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Eliminating cervical cancer from low-and middle-income countries: An achievable public health goal

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Eliminating cervical cancer from low-and middle-income countries: An achievable public health goal

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Editorial: Eliminating cervical cancer from low- and middle-income countries: An achievable public health goal

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cervical cancer, vaccination, low- and middle-income countries, elimination, prevention

Editorial on the Research Topic
Eliminating cervical cancer from low- and middle-income countries: An achievable public health goal

It is possible to eliminate cervical cancer by fully vaccinating 90% of girls by the age of 15, screening 70% of women between the ages of 35 and 45, and treating 90% of cervical cancer patients in low- and middle-income countries. Cervical cancer can now be prevented with HPV vaccination and screening, as well as treated with effective surgery, radiotherapy, and chemotherapy. Nonetheless, over 500,000 new cases were reported worldwide (1).

Every year, half a million women worldwide are diagnosed with cervical cancer, with half of those diagnosed dying as a result. Cervical cancer is strongly linked to socioeconomic development, with the disease affecting low- and middle-income countries disproportionately (2).

Women in low and middle-income countries may not receive prophylactic vaccines or screening due to a lack of adequate logistics and infrastructure, as well as a lack of trained medical services and health education. Aside from political and social issues. It is critical to address these issues and devise strategies to overcome these obstacles. It is necessary to address the social, political, and economic barriers to accessing services, particularly those related to gender. Regardless of supply, cost, delivery, or skepticism, HPV vaccination should be made available to everyone who needs it.

Screening services must be established from scratch in some low-income countries. Screening positive women in countries where chemotherapy or radiotherapy are unavailable necessitate treatment. A large number of radiographers, physicists, nurses, and surgeons must be trained.

A multi-front battle will almost certainly be required to advance cervical cancer prevention. Raising public awareness about the problems caused by cervical cancer, as well as new discoveries about its etiology, is critical. Providing women and their male partners with updated health education appears to be a necessary first step.

Incorporating novel technology in a reasonable manner would reduce the number of visits required and make screening more efficient in terms of the protection provided by each visit. Educating professionals and populations about the vaccination strategy. Adopting an unbiased scientific approach to these issues is a critical responsibility of clinical and public health societies.

We are all capable of eliminating cervical cancer, and we are all aware of the health consequences of inaction. To overcome these challenges, governments, civil society, the private sector, and academia must now collaborate.

This Research Topic is an excellent starting point for the project. It includes nine articles from Nepal (Narasimhamurthy and Kafle), Brazil (Corrêa et al.), Philippines (Lintao et al.), Rwanda and Sierra Leone (Bangura et al.), China (Liu et al.) (Yu et al.), Peru (Shin et al.), Latin American countries (Rol et al.), and Kenya (Mabachi et al.), written by experts on various aspects of the field that describe the issues, options, and outcomes available.

The main focus of these studies from low and middle income countries is the importance of laboratory readiness in the successful implementation of HPV testing. High readiness, however, is insufficient to ensure high continuity capacity for HPV testing, which necessitates the establishment of a quality culture that includes regular training, robust monitoring, and quality assurance systems tailored to the local context. All efforts to improve HPV laboratories are valuable and necessary to ensure the successful implementation of HPV-based cervical screening (Rol et al.).

The incorporation of new technologies and approaches in those fronts is expected to help drive the country toward an elimination target, single-dose HPV vaccination, and HPV self-sampling testing, which are very effective cervical cancer prevention strategies in low- and middle-income countries. Local and international collaborations are also required to improve secondary prevention and management by establishing a reliable infrastructure to treat HPV-related pre-invasive and invasive cancer (Narasimhamurthy and Kafle and Corrêa et al.).

Other studies on the Research Agenda should be conducted, such as implementation research, epidemiological studies, and clinical research on the cost-effectiveness and efficacy of various traditional and novel treatment strategies, in order to develop a locally applicable system for implementing a national cervical cancer screening and HPV vaccination program (Lintao et al.). Improving data quality and completeness, which is a priority among national stakeholders, is critical. Investing in systems to improve the detection and treatment of precancerous lesions can improve patient outcomes and, in the long run, lower the costs associated with the much more expensive treatment of later-stage detection (Mabachi et al.).

Another issue raised by experts from low and middle income countries is awareness. Without policymakers' and the public's awareness and willingness to fund cervical cancer programs, the prioritization of cervical cancer activities, the availability of resources, an adequate health workforce and infrastructure, cross-sectional collaboration and planning, intersectorial, national, regional, and international partnerships, the goal of cervical cancer elimination would not be achievable in countries (Bangura et al.).

Another important issue raised by the experts is socioeconomic inequalities, risk factors, and community-based social entrepreneurship. In low and middle income countries, rural-urban inequality and socioeconomic inequalities continue to be problems (Liu et al.). Age, a history of alcohol consumption, marital status, reproductive diseases, education level, and the number of live births were all risk factors for HPV infection. Therefore, cervical cancer screening should be made available to women over the age of 30 in rural areas, particularly those aged 41–45 (Yu et al.). Future research is required to clarify the relationship between empowerment and worker performance in order to inform the expansion of HPV self-sampling social entrepreneurship programs (Shin et al.).

The completion of such a task at the appropriate time indicates that the international scientific community strongly supports low-income countries in the field of cervical cancer, and thus future scientific support should be available when required. Our challenge is to reduce the mortality rate from cervical cancer, an infectious disease with well-established and highly effective prevention methods. In this regard, the prospects for low and middle-income countries should be brighter than they have ever been.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

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

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Evaluation of Women's Empowerment in a Community-Based Human Papillomavirus Self-Sampling Social Entrepreneurship Program (Hope Project) in Peru: A Mixed-Method Study

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Introduction: Understanding community women's relational and financial empowerment in social entrepreneurship could be the key to scaling up community-based human papillomavirus (HPV) self-sampling programs in low- and middle-income countries. The Hope Project, social entrepreneurship in Peru, trains women (Hope Ladies) to promote HPV self-sampling among other women in their communities. This study aims to evaluate the Hope Ladies' relational and financial empowerment after participating in the program.

Materials and Methods: We evaluated the Hope Ladies' experiences of empowerment in social entrepreneurship using a parallel convergent mixed methods design. The Hope Ladies participated in semi-structured in-depth interviews (n = 20) and an eight-questions five-point Likert scale survey that evaluated their relational (n = 19)/financial (n = 17) empowerment. The interview and the survey questions were developed using three empowerment frameworks: Kabeer's conceptual framework, International Center for Research on Women's economic empowerment indicators, and the Relational Leadership Theory. Deductive content analysis was used to evaluate the interviews with pre-determined codes and categories of empowerment. Descriptive statistics were used to analyze the survey results. Qualitative and quantitative data were integrated through a cross-case comparison of emergent themes and corresponding survey responses during the results interpretation.

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Results: All Hope Ladies reported experiencing increased empowerment in social entrepreneurship. *Interviews:* The women reported challenges and improvement in three categories of empowerment: (1) resources (balancing between household and Hope Lady roles, recognition from the community as a resource, camaraderie with other Hope Ladies); (2) agency (increased knowledge about reproductive health, improved confidence to express themselves, and ability to speak out against male-dominant culture); and (3) achievement (increased economic assets, improved ability to make financial decisions, and widened social network and capital, and technology skills development). *Survey*: All (100%) agreed/totally agreed an increase in social contacts, increased unaccompanied visits to a healthcare provider (86%), improved confidence in discussing reproductive topics (100%), improved ability to make household decisions about money (57% pre-intervention vs. 92% post-intervention).

Conclusions: The Hope Ladies reported improved relational and financial empowerment through participating in community-based social entrepreneurship. Future studies are needed to elucidate the relationship between empowerment and worker retention/performance to inform the scale-up of HPV self-sampling social entrepreneurship programs.

Keywords: cervical cancer, HPV self-sampling, social entrepreneurship, empowerment, community-based cancer screening, Peru

INTRODUCTION

Social entrepreneurship is a highly theorized field of knowledge that has rapidly emerged in recent decades. As such, there has been a proliferation of systematic reviews (1, 2), bibliometric studies (3–5), and other projects (6–8) to explore social entrepreneurship and other efforts to set forth research direction and framework for the future (9–11). Social entrepreneurship could be understood as a phenomenon (12) or organizations (1) that leverage economic activities or innovative business models with the mission of creating or implementing positive social change (13–17) rather than personal or shareholder wealth (18, 19).

Social entrepreneurship activities in low- and middle-income countries have often taken the form of microfinance or microcredit programs designed to advance women's economic development (20). Women working in health-oriented social entrepreneurship programs seek to become financially self-sufficient by promoting health or health products rather than being dependent on or being employed by an organization (21). Women-driven social entrepreneurship programs have been shown to empower the entrepreneurs, not only economically but by widening their social network in their communities, enhancing technical skills with earning potential, and challenging the gender norm and their status in families and society (22). Kabeer explains women's empowerment as a process of changes, "by which those who have been denied the capacity for choice gain this capacity" that entails the inter-related, "indivisible" dimensions of resources (pre-conditions), agency (process), and achievements (outcomes) (23, 24). Kabeer also emphasizes that women are embedded, active members within their society, and hence, their empowerment can create social change in those societies where women lack equal power (24). Some scholars support the claims that the elements of empowerment are inherently and essentially embedded in the for-profit social entrepreneurship models (25–27).

In Peru, cervical cancer is the leading cause of cancer deaths in women aged 15–44 (28). The age-standardized incidence rate in Peru is 23.2 per 100,000 women per year, compared to the world average of 13.1 per 100,000 women (28). Despite the clear need for cervical cancer screening, only 52.4% of the women aged over 30 reported having had a Pap test in the last 2 years, according to the Peruvian Demographic and Family Health Survey from 2015 to 2017 (29). Multiple barriers toward achieving high quality and coverage of cytology (also known as Pap test) programs have been identified in Peru even though it is offered as a free service in the public sector, such as unequal regional concentration of lab facilities and clinics, inconsistency of procedures, distance, fear and shame related to the gynecological examination (30–33). Those screened are often lost to follow-up and/or cannot access the necessary treatment due to prohibitive costs or geography (33). The five-year observed survival rate of cervical cancer in metropolitan Lima is only about 50% (34). HPV self-sampling is an alternative strategy that can overcome barriers to screening because additional providers, facilities, and visits are not required for the initial part of the screening. Using a small cytobrush, women can sample themselves through the vaginal canal in the privacy of their home when it is convenient for them. For this reason, the World Health Organization (WHO) recommends HPV self-sampling as an approach to increase screening uptake for women aged 30–60 years (35).

The Hope Project is a social entrepreneurship program initiated by the Universidad Peruana Cayetano Heredia to promote community-based cervical cancer screening through HPV self-sampling in 2018, following a successful pilot in 2015 (36, 37). It has two components: commercial and social. The commercial component offers HPV self-sampling kits and testing with CareHPV® (Qiagen) online to high- and middle-income women in Peru for a higher price (150 Peruvian Soles [PEN], ∼43 US Dollars [2020 USD]) to create a sustainable platform to offer subsidized testing to women with fewer resources. The geographical coverage of the social component of the Hope Project encompasses the socioeconomically disadvantaged peri-urban districts of Ventanilla and Mi Perú, a special city project within Ventanilla called "Pachacutec" in the region of Callao. Many residents of these communities are migrants from different regions of Peru who live in these districts to work in the metropolitan area of Lima-Callao (38). Some parts of Ventanilla, namely Nuevo Pachacutec, were established in early 2000 when the government resettled over 7,000 migrant families living in informal housing from another metropolitan area (39). About 30% of the population in Ventanilla, Mi Perú, and Pachacutec live in poverty, and one hospital and 13 community clinics serve the population of about 500,000 (40). Only 10 colposcopy, one cryotherapy, and one loop electrosurgical excision procedure instruments to examine and treat precancerous lesions were found in the public health clinics in the Callao region in 2017 (41), pointing to potential difficulty accessing follow-up care for women with positive cytology or HPV testing. To bridge this gap, the Hope Project donated one colposcope and cryotherapy instrument to a public health clinic in the catchment area.

In the social component, women from the communities (known as Hope Ladies) are trained to promote cervical cancer screening through HPV self-sampling and guide other women through the screening pathway in their communities. The program activities have been described elsewhere (42) and also described in **Figure 1**. Briefly, the screening pathway implemented in the Hope Project consists of detecting HPV infection by HPV testing and participants receiving their results via text messages and paper. Women who test negative for HPV are advised to follow up in 3 years, and those who test positive are advised to be evaluated in the public health clinics with visual inspection with acetic acid and colposcopy. HPV positive women with precancerous lesions are treated with cryotherapy if possible or referred to other ablative therapies, and those without lesions are advised to follow up with the public health clinic in 1 year. Women with cancerous lesions are referred for further management in a hospital setting. The Hope Ladies support the participating women through the full screening process by raising community awareness, promoting stigma reduction, distributing kits, and linking women to care with appropriate providers and public health clinics that provide follow-up and treatment as needed.

The concept of women's empowerment has been explored as a mediator between social entrepreneurship and social change (22), but not in the context of HPV self-sampling. Understanding the relationship between these concepts could be the key to informing future program direction and developing scalable social entrepreneurship to increase access to cervical cancer screening. Therefore, we undertook this study to evaluate the Hope Ladies' relational and financial empowerment after participating in the social entrepreneurship. We also developed a causal pathway that can be used to explore empowerment as the mechanism of action and hypothesis generation for the Hope Project intervention in the future.

MATERIALS AND METHODS

Program Setting and Activities

In the social component of the Hope Project, the Hope Ladies initially receive 6 hours of training spanning 2 days on topics including cervical cancer, HPV self-sampling, and project procedures. In addition, the Hope Ladies receive training on effective communication skills, technical skills (e.g., using and managing Whatsapp to communicate with program administrators), and financial skills (e.g., opening and managing online banking, and taxes). Prior to the pandemic, there were monthly monitoring meetings where the Hope Ladies shared their experiences and collectively addressed any challenges from the field.

Upon completion of the training, the Hope Ladies buy the HPV self-sampling kits for five PEN per kit (∼1.50 USD) from the Hope Project and sell the kits door-to-door by leveraging their social networks in their spare time and keep the small profit of the sales (five PEN per kit [∼1.50 USD]) as an incentive for the wide dissemination of the HPV self-sampling kits to their clients. Each kit contains a cytobrush, a collection vial, and a simple instruction that explains how to insert the brush into the vagina and rotate it 3–5 times before placing it into the collection vial (**Figure 2**). The Hope Ladies educate community women about cervical cancer prevention and how to perform HPV self-sampling. The Hope Ladies pick up the samples from the participants and bring them to a designated central location in the neighborhood, which are then transferred to the laboratory once a week. The Hope Ladies deliver printed test results to the screened women and encourage women who screened positive to follow up in the public health clinics to seek evaluation and treatment as needed. As of March 2022, 62 Hope Ladies had been trained since 2018 and 18 (30%) remain active in the program, although the community outreach has been suspended since March 2020 when the country went into lockdown due to the COVID-19 pandemic.

