancer screening and overall, it was successful for all women including under/never screened and those from special populations (rural, indigenous and gender minorities).

Currently, twelve of the 39 LAC countries/territories (30.8%) introduced HPV testing as a primary screening method for


FIGURE 2
Recent HPV self-sampling approach in Latin America and Caribbean countries and territories.

cervical cancer in population-based programs (Argentina, Colombia, Chile, El Salvador, French Guiana, Guadeloupe, Haiti, Mexico, Martinique, Peru, Puerto Rico, and San kitts and Nevis). In addition, at least five countries/territories have developed pilot studies to use the HPV test as a primary screening for cervical cancer (Bolivia, Brazil, Guatemala, Honduras, and Nicaragua) (Supplementary Tables 1). Thus, LAC is moving toward the change to HPV testing for cervical cancer screening, with the endorsement of several regional experiences that resulted in increased coverage and better detection of precancerous lesions using HPV tests. This represents a great opportunity to use the HPV self-sampling for primary cervical cancer screening in the region. Indeed, the recent use of HPV self-sampling as a pilot study (linked to a government initiative in their local, regional or national programs or guidelines) was performed in 9 countries (Argentina, Bolivia, Brazil, Colombia, El Salvador, Guatemala, Honduras, Nicaragua and Mexico) at the time of this review. The HPV self-sampling approach was conducted as research study (not linked to a governmental initiative) in Peru (Table 2). Additionally, no studies from the Caribbean region were found that met our inclusion criteria. This data may suggest that the HPV self-sampling strategy has recently been even less explored for cervical cancer screening in the Caribbean region than in other LAC regions. This hypothesis is reinforced by cervical cancer estimates for the year 2018 in LAC: incidence rates lower in Central America (13.0 per 100,000) than in South America (15.2) and the Caribbean (15.5), and mortality rates higher in the Caribbean (8.5) than in South America (7.1) and Central America (7.0) (41). However, it should be considered that the COVID-19 pandemic may have influenced initiatives to use self-sampling for HPV testing in LAC by changing health systems priorities. Possibly, only in the post-pandemic period will the real impact of the COVID-19 pandemic on LAC approaches to cervical cancer screening by HPV self-sampling be determined.

Barriers to cervical cancer control in LAC include uneven allocation of resources, variable infrastructure and service availability, limited number of population-based cancer registries and scarce distribution of public health centers, which is even more evident in rural areas far from the large urban centers. Taken together, these difficulties result in a scenario of unequal care provided to cancer affected individuals (9). However, at least part of these barriers can be overcome with the introduction of HPV self-sampling. Still, there are several opportunities in LAC that are making the HPV self-sampling approach more feasible and faster than in other word regions. The first opportunity is that most LAC countries/territories (around 72%) already have primary cervical cancer screening programs funded and led by the national government (Supplementary Table 1); this means that countries already have these activities in their national budget, facilitating the process for reallocating some of that funding for HPV testing and self-sampling activities. Other advantages of having such programs already in place is to implement the culture of screening for cervical cancer among women and providers. Also, women will understand the value of prevention and will adopt new options such as self-collecting a vaginal sample. In addition, several LAC countries/territories have started free vaccination programs aimed at girls between the ages of 9 and 13 years in schools and health facilities or health centers (42). Although vaccination coverage is very low (43), this is an important initiative in the region, as both primary prevention (vaccination) and secondary prevention (screening) are needed to resolve the burden of cervical cancer in LAC.

Our findings still show that among the studies that addressed the HPV self-sampling strategy for primary cervical cancer screening, there were many differences between various aspects such as device type, materials and HPV DNA test used, number of participants and target population. Regarding the setting for the self-sampling, only 35% of the studies were conducted exclusively at the participants' homes, which makes it difficult to conclude about the places preferences of the women included. There are few governments HPV self-sampling initiatives from previous periods, as in the case of Argentina. Still, there are few initiatives integrating self-sampling studies between different countries in the region, as in the case of the joint study of Guatemala, Honduras and Nicaragua. Finally, no studies with HPV self-sampling have been conducted in low-income economies of LAC and in the Caribbean. Therefore, our data underscored the need for additional research on self-sampling in LAC. First, we found very few studies from LAC evaluating validity and economic viability in the region. More studies are required across different LAC countries/territories to confirm self-sampling validity and to ensure reliability. In addition, our search found published studies on self-sampling from only 10 of the 54 LAC countries/territories in the past 5 years. Further, only five of the ten LAC countries/territories with the highest rates of cervical cancer globally were represented, highlighting the dearth of research in this area. More studies are needed to improve the applicability and generalizability of results across different LAC contexts.

Despite its potential benefits, the implementation of HPV self-sampling faces some challenges, including training healthcare workers to explain the self-sampling procedure adequately to participating women, transportation of the collected specimens, laboratory technical differences between cervical and vaginal samples processing and finally, skilled clinicians to manage and follow-up positive women (44–46). Regarding follow-up, few of the studies included in this review focused on this theme and used different strategies for the follow-up of HPV+ women by self-sampling (25–27). At the same time, the several opportunities in LAC that can make the process more feasible and faster than in other regions of the world are mainly: most LAC countries/territories already have screening programs funded by their national governments, several countries in the region are already implementing HPV

testing and there is a regional pooled procurement mechanism that could facilitate the purchase of HPV tests at an accessible price. Additionally, the experience from the different LAC countries has created rich information about the barriers and requirements for implementing HPV self-sampling primary screening at large scale in the region.

In summary, the HPV self-sampling approach is now considered a key pillar to reach the WHO cervical cancer elimination target (12). Furthermore, the results of recent studies show that HPV self-sampling is a promising strategy to overcome the multiple barriers to cervical cancer screening in LAC settings and increasing attendance in underscreened women in countries/territories with well-established screening programs. Additionally, this strategy is useful even in LAC countries/territories without organized cervical cancer screening and in special populations such as indigenous, rural and transgender women. Thus, the information generated by the recent initiatives for HPV self-sampling approach in LAC can be beneficial for decision-making in both new and existing programs in the region.

## Limitations

To the best of our knowledge, this is the first study to systematically review the self-sampling approach in LAC countries/territories as a pilot study linked to government initiatives or independent studies, which are those not linked to government initiatives. Findings from this review should be viewed in light of its limitations. We did not include conference abstracts, books, reviews and articles published in other languages than English or Spanish in this review, so our findings may not fully represent the full body of literature on HPV self-sampling in LAC. Also, in the current COVID-19 pandemic scenario, 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 has been discussed (47). On the other hand, economic factors and varying healthcare priorities due to the COVID-19 may have limited studies and the implementation of HPV-based screening in LAC and consequently self-sampling as well.

## Group members of Group PREVENT YOURSELF

Débora M. G. Sant'Ana[1], Sandra M. Pelloso[1], Isabel C. Scarinci-Searles[2], Valquiria C. A. Martins[3], Cláudia M. Carneiro[4], Rita G. Amaral[5], Janaina C. O. C. Freitas[6]

[1]State University of Maringá, Maringá, PR, Brazil

[2]University of Alabama at Birmingham, Birmingham, AL, USA

[3]Amazonas Oncology Control Center Foundation, Manaus, AM, Brazil

[4]Federal University of Ouro Preto, Ouro Preto, MG, Brazil

[5]Federal University of Goiás, Goiânia, GO, Brazil

[6]Federal University of Rio Grande do Norte, Natal, RN, Brazil

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Author contributions

CD, Group PREVENT YOURSELF and MC, conceptualization, investigation, writing-original draft, writing - review and editing. GP, LC, LF, GF, ED, FM, RS: literature search, Study selection, Data Curation, Visualization, Writing - Original Draft. VS: literature search, study selection, Data Curation and Writing - Review & Editing. All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by the Departamento de Ciência e Tecnologia da Secretaria de Ciência, Tecnologia e Insumos Estratégicos do Ministério da Saúde/BR (Decit/SCTIE/MS).

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.948471/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Mini Review
PUBLISHED 26 October 2022
DOI 10.3389/fonc.2022.984449



OPEN ACCESS

EDITED BY
Sarah M. Temkin,
National Institutes of Health (NIH),
United States

REVIEWED BY
Abdelbaset Mohamed Elasbali,
Al Jouf University, Saudi Arabia

*CORRESPONDENCE
Angélica Nogueira-Rodrigues
angelica.onco@me.com

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 02 July 2022
ACCEPTED 10 October 2022
PUBLISHED 26 October 2022

CITATION
Nogueira-Rodrigues A, Flores MG, Macedo Neto AO, Braga LAC, Vieira CM, Sousa-Lima RM, de Andrade DAP, Machado KK and Guimarães APG (2022) HPV vaccination in Latin America: Coverage status, implementation challenges and strategies to overcome it. *Front. Oncol.* 12:984449. doi: 10.3389/fonc.2022.984449



# HPV vaccination in Latin America: Coverage status, implementation challenges and strategies to overcome it

Angélica Nogueira-Rodrigues[1]*, Matheus Gonçalves Flores[2], Avelar Oliveira Macedo Neto[2], Lucélia Antunes Coutinho Braga[3], Carolina Martins Vieira[4], Renata Maria de Sousa-Lima[4], Diocésio Alves Pinto de Andrade[5], Karime Kalil Machado[5] and Andrea Paiva Gadelha Guimarães[5]

[1]Department of Internal Medicine, Federal University of Minas Gerais, Belo Horizontel, Brazil, [2]Federal University of Minas Gerais, Belo Horizontel, Brazil, [3]Fundação Oswaldo Cruz (FIOCRUZ) Minas, Belo Horizontel, Brazil, [4]Clinical Oncologist at Oncoclinicas, Belo Horizontel, Brazil, [5]Brazilian Gynecologic Oncology Group, EVA, São Paulo, Brazil

Cervical cancer remains a leading cause of morbidity and mortality amongst females in Latin America (LATAM). Cervical cancer is a preventable disease and HPV vaccination is a main key strategy towards its elimination. This study analyzes HPV vaccine implementation current status and the main barriers to achieve adequate coverage in the region. Data from the nineteen sovereign states of LATAM (comprised of all Portuguese and Spanish-speaking nations located south of the United States) were collected, including year of HPV vaccine implementation, gender and age targets, the number of doses included in the public program and coverage by dose. Sixteen out of the 19 evaluated countries have already implemented HPV vaccination programs. However, despite its proven efficacy and safety, HPV vaccine uptake in LATAM has been lower than expected. There is an evident decline in adhesion, mainly regarding the second dose. Several reasons are probably involved, of note: limited knowledge of HPV and HPV vaccine, misguided safety concerns, high cost, cultural barriers, and the Covid19 pandemic. Proper strategies to overcome these barriers are needed to ensure successful uptake. Effective policies are: adopting the one dose schedule, delivering the vaccine on both health center and schools, and advising health professionals to recommend the vaccine. Further research regarding HPV vaccine hesitancy in Latin America is needed.

KEYWORDS

**HPV, vaccine, Latin America, coverage, cervical cancer, implementation**

## Introduction

Worldwide, more than half a million women are diagnosed with cervical cancer annually. Currently, more than 300,000 die from the disease[1], at least 85% in low-middle income countries (LMICs) and 10% in Latin America and the Caribbean, where mortality rates are almost five times higher than in North America (1).

Infection with high-risk subtypes of the Human Papillomavirus (HPV) is a necessary, but not sufficient, cause of cervical cancer. The natural history of the disease involves persistent high-risk HPV infection, followed by the development of precancerous cervical lesions and progression to invasive cervical cancer, process that may take some years, providing a window of opportunity for secondary prevention with screening tests. These lesions can be successfully treated when diagnosed early. Besides, the existence of a primary infectious etiologic agent allows primary prevention with prophylactic HPV vaccines capable of reducing the incidence of causative infections. Thus, cervical cancer is considered a preventable and treatable disease (2).

Due to the preventable nature of cervical cancer, in May 2018, the World Health Organization (WHO) made a call to action for the global elimination of the disease as a public health problem. Elimination occurs when incidence rates scale down to less than four cases per 100,000 women, which would be possible through a strategy comprising three targets for 2030: 90% HPV vaccination coverage for girls from 15 years of age, 70% screening coverage with high-performance tests of women by the ages of 35 and 45, and adequate management and treatment of 90% of precancerous lesions and invasive cancers (2).

According to the WHO's predictions, in LMICs, including most countries of Latin America, cervical cancer elimination is possible in the long term, but it will heavily depend on achieving the target for vaccination coverage (3).

This study aims to update the current status of HPV vaccine implementation and coverage in Latin America (LATAM); further, we performed a narrative review addressing local obstacles to achieving adequate numbers and strategies to overcome them.

LA HPV vaccine coverage status has been consistently below WHO's targets (4). Hence, our objective is to provide LA public health officers, researchers, and local governmental organizations with a comprehensive guide with the most relevant references and strategies to improve HPV vaccination in the region, thus contributing to the WHO's Cervical Cancer Elimination Initiative.

To our knowledge, this is the first study to present information on the vaccination status of all countries in latin america individually.

## Materials and methods

Data regarding nineteen sovereign states of LATAM was gathered, including all the Portuguese and Spanish-speaking nations located to the south of the United States - comprising Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela. Our primary source of information was the WHO/UNICEF Joint Reporting Form on Immunization (JRF) online portal (5). When available, the following data for each country was collected: year of HPV vaccine implementation, gender and age targets, the number of doses included in the public program, target (5) population that received the 1 and 2 doses in 2020, and coverage of girls by 15 years of age, and vaccination strategy.

We also conducted a search at PubMed with the terms "(latin america) AND (HPV vaccine)" that found 65 papers published between 2012 and 2022. After also conducting a snowball search, we've selected 15 papers to include at the narrative review.

### Implementation and coverage

The main results are summarized in Table 1.

Out of the 19 evaluated countries in 2022, three - Cuba, Venezuela, and Nicaragua - still have not introduced the HPV vaccine as Public health police (5). Among the 16 nations where HPV vaccination is included, Mexico is the only country that met the target of 90% of girls fully vaccinated with the HPV vaccine by age 15 (5). Furthermore, this indicator was unavailable for Costa Rica, Dominican Republic, El Salvador, and Guatemala. Another relevant trend was the decreasing adherence to the second dose that appeared in all countries with available information.

Although Latin America has a consistent history of high vaccination coverage with highly efficient national immunization programs (4), HPV vaccine uptake has been below expected.

## Discussion

### Elimination of cervical cancer in Latin America is possible

Latin American countries have received support from governments and the Pan American Health Organization (PAHO) to implement vaccination programs, initially focusing on girls. Despite significant advances, vaccine uptake is below

TABLE 1 Coverage Status of HPV vaccination in Latin America.

| LA and the Caribbean Country or Territory | Year of HPV vaccine implementation | Target sex | Schedules | Target population who received the first dose of HPV vaccine - Female (2020) | Target population who received the last dose of HPV vaccine - Female (2020) | HPV Vaccination Coverage by age 15 - Female - First Schedule (2020) | HPV Vaccination Coverage by age 15 - Female - Complete Schedule (2020) |
|---|---|---|---|---|---|---|---|
| Argentina | 2011 | F/M | 2 doses | 72% | 46% | 94% | 69% |
| Bolivia | 2017 | F | 2 doses | 60% | 24% | 78% | 70% |
| Brazil | 2014 | F/M | 2 doses | 88% | 72% | 89% | 66% |
| Chile | 2014 | F/M | 2 doses | 78% | 74% | 80% | 72% |
| Colombia | 2012 | F | 3 doses | 34% | 57% | 57% | 33% |
| Costa Rica | 2019 | F | 2 doses | N/A | 77% | N/A | N/A |
| Dominican Republic | 2014 | F | 2 doses | 18% | 7% | N/A | N/A |
| Ecuador | 2014 | F | 2 doses | 75% | 36% | 100% | 78% |
| El Salvador | 2020 | F | N/A | 27% | N/A | 27% | N/A |
| Guatemala | 2018 | F | N/A | 38% | 20% | N/A | N/A |
| Honduras | 2016 | F | 2 doses | 67% | 47% | 76% | 53% |
| Mexico | 2008 | F | 2 doses | 17% | 5% | 99% | 99% |
| Panama | 2008 | F/M | 2 doses | 67% | 44% | 85% | 57% |
| Paraguay | 2013 | F | 3 doses | 56% | 37% | 69% | 65% |
| Peru | 2011 | F | 2 doses | 79% | 16% | 76% | 74% |
| Uruguay | 2013 | F/M | 3 doses | 38% | 25% | 67% | 49% |

F, female; M, male; F/M, female and male; N/A, not available. Data gathered from World Health Organization report's - Human papillomavirus (HPV) vaccination coverage (5).

expected, and there is no standardized protocol to be adopted regarding the type of vaccine, number and intervals of doses, and age range (6).

The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) was created to facilitate the strategic planning of the global elimination strategy. It consists of three independent models that reproduce the natural history of cervical cancers, which have been used in combination to evaluate the impact of potential intervention scenarios regarding HPV vaccination and cervical cancer screening (3).

Based on that, CCEMC presented three models of protocols for reducing the incidence of cervical cancer in LMICs. Achieving women's vaccination targets can reduce the disease by 60%. Vaccination and screening for HPV, on the other hand, can lead to a 96% reduction; and vaccination associated with two HPV screenings can lead to 100% elimination of the disease in LMICs. 80% of LA and Caribbean countries that already have HPV vaccination implemented could eliminate the disease (3).

Canfell et al. modeled the impact of WHO's strategies on cervical cancer mortality in all 78 LMICs. Estimating a mortality rate of 13.2 per 100,000 women in 2020, they forecasted that vaccination alone would reduce cervical cancer mortality by merely 0.1% in 10 years, compared to the status quo. Additional twice-lifetime screening and cancer treatment would reduce it by 34.2%. In 50 years, the reductions would be 61.7% with vaccination and 92.3% with all three interventions. In 100 years, vaccination alone would reduce mortality by 89.5%, while the implementation of the triple-intervention strategy would reduce mortality by 98.6%, averting more than 60 million deaths (7).

Other groups have demonstrated that scaling up HPV vaccination and screening in LMICs would also be cost-effective. According to a modeling study comprising 50 countries, a comprehensive program could avert 5.2 million cases, 3.7 million deaths, and 22.0 million DALYs (US $ per disability-adjusted life-year averted) over the lifetimes of the intervention cohorts for a total 10-year program cost of US $3.2 billion (8).

## Barries and solutions

The main barriers to HPV vaccination in Latin America are limited knowledge of HPV and its consequences, misguided safety concerns, the cost to constrained health systems, and cultural barriers (4) (9).

As an illustration of this lack of knowledge about HPV, a recent Brazilian cross-sectional study found that 40.0% of participants reported having heard about HPV, and only 8.6% had heard of HPV vaccines. Once informed of the existence of HPV vaccines, about 94% of the participants reported that they would get vaccinated and/or vaccinate their teenage children if vaccines were available in the public health system (10). In the state of Roraima, Brazil, a study that evaluated the parents or

guardians of pre-adolescent girls (between 12 and 14 years of age in 2015) who were students of middle schools in the capital city Boa Vista found out that the knowledge about the vaccine was deficient. Besides that, this deficiency was negatively associated with compliance with vaccination. On the other side, the facts that had the greatest influence on the decision to vaccinate were knowing that HPV infection is not rare, that the HPV vaccine is effective and that its purpose is to prevent cervical cancer (11). In the city of Santo Domingo, the Dominican Republic, a qualitative study with 64 parents of school-age children stated that the main obstacles to vaccine acceptance were low to moderate knowledge of HPV and cervical cancer, especially in the rural and suburban groups, and lack of public awareness of the vaccine (12). In Iquitos, Peru, a study aimed to qualitatively explore vaccination barriers through interviews with eleven nurses and ten teachers involved in vaccine delivery. The professionals considered the lack of parental knowledge about HPV the key barrier to vaccine uptake (13).

Many parents also cite safety concerns as the main reason for refusing to vaccinate their children (9). For example, in Colombia, in the year of the introduction of the HPV vaccine, there was a mass psychogenic response among vaccinated girls in the city of Carmen de Bolivar that made vaccination rates drop from 80% in 2012–2013 to 5% in 2016. The main barriers for vaccine uptake or completion of three doses were the event in Carmen de Bolivar and the consequent fear of adverse effects and fear of needles (14). Nevertheless, data shows that these concerns are misguided. More than 300 million doses of HPV vaccines have been distributed globally as of January 2016, and, to this date, the Global Advisory Committee on Vaccine Safety has not found any safety issue that would alter its current recommendations for the use of HPV vaccination (15).

Besides that, because of the nature of HPV as a sexually transmitted infection and cultural taboos, there is an unfounded belief that the HPV vaccine would increase adolescent sexual activity decreasing vaccine confidence. Parents fear that vaccination would encourage risky sexual behavior (such as not using condoms or having the first sexual intercourse early). However, this association was proven inexistent (16). In 2022, a study confirmed that this relation is inexistent also in an LA Country. The researchers used data from the National Survey of School Health (PeNSE), which is based on a representative sample at the national level, Major Regions, Federation Units, and Capital Municipalities of Brazilian young people who are attending the 9th year of elementary education in public or private schools. The results were consistent with the literature and showed that the vaccination campaign increases the likelihood of girls under 14 years taking the public HPV vaccine, with no significant effects on the beginning of sex life or condom use (17).

According to a systematic review published by the Journal of Pediatric Nurse, the most effective intervention to promote HPV vaccine uptake is strong recommendations by practitioners and nurses. Providers should also inform parents about the vaccine's safety as part of their recommendation to dispel these misconceptions and improve acceptance (18). A cross-sectional study conducted with 200 mothers of Mexican origin in the U.S. Midwest and Xalapa, Veracruz, Mexico, revealed that the odds that a mother vaccinated their child against HPV is higher for mothers that obtain information about the vaccine from their medical provider (19).

According to a cross-sectional study, maternal HPV vaccine acceptance in Argentina was high; however, it substantially decreased when vaccination was not free-of-charge (20). Therefore, HPV vaccines should be offered costlessly to achieve vaccination targets. However, the high cost of the HPV vaccine can represent a substantial burden for Latin American countries with limited budgets. An increase in global financial investment and cooperation is still necessary.

Recently the WHO Strategic Advisory Group of Experts on Immunization (SAGE) published a review that can be game-changing. They concluded that a single-dose Human Papillomavirus (HPV) vaccine delivers protection against HPV that is comparable to 2 or 3 dose schedules. Adopting a single-dose strategy would allow more girls to access this life-saving intervention. Therefore, SAGE recommends updating dose schedules for HPV as follows: one or two-dose schedule for the primary target of girls aged 9-14, one or two-dose schedule for young women aged 15-20, and two doses with a 6-month interval for women older than 21 (21).

Another efficient strategy is school-based vaccine delivery. Large-scale HPV vaccination programs in the United Kingdom, Australia, and New Zealand, achieved better results when using school-based vaccine delivery programs. However, higher adherence rates were achieved utilizing both health facility and school-based compared to the school-based model (4). In Brazil, 2 studies documented successful delivery programs using similar strategies. In the city of Barretos, a study that included girls who were enrolled in public and private schools and regularly attended the sixth and seventh grades of elementary school achieved vaccine uptake rates for the first, second, and third doses of 87.5%, 86.3%, and 85.0%, respectively. The school visits for regular vaccination occurred on previously scheduled dates. The vaccine was also made available at Barretos Cancer Hospital for the girls who could not be vaccinated on the day when the team visited the school (22). In the city of Indaiatuba, a school-based annual HPV vaccination in children between 9 and 10 years old proved itself feasible and increased vaccination coverage, regardless of gender, although the program was vulnerable to competing events (23). Another Brazilian study that interviewed 826 parents through an online questionnaire suggested that low coverage seemed to be due to challenges in vaccine delivery and HPV vaccination barriers at healthcare centers rather than to vaccine refusal. It also identified "No vaccination/missed vaccination at school" as the most common reason for missed vaccinations (24).