Conceptual Framework for Evaluation of Empowerment

We applied three conceptual frameworks to inform the evaluation of empowerment: (1) Kabeer's conceptual model on empowerment (23); (2) International Center for Research on Women (ICRW)'s indicators on women's economic empowerment (43); and (3) relational leadership theory (RLT) (44). We decided to use three frameworks for the analysis because the science of defining and measuring women's empowerment is complex and evolving (45–48), and Kabeer's framework has been successfully used to analyze women's empowerment in social entrepreneurship in developing countries (24, 25).

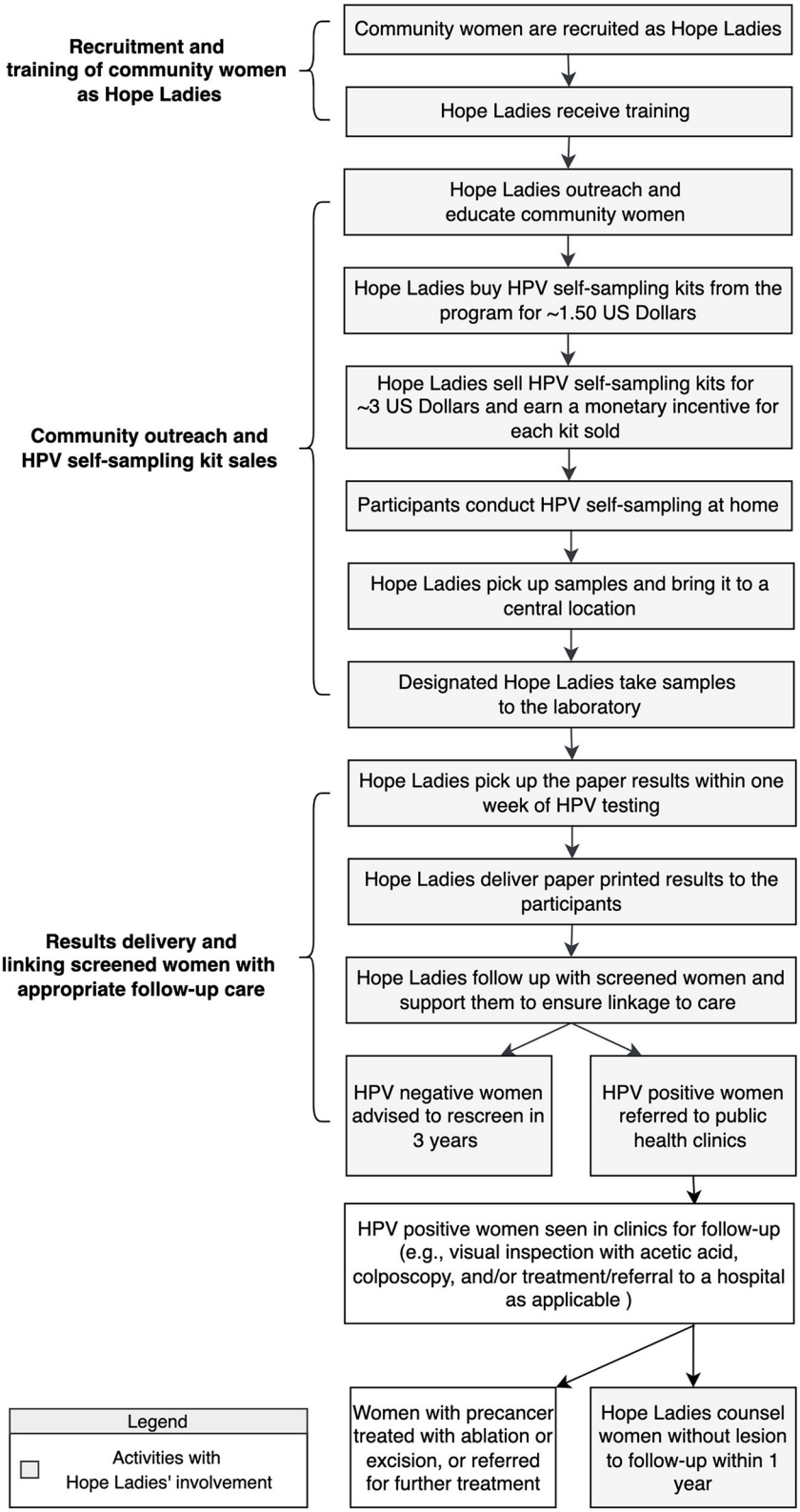

FIGURE 1 | Activities within the Hope Project social entrepreneurship.

FIGURE 2 | HPV self-sampling kits sold by the Hope Project.

The relationship between the three conceptual frameworks is depicted in the fishbone matrix diagram in **Figure 3.** The ICRW's framework measures women's economic empowerment by tracking indicators such as control over assets, agency in decision making, autonomy and mobility, self-confidence and self-efficacy, gender norms, and gender roles within the household (43). Although the measurement indicators have not been specifically validated in Peru among women working in healthcare, we chose this ICRW's framework because it was derived from the literature and the field experience in evaluating women's economic empowerment programs in various low-resource settings. The RLT was used to examine empowerment in the context of family, social networks, and communities, with the assumption that power is "developed and exercised through relationships" (49). The constructs related to financial and empowerment from ICRW framework and RLT were organized into individual- and community-level sub-categories, then mapped onto the generic categories of resource, agency, and achievements from Kabeer's conceptual model of empowerment, acknowledging

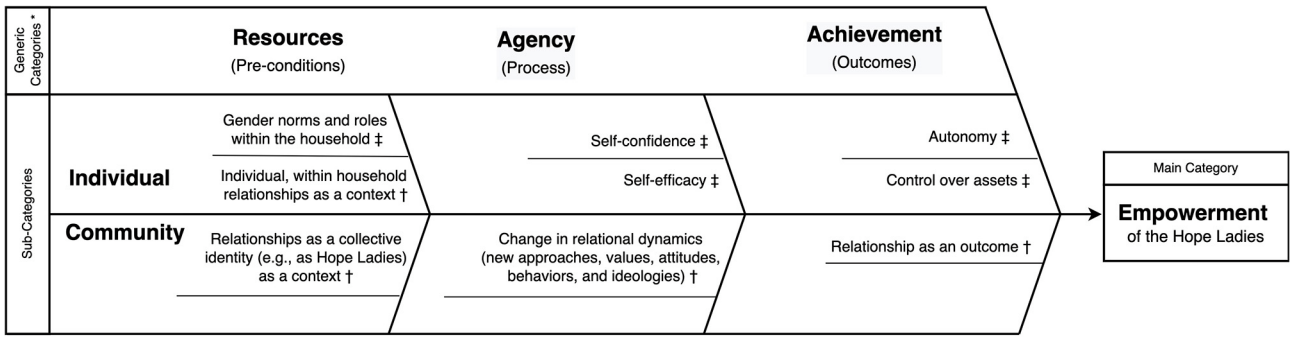

FIGURE 3 | Conceptual framework of financial and relational empowerment.
*, Constructs from Kabeer's conceptual framework of empowerment.
†, Pre-determined codes about the Hope Ladies' relational empowerment, derived from Relational Leadership Theory.
‡, Pre-determined codes about the Hope Ladies' economic empowerment, derived from International Center for Research on Women.

that these constructs are not mutually exclusive but rather inter-related (23).

Data Collection and Analysis

We evaluated the Hope Ladies' experiences of empowerment using a parallel convergent mixed methods design (50). To recruit the participants, we selected (via spreadsheet randomization [Microsoft Excel]) and invited 20 of the 62 Hope Ladies (32%) to participate in an individual in-depth interview and a survey through Whatsapp in early March 2020. Each participant gave written informed consent in Spanish. Participant characteristics were gathered from the administrative data from the project. The study was approved by the International Review Boards of Cayetano Heredia University (#103900), Duke University (#2020-0376), and the University of Washington (STUDY00010676).

The interview guide and the eight-question five-point Likert scale-based survey were derived from the ICRW framework and RLT (available as **Supplementary Data Sheet**). The interview and the survey were designed to take 30 and 10 minutes, respectively, and asked about the Hope Ladies' perceived financial and relational empowerment before and after participating in social entrepreneurship. The interview guide and the survey instruments were prepared in English and translated and reviewed, and piloted by the Hope Project administrators, and amended according to their feedback before finalization.

We conducted individual in-depth interviews and the survey orally in-person in the participants' homes in March 2020. Other family members or program administrators were not present during the interview and the oral survey to minimize bias. Due to the unforeseen logistical challenges and sudden country lockdown due to the COVID-19 pandemic during the week of the data collection, some participants were rescheduled and completed the oral surveys at a later date in June 2021 virtually. The data was collected by at least two trained study personnel, one of whom was fluent in Spanish while the other study personnel took notes.

The interview recordings were transcribed verbatim in Spanish by an independent contractor fluent in Spanish and a resident of a nearby city. Following the structured deductive content analysis method (51), the two authors (MS and MD) independently cleaned the data and organized the emerging themes according to the pre-determined codes from the conceptual framework in **Figure 3**. They iteratively discussed their individual findings from the qualitative data analysis in a series of meetings and discussed discrepancies until reaching consensus. Salient quotes were translated from Spanish to English by MS and verified by other bilingual authors. The number of participants who endorsed the emergent theme and the reference counts were also measured. Qualitative analysis was performed using NVivo 12 (QRS International, Burlington, MA, USA). Basic frequencies and proportions were used to analyze the results of the survey.

Qualitative and quantitative data were integrated through a cross-case comparison of pre-determined codes from the conceptual framework and corresponding survey questions during the results interpretation (**Supplementary Data Sheet**). The emergent themes and the reference counts were arrayed in the joint display, along with salient quotes from specific participants and their responses for the respective survey question. Then, the analysis team discussed convergence, divergence and expansion between the qualitative and quantitative data to triangulate and interpret their findings (52).

Development of Potential Causal Pathway

We developed an implementation science-based causal pathway that can be used for hypothesis generation and for exploring the Hope Ladies' empowerment as the mechanism of action in the future. Using the Agile Science-informed method specified by Lewis et al. and the findings of our surveys and interviews, we developed a pathway model for the Hope Project to increase HPV self-sampling kit sales (proximal outcome), thereby increasing cervical cancer screening coverage (distal outcome) (53). We followed the definition of the mechanism of action, which was the "process or event through which the implementation strategy operates to affect desired implementation outcomes" (53). The cognitive moderator was defined as individual-level

perception or attitudes that increase or decrease the level of the influence of the Hope Project. In contrast, the organizational moderator was defined as community-level factors such as culture or widely held beliefs. We also defined pre-conditions, or factors necessary for an implementation mechanism to be activated and the proximal outcome to be realized in the Hope Project.

RESULTS

All 20 randomly invited Hope Ladies agreed to participate in the study, and the interviews were scheduled for early March 2020. Overall, the 20 Hope Ladies participated in in-person individual in-depth interviews (approximately 60 mins each). Due to the COVID-19 pandemic, five and 10 participants completed the relational and financial empowerment surveys virtually in June 2021, respectively. Ultimately, 19 women completed the relational empowerment survey, and 17 women completed the financial empowerment survey, from which the analysis was conducted.

The demographics of the Hope Ladies are described in **Table 1**. On average, the Hope Ladies' ages were 45 years old (range: 32–64), had lived in the Ventanilla region for 20 years (range 10–37 years), and had been involved with the Hope Project for 9 months. Most ($n = 11$, 55%) were born in the coastal region, had at least two children ($n = 18$, 90%). All had at least secondary school education, which is equivalent of high school in the United States, and five (25%) had a job in the informal sector other than the Hope Project. Six (30%) were "active" in the Hope Project, defined as sending weekly samples to the laboratory prior to the pandemic, although the level of sales varied greatly throughout the school year when the participants were tending to their children (42). On average, the participants had sold 151 HPV self-sampling kits, with a profit of 23.50 USD per month (Range: 7.20 to 72.80 USD) from the time they began working as Hope Ladies and the time of analysis (August 2020).

In **Table 2**, we present the results of the relational and financial surveys. The summary of deductive content analysis of the in-depth interviews is available in the **Supplementary Data Sheet** with salient quotes from the participants. We present the results organized according to the conceptual framework presented in **Figure 3**. The cross-case comparison of the qualitative and quantitative data that was used to compare and contrast the emergent themes and the survey responses is available in the **Supplementary Data Sheet**.

TABLE 1 | Characteristics of the interview participants ($N = 20$).

Sociodemographic characteristic	Number (%)
Age (years)	
30–44	10 (50)
45–65	10 (50)
Place of birth	
Andean	7 (35)
Coastal	11 (55)
Amazon	2 (10)
Marital status	
Married/living with partner	16 (80)
Separated	2 (10)
Single	2 (10)
Number of children	
0–2	12 (60)
3–5	8 (40)
Age of last child	
0–5	3 (15)
6–16	12 (60)
17+	6 (30)
Education	
Secondary education	16 (80)
Technical institute	4 (20)
Employment status (informal sector)	
Yes	5 (25)
No	15 (75)

Resources

Resources could be defined as those conditions that enhance the ability to exercise choice (23). The Hope Ladies described the challenge of managing their roles within the household and working as a Hope Lady and the benefit of peer support within the Hope Project, as well as being recognized as a resource for women's reproductive health in their communities.

Gender Norms and Roles Within the Household

Maintaining Roles Within the Household and Working as a Hope Lady

The majority of the Hope Ladies who were interviewed ($n = 15$, 75%) mentioned that it is difficult to manage their time to sell HPV self-sampling kits in their communities due to their various roles in their households, such as childrearing and caregiving. One study participant stated, *"I have a baby. When she grows a little more, I don't think I will have any obstacles with the Hope Project"* (Hope Lady, age 35), and another stated, *"I have my mother-in-law in my care. She needs me to take care of her [...] because she cannot get out of bed. I go [out to sell the kits], but with the thought, 'what if she suddenly falls out of bed,' or I do not know she will urinate on herself. Sometimes I wonder, 'Should I continue [to work as a Hope Lady] or not?' and sometimes I stop [selling the kits]. But my friends [other Hope Ladies] tell me, 'Don't stop, keep going for us.'"* (Hope Lady, age 33). Another study participant stated, *"It's definitely not easy [...] it is a matter of organizing, it is a matter of habit, it is a matter of accustoming the family. It has its consequences, but it is possible to balance."* (Hope Lady, age 33). In contrast, other study participants found it easy or manageable to organize their time. For example, one study participant mentioned, *"It's not difficult for me [to manage my time] because the issue here is to organize ourselves. If we organize ourselves, everything works out for us."* (Hope Lady, age 45). Another study participant emphasized the convenience of

TABLE 2 | Relational and financial empowerment survey results.