In addition to these barriers, which are not new, in 2020, the COVID-19 Pandemic emerged. Research conducted in April 2020 by WHO, UNICEF, and GAVI, in collaboration with the US Centers for Disease Control, Sabin Vaccine Institute, and Johns Hopkins Bloomberg School of Public Health, addressing a VC rate of 107 countries, showed that the Pandemic had already influenced vaccination. In 64% of these countries, their routine immunization programs have been stopped or suspended (25).

In July 2020, WHO published an alert about the impact of the pandemic on vaccine coverage. The Pandemic caused an interruption in vaccine delivery and affected the acceptance of immunization services. It also brought the discussion on vaccination to the spotlight. Although the vaccination campaign has proven itself the most efficient measure to control the spread of the virus, the anti-vax movement and the concerns about the vaccines, in general, have also increased (26).

This anti-vax movement had its first major impact shortly after the H1N1 epidemic in 2009 (27).

According to a meta-analysis, COVID-19 Vaccination Intention in LA's general population is relatively high. While Vaccination Intention in LA's general population is 78%, previous systematic reviews have found global vaccination acceptance rates ranging from 61 to 73% (28). The actual vaccination coverage is also considerable; according to the Our World in Data website, on 4 of January 2022, South America had vaccinated 76% of its people with at least one dose, and 64% of its inhabitants were fully vaccinated, rates higher than Europe (66% and 62%) and the United States (74% and 62%) (29). However, we still don't know how this good acceptance of the COVID-19 vaccine by the LA population and efficient delivery program by the LA government will reflect on HPV vaccine confidence and delivery rates.

An infodemiology study conducted by Eala and colleagues showed that the interest in HPV vaccination increased during the COVID-19 pandemic. They analyzed 9 terms related to cervical cancer care using the Google Trends database between 2018 and 2021. Although terms such as "cervical cancer" or "Pap test" have shown a decline in their search volume index, "HPV vaccine" have increased in LA (30).

As long as we know, there is no research analyzing the impacts of the covid19 pandemics on HPV vaccine confidence. This is very alarming because improvements - such as the expansion of the HPV vaccine to a total of 106 countries globally - are in danger of regressing, as indicated by WHO and UNICEF (31) (42). A catch-up vaccination program should be implemented in all countries to cover age tiers impacted by the COVID pandemic.

## Conclusion

Cervical cancer remains a significant public health issue in Latin-American countries. Most countries have incorporated HPV vaccination into their National Immunization Programs. However, in most countries, vaccine targets were not achieved. Cuba, Venezuela, and Nicaragua have not incorporated HPV vaccination in their health policies so far, and this action is an urgent need for cervical cancer elimination in the region.

Strategies such as health providers' recommendations, school-based associated with health facilities delivery, and one dose schedule could be helpful to achieving universal vaccination coverage in LA countries, contributing to eliminating deaths caused by cervical cancer.

Strategies such as information, providers' recommendations, health centers integrated with school-based delivery, and one dose schedule could be useful to achieve universal vaccination coverage in LA countries, contributing to the goal of eliminating deaths caused by cervical cancer.

## Author contributions

The authors indicated in parenthesis made substantial contributions to the following tasks of research: Conceptualization: ANR, APGG, KKM; methodology: MGF, AMN, ANR, CMV; formal analysis: MGF, AMN; writing-original draft preparation: MGF, AMN, ANR, LCB, DAPA; writingreview and editing: MGF, AMN, DAPA, ANR, RSL, visualization: MGF, AMN, ANR, APGG.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 26 October 2022
DOI 10.3389/fonc.2022.979799



OPEN ACCESS

EDITED BY
Lucely Cetina-Pérez,
National Institute of Cancerology (INCAN), Mexico

REVIEWED BY
Leila Allahqoli,
Iran University of Medical Sciences, Iran
Hamideh Rashidian,
Tehran University of Medical Science, Iran

*CORRESPONDENCE
María-Teresa Urrutia
maria.urrutia@unab.cl

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 28 June 2022
ACCEPTED 13 October 2022
PUBLISHED 26 October 2022

CITATION
Urrutia M-T and Padilla O (2022) Validity of a questionnaire on self-efficacy for Pap test adherence screening. *Front. Oncol.* 12:979799. doi: 10.3389/fonc.2022.979799



# Validity of a questionnaire on self-efficacy for Pap test adherence screening

María-Teresa Urrutia[1]* and Oslando Padilla[2]

[1]School of Nursing, Universidad Andres Bello, Santiago, Chile, [2]Department of Public Health, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

**Introduction:** Self-efficacy has been related to different health preventive behaviors, included adherence to the Papanicolaou test—also called Pap smear or Pap test. The aim of this study is to test construct and criterion validity and reliability of a questionnaire on self-efficacy and the Pap test in Chilean women.

**Method:** This study was carried out on a sample of 969 women of ages from 25 to 64, who are users of the public health care system in Santiago, Chile. The validity of the Self-Efficacy Scale for the Pap Smear Screening Participation (SES-PSSP) questionnaire was done by confirmatory factor analysis, external criteria by t-test, and reliability by Cronbach's alpha.

**Results:** Three models were tested, obtaining a questionnaire with 20 items and 2 dimensions. The criteria validity was confirmed by adherence to the Pap test. The final questionnaire has a reliability of 0.95, measured by Cronbach´s alpha.

**Conclusion:** A valid and reliable questionnaire to measure self-efficacy in relation to the Pap test is a relevant contribution in cervical cancer prevention, especially related to interventions focused on increasing adherence.

KEYWORDS

**uterine cervical neoplasms, Papanicolaou test, self-efficacy, reproducibility of results, surveys and questionnaires. 2**

## Introduction

The need to explain behavior has been the motivation of many health theorists. Bandura's Social Cognitive Theory (1) establishes self-efficacy among its main components, defined as the perception of control that can be exercised over a certain health behavior. The level of self-efficacy affects the choices people make, how much effort they invest, and how long they will persist in carrying out a certain behavior (2).

The higher the level of self-efficacy, the greater the commitment to comply with a certain health behavior and the lower the perception of obstacles to carrying it out (1).

Self-efficacy has been related to different preventive health behaviors, such as screening for breast cancer (3–8), colon cancer (7, 9–11) and certain preventive practices in skin cancer (12). Regarding cervical cancer (CC), its relationship with adherence to the human papillomavirus vaccine (13, 14), adherence to the Papanicolaou (Pap) test—also called Pap smear or Pap—and to colposcopy (15), to educational interventions (16–21) and to depressive symptoms in women with the disease (22) has been studied.

The relationship between self-efficacy and adherence to Pap tests has also been studied (23–32) and found to establish that high levels of self-efficacy predict both the behavior of adhering to screening (33–41), as well as the intention (35, 42, 43). The participants' CC and Pap test screening knowledge levels increased as their self-efficacy levels increased (44).

Given the importance of CC prevention and the relationship with self-efficacy, it is relevant to have a valid and reliable instrument in a commonly spoken and understood language that allows measurement of the self-efficacy of women in relation to adherence to CC screening. The aim of this work is to validate an instrument on self-efficacy related to Pap tests in Chilean women, written in Spanish.

## Materials and methods

The study is part of the FONDECYT #11130626 grant, "Social determinants for adherence to CC screening." The universe of study corresponds to women from ages 25 to 64 years, belonging to the Chilean public health system—National Health Fund (FONASA)—and registered in one of the four primary health care centers of the Puente Alto commune in Santiago, Chile. The sample was selected and stratified by health centers and Pap test coverage levels. According to Pap test coverage data, four primary health care centers were randomly selected, with probabilities proportional to their size, one from each group: with the highest coverage, medium-high coverage, medium-low coverage, and low coverage. The sample size was calculated for a broader study using structural equation models, in which several instruments are related, such as beliefs, knowledge, activity planning, and self-efficacy. Using an online calculator and the methodology described by Soper (2003) (45), for a small effect size of 0.1 (relationship between the instruments), a power of 80%, a number of 15 latent and 40 observed variables, and a level of reliability of 95%, it was estimated that at least 850 women needed to be interviewed. The sample size corresponding to 969 women also meets the requirement regarding instrument validation (46). The inclusion criteria were the characteristics of the universe previously. The exclusion criteria were the presence of CC and/or total hysterectomy. Recruitment was carried out by telephone or by home visit. The interviews were conducted by previously trained personnel.

The sociodemographic variables, adherence to the Pap test, and self-efficacy in relation to screening were measured during the interview. The self-efficacy variable was measured with the SES-PSSP questionnaire (Self-Efficacy Scale for Pap Smear Screening Participation) (47). This questionnaire, validated in the North American population, has 20 items distributed in two dimensions: the first, on personal costs, includes aspects such as time, money, transportation and interruptions of life; and the second, on relationships, which includes the opinion of family members and peers. According to the original recommendation of the author of the instrument, 2 items can be added in case the interviewed woman has children and can leave them alone; given that these items are not applicable to all women, the author of the instrument does not include them in the dimensions described above and therefore they were not included in this research either. The answers are measured on a 5-point Likert scale (1 corresponding to "I would definitely do the Pap test" and 5 corresponding to "I would definitely not do the Pap test").

For the validation of the instrument, the translation and back-translation of the questionnaire was carried out by two professionals in their respective native languages (English and Spanish); it was later submitted for determination of validity of cultural content to five thematic experts. First, the original questionnaire was translated into Spanish by a bilingual (Spanish/English) and native Spanish professional and researcher, and the "Spanish version" was obtained. Second, a bilingual native English professional researcher translated the "Spanish version" into English. Third, another bilingual researcher compared the original and translated versions of the instrument to ensure that the meaning of each item was not altered. In this case, both versions matched; thus, no changes to the translated version were needed. In relation to content validity, the reviews by the five researchers—who analyzed the characteristics of each of the items in terms of their understanding and applicability to the context in which the instrument would be used—were considered. There were no suggested changes. Subsequently, the questionnaire was applied to 10 women from the population that would be studied, to find out if the questions were understandable and/or if there were any terms that prevented a fluid response; there were no suggested changes.

### Statistical analysis

The continuous variables were described using means and standard deviations, and categorical variables using absolute frequencies and percentages. Construct validity was performed using confirmatory factor analysis (CFA), criterion validity using Student's t-test, and reliability using Cronbach's alpha.

Adherence to the Pap test was used as an external criterion of validity, for which the scores for each of the factors and the total score were calculated using the regression method. The scores of those who adhered to the Pap test were then compared with the scores of those who did not, using the t-Student test for independent samples. The regression method using a multiple ordinary least squares regression to predict each individual's factor score based on their observed variables was used (48). The models were estimated using diagonally weighted least squares. The fit of the models was measured using the chi square statistic and two fit indices: the Comparative Fit Index (CFI) and the Tucker-Lewis index (TLI). The Root Mean Square Error of Approximation (RMSEA) was used as the parsimonious fit index. CFI and TLI values greater than 0.95, with RMSEA less than 0.05 are good; CFI and TLI values between 0.90 and 0.95, and RMSEA between 0.05 and 0.08 acceptable; and CFI and TLI values less than 0.90, or RMSEA greater than 0.08 unacceptable. The data were analyzed with the lavaan and psych packages of the R program. A p value <0.05 was considered significant.

The study was approved by the Ethics Committee of the Southeast Metropolitan Health Service, Santiago, Chile. Their signature of the informed consent document was requested from each of the women in the study.

## Results

The average age of the study group is 43.37 ± 10.77 years, and educational level is 10.97 ± 3.4 years. 63.7% of the women work for pay; 79.2% have a partner; 74.5% maintain sexual activity, with 2.69 ± 2.73 (range 1 to 40) being the number of sexual partners; 93.3% have children; and 58.9% use some method of family planning.

76.5% of the women (n = 741) reported having adhered to the Pap test in the last three years. Of the group of women who did not have a Pap test in that period (n = 228), 14% had never had a Pap test, and the remaining 86% reported having it for more than 3 years.

The items with their respective means and standard deviations are presented in Table 1.

For construct validity, the first model tested considered the distribution of the 20 items in the two factors of the original instrument. Given that the fit indices were not good, and the modification indices suggest transferring item 1.3 to the personal costs dimension, a second model was tested. The change of the item is welcome since the meaning of this corresponds to a personal cost. The second model showed acceptable adjustment indices; however, a correlation of 0.857 between both factors was presented, which suggested testing a second-order model. The third model tested was second-order; the results indicated acceptable adjustment indices, so it was decided to retain it. The fit indices of the three models tested are presented in Table 2. The standardized parameters of the final model and the significant correlations between the items are presented in Figure 1. Cronbach's alpha for the total instrument is 0.95, 0.94 for the personal costs dimension, and 0.91 for the relationships dimension. The results of criterion validity are presented in Table 3.

## Discussion

The reduction of mortality and morbidity due to CC requires, among other things, the identification of factors that allow predicting adherence to Pap test; self-efficacy is a construct that had been related to CC screening. The main contribution of this study is the validation of an instrument to measure self-efficacy for taking Pap test, which can be very useful in both health care and research. Although there is another instrument validated in the Latino population that measures self-efficacy on this same topic (49), the SES-PSSP is important since it measures different situations that women could hypothetically face when deciding whether to adhere to screening. The possibility of posing different situations is a necessary condition to efficiently measure self-efficacy (2).

CC is an important public health problem in Latin America and the Caribbean. Therefore, having a questionnaire in Spanish will be very useful in measuring the self-efficacy of women and developing interventions to increase it because enhancement programs result in increased screening rates (50–52). Findings suggest that the inclusion of self-efficacy information in entertainment programming may lead to beneficial health outcomes (35).

Although the questionnaire was validated in the Chilean population, its usefulness transcends borders, since the Latino population shares cultural values that explain many health behaviors, including barriers to adherence to CC screening (53). Latina women in the United States have greater CC mortality rates than non-Latina women because of their low rates of screening (54). Receiving provider advice both directly and indirectly predicted Pap test adherence through greater self-efficacy (55). A systematic review found that self-efficacy is also a facilitator to CC screening in young people (56).

Related to the construct validation, in general, the factor loadings of the CFA are higher than in the PCA. This is a consequence of having a second-order factorial analysis, with different loads for each one of the dimensions, and therefore, the role of the items in each of the dimensions appears a little more precise.

The CFA carried out using a second-order model supports the two original dimensions proposed by the author of the SES-PSSP, and therefore provides sufficient evidence to consider the instrument valid and reliable. The confirmatory analysis in the Chilean population provides new evidence that both factors, validated in the original instrument, are explained by a second-order factor, self-efficacy. Although there is a difference between

TABLE 1 Means and standard deviations of items of the questionnaire.

| How likely are you to get a Pap smear if:(¿Que tan probable es que usted se haga un Papanicolaou si): | Mean | Standard Deviation |
|---|---|---|
| 1.1. How likely are you to get a Pap smear if your last Pap was normal?(¿Que tan probable es que usted se haga un Papanicolaou si Su último Papanicolaou fuese normal)? | 1,58 | 0,932 |
| 1.2. How likely are you to get a Pap smear if you need a ride to your appointment?(¿Que tan probable es que usted se haga un Papanicolaou si alguien tuviera que llevarla a su cita para tomarse el Papanicolaou)? | 1,88 | 1,174 |
| 1.3. How likely are you to get a Pap smear if you are too busy during clinic hours?(¿Que tan probable es que usted se haga un Papanicolaou si usted estuviera ocupada durante el horario de atención del consultorio)? | 2,43 | 1,384 |
| 1.4. How likely are you to get a Pap smear if without applicable health insurance?(¿Que tan probable es que usted se haga un Papanicolaou si usted no tuviera seguro de salud para pagar el Papanicolaou)? | 2,31 | 1,454 |
| 1.5. How likely are you to get a Pap smear if someone in your family tells you the Pap is unnecessary?(¿Que tan probable es que usted se haga un Papanicolaou si alguien en su familia le dijera que el Papanicolaou no es necesario)? | 1,59 | 1,035 |
| 1.6. How likely are you to get a Pap smear if it is hard to get a provider to take your insurance?(¿Que tan probable es que usted se haga un Papanicolaou si usted tuviera problemas para encontrar un médico o matrón (a) que atienda con su seguro de salud)? | 2,11 | 1,327 |
| 1.7. How likely are you to get a Pap smear if you have a frequent change of residence?(¿Que tan probable es que usted se haga un Papanicolaou si usted se cambiara de casa frecuentemente)? | 1,92 | 1,236 |
| 1.8. How likely are you to get a Pap smear if a close male friend or your husband tells you a Pap is not needed?(¿Que tan probable es que usted se haga un Papanicolaou si un amigo cercano o su pareja/marido le dijera que el Papanicolaou no es necesario)? | 1,51 | 0,960 |
| 1.9. How likely are you to get a Pap smear if you have irregular vaginal bleeding?(¿Que tan probable es que usted se haga un Papanicolaou si usted tuviera sangramiento vaginal irregular)? | 1,30 | 0,692 |
| 1.10. How likely are you to get a Pap smear if without permanent housing?(¿Que tan probable es que usted se haga un Papanicolaou si usted no tuviera un lugar donde vivir de manera permanente)? | 1,98 | 1,292 |
| 1.11. How likely are you to get a Pap smear if friend(s) tells you a Pap is unnecessary?(¿Que tan probable es que usted se haga un Papanicolaou si su amiga(s) le dijera que el Papanicolaou no es necesario)? | 1,50 | 0,946 |
| 1.12. How likely are you to get a Pap smear if your Pap is self-pay?(¿Que tan probable es que usted se haga un Papanicolaou si usted tuviera que pagar por el Papanicolaou)? | 1,84 | 1,242 |
| 1.13. How likely are you to get a Pap smear if you are drinking alcohol heavily?(¿Que tan probable es que usted se haga un Papanicolaou si usted bebiera mucho alcohol)? | 2,36 | 1,490 |
| 1.14. How likely are you to get a Pap smear if you would lose work time?(¿Que tan probable es que usted se haga un Papanicolaou si usted tuviera que faltar al trabajo)? | 2,05 | 1,375 |
| 1.15. How likely are you to get a Pap smear if you are living in a drug treatment place?(¿Que tan probable es que usted se haga un Papanicolaou si usted estuviera en un centro de rehabilitación por drogas)? | 2,39 | 1,481 |
| 1.16. How likely are you to get a Pap smear if without a regular health care provider?(¿Que tan probable es que usted se haga un Papanicolaou si usted no tuviera un profesional de salud que la atienda regularmente)? | 2,01 | 1,298 |
| 1.17. How likely are you to get a Pap smear if on street drugs?(¿Que tan probable es que usted se haga un Papanicolaou si usted estuviese usando drogas)? | 2,63 | 1,552 |
| 1.18. How likely are you to get a Pap smear if you had a past abnormal Pap?(¿Que tan probable es que usted se haga un Papanicolaou si usted hubiese tenido un Papanicolaou alterado/anormal en el pasado)? | 1,17 | 0,576 |

The Spanish version is shown in parentheses.

TABLE 2 Fit indices in the three tested models of the SES-PSSP questionnaire (n = 969).

| Models | $\chi^2$ | gl | p value | CFI | TLI | RMSEA(CI 95%) |
|---|---|---|---|---|---|---|
| First (Original questionnaire) | 1831,976 | 134 | <0,001 | 0,952 | 0,945 | 0,114 (0,110–0,119) |
| Second (Change ítem 1.3) | 592,374 | 131 | <0,001 | 0,987 | 0,985 | 0,060 (0,055–0,065) |
| Third (Second-order) | 591,810 | 131 | <0.001 | 0,987 | 0,985 | 0,060 (0,055–0,065) |

the characteristics of the women in the validation of the original instrument (47) and the Chilean sample, the instrument was maintained with the same items with high factor loads.

The change in item 1.3 from the relationship dimension to the personal cost dimension may be explained by the differences that exist between the women in both studies. The North American sample is an institutionalized population (inpatient), while the Chilean sample was drawn from the population belonging to primary health centers. Therefore, the fact of "being busy during office hours" is a personal cost for the

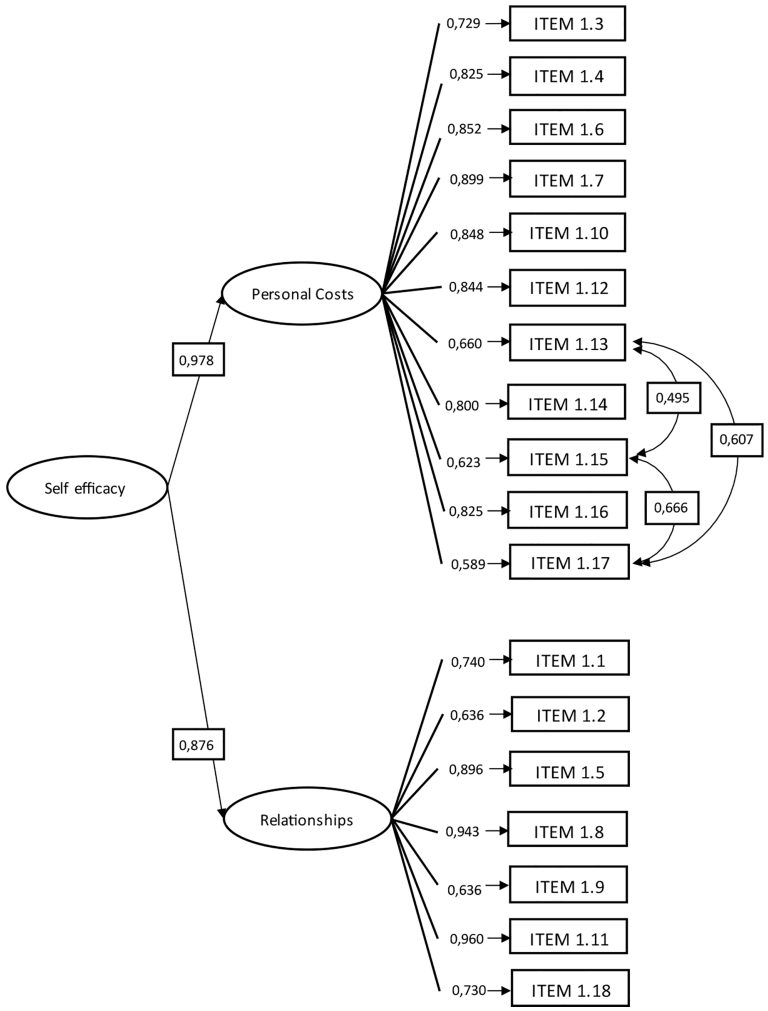


FIGURE 1
Factor loadings of first and second-order and correlations between items of the final model (n = 969).

TABLE 3 Criterion validity by comparing groups according to adherence to the Pap test.

| | Pap test in the last three years | | |
|---|---|---|---|
| **Factor** | **Yes M ± DE†** | **No M ± DE†** | **p value (*)** |
| 1. Personal Costs | 0,461 ± 0,722 | −0,139 ± 0,753 | <0,001 |
| 2. Relationships | 0,495 ± 0,802 | −0,128 ± 0,809 | <0,001 |
| Total score | −0,448 ± 0,694 | −0.133 ± 0,725 | <0,001 |

†M ± DS: Media ± Standard deviation (*) Student's t-test was used to compare groups.
The standardized scores for each of the factors do not have an absolute meaning but a relative one. Being significantly different, it is to be expected that some will be positive and others negative.

Chilean woman, while for the North American, she is dependent on others. It has been previously described in the Chilean population that both office hours and waiting time are a difficulty for women when deciding to adhere to screening (57). The context in which each woman finds herself determines this difference.

When analyzing the moderate correlations between the items that are not explained by belonging to the personal costs

factor, these could be explained by the three items referring to the use of alcohol or drugs. Since none of the correlations presented values above 0.8, all the items were kept in the instrument.

Finally, the results of the criterion validity provide additional strength to the instrument since higher scores in the total and in both dimensions of the instrument are significantly associated with adherence to the Pap test.