Question	Number of responses	Responses	*N* (%)
Relational empowerment			
RLT 1.a. Would you say that your number of social contacts within and outside the family has increased since the beginning of your Hope lady journey?	*N* = 19	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	3 (21)
		Totally agree	16 (84)
RLT 1.b. Would you say that you have been able to help other women in moments of need since the beginning of your Hope lady journey?	*N* = 19	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	5 (36)
		Totally agree	14 (74)
RLT 1.c. Since becoming a Hope Lady, would you say that you have been able to visit the health care provider to meet your personal needs without your family members or friends accompanying you more easily?	*N* = 19	Totally disagree	0 (0)
		Disagree	2 (14)
		Agree	10 (53)
		Totally agree	7 (37)
RLT 1.d. Would you say that you have felt confident because of learning about your reproductive health and how to prevent certain diseases compared to starting your job Hope lady?	*N* = 19	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	8 (42)
		Totally agree	11 (58)
Financial empowerment			
ICRW 2.a. Currently, do you decide how to spend money in your household?	*N* = 17	Always	16 (94)
		Sometimes	0 (0)
		Rarely	1 (8)
		Never	0 (0)
ICRW 2.b. In the past before joining the Hope Project, did you decide how to spend money in your household?	*N* = 17	Always	7 (41)
		Sometimes	6 (35)
		Rarely	3 (18)
		Never	1 (6)
ICRW 2.c. Currently, are you allowed to comment on the purchase of large domestic assets in the household?	*N* = 17	Always	14 (82)
		Sometimes	1 (6)
		Rarely	2 (12)
		Never	0 (0)
ICRW 2.d. In the past before joining Hope project, were you allowed to comment on the purchase of large domestic assets in the household?	*N* = 17	Always	9 (53)
		Sometimes	6 (35)
		Rarely	2 (12)
		Never	0 (0)

setting their own schedule saying, "*Without having to have an obligatory schedule, in my free time I can go to work myself.*" (Hope Lady, age 33). There were five salient quotes in this theme, and the survey questions corresponding to this theme were RLT 1.a. and RLT 1.b., which asked if the number of social contacts within and outside the family has increased and whether the participant had been able to help other women in the community as a Hope Lady. While all five participants totally agreed/agreed on both survey questions, only one was actively working as a Hope Lady because they were unable to meaningfully engage in the increased social contacts due to their conflicting household roles. Those who paused their Hope Lady role expressed a sense of guilt because they could not continue helping community women. The qualitative and quantitative data diverged in this theme.

Relationships at the Community-Level as the Collective Identity of Hope Ladies

Hope Ladies as a Resource for the Communities

In the relational empowerment survey, all participants responded "agree/totally agree" ($n = 19$, 100%) to the question, "would you say that you have been able to help other women in moments of need since the beginning of your Hope Lady journey?" (RLT 1.b., **Table 2**). Half of the Hope Ladies interviewed ($n = 10$, 50%) reported being recognized for their knowledge about cervical cancer in their communities and said, *"They [the community women] talk to me more because you know in the hospital, they [the doctors] will hardly talk to them like we [Hope Ladies] talk to them."* (Hope Lady, age 45). Both the interview and the survey data showed that being valued as leaders and resource for the community was important to the Hope Ladies.

The Camaraderie With Other Hope Ladies

Nearly half (n = 9, 45%) of the Hope Ladies interviewed commented on enjoying the peer support with other Hope Ladies and started collaborating with other colleagues helped sell their kits. One study participant said, *"We would agree with other colleagues [Hope Ladies], and we would go out in a group because it is less tedious [than] when you are alone."* (Hope Lady, age 64). Another study participant commented they look forward to the growth of the Hope Project, saying, *"we are working with the Cayetano [University], so that [the Hope Project] grows and we can amplify the good work."* (Hope Lady, age 54).

Agency

Agency is defined as the capability to define one's goal and act upon it (23). The Hope Ladies reported an increased sense of confidence and efficacy in themselves stemming from increased knowledge about reproductive health and improved communication ability and express themselves. They also discussed changes in behaviors, values, attitudes, and ideologies, such as advocating for their clients (other community women) to make autonomous decisions about HPV self-sampling against male-dominant culture (*machismo*).

Individual-Level Self-Efficacy and Self-Confidence

Increased Knowledge and Self-Efficacy

All (n = 20, 100%) of the Hope Ladies said the increased knowledge and education about cervical cancer helped them to make informed decision-making for themselves, as well as other community women. 53% (n = 10) agreed, and 37% (n = 7) totally agreed that they have been able to increase unaccompanied visits to a healthcare provider to meet their personal needs since the beginning of your job as a Hope Lady?" (RLT 1.c.) One study participant stated, *"It has empowered me, and I have gained a lot of experience [. . .] It taught me to express myself, to reach the families who are the most in need, and I saw that there is a lot of need in the communities that I have visited, and others thank you and tell you, 'Thanks for coming! Thank you for remembering me!' And all that makes your self-esteem rise, and you have more desire to continue working, for them, for them more than anything."* (Hope Lady, age 47). The four salient quotes in this theme also discussed that many of their HPV positive clients do not want to go to the public health clinic for further evaluation due to fear of cancer diagnosis, encountering a male provider, and long wait time. The interview and the survey data converged in this theme, which demonstrated that the Hope Ladies felt the increased knowledge about the reproductive health gave them confidence to accompany the HPV positive clients to emotionally support and advocate for them during the clinic visits in addition to increasing unaccompanied visits to the healthcare providers for their personal needs.

Improved Self-Confidence and Ability to Communicate and Express Thoughts

All study participants agreed (n = 8, 42%) or totally agreed (n = 11, 58%) in the relational empowerment survey that they felt more confident than before working as a Hope Lady because they learned about the female reproductive health system (RLT 1.d., **Table 2**). One study participant mentioned, *"If it weren't for this [the Hope Project], I wouldn't even have taken the test,"* (Hope Lady, age 44). More than half (n =12, 60%) of the study participants reported improved communication abilities to express themselves. One reported, "*It has helped me to have more confidence in words, that is, in being able to express myself with confidence what I am talking about.*" (Hope Lady, age 33). Another study participant emphasized the importance of ongoing support and training by the Hope Project to her and said, "*I have lost the shame of communicating with people, because before I was not capable. When I started, I was very shy, but now I have enough skills. I have acquired that with [Hope Project] because of the training that they also give us. They support us in everything that we do, we also consult with them.*" (Hope Lady, age 46). The interview and the survey data converged in this theme, which demonstrated that the improved knowledge about reproductive health enhanced the participants' confidence in their ability to learn and perform their roles as Hope Ladies.

Change in Relational Dynamics in the Community

Advocating for Women Against Male-Dominant Culture

Almost all (n = 18, 90%) of the Hope Ladies who were interviewed mentioned male-dominant culture (*machismo*) in the households as a barrier to selling the HPV self-sampling kits. One reported, *"Many times [the women] say, 'No, my husband does not want [me] to,' and they have to talk with the husband [to buy the kit]. That is, more than anything,* machismo." (Hope Lady, age 50). Another participant cited fear as a barrier to screening saying, *"Some women don't do [the HPV self-sampling] out of fear of [their spouses]. They say, 'my husband will ask me why I'm taking the test! He might think it's because I doubt [his fidelity].'"* (Hope Lady, age 33). A few (n = 3, 15%) Hope Ladies reported clients who buy the HPV self-sampling kits in secret, without informing their spouses.

The Hope Ladies stated they advocate for women to make autonomous decisions about their bodies without obtaining permission from their spouses by educating them about the importance of cervical cancer screening. One stated, *"We help them so that they can become aware that the decision is in themselves, and that we do not depend on anyone. We say, 'We have come alone, and we are going to leave alone, so each one is the owner of what to do and what decisions to make.' And that is what I have learned with Hope Project."* (Hope Lady, age 46). Another study participant said, *"The empowerment that [the Hope Project] brings to us, that other institutions cannot, is women's self-realization, their power to decide themselves, not to ask their partner."* (Hope Lady, age 48). Although the interviewers did not solicit information about domestic violence, a quarter of all study participants (n = 5, 25%) mentioned their clients shared that they sometimes experience it.

Achievements

Achievement can be seen as the outcome of the resources and agency (23). The Hope Ladies reported increased economic assets and expanded social network since joining the Hope Project.

Control Over Assets

Increased Economic Assets

All (n = 20, 100%) study participants reported that the supplemental income from selling HPV self-sampling kits was economically helpful. One study participant responded, *"Of course, it has helped me a lot [. . .] It helps me for my children's bus fares, which is daily for school."* (Hope Lady, age 45). Another study participant stated, *"Yes, it helps [financially]. It is a job that helps you financially and that you are also helping other people, other women."* (Hope Lady, age 51). There were three salient quotes in this theme, and the survey questions corresponding to this theme asked if the participant decides how to spend money in their household currently (ICRW 2.a.) and in the past before joining the Hope Project (ICRW 2.b.). All three answered that they "often" make spending decisions currently, whereas their responses varied from "never" to "sometimes" on how often they made spending decisions before joining the Hope Project. The interview and the survey data converged in this theme in that while the participants said financial gains are not the primary motivation for working as Hope Ladies, they derive a sense of achievement from financially contributing to the household.

Financial Autonomy

Improved Financial Autonomy

Most study participants of the financial empowerment survey (16 of 17, 94%) reported that currently, they "always" decide on how to spend money in their household (ICRW 2.c., **Table 2**). In contrast, when asked the same question before starting the Hope Project, 41% (7 of 17) responded "always" (ICRW 2.d.). In the individual interviews, the change in the ability to make financial decisions since working as a Hope Lady was more subtle. One study participant who is a single-parent stated, *"I'm the one who works. I am a mother and father, I have a daughter, and I am the one who says how much money comes into my house and how much I am going to spend. I try to balance what is my priority."* (Hope Lady, age 47). Another study participant stated, *"Although I don't [work], I have always tried to solve all the house expenses. [My husband] is the one who contributes."* (Hope Lady, age 33). Qualitative and quantitative data diverged in this theme in that little change in perceived financial autonomy was observed in the interviews as it was in the survey results.

Relationship as an Outcome

Widened Social Network and Gaining Technology Skills

In the relational empowerment survey, all study participants responded either "agree" (n = 3, 16%) or "totally agree" (n = 16, 84%) that the number of social contacts within and outside the family has increased since working as a Hope Lady (RLT 1.a., **Table 2**). One study participant stated, *"They [the community women] comment on the program and they look for us, and they call us about this topic [of HPV self-sampling]. They call us, they leave our numbers, and other people who have never met call us, and you get to know more people."* (Hope Lady, age 45).

The widened social network was often discussed in the context of social media and technology skills development. Many study participants mentioned they had limited experience with social media or touchscreen phones before joining the Hope Project. One study participant stated, *"I didn't know how to use [a touchscreen phone] at all. And when I joined the Hope Project, it was practically indispensable. . . [the program administrators] themselves have taught me to use it, they have taught me to enter the page, to enter the data [. . .] I have learned everything about technology with the Hope Project, because before I didn't even care to pick up a phone, but now I do."* (Hope Lady, age 46). Another study participant stated, "*Social networks...the cell phone for me was nothing more like the phone that you go and answer, nothing at all! Now I know, well, I chat everything.*" (Hope Lady, age 33). The interview and the survey responses converged in that the combination of technological skills and the widened social network increased the Hope Ladies' sense of achievement.

Empowerment as the Mechanism of Action

We developed a causal pathway model for the Hope Project based on the mixed methods findings (**Figure 4**) that can be used for hypothesis generation and testing for the future. We designated the individual and collective improvement of resources, agency, and achievement as the pre-condition for the mechanism of empowerment to be activated because the Hope Ladies discussed how their collective identity of being a resource for their communities, improved self-confidence/efficacy through training and newly gained skills, and financial autonomy helped them to feel empowered in their work as Hope Ladies. We designated the perceived value of financial and relational incentives as cognitive moderators, as they "interact" with the mechanism of empowerment (e.g., widened social network leading to feeling more empowered). Logistical and sociocultural barriers to HPV testing were designated as organizational moderators because the participants discussed how they impacted the numbers of kits sold (e.g., the male-dominant culture in the community interfering with women's ability to buy the kits). The study participants discussed how financial and logistical accessibility was necessary to buy and sell the kits, therefore, we designated it as the pre-condition. We posit that the implementation strategy of microfinancing, training and peer-education operates through the process of Hope Ladies' empowerment to achieve increasing HPV self-sampling kit sales and cervical cancer screening in the Hope Project (proximal and distal outcomes, respectively), which can be tested in future research studies.

DISCUSSION

We evaluated the relational and financial empowerment of women participating in social entrepreneurship called the Hope Project in Peru using surveys and in-depth interviews and created a pathway model to inform future program direction and scaling of this community-based HPV self-sampling intervention. We found that the Hope Ladies individually and collectively experienced meaningful improvement of resources, agency, and achievement in varying degrees and forms, which expanded their capacity to make strategic and meaningful choices in their households and communities. Using a pathway model, we show how HPV self-sampling kit sales could be achieved through the

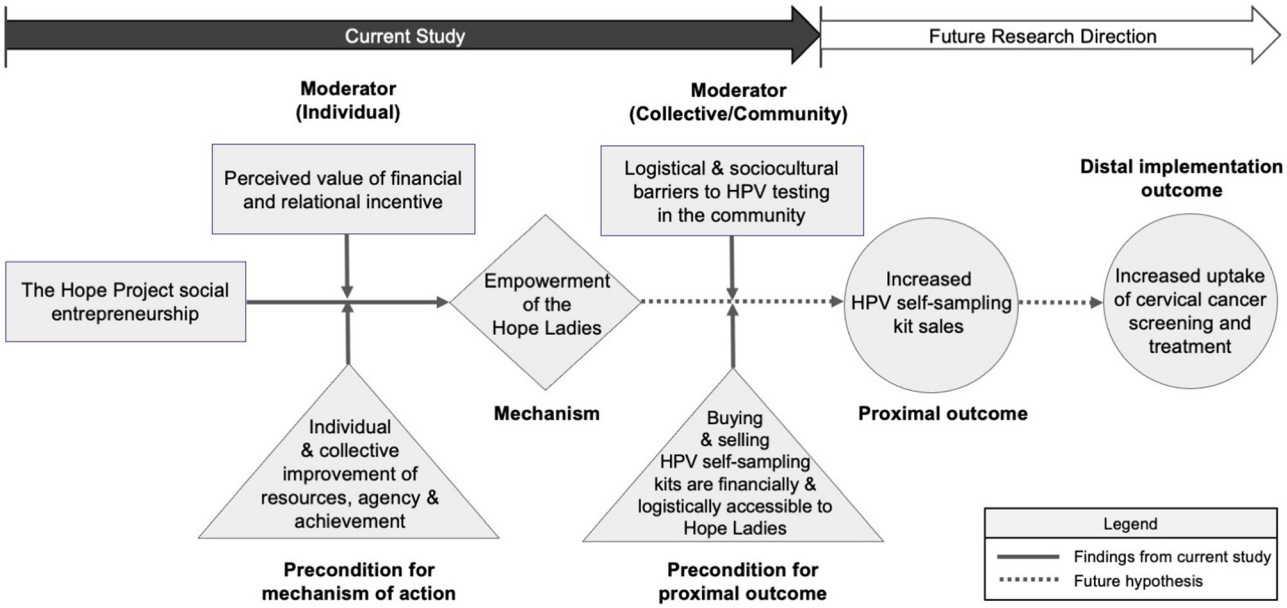

FIGURE 4 | Empowerment as the potential mechanism of action for the Hope Project.

empowerment of the Hope Ladies, which would function as the mechanism of action for the Hope Project.