## Conclusions

The World Health Organization's efforts to eliminate CC by 2030 with a target of 70% screening coverage using a high-performance test necessitate that women increase participation in screening (58). Self-efficacy is a construct that has proven to be very useful in explaining health behaviors, and specifically to be included in interventions aimed at increasing women's adherence to CC screening. Therefore, having a validated and reliable instrument in the Spanish language is very useful, both for professionals in the clinical field and those who carry out research in the area.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Southeast Metropolitan Health Service, Santiago-Chile. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

MT-U and OP contributed to conception and design of the study. MT-U and OP organized the database. OP performed the statistical analysis. MT-U wrote the first draft of the manuscript. Both authors contributed to manuscript revision, read, and approved the submitted version.

## Funding

FONDECYT #11130626 "Determinantes Sociales para la Adherencia al Tamizaje de Cáncer Cervicouterino"/Social determinants for adherence to Cervical Cancer screening"

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 30 November 2022
DOI 10.3389/fonc.2022.1028291



OPEN ACCESS

EDITED BY
Kingston Rajiah,
School of Pharmacy, Gandhi Institute of Technology and Management University, India

REVIEWED BY
Roshankumar Patil,
Cancer Centers of America, India
Afza Ahmad,
Research Scholar, Integral Yniversity, India

*CORRESPONDENCE
Alfonso Duenas Gonzalez
alfonso_duenasg@yahoo.com

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 25 August 2022
ACCEPTED 14 November 2022
PUBLISHED 30 November 2022

CITATION
Arango-Bravo EA, Cetina-Pérez LdC, Galicia-Carmona T, Castro-Eguiluz D, Gallardo-Rincón D, Cruz-Bautista I and Duenas-Gonzalez A (2022) The health system and access to treatment in patients with cervical cancer in Mexico.
*Front. Oncol.* 12:1028291.
doi: 10.3389/fonc.2022.1028291



# The health system and access to treatment in patients with cervical cancer in Mexico

Eder A. Arango-Bravo[1,2,3], Lucely del Carmen Cetina-Pérez[1,2,3,4], Tatiana Galicia-Carmona[1,2,3], Denisse Castro-Eguiluz[5], Dolores Gallardo-Rincón[3], Ivette Cruz-Bautista[6] and Alfonso Duenas-Gonzalez[7,8]*

[1]Department of Clinical Research, Instituto Nacional de Cancerología, Mexico, Mexico, [2]Integral program for the care of locally advanced and metastatic cervical cancer (MICAELA), Instituto Nacional de Cancerología, Mexico, Mexico, [3]Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico, Mexico, [4]Department of Oncology, Hospital Médica Sur, Mexico, Mexico, [5]Investigador por México CONACYT- Department of Clinical Research, Instituto Nacional de Cancerología, Mexico, Mexico, [6]Department of Metabolic Diseases Research, INCMNSZ, Mexico, Mexico, [7]Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico, Mexico, Mexico, [8]Division of Basic Research, Instituto Nacional de Cancerologia, Mexico, Mexico

Cervical cancer (CC) is tightly related to a low Human Development Index. Mexico is an upper-middle-income country with 126 million inhabitants, and its public health system aims to provide universal health coverage. Currently, employment-based social insurance covers approximately 60% of the population, and the scope of the remaining 40% is on course *via* the "IMSS-Bienestar" Institute. However, the annual government spending on health remains at 3% of the Gross Domestic Product, which is well below the 6% recommended by the Organization for Economic Cooperation and Development. CC is the second in incidence and mortality among women. Regarding primary prevention with the Human Papilloma Virus-vaccine, the current coverage for girls aged 9 to 14 years is only around 7%. Among secondary prevention with screening, the program is yet to cover the total number of women at risk; nevertheless, the age-standardized CC mortality rate has decreased from 12 per 100,000 women in 1979 to 5.7 per 100,000 women in 2020 due in part to increased screening coverage. Still, around two-thirds of patients present with locally advanced disease at diagnosis. Data from our country demonstrate that even socially disadvantaged CC patients achieve "standard" survival outcomes if treatment is granted. Nevertheless, there is a shortage in almost every aspect regarding CC treatment, including oncologists, chemotherapy units, medical physicists, radiation technicians, and both teletherapy and brachytherapy facilities. In conclusion, advances in the public health system in Mexico are urgently required to achieve CC control and reduce the mortality from this neoplasia that mainly targets socially disadvantaged women.

KEYWORDS

**cervical cancer, Mexican healthcare system, HPV vaccination, pap smear, oncological resources**

## Global burden of cervical cancer

Cervical cancer (CC) is the fourth most incident cancer and the fourth cause of death by cancer in women, with approximately 604,000 new cases and 342,000 deaths worldwide by 2020. In addition, it is the most diagnosed malignant disease in 23 countries and the leading cause of death in 36 countries. Most of these are in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia (1).

The Human Development Index (HDI) is strongly negatively associated with CC incidence and mortality. The rates in developed and developing countries vary from 18.8 vs. 11.3 per 100,000 and 12.4 vs. 5.2 per 100,000 for incidence and mortality, respectively. The difference occurs even within high-income countries such as the United States of America (USA), where the death rate from CC is twice as high among women living in high poverty than those in low-poverty areas (1, 2).

## Cervical cancer in Mexico

Mexico is an upper middle-income country (UMIC) in the current World Bank classification of countries by income. Mexico had a population of 126,014,024 inhabitants in 2020. The adjusted incidence of CC in 2020 was 12.6 per 100,000 women. Data from the National System of Statistical and Geographical Information (INEGI), which registers mortality, indicates that CC mortality rates have decreased from 12 to 5.7 per 100,000 from 1979 to 2020. Still, this neoplasia represents the second cause of cancer in Mexican women, with 9,439 new cases per year, and the second cause of death, with 4,335 cases. Among women with invasive CC, around 70% are diagnosed with locally advanced disease. These figures speak on deficiencies in coverage and timely diagnosis and treatment of detected preinvasive and invasive lesions (2–4).

Information regarding the number of CC patients attended at major public institutions is scarce. A retrospective study that included 346 women diagnosed with CC from an Oncology Center showed that 65.32% of patients were stage II and III according to the International Federation of Gynecology and Obstetrics (FIGO, 2009) (5). Likewise, a third-level hospital of another Oncology Center reported that of 111 patients, 76.4% were in stages II and III (6). In 2020, a cohort of 2,982 women diagnosed with CC treated at the National Cancer Institute of Mexico (Incan) from 2005 to 2015 was reported. The study showed that most patients were diagnosed with locally advanced disease (1B2 –IVA, FIGO), 73.10% in women younger than 40 and 78.1% in women older than 40. Early disease (IA1 –IB1, FIGO) represented 15% of women younger than 40 years compared to 19.3% in those older than 40 years, and advanced disease (IVB, FIGO) corresponded to 7.58% in young women compared to 6.93% in older women (7). Recently, in 2022, a retrospective analysis was published that included more than 20,000 patients diagnosed with CC, whose treatment was financed by the Popular Insurance Catastrophic Expenditure Protection Fund (FPCGC). The prevailing clinical stage at the time of diagnosis was locally advanced disease (FIGO) in 14,782 women (68.5%), followed by early disease in 5,286 patients (24.5%) and advanced disease in 1488 women, corresponding to 6.9% (8). Among 346 CC patients treated at an oncology hospital, more than half of the women did not have a formal job (57%), two-thirds of the women had social security through a family member or their retirement, and 32% had social security coverage through their employment. Nine percent of these women were illiterate, and most did not complete middle school (77%) (5).

## Public health system of Mexico

In Mexico, article 4 of the Mexican Political Constitution, amended in May 2020, establishes: "*…every person has the right to health protection.*" Accordingly, the health system in Mexico is public, intended to provide medical care to all, and it is currently transitioning to accomplish what is written by Law. Up to now, the Mexican public health system has two main components operating in parallel:

1) Employment-based social insurance schemes. These include 1.1. The Mexican Institute of Social Security (IMSS), 1.2. The Institute of Social Security and Services for State Workers (ISSSTE), 1.3. The Social Security Institution of Federal Entities (ISSES), 1.4. The employee of the Mexican Petroleum Public company (PEMEX), and 5.1. The Social Security Institute of the Armed Forces (ISSFAM).

2) The Population with no Social Security Services, which several public funds serve. 2.1. The Federal Entities Spending on Health (Field 12 from Health Secretary), 2.2. The Fund for Health Services (Field 33-FASSA), 2.3. The IMSS-Bienestar, 2.4. The Armed Forces Secretary (SEDENA), and 2.5. The Marine Secretary (SEMAR). Accordingly, the public spending on health by the Mexican government is channeled to 5 institutions of the Employment-based subsystem and 5 Institutions of the Population with no social security services. According to the 2020 data from the INEGI, Mexico has a total population of 126,014,024 million, and the percentages of public insurance are as follows:

1. Employment-based social insurance schemes: IMSS 51%, ISSSTE, and ISSES 8.8%, PEMEX and ISSFAM 1.3%. This subsystem covers 61.1% of the population.
2. Population with no Social Security Services served by several public funds: INSABI 35.5%, IMSS-Bienestar 1%, others 1.2%, covering 37.7% of the population.

Thus, in theory, the total population covered by public health services in Mexico is almost 100%. However, the actual coverage for people with no Employment-based Social Security

Services (37.7%) is yet to occur. Currently, the government is reorganizing the IMSS-Bienestar Institute to make this subsystem the primary public health Institution to cover every individual lacking Employment-based social security (9, 10).

As in many countries, the private health sector is operating as well. The INEGI 2020 data discloses that 2.8% of the population has private insurance, mostly individually contracted and also granted by some private companies to their employees (11). It also must be noticed that many pharmacy chains throughout the territory sell medicines and have a general practitioner physician consultation service for free or a small fee. This system of pharmacies with their primary care physicians represents an affordable option for a population segment (with or without access to public health services). Some people with access to public health services would prefer to pay a relatively small fee than wait in long lines to access their public health clinic that does not always have medicines in stock. Of course, this system works only for relatively simple health issues that do not require hospitalization or a specialized level of care. The overall impact of this private subsystem on the government's public health service remains to be determined (12).

This work does not intend to analyze the Mexican Public Health system deeply. Still, for any informed citizen, the public health system in Mexico has two fundamental flaws that, when combined, explain why it is deficient. The insufficient public resources allocated and its fragmentation into several subsystems. From a comparative perspective, resources allocated to public health by the Mexican government fall well below the spending average of the countries of the Organization for Economic Cooperation and Development (OECD) and of international recommendations, which, according to the World Health Organization (WHO), it should be 6% of the Gross Domestic Product (GDP). In 2019, the OECD countries spent, on average, 6.6%, while public spending on health by the Mexican State represented only 2.7% of GDP. This data implies a per capita expenditure of 555 USD, which places the country well below the OECD average (3,040.55 USD).

Regarding private expenses as a percentage of the GDP, the average for countries of OECD was 2.2% (6.6% public, 2.2% private, a total of 8.8%). In Mexico, the average personal expense was 2.8%, similar to the public expense of 2.8% for a total of 5.6%. The current perspectives on the public expense on health are not very encouraging. Between the years 2004-2021, the average was 2.86%. The lowest was 2.5% in 2005 and 2006, and the highest was 3.1% in 2009, 2010, 2011, 2012, and 2013. The estimates for 2020 and 2021 were 2.9%. The expending for the Employment-based systems and those services for the population with no Social Security Services remained the same at 1.7% and 1.2%. Thus, despite the Law that states that all individuals must have medical service coverage, many do not have it, or if they do, it is suboptimal. These figures on federal spending on health have dramatic consequences. The availability of health resources such as beds, medicines, medical supplies, and health professionals (medical and nurses) is poor—for example, the ratio of beds and staff doctors for every thousand inhabitants. In Mexico, we had only 1.8 beds per thousand inhabitants in 2000, a figure well below the 4.5 beds per every thousand in OECD countries. Regarding medical personnel in Mexico, there are only 2.4 doctors for every thousand inhabitants, compared to the OECD countries with 3.6. With this scenario on public health, it is not surprising that the oncology infrastructure is also deficient (10).

A recent report in Mexico establishes that most cancer services (81%) were delivered by the public while 19% by the private sector (13). The numbers of specialized cancer units are 118 establishments in total. Of these, 65 are public, 48 are private, and 5 are mixed. Regarding equipment for diagnosis, 31 positron emission tomography-computed tomography (PET-CT) equipments, 793 Computed Tomography (CT) scanners, and 316 magnetic resonance imaging (MRI) equipments are available (14). The IMSS alone which is the main employment-based social insurance has medical units for the first, second, and third level of care. The first level units are located throughout the national territory, and most preventive actions are related to the timely detection of breast cancer and CC. From the third level units, it has only 20 specialized centers providing oncological care (15).

According to the Mexico Radiation Oncology Certification Board, a national census revealed Mexico's infrastructure and radiotherapy (RT) units. One hundred and three RT centers were documented. These centers contain a total of 162 RT machines, 141 linear accelerators, and 21 radionuclide therapy units—19 are teletherapy cobalt-60 (90.5%) and 2 radionuclide stereotactic units (9.5%), both GammaKnife. This data represents a median of 3 machines by federal entity (except in Tlaxcala, which has no radiotherapy, and 46 are located in Mexico City). Eighteen federal entities have less than 3 machines (56.25%). The total density of RT machines per million inhabitants is 1.32, ranging from 0 in Tlaxcala to 5.16 in Mexico City. Of the 103 RT centers, 59 (57.3%) have brachytherapy units (median of 1 center with brachytherapy units by state). Five states have no brachytherapy units (15,6%), 11 states have 1 unit (34,4%), 8 states have 2 units (25%), 5 states have 3 units (15,6%), and 1 state has up to 15 units (3,1%). The global rate of brachytherapy units per million inhabitants is 0.55. Thirty-seven brachytherapy units (56.1%) use automated high-rate dose, and 29 units (43.9%) use low-rate dose (16). Mexico stands last with only 1.3 RT machines per million inhabitants, while there are 18.7 for Switzerland and 11.3 for the USA.

Regarding cancer specialists, there were 945 surgical oncologists for adults and 24 surgical oncologists for children, 473 medical oncologists, 174 gynecological oncologists, and 264 pediatric oncologists. In a list of selected countries, the USA heads with 161 oncologists per million inhabitants, followed by the United Kingdom and Italy with 131 and 122, while Mexico has only 16 per million (17). The report from the Mexico

Radiation Oncology Certification Board stated that since 1988, 368 radiation oncologists had been certified. Of these, 346 remain active in oncologic institutions. This fact translates into 1 radiation oncologist per 345,000 inhabitants (16). Altogether, these data indicate that Mexico's public health system cannot provide coverage to the whole population promptly and efficiently. Much work needs to be done to increase government spending on health and, at the same time, to be organized in a centralized manner to optimize the scarce existing resources.

## Primary prevention in Mexico (HPV vaccination)

In Mexico, vaccination against HPV was first introduced in 2008 with low coverage to girls aged 12-16 years using a 0 to 6-month schedule. One year later, an extended dosing schedule was introduced to target girls aged 9-12 for the first 2 doses, applied 6 months apart, followed by a third dose 60 months later. The vaccine was included in the national vaccine program until 2012. The coverage has increased over time; according to the last reported data in 2018, about 1 million doses were applied in Mexico (18). However, this number is still meager (around 7%) considering the population of 126 million, from which 5.7% are females between 9 and 14 years old (19). In this regard, Mexico faces, like many other countries with limited resources for public health, many obstacles to implementing vaccination schedules. Those barriers are multifactorial and include limitations in costs, infrastructure, and even social stigma (20). Due to these difficulties, the prevalence of HPV infections remains high in Mexico. Mexico is a region with a high rate of HPV infection (21, 22). Moreover, a high prevalence of HPV in women younger than 25 that attend college is likely related to risky sexual behavior, lack of knowledge of HPV infection, and other cultural factors (23). Because of that, even in the best scenario, the prospects for reducing CC mortality *via* primary prevention are discouraging.

## Secondary prevention in Mexico (screening)

In Mexico, despite historical efforts, CC continues to represent a high burden of cancer. The first actions for the timely detection of CC were implemented at the General Hospital of Mexico in 1974. In 1994, the official Mexican standard OM-O 14-SSA2-1994 for Prevention, Treatment, and Control of CC and Breast Cancer was established. According to the Norm, the Papanicolaou would have to be performed annually, and women whose cytology diagnosis was compatible with HPV infection would be referred to a colposcopy service. By then, it was not known that there was no treatment for HPV infection in the absence of lesions. Also, referring a woman with a morphological image suggestive of HPV infection to a colposcopy clinic unnecessarily increases costs and carries other issues like overdiagnosis and negative psychological consequences in women. In 1998 it was decided that the frequency of cervical cytology would be every three years in women with two consecutive annual negative results for HPV infection, dysplasia, or cancer; while women positive for HPV infection or dysplasia would be followed up in the clinic. After being discharged, they would start the annual periodicity again. On the other hand, women with positive results for nonspecific inflammatory processes should continue with annual exams until they have two consecutive negative results. In 2007, the Modification to the Mexican Official Standard (NOM-O 14-SSA2-1994) for the Prevention, Detection, Diagnosis, Treatment, Control, and Epidemiological Surveillance of CC privileged CC detection in women residents of rural and indigenous areas and marginalized urban areas (24–26).

Based on these experiences, in 2009, the norm incorporated vaginal self-sampling for high-risk HPV DNA testing. The main difficulty with this method lies in achieving, once the self-collection is done, that the sample arrives at a trained laboratory, that the sample is analyzed and that the results return promptly to the place of origin, where trained personnel must come to provide treatment and follow up on each case. Again, the main obstacle lies in the scarce availability of resources in marginalized areas. It was assumed that the incorporation of the high-risk HPV DNA test as a diagnostic complement to Pap smear could help reduce inequity in the quality of detection, modernize prevention and control strategies, increase coverage –without losing certainty in detection—and expand the detection coverage in areas with difficult access to health services. However, this can only be achieved if the institutional responsibilities in each case are precisely defined and fully adopted by the health services (27). They must ensure that the samples reach the laboratories, that they will be processed and sent promptly to those responsible for the treatment and follow-up of the patients, and that women can be treated appropriately. Though existing resources have recently increased, including regional molecular laboratories in several Mexican states, a pending issue is the lack of an integrated information system for accurate data on CC.

Currently, the fragmented information causes inaccurate epidemiological information. It makes it challenging to cross-reference information to understand better the problem, including the lack of data incorporation from private medical units. Consequently, there is only a partial diagnosis of the problem, which affects the design of programs and the allocation of resources to address them. Despite all these caveats, some progress has been made. The age-standardized CC mortality rate in Mexico in 1979 was 12 per 100,000 women, and the estimates for 2020 were 5.7 per 100,000. According to the current program (28), further progress can be expected if the program is better

organized and adequately funded to increase coverage while reducing the high proportion of women lost to follow-up who do not receive treatment for their cervical lesion.

## Tertiary prevention in Mexico (treatment)

CC treatment is determined by clinical staging. Early-stage CC (IA1 to IB1) is primarily surgically treated. Locally advanced disease (IB2 to IVA) is treated with cisplatin-based concurrent chemoradiation followed by brachytherapy (either low-rate or high-rate dose). Advanced disease (IVB) is usually treated with carboplatin-paclitaxel doublet chemotherapy. Bevacizumab is only employed in selected patients (29). The lack of a cancer registry at the National level in Mexico is a severe drawback to having reliable epidemiological data on percentages of invasive CC patients regarding the FIGO clinical stage at presentation. Likewise, no information exists at the national level on the percentage of patients that receive optimal care. Available data are summarized in Table 1. Recent data from the ISSSTE informs that only 1.8% of the patients underwent surgery as a single modality; 6.7% underwent surgery plus adjuvant cisplatin-based concurrent chemoradiation; and 51.8% received definitive treatment with cisplatin-based concurrent chemoradiation, of which 77.6% completed treatment with brachytherapy. The most common treatment modality was radiotherapy alone in 28%; surgery followed by radiotherapy in 10%; 6% in the advanced disease subgroup received bevacizumab in combination with chemotherapy. The following drugs are available in this institution for managing locally advanced, recurrent, or metastatic disease: carboplatin, cisplatin, capecitabine, docetaxel, 5-fluorouracil, gemcitabine, and bevacizumab (6).

It can be inferred from the shortage in oncological infrastructure that not all CC patients are treated effectively and on time. Despite those caveats, it can be suggested that the outcomes of patients in Mexico treated for invasive CC are within the expected, according to a recent study (8). To place this study in perspective, currently, the population with no Employment-based Social Security Services in Mexico is 37.7%, and the goals of the current Federal Administration are to cover this population with medical services *via* the IMSS-Bienestar subsystem. Before 2003 this population had no access to gratuity for medical services, and the Mexican government created the Social System for Health Protection called "Seguro Popular" through the Fund for Protection against Catastrophic Expenses (FPGC). The FPGC provided monetary resources through a trust to accredited service providers (public and private) at the country level to care for 66 high-cost diseases, including CC, from 2005 to 2018. The study reported the treatment outcome of 38,187 women with CC from 2006 to 2014 covered by FPGC (8). For this analysis, the survival analysis was done in 25,556 women only as 16,619 were excluded (12 with poor-prognosis histology, 8,544 preinvasive diseases, 1,130 recurrent or progression, 1,619 unconfirmed diagnoses, 2,284 and 3,043 had no 5-year follow-up because data on deaths were available until 2019). The results indicate that the FIGO stage distribution was 24.5% for early stages (1A-IB1), 68.5% for locally advanced stages (IB2-IIIB), and 7% for advanced stages (IVA-IVB), with a median age of 51.2 ± 13.8, 49.8 ± 13.6 and

TABLE 1 Summary of resources for diagnosis and treatment of Cervical Cancer in Mexico.

| Diagnosis | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| **Imaging equipment (number of units in Mexico)(15)** | **Clinical Stage** | **Patients diagnosed at each clinical stage (8)** | **Modality (31)** | **Oncologists (number) (17,18)** | **Infrastructure (17)** | **Pharmacological treatment (6)** | **Five year-Overall survival (8)** |
| Computed tomography scanners (793)<br>Positron emission tomography-Computed Tomography (31)<br>Magnetic resonance imaging (316) | Early Diasease | 24.5% | Surgery<br>Surgery and adjuvant radiation or adjuvant chemoradiation | Surgical oncologists (945); Gynecological oncologists (174) | | Cisplatin | 88% |
| | Locally advanced Disease | 68.5% | Concurrent chemoradiation and brachytherapy | Medical oncologists (473);<br>Radiation oncologist (346) | Teletherapy equipments (162); brachytherapy units (59) | Cisplatin<br>Gemcitabine<br>Carboplatin | 63.9% |
| | Advanced Disease | 6.9% | Doublet chemotherapy with/ without bevacizumab | Medical oncologist (473) | | Cisplatin<br>Carboplatin<br>Paclitaxel<br>Bevacizumab<br>5-Fluorouracil<br>Docetaxel<br>Capecitabine | 43.6% |

51.6 ± 13.8 respectively. In the multivariate analysis, only the age and clinical stage were significant. For each year of increase in women's age, the risk of dying increased by 0.3%, while the risk of dying was 2.76 and 5.39 times higher for women with locally advanced and advanced disease, respectively, compared to early stages. Overall survival (OS) at 5 years was 68.5%. The OS analysis by clinical stage was 88% in early stages, 63.9% in locally advanced disease, and 43.6% for advanced disease (8). The results of this study found 5-year survival rates comparable to the reported for other countries, which are 63%, 66%, 67%, and 58.8% for Spain, the USA, Chile, and Colombia, respectively. These outcomes are consistent with others reported by specialized hospitals with oncology departments and cancer centers (5–7, 30). Regarding the factors that affect the survival of patients, a retrospective study that included a cohort of 2,982 women diagnosed with CC, and treated at the INCan, from 2005 to 2015, shows that age at diagnosis is not a prognostic factor for OS or PFS. OS at 5 years in the early stage (FIGO) in women younger than 40 years was 93.4% vs. 92% in women older than 40 years, while in locally advanced disease, it was 62.9% vs. 63.4%, respectively; and advanced disease was 47.5% vs. 46.6%, respectively. The multivariate analysis identified adverse factors contributing to OS and disease-free survival: clinical stage, histological subtype, presence of hydronephrosis, and lymph node involvement (7).

From here, it is clear the importance of providing access to CC treatment in specialized centers to all women, especially those with social disadvantages (8).

## Conclusions

CC is a model of preventable cancer, as demonstrated by the dramatic mortality reduction observed in high-income countries that have successfully implemented screening programs. CC incidence and mortality are closely related to socially disadvantaged women, and such an association remains even in high-income countries. The case of Mexico, an upper-middle-income country, illustrates that CC incidence and mortality are heavily related to the public health system. A universal and efficient health system and a nationwide cancer control program are needed to control CC in Mexico. Despite numerous analyses from epidemiological and medical perspectives, the fact is that this neoplasia still represents a heavy health burden in the world derived from global social and economic inequalities.

## Future perspectives

The eradication of CC remains challenging. From the primary prevention perspective, we must consider statistical models that predict the ability of HPV vaccination to reduce CC mortality. More decades to come are needed to confirm these predictions. Unfortunately, the world population coverage of HPV vaccination is around 15%, which is still far from the threshold of 70% proposed by the WHO. Not all is known regarding HPV vaccination. Some reports have associated vaccination with reductions in the prevalence of HPV infection in unvaccinated women residing at the same geographical location as vaccinated women, presumably by sexual dissemination of these changes. However, vaccine-covered, high-risk HPV types may be replaced by not covered HPV types. In light of these observations, it is not entirely clear what effects vaccine-associated HPV type replacement may be seen in the future (31). Safety issues of HPV vaccination and continued research to ratify the risk-benefit analyzes of these vaccines is desirable (32–34).

Regarding secondary prevention, the Pap test remains widely recommended in most countries though the WHO advocates using HPV-DNA testing primarily or combined with cytology as the primary screening tool for CC, subject to the available resources and infrastructure. The research on alternative simple and effective approaches, such as see-and-treat strategies with visual inspection with acetic acid, must continue, particularly in those countries where HPV testing/Pap smears are unaffordable (35). We must critically analyze the cost-benefit challenge in changing the field of CC screening toward molecular tests (36).

The treatment of CC is perhaps the one facing more problems worldwide. The shortage of trained gynecological surgeons in many countries and regions directly threatens the treatment of patients at early stages (37). For radiotherapy, the situation could be worse. While in high-income countries, one radiotherapy machine is available for every 120,000 people, in middle-income countries, one machine serves over 1 million people and about 5 million people in low-income countries. Cancer patients cannot access radiotherapy in 51 countries, independent territories, and islands (38).

Regarding chemotherapy, low affordability for cancer drugs and medical oncologist specialists seems constant in developing countries (38). Nevertheless, patients from socially disadvantaged conditions attain satisfactory survival rates when they access appropriate cancer care. Therefore, very clever use of resources is required from the view of public health to employ treatments with the highest cost-benefit in settings where resources are insufficient.

## Author contributions

EB: Investigation, Writing-Original Draft. LC-P: Conceptualization, Project administration, Supervision. TC: Investigation. DC-E: Writing-Reviewing and Editing. DR: Supervision. IB: Resources. AD-G: Writing-Original Draft. All

authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 07 December 2022
DOI 10.3389/fonc.2022.997030



OPEN ACCESS

EDITED BY
Lucely Cetina-Pérez,
National Institute of Cancerology (INCAN), Mexico

REVIEWED BY
Lichun Wei,
The First Affiliated Hospital of Air Force Medical University, China
Stefano Restaino,
Ospedale Santa Maria della Misericordia di Udine, Italy

*CORRESPONDENCE
Xiaobing Qin
qin_xiaobing@163.com
Zhengxiang Han
cnhzxyq@163.com

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 18 July 2022
ACCEPTED 21 November 2022
PUBLISHED 07 December 2022

CITATION
Liu H, Ma X, Sun C, Wu M, Xu Z, Zhou S, Yao N, Liu S, Qin X and Han Z (2022) Concurrent chemoradiotherapy followed by adjuvant chemotherapy versus concurrent chemoradiotherapy alone in locally advanced cervical cancer: A systematic review and meta-analysis.
*Front. Oncol.* 12:997030.
doi: 10.3389/fonc.2022.997030



# Concurrent chemoradiotherapy followed by adjuvant chemotherapy versus concurrent chemoradiotherapy alone in locally advanced cervical cancer: A systematic review and meta-analysis

Haonan Liu[1], Xiao Ma[1], Chenyu Sun[2], Meng Wu[1], Zhiyuan Xu[3], Shuang Zhou[1], Nan Yao[1], Suya Liu[1], Xiaobing Qin[1*] and Zhengxiang Han[1*]

[1]Department of Oncology, The Affiliated Hospital of Xuzhou Medical University, Jiangsu, China, [2]Department of Internal Medicine, AMITA Health Saint Joseph Hospital Chicago, Chicago, IL, United States, [3]Department of Emergency, The Affiliated Hospital of Xuzhou Medical University, Jiangsu, China

**Objective:** This study aimed to assess the efficacy and safety of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) in patients with locally advanced cervical cancer (LACC) *via* meta-analysis.

**Methods:** A systematic literature search of MEDLINE, PubMed, Web of Science, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted from January 10, 1966 to May 20, 2022. Randomized controlled trials and observational studies comparing the CCRT alone with CCRT plus ACT were included. The literature search, quality assessment, and data extraction were conducted by two reviewers independently. The primary endpoints were 3-year rates of overall survival (OS) and progression-free survival (PFS). Complete response rate, local recurrence, distant metastasis, and adverse events were secondary outcomes. The hazard ratios (HRs) and relative risk (RR) were pooled.

**Results:** Nine studies with a total of 2732 patients were included in this meta-analysis, including 1411 patients in the CCRT group and 1321 in the CCRT plus ACT group. The HR for 3-year rates of OS and PFS of the CCRT group compared with the CCRT plus ACT group was 0.72 [95%confidence interval (CI) = 0.44–1.17] and 0.78 (95%CI = 0.5–1.75), respectively. No significant differences were observed between the two groups in the complete response rate (RR = 1.06, 95%CI = 0.96–1.16). However, local recurrence and distant metastasis were significantly lower in the CCRT plus ACT group than in the CCRT group (RR = 0.63, 95%CI = 0.44 –0.91 and RR = 0.64, 95%CI = 0.47–0.88). Grade 3–4 acute toxicities were more frequent in the CCRT plus ACT group (RR = 1.73, 95%CI =1.19–2.52).

**Conclusion:** Although associated with a decreased risk of local recurrence and distant metastasis, ACT did not significantly improve the survival rate and the complete response rate with increasing grade 3–4 acute toxicities in patients with LACC. Thus, this ACT regimen cannot be recommended for patients with LACC.

**Systematic review registration:** https://inplasy.com/inplasy-2022-9-0089/, identifier INPLASY202290089.

KEYWORDS

concurrent, chemoradiotherapy, adjuvant chemotherapy, cervical cancer, meta-analysis

# Introduction

As the most common gynecologic malignant neoplasm reported in women worldwide, the treatment of cervical cancer remains a challenge due to the lack of health infrastructure. In 2018, there were about 36,000 new cases, with 311,365 cancer-related deaths (1). In many developing countries, patients were diagnosed with cervical cancer at at a locally advanced stage, indicating a poor outcome (2).

For more than two decades, cisplatin-based concurrent chemoradiotherapy has been used as a standard therapeutic regimen for locally advanced cervical cancer (LACC), based on the survival benefit and clinical experience (3–7). Despite the use of concurrent chemotherapy, about 16%–60% of patients with LACC still suffer from tumor recurrence or distant metastasis (8). The mortality rate in patients with LACC remains high, with a 5-year survival rate less than 60% (9). Previous studies found that concurrent chemoradiation (CCRT) may improve the 5-year survival rate by 9%–18% (10). Adjuvant chemotherapy (ACT) after CCRT is another option for patients with LACC. ACT aims at decreasing both the mortality rate and the risk of recurrence by eliminating residual malignant tissues outside the radiotherapy target region and treating occult disease in the pelvis. While the role of additional chemotherapy after CCRT for treating LACC has been explored in many studies (11–15), survival benefits after the addition of ACT to CCRT in patients with LACC remain controversial. With limited data from only two trials, a Cochrane review published in 2014 could not find sufficient evidence to support the use of ACT after CCRT and failed to perform meta-analysis (9). However, a number of original studies have been published since then, which were incorporated to evaluate the efficacy and safety of ACT in patients with LACC through meta-analysis.

# Methods

This meta-analysis was registered on INPLASY website (INPLASY202290089), doi:10.37766/inplasy2022.9.0089.

## Search strategy

We conducted a systematic literature search of MEDLINE, PubMed, Web of Science, EMBASE, and the Cochrane Central Register of Controlled Trials, using the following search terms: (concurrent or chemoradiotherapy or chemoradiation or concurrent chemoradiation or concurrent chemoradiotherapy or adjuvant chemotherapy or addition or chemotherapy or consolidation chemotherapy) and (cervical cancer or uterine cervical neoplasm or uterine cervical cancer or cervical). In addition, we supplemented the search by manually reviewing the reference lists of retrieved articles and relevant reviews and by contacting content experts for additional published or unpublished trials.

## Study selection

Two of the authors (Wu and Yao) carried out a preliminary search, scanning all titles for eligibility according to the predefined inclusion criterion. Duplicate publications or datasets were removed. Each title and abstract were reviewed to determine eligibility. After obtaining full abstracts for potentially eligible studies, two reviewers (Qin and Han) worked independently to assess eligibility. A study was considered ineligible from a review of the title and its abstract. In all other cases, the full study was reviewed.

## Inclusion and exclusion criteria

Studies were considered eligible for meta-analysis if they met the following criteria:

(1) patients diagnosed with LACC of the FIGO (International Federation of Gynecology and Obstetrics) stage IB–IVA with at least one measurable lesion and Karnofsky performance score of 70 (16) (2); randomized controlled trials (RCTs) or observational studies (3); all patients aged 18 years or older who had not been previously treated with immunotherapy (4); all study protocols approved by the institutional ethics committee and performed in accordance with the Declaration of Helsinki (5); at least 30 patients included in the study (6); survival rate and complete response rate as the outcomes of interest; and (7) risk estimates with 95% confidence interval (CI) or data to calculate them.

The major exclusion criteria were as follows (1): patients with other malignant tumors (2); the publication in the format of an abstract, comment, or review; and (3) no sufficient data.

## Data extraction

Two authors (Zhou and Sun) independently extracted data using a standardized data-collection form. The following information was recorded: the first author's name, year of publication, sample size, population demographics, study design, trial length, and country of origin. Our primary efficacy endpoint was the survival rate. Secondary endpoints included complete response rate, local recurrence, distant metastasis, and adverse events. Disagreements were resolved by discussion with the third author (Han). The quality assessment of the RCTs was evaluated using the Cochrane Handbook of 6.2 (17).

## Statistical analysis

We evaluated the efficacy and safety of ACT after CCRT in patients with LACC. Qin and Liu performed all statistical analyses. The hazard ratio (HR) and the 95% CI were used to assess the survival rate of patients with LACC who underwent ACT after CCRT. Because of the lack of information on HR, the estimation of data from the Kaplan–Meier curves were used (18, 19). The risk ratio (RR) was used as the summary statistic for statistical analyses of dichotomous variables. The homogeneity of effect size across studies was tested using Q statistics at the statistically significant level of $P < 0.10$. The $I^2$ statistic, which is a quantitative measure of inconsistency across studies (20), was also calculated. We further conducted the sensitivity analysis to explore the possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate. Finally, potential publication bias was assessed using Begg's funnel plots and Egger's regression test (21, 22). All analyses were carried out using Stata 12.0. P value < 0.05 was considered to be statistically. All data analyses were performed according to the PRISMA statement (23).

# Results

## Literature search

Initially, 791 unique citations were identified. After the removal of duplicates, 345 studies remained eligible. By screening the titles and abstracts, 178 of 345 studies were excluded and 167 were selected for further assessment. Of these publications, 63 studies were excluded for the following reasons: 33 studies did not meet the selection criteria, 14 studies did not provide sufficient data, and 16 studies reported different outcomes. Finally, 9 studies involving a total of 2732 patients (1321 in the CCRT plus ACT group and 1411 in the CCRT-alone group) were included in this meta-analysis. The search process and strategy adopted for this study are shown in Figure 1.

## Study characteristics

The characteristics of the included studies are listed in Table 1, which were published between 2003 and 2019. Four studies were on RCTs, while the remaining five were observational studies. Of these, two studies were conducted in Thailand (25, 29), two in Korea (27, 30), one in Mexico (28), one in Turkey (24), one in Japan (32), one in Brazil (31), and one in China (26). The median length of the follow-up period ranged from 21.5 to 89 months. This study analyzed 2732 patients with FIGO stage IB–IVA cervical cancer, with the majority of the studies (8/9) using cisplatin-based chemoradiotherapy.

## Quality assessment

The quality of observational studies was determined using the Newcastle-Ottawa Scale. Any study that scored over seven stars was regarded as a high-quality study, while a score of four to six stars was regarded as a moderate-quality study (33). A quality assessment of the RCTs was carried out using the Cochrane risk of bias tool (Figures 2, 3). High risk was mainly attributed to blinding methods. Most studies had either low or unclear risks of bias due to missing information on the protocols of the trials or inclusion criteria.

## Sensitivity analysis

Large heterogeneity was observed among studies in this meta-analysis. Thus, we conducted sensitivity analyses for the

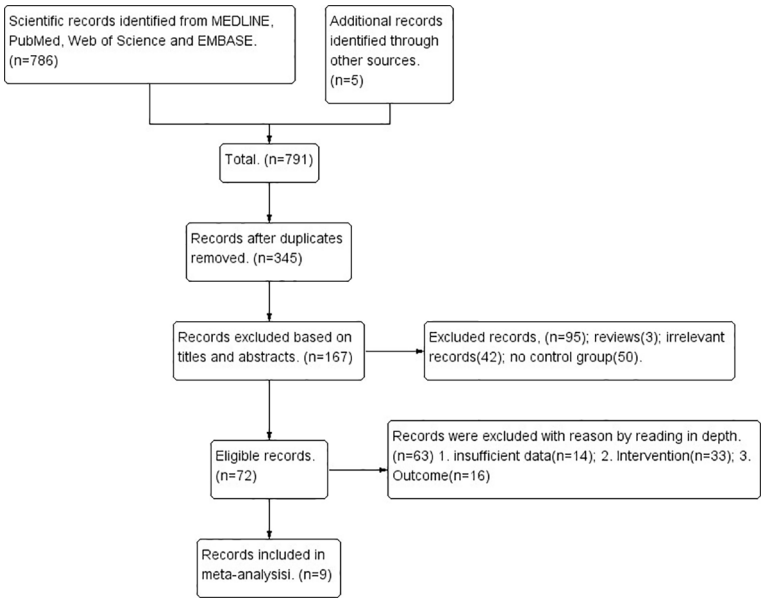


FIGURE 1
PRISMA flow diagram showing a selection of articles for meta-analysis.

TABLE 1 Details of the previous studies included in this meta-analysis.

| Author/ year | Country | Research type | Sample size | Follow-up time (median) | Stage | Histopathology | Concurrent chemotherapy | Adjuvant chemotherapy | NOS score |
|---|---|---|---|---|---|---|---|---|---|
| Yavas (2019) (24) | Turkey | Observational study | 109 | 24.5 months | IB to IVA | SCC,ACA,AS,small-cell, large-cell | Cisplatin in both arms | Paclitaxel/carboplatin median 6 cycles (range 3–6 cycles) | 6 |
| Tangjit (2019) (25) | Thailand | RCT | 259 | 27.4 months | IIB to IVA | SCC, ACA, AS | Cisplatin in both arms | Paclitaxel/carboplatin 3 cycles | – |
| Tang (2012) (26) | China | RCT | 880 | 60 months | IIB to IVA | ACA only | Cisplatin in both arms | Paclitaxel/cisplatin 2 cycles | – |
| Choi (2011) (27) | Korea | Observational study | 78 | 35 months | IIB to IVA | SCC, ACA | 5-FU and cisplatin or cisplatin in both arms | 5-FU and cisplatin 3 additional cycles | 8 |
| Duenas (2011) (28) | Mexico | RCT | 515 | 46.9 months | IIB to IVA | SCC, ACA, AS | Cisplatin in CCRT arm Cisplatin/gemcitabine in CCRT+ACT arm | Cisplatin/gemcitabine 2 cycles | – |
| Lordvith (2003) (29) | Thailand | RCT | 463 | 89 months | IIB to IVA | SCC, ACA | Mitomycin/oral 5-FU in both arms | Oral 5-FU 3 cycles | – |
| Kim (2007) (30) | Korea | Observational study | 205 | 64 months | IB to IIB | SCC, small-cell, large-cell | Cisplatin/carboplatin in both arms | Cisplatin/carboplatin 3 cycles | 8 |
| Fabri (2019) (31) | Brazil | Observational study | 186 | 37.7 months | IB2,IIA2, or IIB to IVB | SCC, ACA | Cisplatin in both arms | cisplatin and gemcitabine 2 cycles | 7 |
| Abe (2011) (32) | Japan | Observational study | 37 | 21.5 months | IB to IVA | SCC, ACA | Cisplatin in both arms | carboplatin and paclitaxel for 3-6 cycles | 7 |

ACA, adenocarcinoma; ACT, adjuvant chemotherapy; AS, adenosquamous carcinoma; CCRT, concurrent chemoradiation therapy; NOS, Newcastle–Ottawa Scale; RCT, randomized controlled trial; SCC, squamous cell carcinoma.

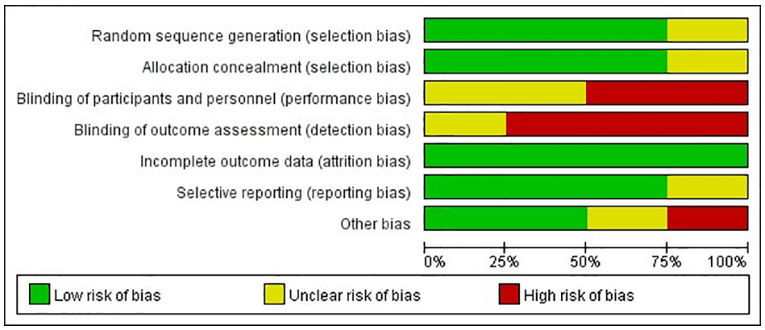


FIGURE 2
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across RCTs.

3-year rates of overall survival (OS) to explore the underlying reasons for heterogeneity (Figure 4). The pooled HR did not change significantly after sensitivity analysis with the removal of one study at a time, which indicated that the results were relatively stable.

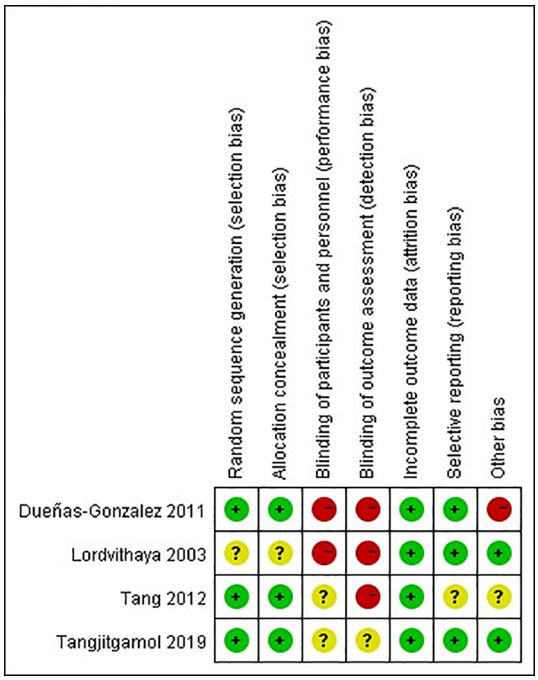


FIGURE 3
Risk of bias summary: review authors' judgments about each risk of bias item for RCTs.

## Primary endpoints: 3-year OS and progression-free survival

The 3-year OS was evaluated in eight included studies (24, 25, 27–32), and significant heterogeneity was observed among the studies ($P = 0.001$, $I^2 = 72.8\%$). No significant difference was observed between the CCRT group and the CCRT plus ACT group (HR = 0.72, 95%CI = 0.44–1.17) (Figure 5A).

Five studies reported the HR for 3-year progression-free survival (PFS) (25, 27–29, 31). The results revealed no significant difference in 3-year PFS between the two groups (HR = 0.78, 95%CI = 0.53–1.15), with high level of heterogeneity between studies ($P = 0.010$, $I^2 = 70.0\%$) (Figure 5B).

## Secondary endpoints: complete response, local recurrences, distant metastases, and adverse events

Four studies were included in this meta-analysis, which assessed the complete response rate (24, 25, 27, 28). No heterogeneity was observed among the studies ($P = 0.372$, $I^2 = 4.2\%$). No noticeable differences were observed between the two groups in the complete response rate (RR = 1.06, 95%CI = 0.96–1.16) using a fixed-effects model. (Figure 6).

Eight studies were pooled into the analysis of local recurrence rates (24–30, 32). The results indicated that the CCRT plus ACT group had a significantly lower risk of local recurrence than the CCRT group (RR = 0.63, 95%CI = 0.44 – 0.91) with moderate between study heterogeneity ($P = 0.024$, $I^2 = 56.5\%$) (Figure 7A).

Eight studies were eligible to analyze the risk of distant metastasis (24–30, 32). The results suggested that the risk of distant metastasis was significantly lower in the CCRT plus ACT group than in the CCRT group (RR = 0.64, 95%CI = 0.47–0.88)

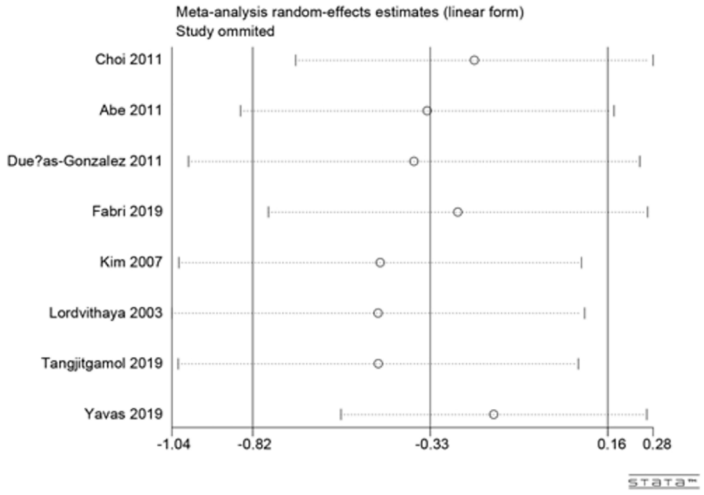


FIGURE 4
Sensitivity analysis of the 3-year rates of OS.

with moderate heterogeneity ($P$ = 0.063, $I^2$ = 47.8%) between studies (Figure 7B).

Six studies reported grade 3–4 acute toxicities in two groups (25–30). The meta-analysis showed that grade 3–4 acute toxicities were more frequent in the CCRT plus ACT group (RR = 1.73, 95%CI = 1.19–2.52) with high between study heterogeneity ($P$ = 0.001, $I^2$ = 88.9%) (Figure 8). Next, we conducted a subgroup analysis, in which grade 3–4 gastrointestinal system toxicities were more frequent during the treatment of the CCRT plus ACT group (RR = 1.33, 95% CI = 1.01–1.75). However, no noticeable differences were observed between the two groups in grade 3–4 hematological adverse events (RR = 1.92, 95%CI = 0.94–3.90) and genitourinary system toxicities (RR = 1.58, 95%CI = 0.80–3.10).