There is strong evidence linking women's economic empowerment to improved health outcomes for both women and their families. Benefits include uptake of family planning, improved nutrition, and reduced maternal and child mortality (43). The social entrepreneurship model has been used successfully to create incentives for the uptake of health services and behavior change in the context of HIV (54, 55), syphilis (56), and malaria (57). Social entrepreneurship programs are uniquely positioned to empower women who are vulnerable to sexually transmitted infections such as HIV due to gender disparity in social structures and relationships, such as income inequality, violence, and educational opportunities (58, 59). For example, Haitian women who participated in a microfinance program were less likely to report partner infidelity and more likely to report condom use with their partners than those who did not participate in the program (60). A micro-grant intervention called the SHAZ! Project reported a significant improvement in economic security and decreased HIV risk factors such as transactional sex or gender-based violence among the adolescent female orphans in Zimbabwe (61).

As noted in the conceptual model, resources, agency, and achievements were interrelated and indivisible for the empowerment of the Hope Ladies in our study. The Hope Ladies reported that improved resources in the form of supplemental income improved their ability to participate in financial and household decisions. The recognition of the Hope Ladies as a community resource for reproductive health widened their social network and gave them more social capital. Increased knowledge, self-confidence, and expanded social network empowered the Hope Ladies to see and advocate for the women in their communities by speaking out against the unequal power relations with their spouses, disparate access to healthcare, and fear of stigma in being diagnosed with cervical cancer.

As we posit in our causal pathway, the relational and economic empowerment of the Hope Ladies may be necessary but not sufficient to produce the pre-conditions of financial and logistical means of buying and selling HPV self-sampling kits. For example, the empowerment of the Hope Ladies alone cannot protect their time against competing household priorities such as caring for another family member. Leveraging the social entrepreneurship structure by increasing their financial incentives or providing resources that could reduce conflicting household roles (e.g., childcare) would bolster their empowerment and protect the Hope Ladies' time to sell more kits which would modify the effects of the contextual moderators.

Our study has several limitations. Our sample size was small, and the number of respondents varied in some survey questions because the data collection took place during the week Peru closed its borders due to the COVID-19 pandemic. These factors may negatively impact the generalizability of our findings. Secondly, the interviews took place in the participants' homes, which may have biased their responses due to privacy concerns. Although the interviewers were fluent in Spanish and the Hope Project administrators were not present during the interview, the presence of other study personnel may have contributed to social desirability bias. Third, because some of the survey data were collected 1 year later virtually due to the country lockdown, this may have introduced more recall bias. However, because our sample size was small and the Hope Ladies have not been working in the communities since interviewing in accordance with the pandemic precautions, we took the opportunity to strive for data completion. Despite the limitations, we rigorously

evaluated the financial and relational empowerment of the Hope Ladies, using multiple well-established conceptual frameworks and mixed methods.

In conclusion, the participants in the community-based HPV self-sampling social entrepreneurship experienced improved financial and relational empowerment in the program. More research is needed to test and demonstrate the association between the Hope Ladies' empowerment and cervical cancer screening uptake by community members to scale this intervention to a broader population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was approved by the International Review Boards of Cayetano Heredia University (#103900), Duke University (#2020-0376), and University of Washington (STUDY00010676). All participants gave written consent in Spanish. All methods were carried out in accordance with relevant guidelines and regulations.

AUTHOR CONTRIBUTIONS

MS, PG, RB, and SG made substantial contributions to the conception and the design of the work. MD, MV, MC, and PG contributed to data acquisition. MS and MD conducted data analysis, interpretation of the data, and drafted the original manuscript. PG, NR, MK, KÁ, RB, SI, and SG provided substantial review and revision to the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.858552/full#supplementary-material

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Current Status of Human Papillomavirus Infection and Cervical Cancer in the Philippines

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Cervical cancer is estimated to cause 341,831 deaths each year, with 9 of 10 deaths occurring in developing countries. Over the past decade, there has been a significant increase in cervical cancer incidence among women in the Philippines. Persistent infection with high-risk human papillomavirus (HPV) is the well-established necessary cause of cervical cancer. Based on limited studies conducted in the Philippines, the prevalence of infection with any HPV genotype was 93.8% for cervical squamous cell carcinoma and 90.9% for cervical adenocarcinomas. HPV types 16 and 18 were the most common HPV genotypes among Filipino patients with cervical cancer. On the other hand, the incidence of HPV infection among Filipino women with normal cervices was 9.2%. The World Health Organization has launched a global agenda of eliminating HPV infection by 2030. One of its key milestones is to vaccinate 90% of girls with the HPV vaccine by 15 years. However, the HPV vaccination rate among Filipino women remains to be unsatisfactory. HPV vaccination has only been included in the Philippine Department of Health's community-based National Immunization Program in 2015. Despite these efforts, the Philippines currently ranks last on HPV program coverage among low-middle income countries, with coverage of only 23% of the target female population for the first dose and 5% for the final dose. The principal reason for the non-acceptance of HPV vaccines was the perceived high cost of vaccination. The low utilization of available cervical cancer screening tests such as Pap smear and visual inspection with acetic acid hampered the Philippines' control and prevention of HPV infection and cervical cancer. Among those diagnosed with cervical cancer in the Philippines, only an estimated 50% to 60% receive some form of treatment. To this end, we summarize the burden of HPV infection and cervical cancer on Filipinos and the risk factors associated with the disease. We present the current screening, diagnostics, treatment, and prevention of HPV-related diseases in the Philippines. Lastly, we also propose solutions on how each building block in health systems can be improved to eliminate HPV infection and reduce the burden of cervical cancer in the Philippines.

Keywords: human papillomavirus, cervical cancer, epidemiology, vaccination, screening, treatment, Philippines

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INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. Aside from causing anogenital warts, persistent infection with high-risk HPV genotypes is the well-established necessary cause of cervical cancer (1). It is estimated that 604,127 new cases of cervical cancer occur each year, 88% of which occur in low- and middle-income countries. Cervical cancer is also estimated to cause 341,831 deaths each year; 9 of 10 deaths occur in developing countries (2).

Currently, cervical cancer is the fourth leading cancer in women worldwide and the second most common cancer among women of reproductive age (2). Cervical cancer is a preventable disease, owing mainly to HPV vaccines, screening, and treatment for early premalignant lesions. Three HPV vaccines have been approved for clinical use—a quadrivalent vaccine derived from HPV types 6, 11, 16, and 18; a bivalent vaccine derived from HPV types 16 and 18; and a nonavalent vaccine that provides additional coverage to HPV types 31, 33, 45, 52, 58—to prevent cervical, vulvar, and vaginal cancers and their precancerous lesions. All three vaccines have been effective in decreasing infection rates of high-risk vaccine genotypes (3–5).

The World Health Organization (WHO) has launched a global agenda of eliminating HPV by 2030. One of its key milestones is to vaccinate 90% of girls with HPV vaccines by 15 years of age (6). Despite the availability of HPV vaccines since 2006, only 107 (55%) of the 194 WHO member states have introduced HPV vaccine in their national immunization program. The Americas and Europe are the regions with the most introductions (85 and 75%, respectively), whereas Asia and Africa have the least (40 and 31%, respectively) (7).

In the Philippines, 37.8 million women are at risk for cervical cancer. The country has an annual burden of 7,897 cervical cancer cases and 4,052 deaths (8). However, HPV vaccination has only been included in the Department of Health's community-based National Immunization Program in 2015 (9). This was followed by a school-based HPV vaccination program in pilot elementary schools launched in 2017 to reach school-age girls (10). Despite these efforts, the Philippines currently ranks last on HPV program coverage among low-middle income countries (7), with coverage of only 23% of the target female population for the first dose and 5% for the final dose (11). Thus, there is much to do to achieve the goal of HPV elimination. There is a need to strengthen monitoring of HPV infection and disease, assess the progress of HPV vaccination programs, and assess the impact of current treatment practices on the Filipino population. To this end, we summarize the existing data on the burden of HPV and cervical cancer on Filipinos and the risk factors associated with the disease. We present the current screening, diagnostics, treatment, and prevention of HPV-related diseases in the Philippines. Lastly, we also propose solutions on how each building block in health systems can be improved to meet the global HPV agenda.

HPV: THE NECESSARY CAUSE

The causal link of HPV infection with cervical cancer has long been established (12). HPV has a global prevalence of 11% in women without cervical abnormalities and 99.7% in women with cervical carcinomas (1, 13). There are numerous genotypes of HPV, causing anogenital and non-genital warts, but carcinogenesis is mostly seen in high-risk or carcinogenic genotypes. Specifically, HPV types 16 and 18 are responsible for at least 70% of cervical cancer cases worldwide, while HPV types 31, 33, 35, 45, 52 and 58 contribute around 20% of the cases (1, 11, 14). In the Philippines, a pioneer case-control study showed that HPV DNA was detected in 93.8% of squamous cell cervical carcinoma cases and 90.9% of cervical adenocarcinoma cases compared with 9.2% of controls. HPV type 16 was the most common genotype found in patients with cervical cancer, followed by HPV types 18 and 45 (15). HPV types 16 and 18 have a prevalence of 21.2% among those with low-grade squamous intraepithelial lesions (LSIL) determined *via* cervical cytology, 42.1% among those with high-grade squamous intraepithelial lesions (HSIL), and 58.6% among women with cervical cancer (7, 15). A more recent case-control study showed that 75% of cervical cancer patients were positive for HPV types 16, 18 or 52. On the other hand, 25% of patients with non-malignant cervices were also positive for HPV types 16, 18 or 52. HPV types 18 and 52 were only detected in cervical cancer patients and not in control (16).

Persistent infection by high-risk genotypes has been implicated in malignant transformation in cervical cancer, facilitated by viral oncoproteins E6 and E7 (17–19). Both proteins function in shifting the infected cell to a proliferative state needed to support viral replication. HPV E6 induces degradation of p53 *via* the ubiquitin-proteasome pathway, resulting in inhibition of apoptosis in the infected cell despite eventual accumulation of genetic mutations (17, 20). HPV E7, on the other hand, is associated with retinoblastoma protein (pRB) (21, 22). In a normal cell, pRB acts as a repressor of E2F, a critical factor in cell cycle progression from G1- to S-phase. Association of HPV E7 to pRB releases E2F, which acts as a transcription factor to activate cellular entry to S-phase (23, 24). Furthermore, the integration of viral genes into the host chromosome further contributes to continuous E6 and E7 expression, subsequent genomic instability, and accumulation of mutations (25).

While the mechanism behind progression of cervical intraepithelial neoplasia (CIN) 1 to CIN 3 remains unclear, it is hypothesized that increased expression of E6 and E7 by high-risk HPV genotypes influences cellular progression to carcinogenic phenotypes. This contrasts with the low E6 and E7 expression levels in CIN 1 lesions (13). Accumulated genomic disturbances in high-grade lesions also allow the integration of viral genomes into the chromosome of host cell. This leads to further destabilization of chromosomal areas and increased expression of HPV oncogenes (26, 27). Cells with integrated viral genomes lose multiple gene regulatory mechanisms, and clones are later selected for neoplastic growth (28, 29).

RISK FACTORS FOR HPV INFECTION AND CERVICAL CANCER IN THE PHILIPPINES

Cervical cancer is the second leading cancer among women in the Philippines despite being the fourth leading cancer among women globally, next to breast, colorectum, and lung cancers (30). This may be due to a higher prevalence of risk factors, which are related to increased exposure to HPV or decreased immunologic ability to clear the virus, or a lack of access to essential health services in the country (31). There are no extensive, consolidated studies investigating the burden of risk factors for cervical cancer in the Philippines. However, it is said that risk factors in the Philippines are like those reported in other countries (32). We summarized the potential host and environmental risk factors that contribute to persistent HPV infection and cervical carcinogenesis in Filipino women (**Figure 1**).

Microbial Risk Factors

Human immunodeficiency virus (HIV) infection is a significant risk factor for HPV infection, persistence, and associated cancers. This is related to suppression of the immune system, which usually clears HPV in most infected women, and increases the risk of exposure among sexually active adults (33). A meta-analysis showed that an estimated 33,000 new cases of cervical cancer, corresponding to 5.8% of new cases, occurred among women with HIV—a six-fold higher risk than those without HIV. This was lower in the Southeast Asia region, with 1.4% of new cases in people living with HIV (PLHIV) (34). However, this is of paramount concern in the Philippines since the country faces the fastest growing HIV epidemic in the Western Pacific region, increasing from 1 case per day in 2008 to 28 cases per day in 2022. In 2020, around 5% of the 16,700 new cases were females. There were around 115,100 PLHIV in the Philippines in 2020, which is estimated to rise to 331,500 by 2030 (35, 36).

Chlamydia infection caused by *Chlamydia trachomatis* is also an essential co-factor for cervical carcinogenesis. It can cause chronic inflammation, disrupt epithelial integrity, and induce cervical metaplasia. These effects may lead to HPV viral load enhancing, genome integration, and genomic instability, synergizing cervical cancer transformation (37). A hospital-based case-control study from 7 countries, including the Philippines, showed that the odds of squamous cell invasive cervical carcinoma was higher in *C. trachomatis* seropositive women (odds ratio (OR) 1.80; 95% confidence interval (CI) 1.22–2.66), which increased with higher *C. trachomatis* titers in women under 55 years of age (38). Another case-control study conducted on Filipino women showed no significant difference in the prevalence of other sexually transmitted infections (*Ureaplasma* spp., *Mycoplasma* spp., and *C. trachomatis*) between cervical cancer and control group (chronic cervicitis patients). However, this study showed that 22.73% of HPV-positive patients were co-infected with *Ureaplasma* spp. and 9.09% with *Mycoplasma* spp. (16).

Behavioral Risk Factors

HPV infection is a sexually transmitted infection, hence sexual behavior determines exposure to the virus (39). In the Philippines, around 12% of 15–19 years old were sexually active, increasing to 40% among 20–24 years old, and 47% among 25–27 years old (40). The median age at first sexual intercourse among women of reproductive age was 21.2 years in 2017. In this cohort, 18%, 56% and 73% engaged in sexual intercourse before the age of 18, 22 and 25, respectively (41). In addition, an interval of fewer than 3 years between menarche and coitarche may represent a critical time window for establishing persistent infection and the development of precancerous lesions. In one study, women who had their first sexual intercourse within 3 years of menarche had greater odds of cytologic abnormalities (OR 1.65; 95% CI 1.02–2.68) and CIN 2/3 or adenocarcinoma *in situ* (OR 3.56; 95% CI 1.02–12.47) (42). Proposed mechanisms for this include decreased cervical mucus from decreased progesterone during anovulatory cycles in the initial years following menarche, and elevated estrogen after puberty, which is accompanied by rapid changes in the squamo-columnar junction that increase susceptibility to sexually transmitted infections. The immature cervix may also have increased areas of metaplastic epithelium, thus posing greater vulnerability to HPV infection and neoplastic changes (42, 43).

Early age at first sexual intercourse is associated with an increased risk of HPV infection due to increased exposure and riskier sexual behavior such as having unprotected sex and having multiple sexual partners (39). A meta-analysis including 41 studies showed that the number of sexual partners was associated with the occurrence of non-malignant cervical disease (OR 1.82; 95% CI 1.63–2.00) and invasive cervical carcinoma (OR 1.77; 95% CI 1.50–2.05) (44). In the Philippines, around 34% of sexually active young Filipinos have multiple sexual partners, representing around 1.6 million in the 15–27 years cohort (40).