## Publication bias

Visual inspection of Begg's funnel plot did not identify substantial asymmetry (Figure 9). The publication bias was examined using Egger's ($P$ = 0.289) and Begg's tests ($P$ = 0.266), and no publication bias was found.

# Discussion

In 2021, the American Society of Clinical Oncology announced the latest results of the OUTBACK trial (34), which indicated that the addition of ACT to standard CCRT did not improve the survival outcomes of patients with LACC,

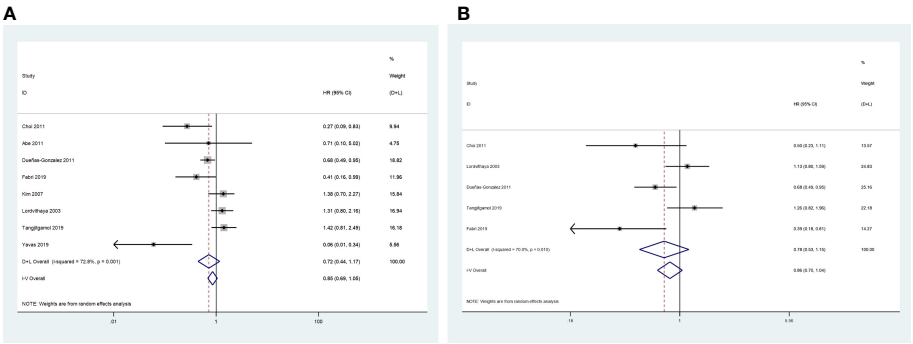


FIGURE 5
Forest plot of the survival rates. **(A)** 3-year rates of OS; **(B)** 3-year rates of PFS.

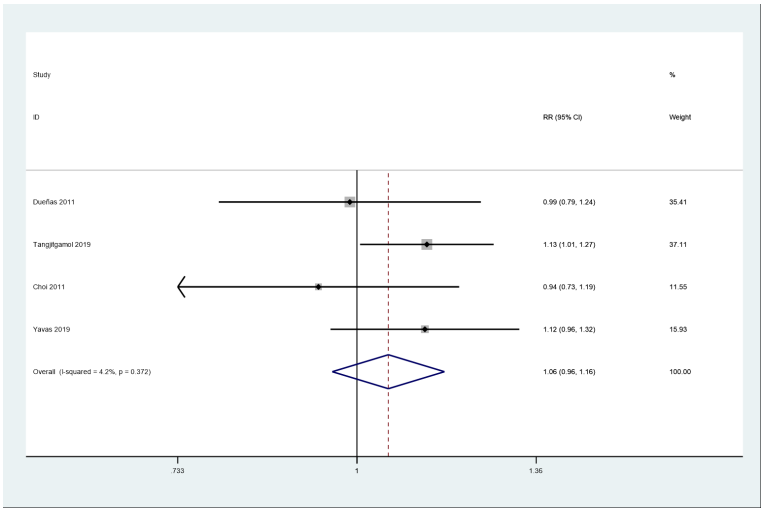


FIGURE 6
Forest plot of the complete response rate.

and the incidence of adverse events was higher. This was a phase III multi-center clinical study with patients from developed countries, such as the United States and Canada. However, due to the limited medical facilities and detection capacities in developing countries, the incidence of LACC is higher. Most of the included studies (6/9) in this meta-analysis were from developing countries. This is the first meta-analysis aimed at comparing the tumor response, survival benefit, and tolerability between the CCRT plus ACT and CCRT-alone groups for patients with LACC. The results revealed that CCRT plus ACT was associated with the reduced risk of local recurrence and distant metastasis, yet at the expense of some additional toxicities. Nevertheless, the addition of ACT had no advantage in increasing the survival and complete response rates.

In recent years, ACT has been applied in different types of tumors, and its efficacy has been confirmed. In contrast, accurate data on the effects of ACT when added to CCRT in patients with LACC, still remain unclear (35). Despite the benefits of ACT reported in a number of previous studies (36–38), we failed to find any improvement in the survival or the complete response rate with increasing the incidences rates of grade 3–4 acute toxicities.

Reviews exploring the role of ACT after CCRT in patients with LACC have been limited. A 2021 systematic review did not demonstrate the effectiveness of ACT because the purpose of this review was to emphasize the importance of adjuvant systemic treatment (chemotherapy, immunotherapy, and hormone therapy) (39). Moreover, the control group in this review was not the CCRT-alone group. Because of the significant clinical

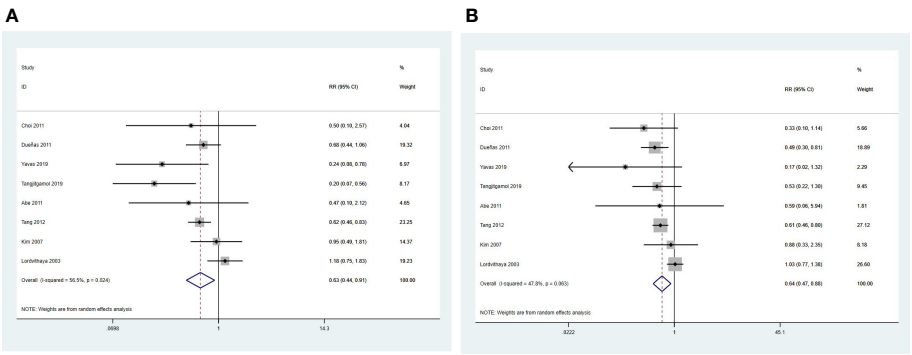


FIGURE 7
Forest plot of total failure: **(A)** local recurrences; **(B)** distant metastases.

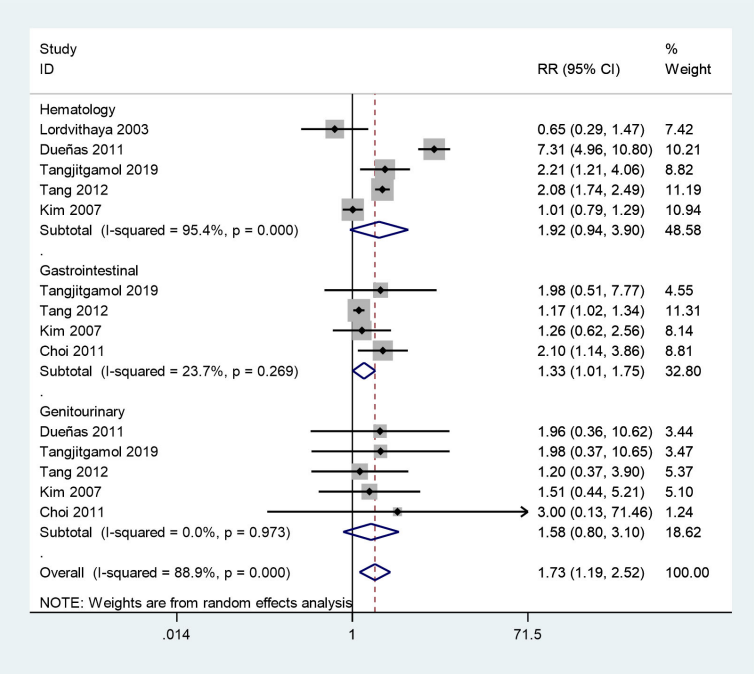


FIGURE 8
Forest plot of adverse events.

differences between the included studies, no meta-analysis was conducted in the 2014 Cochrane review (9). This review only incorporated two RCTs, and one of the trials did not use platinum-based chemotherapy as adjuvant chemotherapy. Besides this, in the Cochrane review, concurrent chemotherapy regimens were not the same in the treatment group (gemcitabine plus cisplatin) and the control group (cisplatin). Thus, some limitations were found in applying their results to guide the application of ACT in clinical practice. This meta-analysis included more high-quality RCTs and other original studies, and provided more powerful and reliable results compared with the two previous studies.

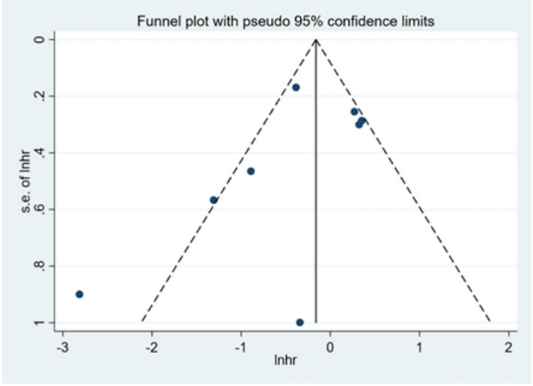


FIGURE 9
Begg's funnel plot for detecting publication bias.

It is noteworthy that three additional studies also investigated the role of ACT in patients with LACC. Jelavić et al. reported that ACT consisting of four cycles of cisplatin and ifosfamide after CCRT could potentially improve distant control of LACC (40). Mabuchi et al. observed that using three cycles of ACT with paclitaxel plus carboplatin after CCRT in patients with LACC of stage IIIB/IVA improved local control and reduced distant metastasis (36). However, the OUTBACK trial showed that four cycles of carboplatin combined with paclitaxel after concurrent chemoradiotherapy did not differ in local recurrence and distant metastasis compared with concurrent chemoradiotherapy alone (34). This meta-analysis found that local recurrence and distant metastasis were significantly lower in the CCRT plus ACT than in the CCRT group (RR = 0.63, 95%CI = 0.44 –0.91 and RR = 0.64, 95%CI = 0.47–0.88). One of the reasons might be that the systemic cytotoxic effects of ACT are enhanced by CCRT due to radiosensitization, rather than the effects of ACT alone (40).

The overdiagnosis and overtreatment of a malignant tumor is a serious issue and has been debated globally over the last few years (41). In principle, it should be emphasized that the superior

treatment effect can be achieved only if moderate treatment is adopted. Overtreatment results in the waste of resources and places patients at risk of adverse events. For example, in this meta-analysis, grade 3–4 gastrointestinal system toxicities were found more frequent during the treatment of CCRT plus ACT than that of CCRT alone. Moreover, the total incidence of grade 3–4 adverse advents was more common in the CCRT plus ACT group than in the CCRT-alone group. Furthermore, ACT could not improve the survival rates in LACC, and therefore, ACT could be considered overtreatment. Multiple factors that might affect therapeutic options in patients with LACC should be taken into consideration when clinicians determine the appropriate therapeutic regimen to avoid overtreatment.

The treatment of patients with LACC has been under investigation. According to the National Comprehensive Cancer Network clinical guidelines, CCRT is still the preferred treatment option for stage IB3 and IIA2 cervical cancer, followed by radical hysterectomy combined with pelvic lymphadenectomy (42). For stage IIB cervical cancer, CCRT remains the only option (42). However, radiotherapy can impair the ovarian function and vaginal elasticity in young patients and reduce the quality of their sexual life (43). In recent years, some studies have shown that radical surgery after neoadjuvant chemotherapy can be an important treatment option for patients with LACC, and may have better performance than CCRT, especially in relatively early-stage patients (44–46).

This meta-analysis had several limitations. First, about half of the included studies (5/9) were observational, indicating that recalling bias and selection bias were hard to avoid. Second, in this meta-analysis, some survival outcomes extracted from the Kaplan–Meier curve might not accurately reflect the true values. Third, the ACT regimens differed slightly between studies; Lorvidhaya (2003) used non-platinum regimens (29). Fourth, only 2732 patients were included in trials, and the sample size in this meta-analysis needed to be further expanded. Fifth, the loss to follow-up in these studies might affect the results. Although most of the loss to follow-up in the four RCTs and five observational studies were balanced across treatment arms, the risk of selection bias could not be completely ignored, and the individuals who participated in these studies might not be representative of the randomized sample. Sixth, the length of the follow-up time of the included studies was relatively short. Finally, a large heterogeneity was observed in this study. However, the sensitivity analysis showed that the results were relatively reliable. The causes of heterogeneity might be different follow-up periods, small sample size, different study designs, and different chemotherapy regimens.

## Conclusions

Compared with CCRT, ACT did not significantly improve OS and PFS rates with increasing unmanageable toxicity in the treatment of patients with LACC. The CCRT plus ACT treatment should not be considered over CCRT alone for LACC. Future studies need consideration of higher-quality RCTs to confirm this result.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

## Author contributions

HNL, XBQ and ZXH contributed to conception and design of the study. CYS, NY and MW collected and assessed the literature. HNL, SZ and ZYX performed the statistical analysis. HNL and SYL wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 20 January 2023
DOI 10.3389/fonc.2022.1020205



OPEN ACCESS

EDITED BY
Sophia George,
University of Miami, United States

REVIEWED BY
Olugbenga Akindele Silas,
University of Jos, Nigeria
Onyi Balogun,
New York University, United States

*CORRESPONDENCE
Emma McKim Mitchell
emm6z@virginia.edu

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 15 August 2022
ACCEPTED 29 December 2022
PUBLISHED 20 January 2023

CITATION
Mitchell EM, Hall KM, Doede A, Rong A, McLean Estrada M, Granera OB, Maldonado F, Al Kallas H, Bravo-Rodriguez C, Forero M, Pokam Tchuisseu Y and Dillingham RA (2023) Feasibility and acceptability of self-collection of Human Papillomavirus samples for primary cervical cancer screening on the Caribbean Coast of Nicaragua: A mixed-methods study. *Front. Oncol.* 12:1020205. doi: 10.3389/fonc.2022.1020205



# Feasibility and acceptability of self-collection of Human Papillomavirus samples for primary cervical cancer screening on the Caribbean Coast of Nicaragua: A mixed-methods study

Emma McKim Mitchell[1]*, Katherine M. Hall[1], Aubrey Doede[2], Anneda Rong[3], Michelet McLean Estrada[1], Orlando Benito Granera[4], Francisco Maldonado[4], Hala Al Kallas[5], Cassandra Bravo-Rodriguez[1], Mariana Forero[6], Yolande Pokam Tchuisseu[7] and Rebecca A. Dillingham[8]

[1]Department of Family, Community & Mental Health Systems, University of Virginia School of Nursing, Charlottesville, VA, United States, [2]Department of Family Medicine, University of California San Diego, La Jolla, CA, United States, [3]School of Data Science, University of Virginia, Charlottesville, VA, United States, [4]Fundación Movicancer, Managua, Nicaragua, [5]St. George's University School of Medicine, Great River, NY, United States, [6]School of Arts and Sciences, University of Virginia, Charlottesville, VA, United States, [7]Duke-Margolis Center for Health Policy, Washington, DC, United States, [8]Department of Infectious Disease, School of Medicine, University of Virginia, Charlottesville, VA, United States

**Background:** Cervical cancer is the primary cause of cancer death for women in Nicaragua, despite being highly preventable through vaccination against high-risk genotypes of the Human Papillomavirus (hrHPV), screening for hrHPV, and early detection of lesions. Despite technological advances designed to increase access to screening in low resource settings, barriers to increasing population-level screening coverage persist. On the Caribbean Coast of Nicaragua, only 59% of women have received one lifetime screen, compared to 78.6% of eligible women living on the Pacific and in the Interior. In concordance with the WHO's call for best practices to eliminate cervical cancer, we explored the feasibility and acceptability of self-collection of samples for hrHPV testing on the Caribbean Coast of Nicaragua through a multi-year, bi-national, community-based mixed methods study.

**Methods:** Between 2016 and 2019, focus groups (n=25), key informant interviews (n=12) [phase I] and an environmental scan [phase II] were conducted on the Caribbean Coast of Nicaragua in partnership and collaboration with long-term research partners at the University of Virginia and community-based organizations. In spring 2020, underscreened women on the Caribbean Coast of Nicaragua were recruited and screened for hrHPV, with the choice of clinician collection or self-collection of samples.

**Results:** Over the course of the study, providers and potential patients expressed significant *acceptability* of self-collection of samples as a strategy to reduce

barriers currently contributing to the low rates of screening (phases I and II). Ultimately 99.16% (n=1,767) of women chose to self-collect samples, demonstrating a high level of acceptability of self-collection in this pilot sample (phase III). Similarly, focus groups, key informant interviews, and the environmental scan (phases I and II) of resources indicated critical considerations for *feasibility* of implementation of both HPV primary screening and subsequently, self-collection of samples. Through phase III, we piloted hrHPV screening (n=1,782), with a 19.25% hrHPV positivity rate.

**Conclusion:** Self-collection of samples for hrHPV testing demonstrated high acceptability and feasibility. Through concerted effort at the local, regional, and national levels, this project supported capacity building in reporting, monitoring, and surveilling cervical cancer screening across the continuum of cervical cancer control.

KEYWORDS

HPV, cervical cancer, self-collection HPV test, Nicaragua, underscreened

## Introduction

Almost entirely preventable through vaccination against high-risk genotypes of the Human Papillomavirus (hrHPV) and through screening and early detection, cervical cancer is a cancer of disparities, with disproportionate mortality in women living in low- and middle-income countries (LMICs). The World Health Organization (WHO) estimates that 85% of global cervical cancer deaths are in LMICs, where women carry a risk of dying from cervical cancer three times higher than that of women in high-income nations (1). In Latin America, cervical cancer is the third most common cause of cancer death for women, but in Nicaragua, it is the leading cause of cancer death for women (2). Within Nicaragua, access to healthcare and preventive services varies geographically, with women living on the rural and remote Caribbean Coast less likely to engage in cervical cancer prevention efforts (3).

Invasive cervical cancer incidence and mortality can be dramatically reduced through early detection and treatment, but many women do not complete screening at recommended intervals (4). Significant decreases in cervical cancer incidence and mortality rates globally are directly attributed to increased screening and early detection (1). The WHO has developed a plan for the elimination of cervical cancer within the next 100 years with specific targets to be reached by 2030, including: reaching 90% of girls by age 15 for vaccination against high risk Human Papillomavirus (hrHPV); 70% of women receiving a high-quality screen for cervical cancer by age 35 and again by age 45; and 90% of women receiving treatment (whether for precancerous or cancerous lesions) (5–7). Researchers have indicated that in some LMICs, a single lifetime screen may be all that is currently feasible (7).

While the HPV vaccine is available in Nicaragua for purchase (8), there is not currently a National HPV vaccination program (9). The cervical cancer control program in Nicaragua therefore centers on organized, opportunistic, population-based screening, and early detection through annual Pap testing/cytology for women ages 25-65, and annual cervical visual inspection with acetic acid (VIA) recommended for women ages 30-50 (9). Intra-country variability in screening coverage is significant. While screening efforts in the Pacific region cover an estimated 34.7% of eligible women within a given year, and where 78.6% of women have been screened in their lifetime, it is notable that screening coverage drops significantly when disaggregating the Caribbean Coast of Nicaragua, where 27.1% of eligible women are estimated to be screened in the span of a year and only 59% of women have had a lifetime screen (9).

In line with the WHO's call to eliminate cervical cancer, there are innovative technologies and community-based implementation models being trialed globally. Self-collecting samples to screen for hrHPV provides particular promise at mitigating some known barriers to screening engagement found in the literature, where in Latin America specifically embarrassment, privacy concerns, machismo of male partners, and the time or difficulty involved with attending a clinic are well documented in the literature (10). As cost is often a significant barrier for feasible implementation of community-based hrHPV testing, it is important to note that research specifically in Nicaragua, as well as in many other countries, has found community-based hrHPV testing to be a cost-effective approach for cervical cancer control (11).

Perhaps one of the largest benefits, is that shifting community based screening models from Pap/cytology testing or VIA to primary hrHPV screening allows for participants to collect their own sample for testing for the presence of hrHPV, the greatest risk factor in developing pre-cancerous or cancerous lesions (12, 13). hrHPV self-collection is an empirically based strategy shown to increase cervical cancer screening for women in lower resourced settings (4), has been found to have comparable sensitivity and specificity to clinician collection for hrHPV testing (12, 13), and has particular relevance for women who are under- or never-screened (14). In studies conducted with diverse populations, self-collection has shown great promise for improving access to screening for vulnerable populations who live in areas where there is poor access and fewer service

providers (12–14). The ability to self-collect samples addresses some individual reasons for not participating in screening at recommended intervals (4, 13). Several European studies found higher screening completion rates in underscreened women who received mailed at-home HPV self-collection kits when compared to mailed reminders to come for in-clinic screening (12–14).

Several studies of women in Latin America have shown promising results regarding acceptability of HPV self-collection from both participant and provider perspectives, citing the increased ease and comfort of self-collection versus clinician-collection (15, 16), as well as the benefit of time, with respect to both travel and personal obligations when kits are delivered through community-based implementation programs (10). The introduction of HPV self-collection has been shown to increase screening coverage, particularly in rural and remote areas (15).

While self-collection of samples have been found to have high levels of acceptability in disparate global settings, variability remains. Nicaragua is an important case-study for examining the acceptability of self-collection. In 2014, Bansil et al. found lower levels of participant acceptability for self-collection of samples for hrHPV testing in Nicaragua when compared to participants in Uganda and India, specifically as acceptability was influenced by fear of pain/discomfort, and by concerns about womens' ability to collect sufficient samples for testing (17). A 2020 study involving the scaling-up of the same HPV-based primary screening assay/platform (*care*HPV) used in the Bansil, et al., study in Nicaragua recruited and screened 44,635 participants over four years (18). While there was a high level of acceptability for self-collection of samples with participants in Nicaragua (and also with participants in the larger study which included community-based HPV testing in Honduras, El Salvador, and Guatemala), it is important to note that there was no inclusion of women from the Caribbean Coast of Nicaragua in the sample, demonstrating a critical need to explore screening barriers and efforts on the Caribbean Coast (18, 19).

## Caribbean Coast of Nicaragua: Contextual factors impacting acceptability and feasibility

Bluefields is the largest city on the Caribbean Coast of Nicaragua and is the political seat of the Southern Caribbean Coast Autonomous Region (RACCS) which is ethnically, linguistically, and culturally distinct from the rest of the country (20). Mestizo, Creole, Miskitu, Garifuna, Rama, and Mayagna ethnic groups are represented (20). Only within the last three years has there been an overland route connecting Nicaragua's capital of Managua directly to Bluefields (21, 22).

Barriers to cervical cancer screening, diagnosis, and access to treatment persist in the RACCS, though efforts are underway by the Ministry of Health (MINSA) to increase screening and preventive services (23). Within the city of Bluefields, screening services are provided at no cost through a network of primary care clinics or at the region's only hospital. For rural surrounding communities, screening services are provided at no cost through MINSA brigades, where healthcare providers travel to these remote areas to provide screening and return for follow-up (23).

In the context of the notable disparity and in-country variability in annual population cervical cancer screening coverage on the Caribbean Coast of Nicaragua, decreased likelihood of a lifetime cervical cancer screen, and findings in other parts of the country that there is not only high levels of participant (18) and provider (17) acceptability, but also cost-effectiveness in implementation (11), further research of this model in the regionally-specific context of the Caribbean Coast is warranted. The purpose of this study was to explore the feasibility and acceptability of community-based hrHPV screening with self-collection of samples among underscreened eligible women and their healthcare providers living on the Caribbean Coast of Nicaragua.

# Materials and methods

We collaborated with several long-term educational and research community-based partners in Bluefields, Nicaragua and the international research team at the University of Virginia (UVA) School of Nursing. Partners instrumental in this study include: the Comisarías de la Mujer, charged with representing and providing services for women and families experiencing intimate partner violence (24); the Bluefields Indian and Caribbean University (BICU) School of Nursing, which is the only school of nursing within the RACCS and has collaborated for over a decade on health and development investigations integrating nursing students from both BICU and UVA (20, 22, 25, 26); and the Centro de Derechos Humanos Ciudadanos y Autonómicos (CEDEHCA), a long-term collaborator with the research team, which supports human rights campaigns with vulnerable populations throughout the Caribbean Coast of Nicaragua. These partnerships reflect a long-term commitment to research capacity building within Bluefields in conjunction with these key governmental and non-governmental organizations.