Age at first parity is a significant risk factor in cervical cancer (45). One possible mechanism being proposed is that during the first pregnancy, the transformation zone gains atypical features with neoplastic potential due to increased size and increased amounts of metaplastic epithelium, similar to changes and vulnerabilities of hormones and the cervix during menarche (42, 43). In a pooled analysis of case-control studies from eight developing countries, including the Philippines, there was an increased risk of cervical cancer as the age at first pregnancy decreased, associated with sexual activity. For those who had an age of sexual debut and first pregnancy on or before 16 years old, the OR was 2.36 (95% CI 1.82–3.07), while for those with coitarche and first pregnancy at 17–20 years old, the OR was 1.93 (95% CI 1.58–2.36) (39). This is of significant demographic repercussions in the Philippines as 15% of women aged 25–49 years were married by age 18, and 1 in 3 women were married by age 20. Childbearing came within 1 year of marriage, and 7% of women had their first birth by age 18 (41).

High parity is also considered a significant risk factor for cervical cancer, as shown in a multi-center study from eight case-control studies showing a direct association of high parity with HPV infection. The odds ratio for seven full-term pregnancies or

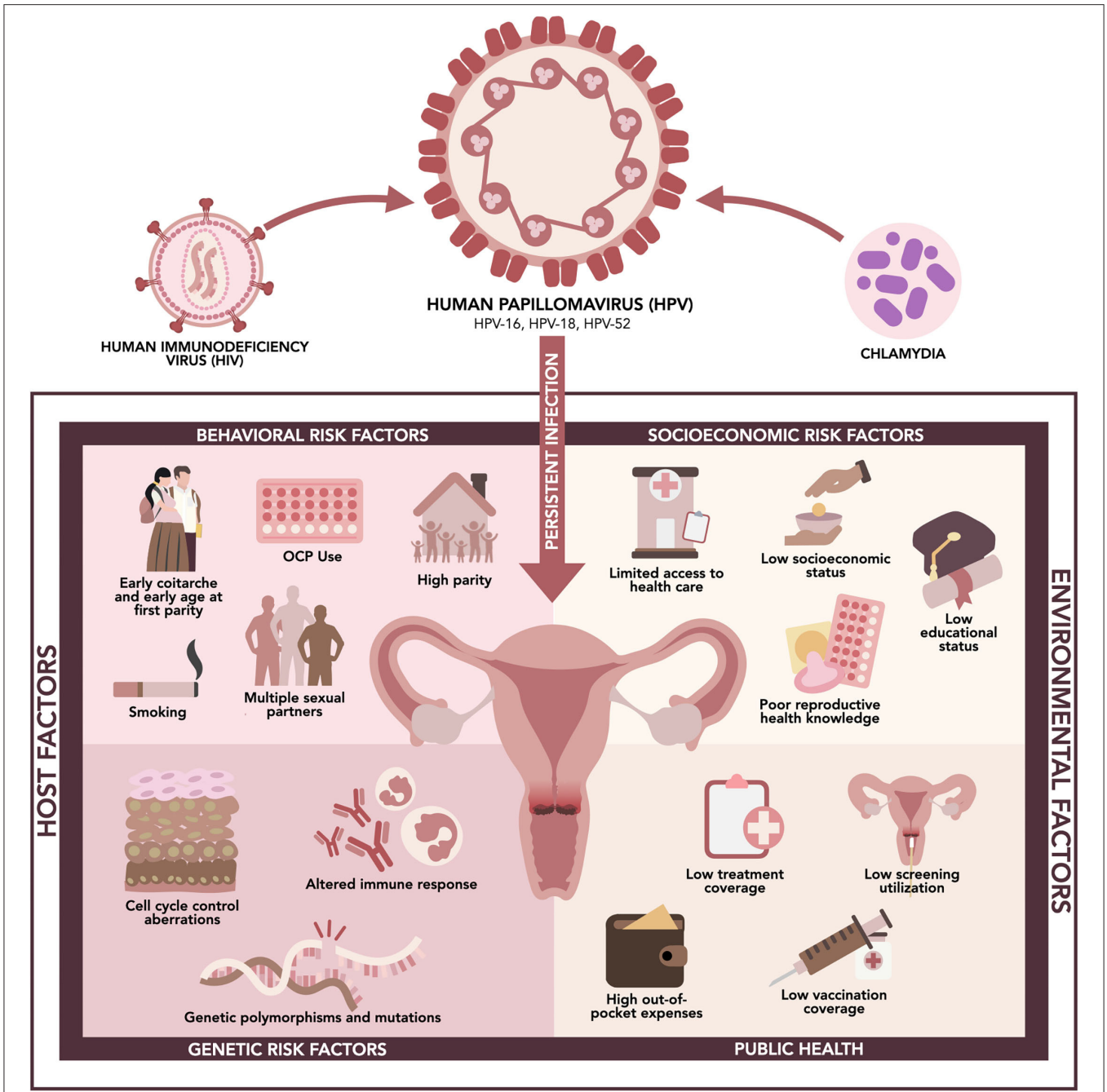

FIGURE 1 | Risk factors associated with high-risk HPV infection and cervical cancer in the Philippines.

more was at 3.82 (95% CI 2.66–5.48) as compared to nulliparous women, and 2.25 (95% CI 1.57–3.22) as compared to women with one or two pregnancies (45). This was consistent with another study where nulliparity served as a protective factor with a relative risk (RR) of 0.69 (95% CI 0.60–0.78) and 0.94 (95% CI 0.74–1.18) for squamous cell and adenocarcinoma, respectively, as compared to the RR of 1.50 (95% CI 1.43–1.59) and 1.36 (95% CI 1.22–1.52) for those with 3–4 full-term pregnancies, and 2.08 (95% CI 1.95–2.23) and 1.61 (95% CI 1.37–1.90) for those with ≥5 full-term pregnancies (46).

The use of oral contraceptive pills (OCP) is associated with an increased risk of invasive cervical cancer. This risk increases with increasing duration of use and declines after cessation of OCP use. In less developed countries, the use of OCP for 10 years from around age 20–30 was estimated to increase the cumulative incidence of invasive cervical cancer from 7.3 cases

per 1,000 women to 8.3 cases per 1,000 women by age 50 (31). A multi-center hospital-based case-control study, including the Philippines, reported an OR of 2.82 (95% CI 1.46–5.42) with 5–9 years of OCP use, increasing to 4.03 (95% CI 2.09–7.79) with 10 years of use or longer (47). A possible explanation is that sex steroids such as estrogen and progesterone may bind to transcriptional regulatory regions on the HPV DNA, which causes an increase in transcription of oncogenes. Since these hormones also interact with hormone receptors in cervical tissue, they may enhance the expression of E6 and E7 oncogenes of HPV (48, 49).

Smoking is a well-established risk factor for cervical cancer, as supported by several studies (31, 50–53). A pooled analysis of 10,577 women showed that current tobacco smoking is associated with a significant risk of HPV infection with an increasing OR as the number of cigarettes smoked per day increases compared with never-smokers. For <5 cigarettes, 5–14 cigarettes, and >15 cigarettes per day, the corresponding ORs were 1.21 (95% CI 0.95–1.54), 1.39 (95% CI 1.04–1.87), and 2.01 (95% CI 1.32–3.08), respectively (52). Another study showed higher HPV types 16 and 18 DNA load in current smokers (53). Possible mechanisms include direct exposure of DNA in cervical epithelial cells to components of cigarettes and abnormalities in the immune system of smokers, which may cause a substantial decrease in the number of Langerhans cells in the cervices of smokers (54). In the Philippines, around 5% of women of reproductive age smoke a tobacco product, of which 41% smoke <5 cigarettes daily, 23% smoke 5–9 cigarettes, 24% smoke 10–14 cigarettes, and 12% smoke more than 15 cigarettes. However, many women have secondhand smoke exposure: 28% were exposed to secondhand smoke inside the home daily, and an additional 8% were exposed on a weekly basis (41).

Genetic Risk Factors

Although the molecular mechanisms of HPV-associated cancer development are not well established, there have been several immune response genes from host innate immunity and adaptive immune response associated with regression, persistence, or progression of HPV. Since most individuals can eliminate the virus in 12–24 months without intervention, the role of host genetic differences will be deemed necessary in determining the risk of developing cancer. Polymorphisms and variations in these genes may confer susceptibility or prediction to the development of cervical cancer. However, these findings need further evaluation (55). To our knowledge, there was only one study from the Philippines that investigated these genetic factors (56).

Genes that interact with HPV E6/E7 oncoproteins have been investigated with cervical cancer development (55). Of particular importance is the role of mutations in the tumor suppressor gene *TP53* on HPV-related cancers. *TP53* codes for p53, a nuclear transcription factor which activates target genes that facilitate cell cycle arrest, allowing cells to either repair damaged DNA or undergo apoptosis in the presence of irreparable DNA damage (57, 58). It plays a key role in almost all cancers by regulating and maintaining genomic integrity, and it is reported that over 50% of human cancers carry loss-of-function mutation in p53 (57). The ability of E6 oncoprotein to cause degradation of p53 is important in the survival of HPV-positive neoplastic cells. Indeed, this is a special feature of high-risk HPV types and is seldom associated with malignant lesions in low-risk HPV genotypes (59). A meta-analysis by Tornesello et al. (59) which included 1,353 cervical tumors found that non-synonymous mutations in the DNA-binding domain of *TP53* were found in 13.3% for adenocarcinoma and 5.9% in squamous cell carcinoma (59). The mutations in codons 175, 248, and 273 were commonly mutated in both types of cervical cancers. Additionally, the frequency of *TP53* mutations was highest in Asians at 19% compared to those in North America at 4% (59). However, there are no studies from the Philippines that investigate the frequency of *TP53* mutations in cervical tumors. Aside from *TP53* gene, polymorphisms in breast cancer susceptibility gene 1 (*BRCA1*), BRCA1-associated ring domain protein 1 (*BARD1*) gene, primary microRNA-218 (*pri-miR-218*), and laminin-5 β3 (*LAMB3*) were also associated with increased risk of cervical cancer (55, 60–62).

Pro-inflammatory cytokines, including interleukin 1-beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin 12 (IL-12), have been implicated in cervical carcinogenesis (55, 63–67). Interestingly, IL-10, an anti-inflammatory cytokine, and B-cell proliferation factors have also been associated with the risk of cervical cancers (55, 68, 69). Polymorphisms in human leukocyte antigen (HLA) genes have also been associated with cervical cancer risk (70). HLA is critical in presenting viral antigens and in inducing of adaptive immune response (70, 71). A variant allele of *IFNG* gene coding for interferon-gamma (IFN-γ), which is essential in defense against viruses and intracellular pathogens and induction of immune-mediated inflammatory responses, has also been associated with increased cervical cancer risk (55, 72). Studies have also identified polymorphisms of *CTLA4* gene associated with increased cervical cancer risk. Cytotoxic T-lymphocyte associated protein 4 encoded by *CTLA4* gene functions as an immune checkpoint and downregulates immune responses (73, 74).

Previous reports showed the association of several gene mutations and polymorphisms with poor prognosis of cervical cancer. *PIK3CA* mutation is associated with poor treatment response and low survival rate, while *MDM2* is associated with the development of cervical cancer and poor prognosis (59, 75). A previous case-control study in the Philippines showed that the *PIK3CA* gene was found mutated in 10.71 % of cervical cancer patients. Around 28.57 % of HPV-negative cervical cancer patients were positive for *PIK3CA* mutation, and 4.76 % tested positive for this mutation among the HPV-positive cervical cancer patients. *MDM2* SNP309 analysis revealed that TG genotype ($p = 0.03$; OR 0.18; 95% CI 0.04–0.76) was associated with lower cervical cancer rates than TT genotype (56).

Sociodemographic Risk Factors

Often, socioeconomic factors (e.g., income, education, and occupation) are overlooked health factors. However, the most fundamental causes of health disparity can be attributed to socioeconomic inequalities (76). Socioeconomic status underlies three significant determinants of health: access to, use of, and

quality of health care; environmental exposure, and health behavior (77).

Poor accessibility of health care is reflected in the high mortality of patients with cervical cancer. The Philippines has the fourth highest age-standardized mortality rate in Southeast Asia with 7.89 per 100,000 women per year, next to Myanmar and Indonesia (14.4), Timor-Leste (8.76), and Cambodia (8.33) (8). This rate is higher than the global age-standardized mortality rate of 7.3 per 100,000 women (30). The overall 5-year survival rate for cervical cancer in the Philippines was reported to be 44%. The low survival rate was attributed to cancer being diagnosed at later stages, in addition to treatment being unavailable, inaccessible, or non-affordable (32, 78). This may be reflective of the poverty incidence in the Philippines estimated at 23.7% or 26.14 million Filipinos who live below the poverty threshold of around PHP 12,082 (USD 232) on average for a family of five per month, as of the first semester of 2021(79). Furthermore, with out-of-pocket expenditure comprising 44.7% of health financing in the country as of 2020, any health-related concerns may lead to financial catastrophe and impoverishment, thus serving as a massive barrier to health in many Filipinos (76, 80).

Related to health care access is health-seeking behavior and health literacy, as they are also intimately linked to socioeconomic factors. Health literacy is described as the ability to access, understand, appraise, and apply health information in terms of health care, disease prevention, and health promotion (81). According to the maiden National Health Literacy Survey, 51.5% have limited health literacy, reflecting the inadequate and poor distribution of health care services and high cost of healthcare in the country (81). It was also shown that the proportion of people with limited health literacy increased with decreasing levels of educational attainment. This is further seen in a community cross-sectional study on the knowledge, perceptions, and screening behavior on cervical cancer in rural health centers in the Philippines, which showed that only 13.9% of participants had ever had cervical cancer screening (82). The majority of those who had never had cervical screening were higher among those with no formal or primary education, currently unemployed, and household monthly income of less than PHP 5,000 (USD 96). Furthermore, the most common reasons listed for not having screening are lack of money, no signs or symptoms, misconceptions about the procedures, and have never heard or do not understand the meaning of cervical cancer screening (82). In the country, we note that the estimated cost of screening is PHP 1,000 (USD 19), which often requires two to three hospital visits for a pap smear. This limits the access to screening utilization and as such, it is significantly associated with higher education status and financial capability. Vaccination for HPV is also expensive with an estimated cost of PHP 2,400 (USD 46) per vaccinated person (83). Thus, it comes as no surprise that socioeconomic disparities become barriers to essential preventive measures against HPV infection and cervical cancer in the country.

Finally, the social environment, which is greatly affected by socioeconomic status, largely affects the behavioral risk factors for HPV infection as previously discussed above. The risk of sexually transmitted infections may increase due to lack of access to condoms and health education, and early pregnancy and marriage are related to education (40). According to WHO, two out of ten young women gave birth before age 20 in the Philippines, and this was increased to four out of 10 among less-educated women. Out-of-school youth, which is primarily concentrated in urban areas, have a higher risk of teenage pregnancy; however, rural women are twice as likely to become pregnant (40).

Overall, there is a lack of local studies that portray how sociodemographic disparities directly contribute to the high burden of cervical cancer in the Philippines. However, their proxy variables, e.g., low income and educational attainment, high poverty incidence, and poor health literacy, may reflect how women of lower socioeconomic status in the country are rendered more vulnerable to cervical cancer.