Beginning in 2016 and continuing to 2022, we conducted a three-phased iterative research study exploring the feasibility and acceptability of self-collection for primary HPV screening in underscreened women on the Caribbean Coast of Nicaragua. Phases I and II involved a mixed-methods, community-based needs assessment conducted through key informant interviews, focus groups, and a systematic environmental scan. In partnership with the Nicaragua Ministry of Health, Phase III involved implementation of HPV primary screening in underscreened women in Bluefields, Nicaragua (please see Figure 1). We report herein on specific time points where data were collected, however, it is important to note that this study is embedded within a larger decade-long program of collaborative research and bilateral education initiatives between University partners and community-based organizations and institutions.

## Phase 1: Key informant interviews and focus groups

In the summer of 2016, study team members partnered with the Ministry of Health and conducted a mixed-methods community-based needs assessment through key informant interviews (n=12) and focus groups (n=25 across 5 focus groups). Key informant interviews included Ministry of Health officials, nurses, traditional medicine experts, as well as youth educators. Five focus groups were conducted with cancer survivors, nurses, college students, and women who

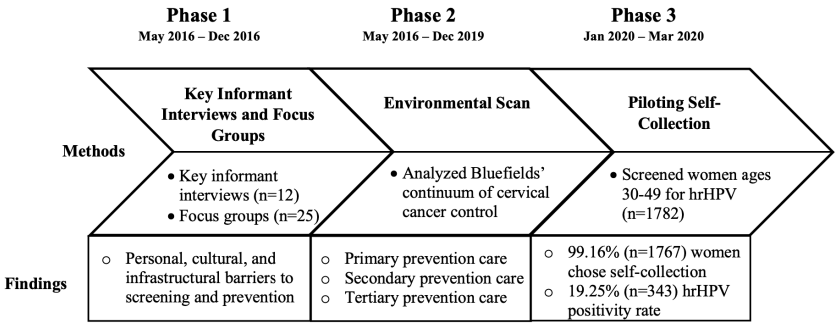


FIGURE 1
Study phases and timeline.

would be eligible for HPV-based primary screening. To facilitate transparency and fluency, all investigators spoke Spanish and English and a language and cultural interpreter from Bluefields was present during all interviews. The language used in each interview (Spanish or English) was dependent on the preference of the participants. All data were audio-recorded and transcribed verbatim. Using thematic analysis (27), we analyzed the data collected through key-informant interviews and focus groups. Throughout this process, we generated initial codes from our transcripts, and, upon reaching saturation of our data, we identified emerging themes, which are categorized under prevention, screening, and treatment. A sub-analysis was then conducted using the Socio-ecological Model (SEM) (28) to identify barriers to engaging with or accessing screening services at the individual, interpersonal, institutional, and community levels. These findings were used to inform study procedures and considerations for Phase III.

## Phase 2: Environmental scan

From May 2016 through December 2019, we conducted an environmental scan of the continuum of cervical cancer control from awareness of cervical cancer as a public health issue, through engagement with screening and through treatment, guided by the Socio-ecological model (SEM) (28). The SEM framed explorations into barriers and areas for potential intervention at the individual, inter-personal/clinician, institutional, community, and policy levels. From early 2018 through 2019, the environmental scan was also guided by the WHO publication of *Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes* (29). The latter in particular guided our clinician and institutional level indicators, through structured comprehensive collection of data points with the goal of identifying enough contextual practical data for feasible implementation of other models and interventions.

We analyzed clinics in the area to identify the continuum of cervical cancer control through existing preventive services. To address primary prevention for cervical cancer, we systematically assessed all pharmacies in Bluefields to determine how many offered HPV vaccination and what the process was for obtaining it. For secondary prevention, we assessed clinical resources for preventive services, including public and private clinics. We subsequently assessed tertiary prevention to explore follow up procedures through local clinics for follow-up care if a woman were to test positive for hrHPV. Along with data from Phase I, we integrated findings from Phase II to inform development of procedures for Phase III.

## Phase 3: Implementation of HPV self-collection

The UVA research team worked with Managua-based NGO Fundacion Movicancer (Movicancer for short) to explore acceptability and feasibility of implementation of HPV primary screening and self-collection of samples from a procedural and policy perspective, at a regional level in the RACCS and at a National level in the context of the Ministry of Health (MINSA). Between January 2020 and March 2020, we partnered with Movicancer and the MINSA to recruit and screen 1,782 women ages 30-49, who were not pregnant, and were due for cervical screening per existing Nicaraguan National screening guidelines. Women were provided culturally tailored teaching on the procedure for collecting their own sample for HPV primary screening, processed through the *care*HPV platform. Women were then given the choice to have the healthcare provider collect the sample for HPV testing, or to self-collect the sample. Samples were then transported to a laboratory setting and batched for results through the *care*HPV platform. All results were communicated to participants in-person by healthcare providers from the Ministry of Health (MINSA).

# Results

## Phase 1: Key informant interviews and focus groups

Interview participants consisted of key informants (n=12) and focus group participants (n=25 across 5 focus groups). Thematic analysis of interview data indicated several personal, cultural, and infrastructural barriers to cervical cancer prevention and screening (please see Table 1). Personal challenges included shame, embarrassment, women's role as caretakers for others, and past

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TABLE 1 Emergent themes and exemplary quotes related to barriers to screening (N=12).

| Emergent theme | Exemplary quotes |
|---|---|
| **Personal barriers** | |
| Shame, embarrassment, and shyness | *It's hard because either they already have kids, and it kind of makes them feel embarrassed because they feel mature to be exposed.* |
| Negative past experiences | *It is quite difficult, yes, because….they have their experiences with a woman who said that it had been maybe ten years since she had a Pap because when she went to have the Pap, generally in good hospitals … the young male medical students did [the exam] for practice … so when they were using the apparatus to perform the exam, it became caught and unable to be removed, and it perforated. So she was traumatized and never again returned to have the Pap done.* |
| Role as caretakers in the home, putting family before self | *Because imagine you have a school or a church, and people who are in that area that come to the brigade, and a lot of times it's mainly men with the children and the boys, a lot of time it's the sacrifices from the women because she's pregnant, because she has to take care of the small children.* |
| **Cultural barriers** | |
| Machismo | *Women are not empowered in the rural settings, and it's incredible, they don't make any decision at all. They would always come [to their medical appointments] with their man and they are not talking at all—not a word.* |
| Taboo topics | *You know cancer here, it's a taboo, people do not like to speak about it, so it's difficult to know exactly if she has cancer, cervical cancer because people do not like to speak about it … people are more reserved in that sense, sometimes when you hear people pass away, it's then that you know, ahh she had cancer, but family or friends do not like to speak about it.* |
| Preference for traditional medicine | *There are people who, yes, especially people from the [rural surrounding] community, when they realize they have this disease, sometimes they do not return because they may have to have chemotherapy. Whatever it is, they don't return. Rather, they go to their community and begin natural medicines that are safe.*<br>————————————<br>*Traditional doctors are from your background [and culture], if you have a headache, they start to ask you so many questions and you end up finding yourself so relaxed and, if you go to a doctor maybe because of the high demand we have here especially in Bluefields, they don't have much time to take care of you. We have these, if you've been to the health center, you have, she's a doctor, I'm a doctor, and you have another doctor here, the patient sit here and we ask them all the questions, so people don't really want to answer, because of the fear of my neighbor is listening to what I'm going to answer, so these are some of the points that people refer they go to traditional doctors because of the care, the ethical part, and the confidence.* |
| Condom use | *I know several people that have told me they use [condoms] only if they do not know if she has something, but after six, five months that they are together, I ask 'Are you using protection' and they respond 'No'.* |
| **Infrastructural barriers** | |
| Long travel times | *There, they are difficult, depending on the road, it will change a bit, because Bluefields has territory, that is 1-day drive, one-day travelling, two day travelling just to get to a certain point, because then you can look at Rama, then the Curba, then Nueva Guinea, then……, then like 8 hours, 4 hours, 5 hours travelling, it's difficult, and in the rain, the accessibilities is like 0, with water is high, and then with the cars there are problems, to get to them is difficult.*<br>————————————<br>*One of the larger problems is the distance. The geographic location between here and the Coast or because here, all transport is by water. It's nothing like Managua, where you can catch a bus and go to Granada or wherever. Here, no. Here, everything is by boat, and it costs a lot, and it isn't every day. For example, for the women who [live far away from the river], there is only transportation on Mondays, Wednesdays, and Fridays, and if there is a problem, they have to wait until Friday or until Monday when the boat leaves. So that is an obstacle.*<br>————————————<br>*For example, for Corn Island, there it is by airplane, there it is worse because by boat, it's a travesty, like four to five hours on the ocean, and by airplane, maybe $120 to go and return. The [boats] from the estuary … they cost 600 Córdobas to go, 600 Córdobas to return. If she comes alone or if she comes with someone because she doesn't want to go alone, they need to come with another person….La Cruz de Río Grande [municipality] as well, I believe the journey is more expensive than the river and much more expensive, than the one from Kukra Hill [municipality]. So while it could be 100 Córdobas to leave and return from the center of town, the women who are more inland [in rural communities surrounding] Kukra Hill who have to come by truck and leave their community and return….generally, that is the challenge with this group of women – those who live more inland are those who have more problems with access.* |
| Vaccination availability | *There's a vaccine, it came out in 2006, but there's no national program in Nicaragua. And it's available in some pharmacies, but it's very expensive because you have to get it from Managua, and you have to get it before a woman is sexually active. So by the time the women know that there was a vaccine, usually it's a bit late to get the vaccine.* |
| Long wait times for results | *But they have to wait when it come from Managua … so then that's the reason why it takes two months, two months and a half and then you will call the health center you have to go and ask for the thing.* |

negative experiences with the screening procedure. In terms of healthcare infrastructure, women must overcome institutional-level barriers to access, both physically and financially. Cultural barriers were some of the most significant in gaining access to health care, due to complex issues such as Machismo, cancer and condom use taboos, misconceptions about contraception, and the preference for traditional medicine versus medical-model clinics. In many cases, these barriers are more prominent for women in rural areas.

From a prevention standpoint, themes related to primary prevention (before exposure occurs), secondary prevention (screening), and tertiary prevention (prevention of further progression of the disease) emerged. For primary prevention, limited

access to HPV vaccination (only available for pre-ordered purchase) was compounded by decreased access to comprehensive sexual and reproductive health education in schools or at the community-level. Participants emphasized the need for more health education related to primary prevention of hrHPV and subsequently cervical cancer.

Secondary prevention (screening) and engagement with existing Pap-based cervical screening services, was described in interviews and focus groups as challenging due to individual and clinic-level barriers, including potential for poor previous experiences, perceptions of a lack of confidentiality at clinics, limited clinic staff and hours, and the significant delay in receiving results after screening (estimated by some key informants to be between 30-90 days before results communication to patients with the current model). Impacting engagement with secondary prevention as well as tertiary prevention (preventing further progression of pre-cancerous or cancerous lesions once identified) were both perceived to be significantly more challenging based on the gender of the healthcare provider, from the patient and often also from their partner's perspective. Further, if a pre-cancerous or cancerous lesions were identified, engagement with tertiary prevention and treatment remained challenging. At the time of data collection, treatment options for anything beyond a pre-cancerous lesion (CIN1) were not available on the Caribbean Coast. For pre-cancerous lesions (CIN1), colposcopy followed by cryotherapy were the recommended treatment pathway. However, with limited trained colposcopists and availability of one colposcope to perform the procedure, as well as delays in accessing gas needed for cryotherapy, this treatment pathway could take a significant amount of time. For more advanced lesions (CIN II/III, ASCUS), women would need to travel to the capital city of Managua for further treatment (it is important to note that during the time span of the phase 2 environmental scan, chemotherapy and later thermal-ablation became available in Bluefields for all women living on the Caribbean Coast). Sub-analyses guided by the Socio-Ecological Model (SEM) are presented in Table 1 to indicate individual, interpersonal, institutional, and societal level barriers with demonstrative quotes.

In describing challenges and barriers to accessing screening and treatment services in the existing cervical cancer control model, participants clearly indicated the potential role self-collection of samples could play. Self-collection appeared to be a both feasible and culturally acceptable method of HPV testing and a better, more accessible method for screening. Interviewees also provided insight into how self-collection might be best initiated and implemented, with recommendations centered on accessibility. For example, self-sampling kits should be both physically accessible to women through clinics and pharmacies in the area, and the kits must be affordable to the general population. In addition, the process of self-collection must be accessible in terms of clear instructions on how to properly use the kits so that a woman is able to successfully perform the test by herself at home. Finally, women should be able to obtain their results in a timely manner, especially compared to the longer wait times that women currently face using Pap testing.

## Phase 2: Environmental scan

In 2016, study team members analyzed 9 public health clinics, one private health clinic, and two community-based agencies (one targeting comprehensive sexual and reproductive health education, one tracking healthcare service delivery, n=12). Using data collection forms tailored to each type of institution, data were collected on: demographics of catchment areas for each clinic; specialties provided in each (and whether these differed between the public and private clinics); healthcare providers available (nurses, physicians, gender break-downs of each); whether Pap testing/cytology and VIA were both offered for cervical cancer screening; whether colposcopy and follow up treatment were offered at that location; patient costs or fees; and where cervical samples were transferred for processing once collected. Further, at each location study team members explored procedures for identifying underscreened patients, learning that most screening is opportunistic, where patients attend the clinic for another reason, are asked whether they've had a Pap test within the last year (verified by chart after self-report), and then offered Pap testing if due. Researchers discussed clinic procedures for a patient who may or may not have been screened previously, and how this data were tracked at a regional level.

For the 10 healthcare clinics in Bluefields targeted, there was a high level of concordance with both regional and National recommendations and guidelines, in terms of initiating screening, screening types (Pap and VIA), recommended screening intervals (yearly), and recommended follow up (colposcopy and cryotherapy when available).

A significant challenge identified consistently was the time interval between sample collection, transportation to the central lab at the regional hospital, and turnaround time for results to be communicated to patients. Adding to phase 1 findings, key informants in phase 2 confirmed wait times of anywhere between 30-90 days before participants knew they did or did not need to follow up in a clinic.

These data served to inform procedures and planning for piloting HPV-based primary cervical cancer screening (phase 3), and in this context a limitation was that there was high variability in healthcare provider availability and subsequently specialties available at each clinic site included in the environmental scan analysis. Further, centralized/Ministry of Health service utilization data were more accurate, particularly when comparing over time, for individual clinic catchment area demographics, than individual clinic assessments reported on here.

In 2018 through 2019, study team members traveled to Bluefields to continue the environmental scan (23), now guided by the WHO's toolkit on data collection for cervical cancer control (29). All operational public and private clinics were analyzed (n=13) for: transportation considerations (n=13 accessible through taxis, less accessible for rural surrounding communities); potable water (accessible at n=11 clinics); power sources (consistently accessible for n=12 clinics); wifi (n=0 clinics had this accessible) and landline phone access (n=7 clinics). Each of these components is necessary to implement cervical cancer screening and control efforts per the WHO toolkit.

In assessing where cervical screening could take place, and adding this to previous data collection on demographics of catchment areas, the research team partnered with the Ministry of Health (MINSA) to identify target clinics to pilot HPV-based primary cervical cancer screening. Using regional targets for screening coverage, updated clinic catchment-area demographics and priorities, and data points

from screening services in 2018 and to that point in 2019, 10 priority clinics in Bluefields were identified as strategic for piloting HPV-based primary screening, including emphasis on the age groups of 30-49 and 50-59 (please see phase 3 below and Table 2).

## Phase 3: Implementation of HPV self-collection

In partnership with MINSA, SILAIS, and CEDEHCA, over a 5-week period in early 2020, we conducted hrHPV screening with 1,782 eligible women in Bluefields. Of the 19.25% (n=343) of screened women who required follow-up for hrHPV positivity, only 31 didn't have access to phones and 7 gave landline numbers. The remaining 305 (89%) participants who tested hrHPV positive provided cellular numbers to be reached for follow-up (30). While barriers to accessing existing cervical cancer control screening services persist due to the requirement for clinic-based collection, primary HPV testing for hrHPV allows for self-collection of cervicovaginal samples, previously found to be culturally acceptable in Nicaragua (31). We employed the QIAGEN careHPV ™ assay, and hrHPV positive participants were triaged using VIA and treated, when necessary, with thermoablation (30). We collected study-specific data and utilized the Nicaraguan National Cervical Cancer Surveillance System (SIVIPCAN) to follow patients through the care continuum. We found high provider and patient acceptability of self-collection of samples (99.16% self-collected), but it is important to note that a significant challenge the study team had in monitoring patient follow-up was the coinciding impact of COVID-19 on this region of Nicaragua. Our sample was reflective of the population living in Bluefields and on the Caribbean Coast: 78% identified as Mestiza; 19% identified as Creole; 2.6% identified as Miskitu; 0.3% identified as Rama; and 0.1% identified as Garifuna. Amas de Casa, or women who run their household, were the most represented group in the sample (n=1,269, 71%), indicating this methodology may have particular relevance in targeting groups most at risk for being underscreened, as has been found in prior studies in other locations (10, 13, 16–18).

TABLE 2 Characteristics of study participants (*N=1782*).

| Sociodemographic characteristics | n (%) |
|---|---|
| Ages | |
| < 30 | 2 (0.11) |
| 30-49 | 1775 (99.61) |
| > 50 | 4 (0.22) |
| Ethnicities | |
| Mestizo | 1388 (77.89) |
| Creole | 338 (18.97) |
| Miskitu | 46 (2.58) |
| Rama | 6 (0.34) |
| Garifuna | 2 (0.11) |
| Missing | 2 (0.11) |
| Patient telecommunication method | |
| Cell phone | 1492 (83.73) |
| Landline | 45 (2.53) |
| None | 245 (13.75) |
| Occupations | |
| Ama de casa | 1269 (71.21) |
| Other (including merchant, medical professional, technician, administrator, and food business) | 513 (28.79) |
| **HPV self-collection characteristics** | **n (%)** |
| Collection Method | |
| Self | 1767 (99.16) |
| Health Personnel | 15 (0.84) |
| Results | |
| hrHPV Positive | 343 (19.25) |
| hrHPV Negative | 1435 (80.53) |
| Missing | 4 (0.22) |

# Discussion

Women's access to health services remains a particular challenge to women in rural communities, particularly with reproductive health. The barriers identified in this study are consistent with other studies about cervical cancer screening as well as breast cancer screening (32). Some of these barriers, namely those associated with personal embarrassment, hesitancy to return to a clinic, and machismo, may be reduced or eliminated by providing women with a private and effective method to administer HPV sample collection. In addition, providing a method for self-collection may also address the barriers related to time and personal commitments (travel time to the clinic and the perception that a woman cannot take care of herself because she must care for her family), as this self-sampling may be performed at home and with a significantly reduced time commitment. While some services related to women's health must still be performed in a clinic, HPV self-collection provides a viable and acceptable method for providing women with an alternative method to screen for a preventable disease. Further, it may even help to connect women to sustained primary care (4).

In Nicaragua, the lack of a national HPV vaccination program leaves primary and secondary screening as the mode of cervical cancer prevention on which most women depend. Novel technology, such as self-collection of cervical samples offer one approach to overcome barriers identified in this study; namely, personal and infrastructural factors that may not allow women to seek timely care. This study describes the particular cultural and geographic barriers to care experienced by women on the Caribbean Coast of Nicaragua and the methods used to integrate HPV self-collection into the country's existing healthcare system. The data collected here indicate that the majority of women (99.16%) are willing and able to perform self-collection. However, previous studies addressing the acceptability and feasibility of self-collection among Nicaraguan women have shown varying results. For example, while Jeronimo et al. (33) showed an 80% acceptability rate of self-

collection, Bansil et al. (17) found that only half of women had a preference for self-collection compared with traditional cervical sampling, with women citing concerns such as an unwillingness to touch the genital region because of shyness or a fear of doing harm. Of note, these studies from Nicaragua do not include the Caribbean Coast, a region with different geographic, cultural, and economic considerations compared with the rest of the country. The current study offers insight into the cultural and practical considerations necessary to implement a public health screening program in this region. With a successful demonstration of the integration of HPV primary screening and self-collection of HPV samples into sustained cervical cancer control, it is possible to have a sustainable program as a result of governmental buy-in of an accepted and validated process.

Successful demonstration projects should rely on geographically relevant input for implementation considerations. Sustainability of integration of new modalities is contingent on governmental buyin and integration, and this will only happen if outcomes and objectives for such programs are collaborative designed and successfully met. In this study, this was done through an iterative and collaborative approach to assessment, analysis, and subsequent procedure design. For example, identifying the need to culturally tailor training materials for participants in instruction on self-collection of samples, the study team sought input from key informants and offered training materials with regionally relevant images, and representative languages (Spanish and Nicaraguan Creole).

### Limitations

One limitation was in the timeline of phase III, necessitated through procurement of supplies necessary to perform molecular testing with the *care*HPV© assay. Manufactured in China, these supplies met manufacturer requirements for implementation for 3 months once they arrived in-country. It is an indication of the expert strategies the nurses and physicians involved in the study utilized that we recruited so many participants in such a short period of time prior to expiration. A significant consideration is in the rapidly changing landscape of cervical cancer control technologies in low recourse settings. For example, our research team began systematically collecting data for the phase II environmental scan before the WHO published the data collection toolkit we ultimately used (23). It is important for cervical cancer control researchers to remain current in implementation of evidence-based prevention strategies.

## Conclusions

It is important to recognize that while populations of women in other regions may have similar experiences regarding their ability to access care, the findings from the current study are specific to the study area, and the proposed self-collection is a product of collaborative development with in-country partners in order to produce an intervention that is both culturally tailored and regionally relevant. Therefore, successful demonstration projects for self-collection in a different region must rely on geographically relevant input and must be approached with cultural considerations specific to that population. Community-based primary HPV screening presents multiple opportunities to mitigate barriers and increase engagement with cervical cancer screening and prevention efforts. Self-collection of samples for HPV testing is not a "one-size-fits-all" or universally acceptable approach. Comprehensive assessments into acceptability, feasibility, and implementation of different community-based cervical cancer prevention efforts are necessary to inform procedures and practices that have a higher likelihood of meeting program goals. Continued research is necessary to guide best-practice in prevention efforts to respond to the WHO's call to eliminate cervical cancer.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by University of Virginia SBS IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

EM and MM made substantial contributions to the conception, design, execution, and dissemination of the work. HAK, CB-R, MF, and YP contributed to data collection. KH, AD, AR, OG, and FM conducted data analysis and interpretation. EM, KH, AD, and RD drafted original manuscript. All authors provided substantial review and revision to the manuscript. All authors contributed to the article and approved the submitted version.

## Funding

From 2016, to present this study was supported by University of Virginia Center for Global Health Equity Scholar Awards, and with pilot funding from the University of Virginia Global Infectious Disease Institute.