PREVENTION STRATEGIES TO ADDRESS HPV INFECTION AND CERVICAL CANCER IN THE PHILIPPINES

Current Cervical Cancer Screening Strategies and Challenges in the Philippines

The 5-year survival rate for cervical cancer is 44% due to most cervical cancers being diagnosed in an advanced stage, remaining unchanged between 1980 and 2010; thus, it is crucial to screen for cervical cancer and intervene before the onset of symptoms (83). Cervical cancer screening aims to identify and remove high-grade cervical intraepithelial neoplasia that may be precursor lesions to cancer (84). Currently, there are three methods employed to screen women: cervical cytology, primary human papillomavirus testing, and co-testing. Cervical cytology assesses pathologic changes in cells obtained from the cervix under a microscope (84). Cervical sample obtained for cytology can be fixed directly onto a glass slide (i.e., conventional cytology), or suspended in a transport medium (i.e., liquid-based cytology). Although there is no significant difference in specificity and sensitivity between conventional and liquid-based cytology, the latter provides an added benefit of doing HPV testing and/or genotyping, especially when the result is equivocal (85). Pathologic changes along with non-neoplastic findings such as atrophy or reactive cellular changes are reported *via* the Bethesda system (86). Depending on the results and 5-year risk estimate for developing CIN 3+, patients can be managed *via* immediate treatment with excisions such as loop electrosurgical excision procedure, colposcopy, or surveillance of varying intervals (87).

Since virtually all cervical cancer cases are caused by high-risk HPV, primary HPV testing alone is gaining traction as an acceptable screening method given that HPV testing is more sensitive than Pap smear test, with a small decrease in positive predictive value (88, 89). Currently, there are two primary HPV tests approved by the United States Food and Drugs Administration: Roche Cobas HPV approved in 2014, and BD Onclarity HPV approved in 2018. Cobas HPV assay allows specific identification of HPV types 16 and 18, and pooled detection of HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58,

59, 66, and 68 (90). On the other hand, BD Onclarity HPV assay allows individual identification of HPV types 16, 18, 31, 45, 51, and 52, and concurrent detection of other high-risk HPV types into three groups: 33/58, 35/39/68, or 56/59/66 (91). Lastly, co-testing is a method that combines both cervical cytology and HPV testing. Although co-testing identifies the same number of CIN3+ lesions as HPV testing alone, co-testing has worse specificity and positive predictive value, which in turn requires more colposcopies, hence providing evidence that primary HPV testing may suffice as a cervical screening method (92).

Table 1 shows the current screening guidelines for average-risk women. The latest Clinical Practice Guidelines for the Obstetrician-Gynecologist by Society of Gynecologic Oncologists of the Philippines (SGOP) still includes the 2012 guidelines by Philippine Society for Cervical Pathology and Colposcopy (PSCPC), which contrasts it with the 2012 guidelines by American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP) and American Society for Clinical Pathology (ASCP) (93, 94). The most updated guidelines were released by the American Cancer Society in 2020, with the following significant changes: (1) primary HPV testing as the preferred screening method, and (2) age of first screening changed from 21 to 25 years due to low cervical cancer incidence and mortality, high incidence of transient infection with HPV, higher risk of adverse obstetric outcomes should a lesion be treated, and favorable benefit-to-harm balance as a result of delaying the age of first screening (95).

Visual inspection with acetic acid (VIA) is an acceptable alternative approach to pap smear in low-resource settings. It is a simple test with locally available supplies and can be performed by trained health workers. The result is immediate, appearing as acetowhitening, which allows VIA to be combined with treatment procedures for early cervical lesions such as cryotherapy (96, 97). Numerous studies have been conducted in the Philippines establishing VIA as more sensitive but less specific than pap smear in detecting precancerous lesions (98, 99). In addition to its utility, this screening approach is favored by developing countries because shifting from pap smear to VIA would result in lower healthcare costs with higher health benefits (100). Thus, given its validity and cost-effectiveness, VIA was adopted to be the initial screening approach in the Philippine setting in 2005, with colposcopy with a pap smear or biopsy as confirmatory test following positive VIA. Indeed, in a cost-utility analysis which looked at epidemiologic, cost, and clinical parameters specific to the Philippines from a health systems perspective, high VIA coverage targeting women aged 35–45 years at five-year intervals was found to be the most efficient and most cost-saving screening strategy, reducing cervical cancer cases and deaths by 25% (83).

Despite the introduction of pap smear in the Philippines during the 1990s and subsequent promotion of VIA as an alternative screening approach to a pap smear in 2005, screening utilization remains low. In a household health survey done in 2003, the estimated coverage of cervical cancer screening in women aged 18–69 was 7.7%, with 9.3% coverage in urban areas and 5% coverage in rural areas (101). More recent data showed better yet dismal coverage. In a cohort of women aged 25–55 years residing in an urban area, only 36.8% had undergone pap smears at least once, despite 82.9% being sexually active (102). Among women aged 26–35 years consulting at a private hospital in greater Manila area and a public hospital in southern Philippines, only 48% of the women had undergone pap smear at least once, with even fewer women (31%) undergoing routine pap smear tests (103). Utilization of cervical cancer screening services is even lower in rural areas: a community-based found that only 13.9% of participants had ever had cervical cancer screening, despite 93.8% having heard of screening (82). A health systems survey showed that the average annual coverage of cervical cancer screening using VIA in the urban group consisting of major cities in Metro Manila was 5.50%, while the coverage in the rural group consisting of municipalities in Albay province southeast of Manila was 0.39% (104).

Among the factors identified that can be attributed to the failure of cervical cancer screening were (1) lack of knowledge about symptomatology of cervical cancer, (2) perception that cancer is fatal and lack of awareness that cervical cancer is treatable, (3) unavailable screening and treatment facilities and expertise, and (4) inconsistent patient adherence to follow-up consults and treatment (105). There are also misconceptions regarding cervical screening. In a study which included 400 women aged 26–35 years of age consulting outpatient a private hospital in greater Manila area and a public hospital in southern Philippines, more women believed that pap smear is done for detecting lower genital infections (75%) than pap smear being done for detecting cervical changes that may lead to cancer (57%) (102). Although 64% agreed that sexually active women should undergo a pap smear test, 52% thought it should only be done when women present with symptoms. Only 67% believed that pap smear tests should be done annually. There was also a discrepancy between attitude and practices regarding pap smear: despite the majority agreeing that women should undergo pap smear tests, only 48% had pap smear tests at least once, and 31% had routine testing (102).

Given the burden of disease in the Philippines, the national government, through the Department of Health and local government units, has started advocating for cervical cancer screening starting in 1999 (32, 106). Advocacy to raise awareness regarding cervical cancer prevention was initiated in 2003 *via* Proclamation No. 368, which declares May as Cervical Cancer Awareness Month (107). As part of the Philippine Cancer Control Program, an organized nationwide Cervical Cancer Screening Program was established in 2005 *via* Department of Health Administrative Order 2005–2006, which included public information and health education, sustainable capacity building, and training and professional education of health workers on case-finding with VIA, and diagnosis with the use of pap smear and colposcopy (106). The national recommendation is to target screening women aged 25–55 years *via* VIA every 5–7 years. In 2020, as part of the effort to ensure equitable access to primary care services, the state-owned Philippine Health Insurance Corporation (PhilHealth), which is responsible for implementing universal health coverage, started coverage of basic outpatient services including pap smear (108). However,

TABLE 1 | Latest cervical cancer screening guidelines for average-risk women.

Population	2012 Guidelines PSCPC (89)	2012 Guidelines ACS-ASCCP-ASCP (90)	2020 Guidelines ACS (91)
<21	No screening	No screening	No screening
21–24	Conventional cytology every year OR Liquid-based cytology every 2 years	Cytology alone every 3 years	No screening
25–29	Conventional cytology every year OR Liquid-based cytology every 2 years	Cytology alone every 3 years	Primary HPV testing every 5 years (preferred) OR Co-testing every 5 years OR Cytology every 3 years
30–65	Conventional cytology every year OR Liquid-based cytology every 2 years	Co-testing every 5 years OR Cytology alone every 3 years	Primary HPV testing every 5 years (preferred) OR Co-testing every 5 years OR Cytology every 3 years
Above 65	Conventional cytology every year OR Liquid-based cytology every 2 years OR Co-testing every 5 years Women with a history of CIN2 or worse should continue screening for at least 20 years	No screening if with: (1) 3 consecutive negative prior screening results. (2) 2 consecutive negative co-testing results within the past 10 years. The most recent test should be within past 5 years. Women with a history of CIN2 or worse should continue screening for at least 20 years	No screening if with: (1) no history of CIN2+ within the past 25 years (2) documented adequate negative prior screening in the past 10 years, which may be either: a) 2 consecutive negative HPV tests b) 2 consecutive negative co-tests c) 3 consecutive negative cytology tests Continue screening as previously described until cessation criteria are met in individuals without conditions limiting life expectancy without sufficient documentation of prior screening
After hysterectomy	No screening if without history of CIN2+ or cervical cancer in the past 20 years	No screening if without history of CIN2+ or cervical cancer in the past 20 years	No screening if without history of CIN2+ in the past 25 years or cervical cancer ever

an assessment of health facilities in Metro Manila and Albay province showed a disparity in the implementation of cervical cancer screening between urban and rural areas (104). Although most health facilities in both urban and rural groups are oriented to Cervical Cancer Screening Program, only 31.25% of the facilities in the rural group had a screening protocol, compared to 100% of urban facilities. All facilities in the urban group provided screening services, while only 4 out of 16 facilities in the rural group were screening providers. Despite facilities in both urban and rural groups having available instruments for cervical screening, the trained health personnel-to-population ratio in the rural group was 1:1,751, compared to 1:699 in the urban group. As a result of the decentralization of the health system, financial support for the screening program was reliant on the local health budget. Majority of the facilities in rural areas had no budget item for screening instead of relying on the general budget for health (104).

Various strategies were done in selected places to improve the utilization rate, but these are yet to be implemented nationwide. Opportunistic screening programs where cervical cancer screening is offered to patients in the waiting area during regular health consultation services can be utilized to encourage women. In a study done in a public tertiary hospital, implementation of a month-long opportunistic screening program increased the utilization rate of cervical screening from 2 to 27%, with most women availing of screening being married, with high school education, multiparous, had no previous screening, and was not knowledgeable about cervical cancer (109). Health education is also important: in a cohort of female secondary school teachers from a rural area, providing a lecture increased acceptance of VIA from 0 to 78%, with 71.4% of the participants submitting themselves to free VIA testing following the lecture (110). In a large-scale setting, however, a public health education program that is geared toward identifying factors that facilitate or inhibit consultation and developing a community intervention program to improve screening compliance is essential. Using the Health Decision Model to explain health-seeking behaviors (111), the best predictors of compliance to pap smear screening were found to be civil status, level of education, number of children, family history of cancer, and perceived risk of cancer, while cost was a critical inhibiting factor (112). Using the perceived risk of having cancer as a basis, implementing a health education program increased pap smear consultations. In summary, a focused information education must be coupled with accessible and well-equipped screening centers to ensure the success of any nationwide cervical cancer screening program.

Cervical Cancer Prevention *via* HPV Vaccination

Currently, three prophylactic HPV vaccines are registered with the Philippine Food and Drug Administration: Cervarix, a bivalent vaccine produced by GlaxoSmithKline that prevents HPV types 16 and 18 (4); Gardasil, a quadrivalent vaccine produced by Merck that prevents HPV types 6, 11, 16, and 18 (3); and Gardasil-9, a nonavalent vaccine produced by Merck that prevents against HPV types 31, 33, 45, 52 and 58 in addition to the coverage of Gardasil (5). All three HPV vaccines are given intramuscularly, with two doses administered at 0 and 6 months to persons aged 9–14 years and three doses administered at 0, 2, and 6 months to persons aged 15 years

and older. Cecolin, a bivalent vaccine, which has been licensed in China, is currently undergoing World Health Organization prequalification process (113).

At a population level, HPV vaccination has been found to reduce the prevalence of high-risk HPV types, anogenital warts and high-grade cervical abnormalities, as evidenced by a meta-analysis of 65 studies involving 60 million individuals who followed up for 8 years (114). The prevalence of HPV types 16 and 18 declined by 83% (RR 0.17, 95% CI 0.11–0.25) and 66% (RR 0.34, 95% CI 0.23–0.49) in girls aged 13–19 years and women aged 20–24 years, respectively, while the prevalence of HPV types 31, 33 and 45 also decreased by 54% (RR 0.46, 95% CI 0.33–0.66) in girls aged 13–19 years. HPV vaccination was also a protective factor for two clinical outcomes: (1) anogenital warts, with RRs of 0.33 (95% CI 0.24–0.46) and 0.46 (95% CI 0.36–0.60) in girls aged 13–19 years and women aged 20–24 years, respectively; and (2) CIN 2+ with RRs of 0.49 (95% CI 0.42–0.58) and 0.69 (95% CI 0.57–0.84) in girls aged 13–19 years and women aged 20–24 years, respectively (114).

Prior to the widespread introduction of HPV vaccines in the Philippines, the acceptability of these vaccines was determined in various studies. In an exploratory study involving 195 women consulting at charity clinics in a tertiary hospital with daughters aged 12–15 years, HPV vaccination was acceptable to 75.4% of women despite only 56.4% identifying HPV as a sexually transmitted infection and 31.8% associating HPV with cervical cancer (115). In a cohort of female adolescents aged 14–19 years consulting at a pediatric specialty hospital, 53% heard about the HPV vaccine, and the majority were willing to get vaccinated if given free (116). A study involving commercial sex workers (CSWs) in Angeles City, Pampanga province, reported that despite 87% having poor practices on cervical cancer prevention, which were attributed to inadequate knowledge and poor health-seeking behavior, the majority of the CSWs have favorable attitudes regarding HPV vaccination (117). The principal reason for the non-acceptance of HPV vaccines was the perceived high cost of vaccination. A community-based study involving 435 adult women reported that HPV vaccine acceptance was contingent on affordable pricing, with 54% accepting at a low price and only 30% and 31% accepting at a moderate and high price (118). Vaccine acceptance was lower in men, with 22–39% of men aged 18–31 years old accepting of HPV vaccination. However, it remained contingent on affordable pricing (117). Other reasons included young age, painful injection and sexual inexperience for pediatric patients aged 10–19 years, and concern that HPV vaccination could promote unsafe sexual behaviors (115).

In 2015, the national HPV immunization program was partially introduced in the Philippines with either bivalent or quadrivalent vaccine through Department of Health Memorandum No. 2015-0316 (9). Initially a community-based immunization program, the government changed the protocol to a school-based immunization program targeting young girls aged 9–14 years to ensure high coverage and minimal dropout rate. Despite being free, which was the predominant factor affecting vaccine acceptance (115, 118, 119), the Philippines still ranked last among low- to middle-income countries on HPV program coverage (7). As of 2020, 23% of the female target population received the first dose of the HPV vaccine, virtually unchanged from 2019, while 5% received the last dose, up from 3% (11). Due to the coronavirus disease 2019 (COVID-19) pandemic, which resulted in suspension of in-person classes for most of 2020 and all of 2021, strategies to continuously provide immunization service such as having stations at permanent health facilities or temporary posts at multi-purpose town halls, and door-to-door approach are being employed (120). Once in-person classes resume, the program will be reverted to school-based immunization.

There are limited studies assessing the implementation of the national HPV immunization program. A cost-effectiveness analysis done in 2017, which has yet to be taken into consideration by the implementing health agency, found that the 2-dose bivalent HPV vaccine administration to 13-year-old Filipino girls prevented additional 986 cervical cancer cases and 399 deaths from cervical cancer, with 555 additional quality-adjusted life-year compared to the 2-dose quadrivalent vaccine (121). It also would result in lower health costs, saving PHP 228.1 million (approximately USD 4.4 million). Studies assessing health systems and socio-cultural determinants affecting intent to vaccinate are needed to understand gaps in implementation resulting in low HPV vaccination coverage better.

TREATMENT OF PERSISTENT HPV INFECTION AND CERVICAL CANCER IN THE PHILIPPINES

A persistent HPV infection is defined as having positive HPV tests at two consecutive time points: at baseline and on follow-up. The minimum duration to classify a woman as having persistent HPV infection varies across studies, with 30% using <6 months as minimum duration, 45% using 6–12 months, and 25% using more than 12 months (122). Type-specific HPV persistence (testing positive for the same HPV type), especially with high-risk HPV, is associated with treatment failure resulting in incomplete removal of HPV infection, recurrent cervical intraepithelial neoplasia (CIN), or progression to cancer. This should be differentiated from an incident HPV infection, a re-infection with a new HPV type not associated with the primary cervical lesion. Routine HPV testing after treatment of CIN 2/3 is recommended for early detection of disease recurrence or progression since these high-grade lesions are associated with 60–80% of persistence (123, 124).

A systematic review of 45 studies involving over 6,000 women showed a decline in median post-treatment HPV persistence with increasing follow-up time (123). Reported post-treatment HPV persistence estimates varied depending on treatment type, patient age, HPV type grouping, HPV detection method, and minimum interval between the two testing points to define HPV persistence. CIN treatment successfully removed HPV from the cervical tissue, but this does not preclude cases where HPV is still present in the vaginal mucosa and may cause re-infection of the cervix during follow-up. None of the included studies evaluated the vaginal/vulvar HPV prevalence after treatment.

Overall, when considering the type of treatment, conization and loop electrosurgical excision procedure (LEEP) were able to clear HPV infection within 12 months of procedure better than cryotherapy (123).

Another review included 86 studies providing data on over 100,000 women (125). The investigators found that persistence varied across studies but was primarily mediated by study region and HPV type. HPV types 16, 31, 33, and 52 were the most persistent genotypes with a weighted median duration of HPV detection of high-risk HPV (9.8 months), persisting longer than low-risk HPV (8.4 months). HPV type 16 persisted the longest at 12.4 months and is reported as the most critical risk factor for recurrence. HPV-positive women with normal cytology had a median duration of 11.5 months for any HPV type in general, and 10.9 months for high-risk types (125). Since half of HPV persistent infections persist past 6–12 months, repeat HPV testing at 12-month intervals would be able to identify women at increased risk for CIN 2/3 due to these persistent infections.

Several studies could not find sufficient evidence from randomized controlled trials to provide the best post-treatment surveillance strategy (126, 127). While high-risk HPV testing is more sensitive than follow-up cytology for detecting post-treatment high-grade lesions; there is currently no consensus on how this may be best applied. Studies on algorithms for post-treatment HPV testing should consider the testing interval, follow-up time, number of post-treatment tests, and assays used.

Treatment of HPV persistent infections according to the American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines emphasize a risk-based strategy aligned with current knowledge on HPV natural history and cervical carcinogenesis (87). More frequent surveillance, colposcopy, and treatment are recommended for high-risk patients, while low-risk patients may have a deferral of colposcopy and follow-up at longer surveillance intervals with a return to routine screening. The type of HPV and duration of infection will determine the patient's risk with CIN 3. Current results combined with history and the immediate CIN 3 risk for each patient are examined. A risk >4.0% will require colposcopy or treatment (87). Excisional treatment such as LEEP, cold knife conization and laser cone biopsy is preferred over ablation treatment such as cryotherapy, laser ablation and thermoablation. This risk-based strategy is a challenge to implement in the Philippines as cytology-based testing remains the most frequent screening modality, and actual figures for HPV-based testing based on a broader sample population that is more representative of the current Philippine situation have not been reported (8).

In their clinical practice guidelines, the Society of Gynecologic Oncologists of the Philippines (SGOP) advises post-treatment monitoring after 6 months then annually for 3 years. They further support the use of vaccination against HPV types 16 and 18 as efficacious against persistent HPV infection and CIN 2/3 (93, 128, 129). Due to the ongoing COVID-19 pandemic, local consensus statements on cytology screening and colposcopy have reduced testing to only cases where immediate action is necessary, making it difficult to perform studies that will further elucidate factors involving HPV persistence in the population (130).

Evidence supports post-treatment or therapeutic vaccination to reduce the risk of clinical disease relapse after treatment (131). A study by Ferris et al. further suggests that women older than the age typically targeted by HPV vaccination programs are at risk for incident and incident-persistent HPV anogenital infections, depending on sexual behavior. The latter calls for a possible recalibration of algorithms to include older women for primary and secondary (post-treatment) vaccination (132). Other modes of treatment for persistence still under investigation include antivirals (i.e., cidofovir) and immunomodulators (i.e., imiquimod) (133).

Moreover, newer studies have also uncovered the beneficial effect of the cervicovaginal microbiome, precisely certain *Lactobacillus* spp., in inhibiting cellular cervical pathogenesis by producing bacteriocins, lactic acid, and hydrogen peroxide. Ongoing studies may soon further elucidate the underlying physiology of microbe- and host-microbe interactions with HPV infection (134, 135).

Cervical cancer is diagnosed *via* histopathologic examination of tissue obtained from suspicious-looking cervical mass *via* biopsy (136). Since 2018, imaging studies such as radiography, ultrasound, computed tomography, magnetic resonance imaging may be used in addition to clinical examination in assigning cancer stage. Depending on the stage, cervical cancer is managed *via* surgery, radiotherapy, chemotherapy, or a combination of the three modalities. Specifics of clinical management of cervical cancer were comprehensively discussed in 2018 International Federation of Gynecology and Obstetrics (FIGO) Cancer Report, with an update published in 2021 (136, 137).

In the Philippines, only an estimated 50–60% of cervical cancer patients receive some form of treatment (138). Given that 23.7% of Filipinos live below the poverty threshold, and that 44.7% of health financing in the country comes from out-of-pocket expenses, seeking treatment may be economically catastrophic to many Filipinos (76, 79, 80). Recognizing the massive financial risk, various financial risk protection mechanisms were set in place by numerous government agencies over the years. PhilHealth covers cancer treatment as part of its Z Benefit Packages for Cancer (139). Medicines for gynecologic cancers including cervical cancer not covered by PhilHealth will be given for free *via* the Cancer, Supportive Care and Palliative Care Medicines Access Program (CSPMAP). This program is funded by the Cancer Assistance Fund, established under Republic Act 11215 or the National Integrated Cancer Control Act passed in 2019 (140). Indigent and financially incapacitated patients can avail of medical and financial assistance in accordance with Republic Act 11463 (141).

CONCLUSION

Although the Philippines has achieved significant milestones in the control and prevention of cancer, such as passing the National Integrated Cancer Control Act (NICCA) in 2019 (142), cervical cancer and other cancers related to HPV infection remain important public health problems in the country. Primary

and secondary cervical cancer prevention activities are still implemented locally in the Philippines, with no established national programs on cervical cancer screening and HPV vaccination. Cervical cancer-related services are not widely available in local health centers or units, particularly outside the main urban centers (143). To achieve WHO-specified country targets for cervical cancer and HPV infection by 2030, health policy reforms guided by locally derived research findings should be implemented.

With the information collated and analyzed in this review, we propose the following national research agenda related to cervical cancer and HPV infection in the Philippines. First, implementation research should be done to develop a locally applicable system on how to implement a national program on cervical cancer screening and HPV vaccination. These include highlighting opportunities and addressing challenges in quality of health service delivery, availability of medical supplies including vaccines and screening materials, presence of trained health personnel to administer the services, establishment of a national registry that can provide timely data to implementers and policymakers, and cost-effectiveness of different interventions (144). Second, epidemiological studies should be done to give locally derived data on community-based prevalence, and genotype distribution of HPV infection in women and men since most data in the Philippines are from hospital-based studies. To address this research gap, we are currently conducting a community-based cohort study among Filipino women in rural and urban Philippines to determine the HPV prevalence and genotype distribution and identify factors influencing the acquisition, clearance, and persistence of HPV infection. This study will update the more than 20-year-old data on the population-based prevalence of HPV infection that can be used to strengthen health policies and programs on cervical cancer and HPV infection (83). Third, clinical research on the cost-effectiveness and effectiveness of different traditional and novel treatment strategies should be done to guide the Philippine Health Insurance system on what treatment options should be included in their packages. Lastly, social science studies should also be prioritized to provide data on the perception and acceptability of the different interventions on the target population.

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Changes in High-Risk HPV Infection Prevalence and Associated Factors in Selected Rural Areas of China: A Multicenter Population-Based Study

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Background: The Chinese government has taken action to prevent cervical cancer by implementing the National Cervical Cancer Screening Programme in Rural Areas (NACCSPRA), which was launched in 2009. Numerous studies have demonstrated that long-term cervical cancer screening alters human papillomavirus (HPV) infection rates and cervical disease detection. Nearly 80 million women have been screened over 10 years, representing <30% of the target population; however, in some rural areas, such as Ordos City of Inner Mongolia Autonomous Region, Xiangyuan County of Shanxi Province, and Jinyun County, and Jingning County of Zhejiang Province, programs for prevention and treatment of cervical cancer have been implemented. Numerous studies have demonstrated that long-term cervical cancer screening alters rates of human papillomavirus (HPV) infection and cervical disease detection. In this study, we aimed to determine the infection rates of high-risk HPV (hrHPV) and the detection rate of cervical lesions; and changes in factors associated with cervical cancer, to provide scientific data to inform efforts to eliminate cervical cancer in rural areas.

Methods: This was a cross-sectional, population-based, and multi-center survey. Populations from three rural areas of China (Ordos City of Inner Mongolia Autonomous Region, Xiangyuan County of Shanxi Province, and Jinyun County and Jingning County of Zhejiang Province) were selected and 9,332 women aged 20–64 years old were invited to participate in cervical cancer screening by both cytology and HPV testing. The outcomes assessed were: infection rates with hrHPV, HPV16, 18, 16/18, and other 12 hrHPV types (HPV 31,33,35,39,45,51,52,56,58,59,66 and 68); detection rates of cytological and histological lesions; and factors associated with HPV infection.

Results: A total of 9,217 women aged 45.62 ± 8.02 years were included in this study. Infection rates with hrHPV, HPV 16, 18, 16/18, and other 12 hrHPV types were 16.3%, 3.0%, 1.5%, 4.3%, and 13.6%, respectively. There were significant differences among the age-specific HPV infection rates ($P < 0.05$). Infection rates with hrHPV, 16, 18, 16/18, and the other 12 hrHPV types showed a single peak infection mode, with a peak age of 56–65 years old. Age, marital status,

number of live births, education level, reproductive disease history, and a history of alcohol consumption were risk factors for hrHPV infection. The detection rate of cytological abnormalities was 12.98% in the study and was higher in women older than 56 years old. The detection rates of cervical intraepithelial neoplasia CIN2+ and CIN3+ in the population were 1.45% and 0.77%, respectively. The highest incidence rates of CIN2+ and CIN3+ were 32.12% and 17.51%, respectively, in the 41–45 years old group.

Conclusion: Infection rates with hrHPV, HPV16, and cervical lesions among our screening population were lower than the mean level in rural areas of China. Infection rates with hrHPV, HPV16, 18, and 16/18 showed a single-peak infection pattern, with the peak age of infection being 56-65 years old. Risk factors for hrHPV infection were age, history of alcohol consumption, marital status, reproductive diseases, education level, and the number of live births. Based on these data, we recommend that cervical cancer screening be offered to women older than 30 years in rural areas, particularly those aged 41–45 years.

Keywords: high-risk human papillomavirus, cervical cancer, genotype, risk factors, China demonstration rural areas

INTRODUCTION

Cervical cancer is ranked third among gynecological malignancies in terms of both estimated new cases and deaths of women worldwide. An estimated 604,000 new cervical cancer cases and 342,000 deaths were reported globally in 2020 (1). In China, there were up to 110,000 and 60,000 of new cases and deaths from cervical cancer, respectively, in 2020 (2), representing increases of 3.5% and 23.0% relative to 2018 (3). Hence, prevention and treatment of cervical cancer are urgent, particularly in China.

There has been heavy investment in cervical cancer prevention and control in China in recent years; however, the goal of eliminating cervical cancer, especially in rural areas, remains some way from being achieved (4). The Chinese government has taken action to prevent cervical cancer by implementing the National Cervical Cancer Screening Program in Rural Areas (NACCSPRA), which was launched in 2009 to provide free annual screening for 10 million women aged 35–64 in rural China (5, 6). Over the past decade, screening areas and population coverage have been expanding, with a screening rate for rural women from 2016 to 2018 of 26% (7), which remains far from the 70% screening target proposed by the World Health Organization (WHO). Due to imbalances in economic development, health levels, HPV infection rates, risk factors, and disease detection rates in rural areas of China, successful implementation of the cervical cancer elimination plan for China is challenging in these areas, particularly the prevention and treatment of cervical cancer. The detection and screening rates for precancerous cervical lesions were raised in rural China (8). Good systems for prevention and treatment of cervical cancer have been achieved in some rural areas of China, such as Ordos City, which has high rates of cervical cancer incidence. As the first city in China to implement a policies of screening for cervical cancer in all women aged 35–64 years and to conduct HPV vaccine immunization for all girls aged 13–18 years, the WHO considered the Ordos of the city in China likely to be first eliminate cervical cancer (9)[1], and the region has a high population of people with Mongol ethnicity, who have a higher incidence of cervical cancer. Further, due to its implementation of cervical cancer screening for almost 30 years, Xiangyuan County in Shanxi Province is a rural area that demonstrates the potential for the prevention and treatment of cervical cancer in China, and this rural area was also a clinical experimental site for the bivalent, quadrivalent, and 9-valent HPV vaccines (10). Jinyun County and Jingning County in Zhejiang Province also have a good record of cervical cancer prevention and treatment. In addition, it was the clinical experimental site for the HPV screening kit.

HPV infection rates, particularly the HPV 16 infection rate, were altered by the implementation of cervical cancer screening measures after ten years follow-up (11). The prevention and treatment experience of cervical cancer in Australia and other countries have confirmed that cervical cancer screening and HPV vaccination reduce the detection rate of cervical lesions. Compared with similar published studies, this study focused on the change of selected rural areas, where successful implementation of a cervical cancer elimination plan was

Abbreviations: AGC, atypical glandular cell; ASC-H, low-grade squamous cell-cannot exclude high-grade squamous intraepithelial lesion; ASCUS, atypical squamous cell of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, Human papillomavirus; hrHPV, high risk HPV; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; NACCSPRA, National Cervical Cancer Screening Programme in Rural Areas; NILM, negative for intraepithelial lesion or malignancy; OR, odds ratio; WHO, World Health Organization.