## Acknowledgments

Authors would like to thank community partners, healthcare providers, and participants who ensured regional relevance of this long-term collaborative study.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 09 March 2023
DOI 10.3389/fonc.2023.1008560



OPEN ACCESS

EDITED BY
Alessandra Buja,
University of Padova, Italy

REVIEWED BY
Martin Perez-Santos,
Benemérita Universidad Autónoma de Puebla, Mexico
Paolo Giorgi Rossi,
IRCCS Local Health Authority of Reggio Emilia, Italy

*CORRESPONDENCE
Kirvis Torres-Poveda
kjtorres@insp.mx

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Gynecological Oncology, a section of the journal Frontiers in Oncology

RECEIVED 01 August 2022
ACCEPTED 27 February 2023
PUBLISHED 09 March 2023

CITATION
Cruz-Valdez A, Palacio-Mejía LS, Quezada-Sánchez AD, Hernández-Ávila JE, Galicia-Carmona T, Cetina-Pérez LdC, Arango-Bravo EA, Isla-Ortiz D, Aranda-Flores CE, Uscanga-Sánchez S-R, Madrid-Marina V and Torres-Poveda K (2023) Cervical cancer prevention program in Mexico disrupted due to COVID-19 pandemic: Challenges and opportunities. *Front. Oncol.* 13:1008560. doi: 10.3389/fonc.2023.1008560



# Cervical cancer prevention program in Mexico disrupted due to COVID-19 pandemic: Challenges and opportunities

Aurelio Cruz-Valdez [1], Lina Sofia Palacio-Mejía [2], Amado D. Quezada-Sánchez [3], Juan Eugenio Hernández-Ávila [3], Tatiana Galicia-Carmona [4], Lucely del Carmen Cetina-Pérez [4], Eder A. Arango-Bravo [4], David Isla-Ortiz [5], Carlos E. Aranda-Flores [6], Santos-Regino Uscanga-Sánchez [7], Vicente Madrid-Marina [8] and Kirvis Torres-Poveda [2,8*]

[1]Center for Population Health Research, Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico, [2]Consejo Nacional de Ciencia y Tecnología (CONACYT)—Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico, [3]Center for Evaluation and Surveys Research, Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico, [4]Department of Clinical Research and Medical Oncology, Instituto Nacional de Cancerología (INCAN), Mexico City, Mexico, [5]Department of Oncology Gynecology, Instituto Nacional de Cancerología (INCAN), Mexico City, Mexico, [6]Oncology Department, Hospital General de México "Eduardo Liceaga", Mexico City, Mexico, [7]Gynecologist Oncologist of MAGNI Gineco-Obstetras S.C, Mexico City, Mexico, [8]Chronic Infections and Cancer Division, Center for Research on Infectious Diseases, Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico

**Introduction:** The COVID-19 pandemic disrupted the preventive services for cervical cancer (CC) control programs in Mexico, which will result in increased mortality. This study aims to assess the impact of the pandemic on the interruption of three preventive actions in the CC prevention program in Mexico.

**Methods:** This study is a retrospective time series analysis based on administrative records for the uninsured population served by the Mexican Ministry of Health. Patient data were retrieved from the outpatient service information system and the hospital discharge database for the period 2017–2021. Data were aggregated by month, distinguishing a pre-pandemic and a pandemic period, considering April 2020 as the start date of the pandemic. A Poisson time series analysis was used to model seasonal and secular trends. Five process indicators were selected to assess the disruption of the CC program, these were analyzed as monthly data (N=39 pre-pandemic, N=21 during the pandemic). HPV vaccination indicators (number of doses and coverage) and diagnostic characteristics of CC cases were analyzed descriptively. The time elapsed between diagnosis and treatment initiation in CC cases was modeled using restricted cubic splines from robust regression.

**Results:** Annual HPV vaccination coverage declined dramatically after 2019 and was almost null in 2021. The number of positive Papanicolaou smears decreased by 67.8% (90%CI: -72.3, -61.7) in April–December 2020, compared to their expected values without the pandemic. The immediate pandemic shock (April 2020) in the number of first-time and recurrent colposcopies was -80.5% (95%

CI:−83.5, −77.0) and -77.9% (95%CI: −81.0, −74.4), respectively. An increasing trend was observed in the proportion of advanced stage and metastatic CC cases. The fraction of CC cases that did not receive medical treatment or surgery increased, as well as CC cases that received late treatment after diagnosis.

**Conclusions:** Our analyses show significant impact of the COVID-19 pandemic with declines at all levels of CC prevention and increasing inequalities. The restarting of the preventive programs against CC in Mexico offers an opportunity to put in place actions to reduce the disparities in the burden of disease between socioeconomic levels.

KEYWORDS

**COVID-19, uterine cervical neoplasm, prevention and control, health impact assessment, time series analysis, Mexico**

## Introduction

Cervical cancer (CC) is caused majorly by a persistent infection of high-risk human papilloma virus (HR-HPV). This neoplasm is considered preventable by HPV vaccination, for those cases caused by the genotypes included in the available vaccines and by routine screening for precancerous lesions. However, CC remains a significant cause of cancer-related mortality and a major public health problem, particularly in low- and middle-income countries (LMICs) (1). In 2020, GLOBOCAN estimated the occurrence of 604,127 new cases (particularly in middle-aged women) and 341,831 deaths from CC worldwide, with 80% occurring in LMICs (2). In 2020 9,439 new cases (4.8%) and 4335 deaths were estimated in Mexico, with a 5-year prevalence of 38/100,000, which is equivalent to 25026 prevalent cases (3).

In 2020, the World Health Assembly adopted a strategy for the elimination of CC, with the intention of achieving for all countries an incidence rate of less than 4 cases per 100,000 women by 2030 (4). For this, three strategies have been proposed: prevention (target of 90% of girls aged 15 years or younger fully vaccinated against HPV), early detection (target of 70% of women aged 35–45 years screened by molecular methods to detect HR-HPV DNA), and guaranteed treatment (target of 90% of women) diagnosed with CC.

According to the Mexican standard NOM 014-SSA2-1994 for the prevention, detection, diagnosis, treatment, control, and epidemiological surveillance of CC, a comprehensive control program for CC in Mexico must include all three types of prevention (5). Primary prevention includes specific protective actions through the free delivery of the anti-HPV prophylactic vaccine, in a two-doses vaccination schedule since 2016, as part of a universal program targeting girls in fifth grade of primary school, aged 9-11 years.

Secondary prevention includes early detection of premalignant cervical lesions in women aged 25–34 years either by a Papanicolaou (Pap) smear test or direct visualization with acetic acid when a Pap smear is not available, and biomolecular testing for HPV detection in women aged 35–64 years. These tests should be performed free of charge to all applicant women in public sector health facilities (5).Tertiary prevention includes the follow-up of women with premalignant lesions and CC, and timely treatment (6).

Latin America and the Caribbean (LAC) has been one of the areas most affected by the ongoing COVID-19 pandemic, with Mexico as an epicenter. Mexico has the fifth highest number of COVID-19 deaths in the world, after the United States, Brazil, India, and Russia (7). COVID-19 has affected, either directly or indirectly, all health systems in the world (8–10). Maternal and child health services, among other health services and programs, have reported poorer results and disruptions because of the pandemic (11, 12); sexual and reproductive health services (13, 14) and cancer screening programs have also been impacted (15).

Cancer screening programs worldwide, including CC preventive programs, have been particularly affected by the COVID-19 pandemic, as evidenced by lower HPV vaccination coverage rates (16, 17), fewer histological and cytological samples taken, fewer immunohistochemistry and molecular tests performed (18), fewer supplies available to perform molecular HPV laboratory services (19), a lower proportion of women screened for CC before and during the COVID-19 pandemic (20), excess CC diagnosis (21), and longer delays in treating cancer patients (22–24).

During the pandemic phase, Mexican national health authorities implemented hospital conversion strategies, prioritizing the allocation of human and biomedical resources for COVID-19 patients requiring hospitalization (25). Hospital conversion affected all "nonessential" health services, including public cancer screening programs. Further disruptions to these services came from reduced availability of public transportation, patient fear of going to hospitals, and staffing shortages, as some health workers were reassigned to support COVID-19 response services (26).

Since estimating the effect of COVID-19 on the resilience of health services depends on several assumptions, it is necessary to evaluate the effect of COVID-19 on primary, secondary and tertiary prevention strategies to compensate for opportunities lost due to

the pandemic. Therefore, this study aims to assess the impact of the COVID-19 pandemic on the disruption of activities at all three levels of the CC prevention program in Mexico.

# Materials and methods

## Study design

This is a retrospective time series analysis based on administrative records to evaluate the disruption caused by the COVID-19 pandemic in the CC care program for uninsured population, served by the Mexican Ministry of Health (MoH). Administrative records of health services provided in outpatient and inpatient care in facilities managed by the MoH and clinical records of the National Cancer Institute (INCAN) were analyzed.

## Data source

Data were retrieved from the outpatient services information system (SIS) (27) and the hospital discharges database (SAEH) for the period 2017-2021. Both systems collect information on the part of the population lacking social security (approximately 50% of Mexico's total population) that received medical care in health facilities administered by the MoH. Anonymized data on patients who attended INCAN in the period 2017–2021 were also included. Approval was obtained for access to clinical record information (INCAN/CI/O411/O411/2022/082). INCAN is one of the main oncology referral centers in Mexico, managed by the MoH and serving the uninsured population. Data were aggregated by month; pre-pandemic and pandemic periods were identified, with April 2020 as the start date of the pandemic. Thus, the pre-pandemic period was defined as January 2017 to March 2020 (39 months), and the pandemic period as April 2020 to December 2021 (21 months).

## Measured indicators

Data retrieved from the SIS included HPV vaccination data (primary prevention): vaccination, coverage, first and second doses of HPV vaccine in female students in grade 5 and/or 11 years of schooling, and third dose of HPV vaccine in females aged 14 years and older; data on screening and treatment of precancerous lesions (secondary prevention): total cytology read, positive cytology, first-time colposcopy, and recurrent colposcopy; diagnosis and treatment of invasive cancer (tertiary prevention): CC-related hospital discharges according to ICD-10 leading cause classification. Indicators of the level of tertiary prevention retrieved from the INCAN database included: histopathological diagnosis, clinical stage, type of treatment and time from diagnosis to initiation of treatment.

Five process indicators were selected to evaluate the disruption on the CC care program: total Pap smears read, positive Pap smears, first-time colposcopy, and subsequent colposcopy as indicators of the secondary prevention level, and CC-related hospital discharges according to ICD-10 classification of main cause as indicators of the tertiary prevention level. In Mexico, HPV vaccination is massively administered during the National Health Weeks; thus, these indicators of vaccine administration could not be included in our statistical models; instead, the results of a descriptive analysis are given in the corresponding section. Data on tertiary prevention retrieved from the INCAN database were aggregated by pre-pandemic and pandemic periods and by month to calculate average time between diagnosis and treatment initiation.

## Statistical analysis

A descriptive analysis of all variables was performed; frequencies, percentages, and central tendency and dispersion statistics were calculated, and data were plotted to capture trends. We fitted Poisson regression models using each of the five process indicators as dependent variable. These models were fitted with Newey-West standard errors, which are consistent in terms of heteroscedasticity and autocorrelation (28). Our linear predictor, the logarithm of the mean in a Poisson regression model, included a linear time term and indicator variables for each month of the year (one excluded as a reference category) to model seasonal fluctuations around the trend. The trend model coefficient was expressed as the mean ratio between consecutive months after exponentiation, including a 95% confidence interval. Our models were trained from January 2017 through March 2020, extending the trend to include a seasonality component from April 2020 through December 2021, to estimate expected monthly values for each process indicator under the model and during the pandemic period; these were used to contrast observed values.

The sum of expected values for each of the five process indicators was calculated for four periods: April 2020, April-December 2020, January-December 2021, and April 2020 to December 2021. Standard errors for periods longer than a month were obtained through the delta method, to generate 95% confidence intervals (29). The differences between observed and expected values were then calculated, and confidence limits were mapped from those obtained for expected values to the differences. The differences were also calculated as percentages with respect to the expected values. In this framework, the analyzed process indicators in the pandemic period were considered as realized observations, rather than random variables; therefore, the inference problem focused on estimating baseline values that reproduced a pre-pandemic environment and approximated a counterfactual to the pandemic. A similar approach has been previously applied to estimate excess deaths from different causes in Mexico (30).

The time (number of days) elapsed from diagnosis to treatment initiation from INCAN patient records was modelled as a function of the calendar time (year and month) of patient records using robust regression. Predictors included monthly indicator variables (except for a reference category) to capture possible seasonal fluctuations, and a 4-knot restricted cubic splines function with respect to monthly time (31, 32).

# Results

## Impact on HPV vaccination (primary prevention)

HPV vaccination is administered during National Health Weeks in October or November each year. The observed patterns from 2017 to 2021 are shown in Figure 1, with a significantly reduced vaccine delivery in 2019 compared to previous years. HPV vaccination dropped to near zero after April 2020. This pattern was also evident for the second dose, with no reduction in 2019. The third dose in risk population, in contrast, is delivered throughout the year (Figure 1), although significantly fewer vaccines were applied after April 2020. With respect to HPV vaccination coverage rates in the target population, showed a significant decline for the first dose of 59% in 2018 to 30.1% in 2019, 17.8% in 2020 and 1.2% in 2021.

## Impact on screening and treatment of precancerous lesions (secondary prevention)

Monthly descriptive statistics for selected program indicators are shown in Table 1. In general, the number and variability of services provided were lower during the pandemic than in the pre-pandemic months, except for CC hospital discharges, which showed similar descriptive statistics in both periods.

Observed counts of process indicators related to CC program services along with their differences with respect to their expected values under a pre-pandemic trend are shown in Table 2 for four pandemic periods: a) an immediate shock in April 2020, b) April to December 2020, c) January to December 2021, and d) April 2020 to December 2021. At the beginning of the pandemic period in Mexico (April 2020), the number of Pap smears showed an abrupt reduction of 38.0% (Table 2), followed by a slow upward trend (Figure 2). Results from the Poisson time-series model that adjusted for seasonal fluctuations showed a negative slope during the pre-pandemic period with a monthly reduction of 2.1% (mean ratio [MR] = 0.979, 95% CI: 0.976–0.982) in the number of Pap smears, this corresponds to an annual reduction of 22.5%. Overall, the number of Pap tests decreased by 44.1% in 2020 (April–December) with respect to the number expected as predicted by our model. The number of Pap smears recovered in 2021, exceeding by 12.6% our model predictions. In the period April 2020–December 2021, an overall reduction of 16.1% was observed (Table 2).

With respect to pre-pandemic data, positive results of Pap smears showed an upward trend, although a reduction of 63.9% was observed at the beginning of the pandemic (April 2020). A reduction of 67.8% was found in positive Pap smears in the period April–December 2020, compared with the value predicted by our model. The overall reduction in 2021 was 45.4%, and it was 54.9% in the period April 2020–December 2021 (Table 2).

The number of first-time and recurrent colposcopies showed a downward trend in the pre-pandemic period after adjusting for seasonality; on average, there was a monthly decrease of 0.7% (MR = 0.992, 95% CI: 0.990–0.994) in the number of first-time colposcopies, and a decrease of 0.9% (MR = 0.990, 95% CI: 0.989–0.993) in the number of recurrent colposcopies, corresponding to an average annual reduction of 9.1% and 10.6%,

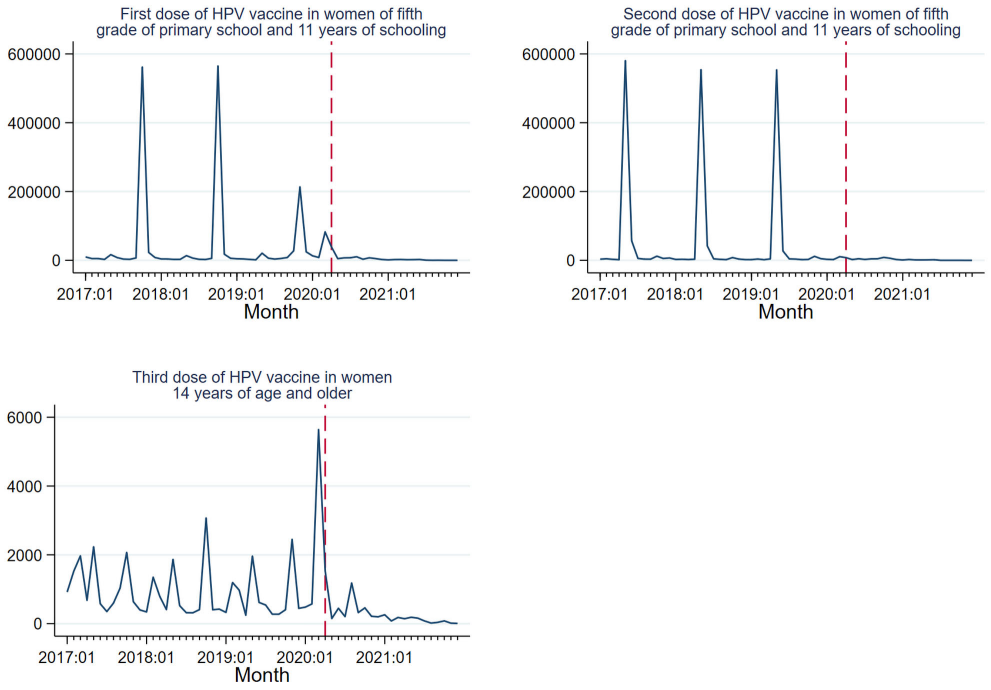


FIGURE 1
HPV vaccination trends 2017–2021. Mexico. Source: Outpatient provided services information system. 2017-2021. DGIS.

TABLE 1 Descriptive statistics of monthly data of selected indicators of the CC program.

| Period | *Observed months (N)* | Monthly mean (SD) | P50 (P25, P75) | Min-Max |
|---|---|---|---|---|
| Pap smears | | | | |
| Pre-pandemic | 39 | 42901 (15215) | 41867 (31252, 53720) | 14934-75683 |
| Pandemic | 21 | 19779 (6477) | 21180 (13633, 24662) | 8413-31380 |
| Positive pap smears | | | | |
| Pre-pandemic | 39 | 2836 (701) | 2829 (2499, 3256) | 1158-4386 |
| Pandemic | 21 | 1691 (728) | 1909 (1070, 2070) | 553-2988 |
| First-time colposcopies | | | | |
| Pre-pandemic | 39 | 4279 (748) | 4350 (3667, 4772) | 2735-5622 |
| Pandemic | 21 | 1872 (879) | 1956 (1116, 2736) | 598-3385 |
| Recurrent colposcopies | | | | |
| Pre-pandemic | 39 | 14130 (2250) | 13655 (12675, 15991) | 9881-19268 |
| Pandemic | 21 | 4942 (1706) | 4920 (3718, 5804) | 1973-7749 |
| Cervical cancer hospital discharges | | | | |
| Pre-pandemic | 39 | 867 (145) | 861 (770, 925) | 562-1226 |
| Pandemic | 21 | 914 (129) | 954 (829, 975) | 670-1228 |

The pre-pandemic period is defined as January 2017–March 2020 (N=39 months); the pandemic period is defined as April 2020–December 2021 (N=21 months). Descriptive statistics of monthly counts are shown: mean, standard deviation (SD), median (P50), 25$^{th}$ and 75$^{th}$ percentiles (P25, P75), minimum (Min) and maximum (Max).
Source: Outpatient provided services information system and hospital discharges. 2017–2021. DGIS.

TABLE 2 Estimation of changes in secondary prevention services and CC hospital discharges in the pandemic period with respect to pre-pandemic projected trends.

| Indicator | Period analyzed | Observed | Expected (95%CI) | Difference observed minus expected | |
|---|---|---|---|---|---|
| | | | | As a count (95%CI) | As percentage (95% CI) |
| Pap smears | Apr. 2020 | 17279 | 27871 (23924, 32470) | −10592 (−15191, −6645) | −38.0 (−46.8, −27.8) |
| | Apr. to Dec. 2020 | 140178 | 250772 (229596, 271949) | −110594 (−131770, −89418) | −44.1 (−48.5, −38.9) |
| | Jan. to Dec. 2021 | 275182 | 244301 (216674, 271928) | 30881 (3254, 58508) | 12.6 (1.2, 27.0) |
| | Apr. 2020 to Dec. 2021 | 415360 | 495073 (446497, 543649) | −79713 (−128289, −31137) | −16.1 (−23.6, −7.0) |
| Positive pap smears | Apr. 2020 | 1258 | 3484 (2900, 4187) | −2226 (−2929, −1642) | −63.9 (−70.0, −56.6) |
| | Apr. to Dec. 2020 | 10713 | 33320 (27972, 38668) | −22607 (−27955, −17259) | −67.8 (−72.3, −61.7) |
| | Jan. to Dec. 2021 | 24795 | 45455 (36300, 54610) | −20660 (−29815, −11505) | −45.5 (−54.6, −31.7) |
| | Apr. 2020 to Dec. 2021 | 35508 | 78775 (64305, 93245) | −43267 (−57737, −28797) | −54.9 (−61.9, −44.8) |
| First-time colposcopies | Apr. 2020 | 598 | 3063 (2594, 3616) | −2465 (−3018, −1996) | −80.5 (−83.5, −77.0) |
| | Apr. to Dec. 2020 | 10301 | 32844 (30790, 34898) | −22543 (−24597, −20489) | −68.6 (−70.5, −66.5) |
| | Jan. to Dec. 2021 | 29020 | 39158 (35933, 42382) | −10138 (−13362, −6913) | −25.9 (−31.5, −19.2) |
| | Apr. 2020 to Dec. 2021 | 39321 | 72001 (66761, 77242) | −32680 (−37921, −27440) | −45.4 (−49.1, −41.1) |
| Recurrent colposcopies | Apr. 2020 | 2270 | 10293 (8881, 11930) | −8023 (−9660, −6611) | −77.9 (−81.0, −74.4) |
| | Apr. to Dec. 2020 | 32638 | 101766 (96147, 107385) | −69128 (−74747, −63509) | −67.9 (−69.6, −66.1) |
| | Jan. to Dec. 2021 | 71153 | 122323 (113649, 130997) | −51170 (−59844, −42496) | −41.8 (−45.7, −37.4) |

*(Continued)*

TABLE 2 Continued

| Indicator | Period analyzed | Observed | Expected (95%CI) | Difference observed minus expected | |
|---|---|---|---|---|---|
| | | | | As a count (95%CI) | As percentage (95% CI) |
| | Apr. 2020 to Dec. 2021 | 103791 | 224089 (209989, 238189) | −120298 (−134398, −106198) | −53.7 (−56.4, −50.6) |
| Cervical cancer hospital discharges | Apr. 2020 | 759 | 873 (800, 953) | −114 (−194, −41) | −13.1 (−20.4, −5.1) |
| | Apr. to Dec. 2020 | 7476 | 8489 (7629, 9348) | −1013 (−1872, −153) | −11.9 (−20.0, −2.0) |
| | Jan. to Dec. 2021 | 11721 | 11600 (10165, 13035) | 121 (−1314, 1556) | 1.0 (−10.1, 15.3) |
| | Apr. 2020 to Dec. 2021 | 19197 | 20089 (17819, 22358) | −892 (−3161, 1378) | −4.4 (−14.1, 7.7) |

Expected values were predicted from Poisson regression models trained during the pre-pandemic period, January 2017–March 2020. The linear predictor included a time linear trend and month indicator variables to model seasonality. Standard errors were heteroskedastic and autocorrelation consistent using the Newey-West methodology with two lags. Source: Outpatient provided services information system. 2017-2021. DGIS.

respectively. The number of first-time and recurrent colposcopies also showed a sudden reduction of 80.5% and 77.9%, respectively, in April 2020, followed by an upward trend (Table 2; Figure 2).

Despite this recovery trend, the number of first-time and recurrent colposcopies was below the expected values throughout the pandemic period, as shown in Table 2. A reduction of 68.6% was observed in the number of first-time colposcopies in 2020, and of 25.9% in 2021, while the number of recurrent colposcopies was lower than the expected value by 67.9% in 2020 and by 41.8% in 2021. During the entire pandemic period, the number of first-time and recurrent colposcopies was lower than expected according to our model by 45.4% and 53.7%, respectively (Figure 2).

## Impact on diagnosis and treatment of invasive cancer (tertiary prevention)

The number of CC-related hospital discharges also showed a reduction at the beginning of the pandemic period, albeit to a lesser extent (13.1%), followed by a recovery trend in 2020 and 2021

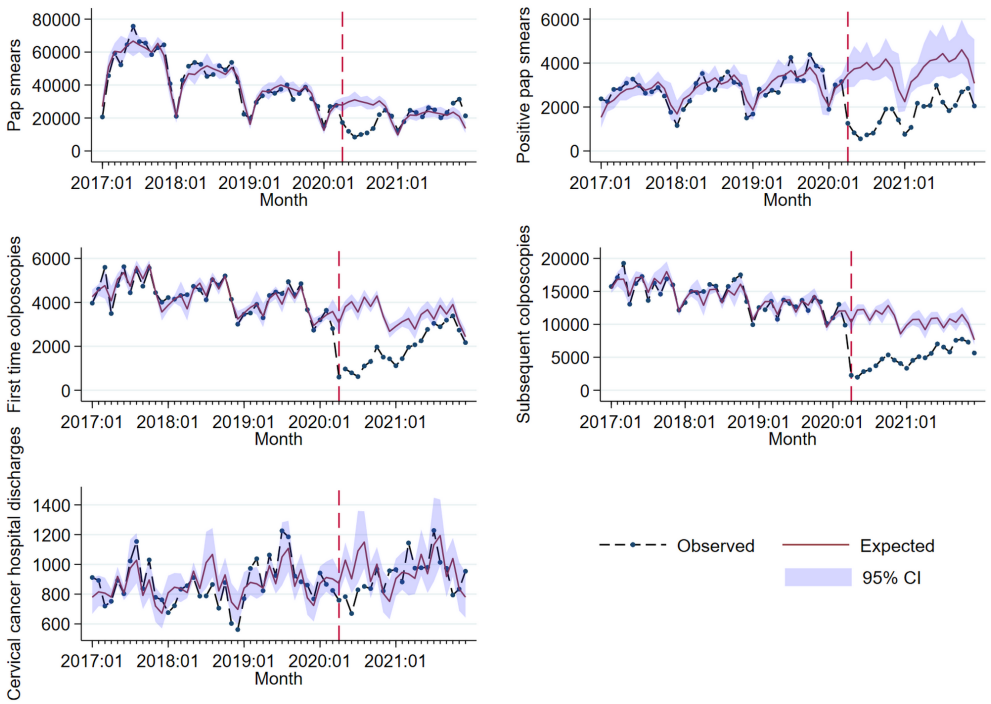


FIGURE 2
Observed and fitted trends for five process indicators to evaluate disruption of the CC program. Source: Outpatient provided services information system and Hospital discharges. 2017-2021. DGIS. The dashed line marks the start of the pandemic period (April 2020–December 2021). Expected trends were obtained from Poisson models trained during the pre-pandemic period (January 2017–March 2020). The linear predictor included a time linear trend and month indicator variables to model seasonality. Standard errors were heteroskedastic and autocorrelation consistent using the Newey-West methodology with two lags. CI, Confidence Interval.

(Table 1; Figure 2). An overall reduction of 11.9% was observed in 2020 with respect to expected hospital discharges in our model. In 2021, no significant differences were observed in the number of hospital discharges with respect to our model in the absence of a pandemic shock.

The distribution of categories of tertiary prevention indicators from patient data of the INCAN database are described in Table 3. An analysis of the number of histopathological diagnoses during the pandemic showed a slight decrease in squamous (from 83.6% to 82.3%) and adenosquamous (from 2.2% to 1.7%) diagnoses compared to the pre-pandemic period, and a small increase in adenocarcinomas (from 10.7% to 11.4%) and neuroendocrine involvement (from 1.6% to 1.9%). While a higher proportion of women were diagnosed in an early stage (21.6%) pre-pandemic; this proportion dropped to 11.4% during the pandemic. A slight increase in the proportion of locally advanced stages was also observed, from 61.8% to 63.6%, while the fraction of metastatic patients increased from 16.6% to 24.5%. The occurrence of untreated cases increased by 3.2 percentage points in the pandemic compared to the pre-pandemic period, and the percentage of women who had access to surgical treatment decreased from 21.1% to 11.7%. With respect to the time elapsed from diagnosis to treatment initiation, the percentage of women who were cared for immediately after diagnosis increased in the pandemic from 5.2% (pre-pandemic) to 8.4%, as did those who were treated within 1-2 weeks. Overall, the fraction of women seen within 2 weeks increased from 6.6% to 9.9%; however, the proportion who received treatment after 8 weeks increased from 36.6% to 46.6% (Table 3).

A robust regression analysis of the average time elapsed between diagnosis and treatment initiation (in days) as a function of the date of patient records is shown in Figure 3. The restricted cubic spline clearly shows an increasing trend in the time between diagnosis and initiation of treatment after April 2020, even though fewer patients were received. The point size of each data point is proportional to the number of patients.

TABLE 3 Indicators of the tertiary prevention level from INCAN database.

| | Pre-pandemic *N* = 1125 | During pandemic *N* = 464 | Overall *N* = 1589 |
|---|---|---|---|
| Histopathological diagnosis | | | |
| Squamous cell carcinoma | 940 (83.6%) | 382 (82.3%) | 1322 (83.2%) |
| Adenocarcinoma | 120 (10.7%) | 53 (11.4%) | 173 (10.9%) |
| Adenosquamous carcinoma | 25 (2.2%) | 8 (1.7%) | 33 (2.1%) |
| Neuroendocrine carcinoma | 18 (1.6%) | 9 (1.9%) | 27 (1.7%) |
| Other | 22 (2.0%) | 12 (2.6%) | 34 (2.1%) |
| Clinical stage | | | |
| Early | 243 (21.6%) | 50 (11.4%) | 294 (18.5%) |
| Locally advanced | 695 (61.8%) | 278 (63.6%) | 992 (62.4%) |
| Metastatic | 187 (16.6%) | 107 (24.5%) | 301 (18.9%) |
| Not specified | 0 (0%) | 2 (0.5%) | 2 (0.1%) |
| Type of treatment | | | |
| None | 58 (5.2%) | 39 (8.4%) | 97 (6.1%) |
| Surgical | 237 (21.1%) | 52 (11.2%) | 289 (18.2%) |
| Concomitant radio-chemotherapy | 689 (61.2%) | 288 (62.1%) | 977 (61.5%) |
| Chemotherapy | 141 (12.5%) | 85 (18.3%) | 226 (14.2%) |
| Time from diagnosis to start of treatment | | | |
| Immediate | 58 (5.2%) | 39 (8.4%) | 97 (6.1%) |
| 1–2 wk | 16 (1.4%) | 7 (1.5%) | 23 (1.4%) |
| 3–4 wk | 108 (9.6%) | 32 (6.9%) | 140 (8.8%) |
| 5–6 wk | 236 (21.0%) | 70 (15.1%) | 306 (19.3%) |
| 7–8 wk | 295 (26.2%) | 100 (21.6%) | 395 (24.9%) |
| > 8 wk | 412 (36.6%) | 216 (46.6%) | 628 (39.5%) |

Observations are patient data during the pre-pandemic (N=1125) and the pandemic (N=464) periods.
Source: INCAN database.

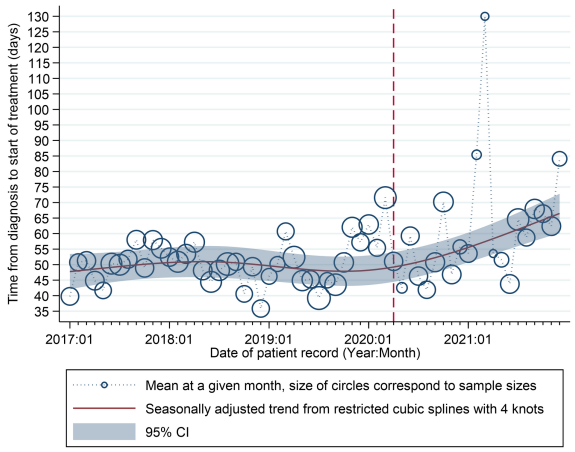


FIGURE 3
Time elapsed from diagnosis to treatment initiation (days) and date of patient records. Source: INCAN Database Relationship between time from diagnosis and start of treatment. The data points show the average time in days between diagnosis and start of treatment for each month in the INCAN database from January 2017 to December 2021 and the solid line are the fitted values from robust regression model. The dashed line marks the start of our defined pandemic period.

## Discussion

The COVID-19 pandemic has disrupted CC screening programs around the world. This study assesses the impacts of the COVID-19 pandemic on CC prevention program in Mexico. It is important to highlight that given the limited availability of data sources and their quality, we organized effects into three levels considering the following indicators: first, the number of HPV vaccine doses and coverage in the target population (primary prevention); second, the number of positive Pap smears and, and the number of initial and subsequent colposcopy examinations (secondary prevention); third, the number of discharges associated with CC, histopathological diagnosis, clinical stage, type of treatment and time from diagnosis to initiation of treatment (tertiary prevention).

Overall, our analyses revealed significant declines in all levels of CC prevention. In primary prevention, the sharp decline in HPV vaccine doses delivered to the target populations between 2020 and 2021 coincides with the COVID-19 pandemic and the shortage of HPV vaccines on the global market due to an increased demand for such vaccines to achieve the elimination of CC as global target (33) In Mexico, this led to a temporary suspension of vaccination efforts and delayed interventions for the 2020, 2021, and 2022 target populations.

According to the WHO/UNICEF report, we found that vaccination was almost nil in 2021 (34). The COVID-19 pandemic has limited access to vaccines (not just against HPV) in many low- and middle-income countries (35). It is unclear whether the vaccine production capacity will meet global demand. Countries that have discontinued routine HPV vaccination can start plans for future catch-up campaigns for young people who missed HPV vaccination during the pandemic. However, the Strategic Advisory Group of Experts on Immunization (SAGE) Committee proposed strategies to address vaccine shortages during this period, including pausing vaccination of older women (> 15 years), establishing multi-age cohorts until sufficient supplies are available to meet global demand and protocols for delaying the second dose of vaccine by 2-3 years (33).

Two previous studies documented the impact of the COVID-19 pandemic on HPV vaccination services. Estimates of the impact of HPV vaccine coverage during the pandemic in the United States reported that coverage declined in March and April 2020, reaching a low of 23% in previous years (17). Another study reported a significant reduction in the average dose of HPV vaccine administered in Brazil from April to September 2019 (16). Many low- and middle-income countries had to delay of introduction of HPV vaccination (35).

In Mexico, as in other LAC countries, efforts to immunize target populations should be pursued in the months and years ahead in order to restore HPV vaccination rates and minimize medium-term consequences (36). In the long term, HPV vaccines accessibility will improve with the development of new, cheaper and faster-to-manufacture vaccines, which are expected to become available in the next few years (35). One government measure is to administrate only one dose of HPV vaccine. It is well known that one dose of HPV vaccine suffices to achieve good HPV serum antibody levels in girls under 12 years of age and is recommended (37). Therefore, this measure suffices to protect the target population of this group of HPV vaccines.

Regarding secondary prevention, the only indicators available for analysis were the number of analyzed/positive Pap smears and the number of initial and subsequent colposcopy examinations. It is important to note that although cervical screening in Mexico includes both cytology and molecular HPV testing, only information on cytology results is available.

Successful secondary prevention of CC is a multistep process that includes screening of the target population, triage of positive results, colposcopy-biopsy to confirm cervical precancer, and treatment of the precancer. Although limited, comparing the number of Pap smears and colposcopies performed during the pandemic with previous periods allows us to estimate the impact of disruptions of CC prevention program.

The number of positive Pap smears dropped at the start of the pandemic a tends to recover in 2021. This recovery coincides with the application of specific technical guidelines and protocols to reduce the risk of contracting COVID 19 issued by national health authorities (38). In Mexico, only one previous study has performed a similar analysis using data from various health services from the Mexican Institute Social Security (IMSS) Health Information System including the number of women screened for CC between January 2019 and December 2020, this indicator fell by 68% (39).

In an international context, the significant decline in cervical cancer screening rates was due to lockdowns and travel restrictions to contain the COVID-19 pandemic (20). In a study conducted in England, a 6.4% deficit was observed in the number of screening samples with respect to expected values before the pandemic (21).

The overall reduction in the number of Pap smear tests during the pandemic in 2020 with respect to historical data found herein

(41.1%) is similar to that reported in Belgium (43.3%) (18) but lower than in Scotland (56%) (40), Italy (64.5%) (41), California (78%) (42), the United States (84%) (43), Canada (85%) (44), and Slovenia (92%) (45).

While our results show that the number of colposcopy procedures performed in Mexico was already declining in the pre-pandemic era, the number of first and recurrent colposcopy procedures decreased further by 45.4% and 53.7% in 2020–2021. A Canadian study reported an average monthly reduction of 39.7% in colposcopy volumes from March to August 2020 compared with the same period in 2019 and a 75.1% reduction at the onset of the pandemic (44). However, other studies that did not provide numerical data reported that colposcopy in women with minor or low-grade cytological abnormalities or persistent HPV infection was delayed worldwide because of the pandemic (40).

According to information from Mexico's Unified Epidemiological Surveillance System, the impact of the COVID-19 pandemic on CC care programs was reflected in the lower number of reported cases of intraepithelial lesion in 2020 (46). We observed a slight recovery in 2021, but the number of cases was still below those reported in 2019. On the other hand, there are no official reports showing the impact of COVID-19 on indicators included in the regulatory documents related to screening coverage, diagnosis, evaluation and treatment of intraepithelial lesions, and efficiency in access to health services.

At the level of tertiary prevention, according to INCAN data, the most frequently diagnosed type of CC in Mexico before the pandemic was squamous cell carcinoma. Unfortunately, the pandemic there was an increase in the number of cases diagnosed at locally advanced and—even worse—metastatic stages. This result is consistent with a comparative analysis of three independent cervical models by the Cancer Intervention and Surveillance Network of the National Cancer Institute, which found that COVID-19-associated disease would cause a small net increase in the number of CC cases by 2027 (47).

Among the most relevant indicators for evaluating tertiary prevention efforts are the proportion of diagnosed CC cases that received treatment and the estimated time to initiate therapy (48). Our analysis shows that between 2020 and 2021, the proportion of untreated CC confirmed cases increased, while the proportion of early-stage CC cases treated with surgery decreased, becoming the scenario predicted by expert groups in hospitals with significant burden of COVID-19 cases (49).

The meantime between the diagnosis of CC and initiation of treatment has increased since the start of the pandemic. Most patients started treatment after eight weeks, and the relative numbers of this group have continued to increase during the pandemic. Evaluation of this indicator is important in Mexico, as the population most affected by COVID-19-related mortality lives in overpopulated and poor areas (50) and is also the most affected by CC (51).

This delay in treatment because of the pandemic has been badly documented, and few studies have described the impact of treatment delay on survival in patients with early-stage CC (22–24). A US study reported that the average wait time from CC diagnosis to hysterectomy was 4 weeks, and longer waiting times of 2 to 12 weeks were associated with an increased risk of all-cause mortality (23). Since the designated treatment procedures for radical hysterectomy in early-stage CC require hospitalization, these procedures will have to be postponed in areas with higher hospital demand (49).

In our study, it was not possible to analyze survival because the follow-up times of patients during the pandemic are still very short. According to a study on survival of delaying the initiation of concurrent chemoradiotherapy in women with locally advanced CC, in the absence of factors related to tumor aggressiveness, a short waiting time for treatment initiation (<10 weeks) may not be associated with an increased risk of mortality in women with this type of cancer (24). This study is relevant in the context of the current COVID-19 pandemic because fluctuating waves of infection force highly specialized hospitals to significantly reduce access to oncology care services, which would mean a delay in the treatment of these patients.

This study identified several areas for improvement at each sub-process or level of CC prevention program in Mexico, which have been affected by disruptions of preventive health and cancer care services because of the COVID-19 pandemic, in order to achieve the WHO goal of eliminating CC by 2030. Considering the cost of human life and suffering, implementing proper management of CC prevention programs should be a top priority for decision-makers and policy makers of CC prevention systems in all LAC countries to improve the performance indicators (52, 53), owing to the high prevalence of CC, the female cancer with the greatest preventive potential given its natural history.

The WHO global strategy to promote the elimination of CC as a public health issue proposes three coverage targets to be achieved (4): HPV immunization coverage in 15-year-old girls (70%); cervical screening coverage in women aged 35–45 years (70%), at least once in lifetime screening with valid evidence; and treatment coverage in women with precancerous lesions or CC (90%).

From 2017 to 2021, coverage of LAC complete HPV immunization schedule remains low (54). In the region, about 74% of women aged 30–49 years have been screened for cervical cancer at least once in their lifetime (55). The reported full coverage of the HPV vaccination program in Mexico was 97%, 96%, 95%, 5%, 5%, and 1% in 2017, 2018, 2019, 2020, and 2021, respectively (34). Screening coverage in 2019 exceeded 50% of the target population for that year. Although diagnostic screening coverage in colposcopy clinics exceeded 50% in 2019, there is no reliable information on the proportion of patients treated within 92 calendar days (56).

A disadvantage of multistep prevention programs is the need for multiple patient visits, including screening, colposcopy, treatment, and surveillance. At each step, there is a possibility that follow-up could be lost because of factors related to the patient, provider or health system, and an untreated precancerous lesion could progress to cancer (57). In this context, we suggest strategies to improve the prevention, diagnosis, and timely treatment program of CC in Mexico and to achieve the goal of CC elimination at the preventive level through their respective components, as well as three main actors for implementing the program, as shown in Figure 4.

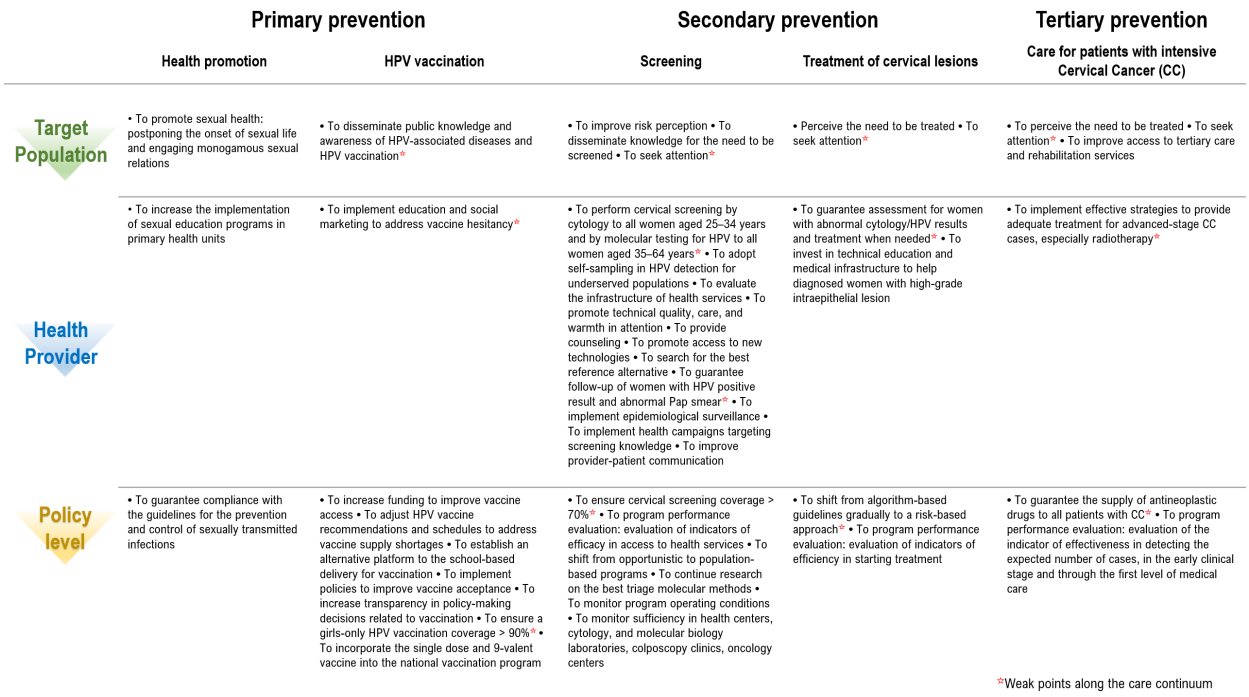


FIGURE 4
Process model of the cervical cancer prevention program in Mexico. The proposed strategies should be considered by health care providers and policymakers along the cascade of care to move toward the goal of eliminating cervical cancer in Mexico, as well as the critical control points in Mexico's cervical cancer prevention program process model. *Weaknesses along the continuum of care.

Our study has strengths and limitations. The main strength and contribution of this work is that it allowed us to identify areas affected by the impact of the pandemic in order to improve CC prevention program and provide recommendations for policymakers involved in the management of this program in Mexico towards the goal of CC elimination.

The main limitation of this study is the use of data sources collected from available administrative records which may have quality issues and lack of opportunity. Unfortunately, data on HPV test positivity, on treatment to premalignant lesions, and diagnostic evaluation were not available. Additionally, our data does not include information on CC-related hospital admissions, and thus does not cover the most negative outcomes (death or continuous in-patient treatment during the observation period). A specific limitation was the use of single center data for analysis of the impact at the level of tertiary prevention, since INCAN does not necessarily reflect what happens in all specialized hospitals in the health sector. However, given that the regulations of cancer programs are similar for the health sector and considering that it is one of the main resolutive hospitals in the CC and with the largest budget, possibly the impact of the epidemic is greater in the hospitals with less infrastructure.

In conclusion, the COVID-19 pandemic had a direct impact on CC prevention efforts at all levels in Mexico. This study documents the deterioration in the performance of the CC prevention program by demonstrating the adverse impacts of the pandemic on effectiveness and access to health services because of a significant reduction in the number of HPV vaccines applied and the lower number of patients attending first-time and recurrent colposcopy exams. The impact on the program's efficiency is also evidenced by the increase in the proportion of cases that started treatment more than 8 weeks after diagnosis and the lower proportion of CC cases detected at an early clinical stage.

Therefore, improving the performance of CC prevention program is crucial to reduce delays in vaccination, to achieve long-term reduction in the incidence of HPV infection, guarantee follow-up of positive cases, promote early detection of invasive cancers, timely initiation of treatment, and to promote disease-free survival. Among other measures, home vaginal self-sampling could offer options for CC prevention and treatment to women with restricted access to health services. These strategies should not only aim to fill the unmet needs created by the pandemic, but also eliminate negative and unnecessary aspects of care for this disease.

In this context, we propose some recommendations that include improving the quality of processes at all three levels of care; for example, improving epidemiological surveillance systems by establishing cancer registries; expand the reach of single-dose immunization; self-collection of vaginal samples for timely molecular diagnostics; early detection in older women; and in according to IARC Handbook, switching from conventional cytology to liquid-bases samples to do HPV as primary screening with cytology triage and typing of the same sample, which could have a large impact on efficacy and maybe on compliance to follow up (58).

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

## Author contributions

Conceptualization, KT-P and AC-V. Data curation, LP-M, JH-A and AQ-S. formal analysis, KT-P, LP-M, JH-A and AQ-S. Investigation, KT-P, AC, CA-F, RU, and VM-M. Methodology, KT-P, AC, LP-M, JH-A and AQ-S. Project administration, KT-P. Resources, LP-M, JH-A, AQ-S, TG-C, EA-B, DI-O and LC-P. Software, LP-M, JH-A and AQ-S. Supervision, KT-P. Validation, KT-P and AC. Visualization, LP-M, JH-A and AQ-S. Writing—original draft, KT-P, AC-V, LP-M, JH-A, AQ-S, CA-F, S-RU-S and VM-M. Writing—review and editing, KT-P, AC-V, LP-M, JH-A, AQ-S, S-RU-S, and VM-M. All authors revised the manuscript. Allauthors contributed to the article and approved the submitted version.

## Funding

This work was funded by the Instituto Nacional de Salud Pública, Mexico, and grants from the Consejo Nacional de Ciencia y Tecnología (CONACYT, Mexico) to KTP (FONSEC SSA/IMSS/ISSSTE-2018 grant # A3-S-49099) and to VMM (grant CATEDRAS-2014-C01-#245520).

## Acknowledgments

The authors thank the General Directorate for Information in Health for making available the database of services provided 2017–2021 hospital discharge and outpatient services dataset and the Unidad de Inteligencia en Salud Pública for integrating of the information used in this manuscript.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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