[1] Available online at: https://m.gmw.cn/baijia/2021-04/21/1302246124.html

introduced and had higher cervical cancer incidence and mortality rates in rural areas of China. There were unreported changes in HPV infection and cervical lesion detection rates and factors influencing these selected rural areas, especially after HPV vaccination in the market. Therefore, we conducted this study to explore the extent of prevention and treatment of cervical cancer in rural China by comparing how HPV infection rates, cervical lesions detection rates, and factors influencing HPV infection have changed. Furthermore, we investigated the effectiveness and relationship with age of cervical cancer screening for women in areas with high incidence rates of cervical cancer to provide a basis for design of follow-up cervical cancer screening strategies. The primary purpose of this study was to evaluate changes in HPV infection and cervical lesion detection rates and factors influencing these in screened women aged 20–65 years in rural areas of China with high incidence of cervical cancer: Ordos City of Inner Mongolia Autonomous Region, Xiangyuan County of Shanxi Province, and Jinyun County, and Jingning County of Zhejiang Province.

METHODS

Setting

This was a multicenter, population-based, and cross-sectional study conducted in rural areas of China from 2016 to 2019. Three rural areas were chosen based on their high incidence rates of cervical cancer, including the Ordos, Inner Mongolia (Hang jin banner and Yi jinholo banner), Shanxi Province (Xiangyuan Country), and Zhejiang Province (Jinyun County and Jingning County). A total of three tertiary hospitals and five maternal and child health hospitals were selected. Ethics approval was obtained from the Cancer Hospital, Chinese Academy of Medical Sciences (No. 16-013/1092), and the study was approved by all institutional review boards of the participating hospitals.

Study Population

In the initial stage of the study, 9,332 women participated, while 9,217 eligible women aged 20 to 64 years who lived in villages or sub-districts participated in the questionnaire survey, gynecological examination, and laboratory testing. All eligible women provided informed consent before enrolment. The investigators carried out procedures, inspecting whether the women complete the questionnaires or met the inclusion and exclusion criteria (**Figure 1**).

Procedure

The survey was conducted face-to-face by trained interviewers. If patients had difficulty reading and completing the scales, trained interviewers helped them read and explain, or family members helped them answer questions. Information collected included: demographic (birth date, sex, location, occupational situation, marital status, education, and annual household income); and other factors, including a history of disease, pregnancy, reproduction, lifestyle (smoking and alcohol consumption), contraceptive measures, menopausal status, and sexual behavior. A strict quality control scheme was adhered to throughout the entire investigation process, including data collection, filing, entry, and checking, revision, and data security. The trained interviewers checked the questionnaires immediately on completion to avoid missing items and logical errors. If the questionnaires had missing items or obvious logical mistakes (such as missing items and errors), the trained interviewers called the patient to amend them and check the information. All procedures were performed by trained local physicians, while the materials for and results of cytology and hrHPV analyses were provided by central hospitals.

Cervical Cancer Screening Process

All women were tested by cytology and for hrHPV using Thin Prep medium and the Cobas 4,800 test (Roche Diagnostics). Women positive for either HPV 16/18 or other HPV genotypes with positive cytology results were deemed to have screened positive; colposcopy and biopsy of suspicious lesions were performed if necessary. Women positive for other HPV genotypes and negative on cytology, and those negative for HPV genotypes, were deemed to have screened negative. The results of cytology show atypical squamous cells of undetermined significance (ASCUS) or higher (including low-grade squamous cell-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and atypical glandular cell (AGC), among others) indicated the need to undergo colposcopy and biopsy of the suspicious lesions. Women negative for intraepithelial lesion or malignancy (NILM) were screened negative, with follow-up observation to be carried out in 3 years.

According to CIN terminology, CIN was diagnosed as one of four stages: NILM, CIN grade 1 (CIN1), CIN2, CIN3; and cervical cancer as micro-invasive carcinoma, invasive carcinoma, and others.

Precancerous lesions diagnosed by cytology were classified into four stages: NILM, ASCUS, LSIL, and HSIL+.

Statistical Analysis

A database was established using Microsoft Access 2007 software. Statistical analyses were performed in SPSS, version 28.0. A χ^2 test was performed to compare proportions in subjects with specific characteristics and incidence rates of hrHPV, HPV16, 18, 16/18, and another 12 high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and cytology. Linear trend tests were used to compare infection rates with total hrHPV, HPV16, 18, 16/18, and the 12 other hrHPV genotypes; detection rates of abnormal cells; and detection rates of cervical precancerous lesions, according to age group.

RESULTS

Sociodemographic Information

Initial screening for cervical cancer was conducted in 9,332 women from rural areas, of which 115 were excluded for various reasons, including an unwillingness to consent, disapproval of gynecological examination, previous uterine surgery, and incomplete data. Finally, 9,217 women completed cervical cancer screening, including 3,082 women from Inner Mongolia, 3,010 from Shanxi, and 3,125 from Zhejiang. The mean age of the

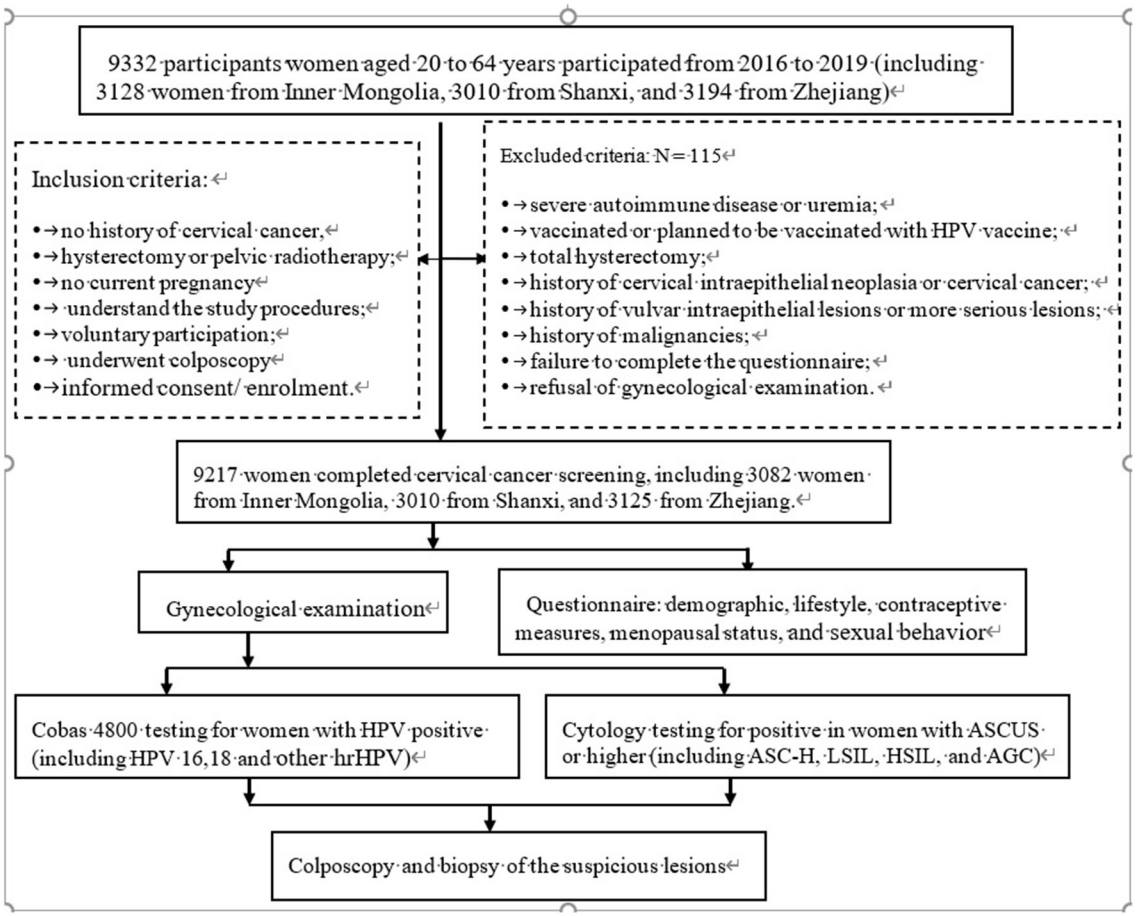

FIGURE 1 | The flow chart of the study procedures carried out on the sites. ASCUS, atypical squamous cells of undetermined significance; ASC-H, higher including low-grade squamous cell-cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cell; NILM, negative for intraepithelial lesion or malignancy.

9,217 women was 45.15 ± 8.74 years, and women aged 41–45-years-old accounted for 20.0% of the screened population. The largest age groups from Inner Mongolia, Shanxi Province, and Zhejiang Province in the screened populations were those aged 51–55 years-old (20.1%), 41–45 years old (19.5%), and 56–60 years old (9.4%), respectively. There were significant differences in age distribution, marital status, and educational level ($P < 0.001$) (**Table 1**).

Distribution of HPV Status

Among the women screened for cervical cancer, the positive rates for the hrHPV types, 16, 18, 16/18, and others (12 high-risk types) were 16.3%, 3.0%, 1.5%, 4.3%, and 13.6%, respectively. Further, the infection rates of HPV16, 18, 16/18, and other types in the total population differed significantly among age groups ($P < 0.05$), with the peak age of infection at 56–65 years old (**Table 2**). The infection rate of hrHPV (17.1% vs. 17.1%), HPV 16/18 (5.0% vs. 4.9%) and other 12 high-risk types (14.1% vs. 21.7%) among the screening population in Inner Mongolia and Shanxi Province were higher than those in Zhejiang Province (14.8%), HPV16 (1.6%), HPV16/18 (3.1%) and other 12 high-risk types (12.6%) ($P < 0.05$).There was no significant difference in infection rate of HPV 18 among the selected areas. Comparing the age groups, the infection rates of hrHPV and HPV 16/18 were statistically different among age groups in Inner Mongolia Autonomous Region and Shanxi Province ($P < 0.05$), except for the infection rates of HPV16. While infection rates of HPV16, 18, 16/18, and other types in the Zhejiang Province were statistically significant ($P < 0.05$), with the peak age of infection at 61–65 years old.

Risk Factors Associated With HrHPV Infection

Among the women screened for cervical cancer, HrHPV infection rates did not differ significantly according to disease history, age at menarche, menopause status, alcohol consumption and smoking ($P > 0.05$). However, the hrHPV infection rate differed significantly according to age at first pregnancy, age at first delivery, number of births and live births, method of contraception, menopause status, and the number of sexual partners ($P < 0.05$). Infection rates were higher in women who were younger at first pregnancy and delivery, had given birth

TABLE 1 | Basic characteristics of the study population.

Characteristic	Total population, N (%)	Inner Mongolia, *N* (%)	Shanxi, *N* (%)	Zhejiang, N (%)	χ^2	*P*-value
Age (years)						
21–25	45 (0.5)	18 (0.6)	16 (0.5)	11 (0.4)	475.3	0.00
26–30	482 (5.2)	127 (4.2)	248 (8.0)	107 (3.4)		
31–35	922 (10.0)	190 (6.3)	488 (15.8)	244 (7.8)		
36–40	1,327 (14.4)	338 (11.2)	508 (16.5)	481 (15.4)		
41–45	1,844 (20.0)	576 (19.1)	601 (19.5)	667 (21.3)		
46–50	1,860 (20.2)	597 (19.8)	554 (18.0)	709 (22.7)		
51–55	1,570 (17.0)	606 (20.1)	405 (13.1)	559 (17.9)		
56–60	862 (9.4)	397 (13.2)	208 (6.7)	257 (29.8)		
61–65	305 (3.3)	163 (5.4)	52 (1.7)	90 (2.9)		
Marital status						
Unmarried	10 (0.1)	0 (0.0)	3 (0.0)	7 (0.1)	90.6	0.00
Married	9,034 (98.0)	3,023 (98.1)	2,925 (97.2)	3,085 (98.7)		
Widowed	126 (1.4)	31 (1.0)	80 (2.7)	15 (0.5)		
Separated	12 (0.1)	2 (0.1)	2 (0.1)	8 (0.3)		
Divorced	32 (0.3)	19 (0.6)	3 (0.1)	10 (0.3)		
Other	4 (0.0)	4 (0.0)	0 (0.0)	0 (0.0)		
Education Level						
Uneducated	641 (7.0)	483 (15.7)	55 (1.8)	103 (3.3)	1692.2	0.00
Primary school	1,885 (20.5)	599 (19.4)	827 (27.5)	459 (14.7)		
Junior school	3,706 (40.2)	689 (22.4)	1,662 (55.2)	1,355 (43.4)		
High school	1,398 (15.2)	432 (14.0)	373 (12.4)	593 (19.0)		
Undergraduate and above	1,587 (17.2)	879 (28.5)	93 (3.1)	615 (19.7)		

TABLE 2 | High-risk HPV infection rate and genotype distribution by age group and areas, *N* (%).

	Types	Amount	21–25 years	26–30 years	31–35 years	36–40 years	41–45 years	46–50 years	51–55 years	56–60 years	61–65 years	*P*-value
Total	HPV	1,504 (16.3)	5 (11.1)	68 (14.1)	137 (14.9)	195 (14.7)	232 (12.6)	283 (15.2)	292 (18.6)	216 (25.1)	76 (24.9)	0.00
	HPV16	278 (3.0)	0 (0.0)	11 (2.3)	28 (3.0)	33 (2.5)	53 (2.9)	45 (2.4)	46 (2.9)	43 (5.0)	19 (6.2)	0.00
	HPV18	136 (1.5)	1 (2.2)	7 (1.5)	12 (1.3)	16 (1.2)	19 (1.0)	20 (1.1)	34 (2.2)	20 (2.3)	7 (2.3)	0.00
	HPV16/18	400 (4.3)	1 (2.2)	18 (3.7)	36 (3.9)	48 (3.6)	71 (3.9)	65 (3.5)	75 (4.8)	61 (7.1)	25 (8.2)	0.00
	Other hrHPV	1,253 (13.6)	5 (11.1)	57 (11.8)	117 (12.7)	164 (12.4)	183 (9.9)	234 (12.6)	252 (16.1)	180 (20.9)	61 (20.0)	0.00
Inner mongolia	HPV	526 (17.1)	2 (11.1)	39 (15.7)	87 (17.8)	90 (17.7)	86 (14.3)	78 (14.1)	79 (19.5)	53 (25.5)	12 (23.1)	0.00
	HPV16	112 (3.6)	0 (0.0)	6 (2.4)	20 (4.1)	16 (3.1)	20 (3.3)	14 (2.5)	20 (4.9)	11 (5.3)	5 (9.6)	0.10
	HPV18	51 (1.7)	1 (5.6)	5 (2.0)	9 (1.8)	5 (1.0)	7 (1.2)	5 (0.9)	10 (2.5)	8 (3.8)	1 (1.9)	0.08
	HPV16/18	155 (5.0)	1 (5.6)	11 (4.4)	25 (5.1)	21 (4.1)	27 (4.5)	19 (3.4)	28 (6.9)	17 (8.2)	5 (11.5)	0.03
	Other hrHPV	434 (14.1)	2 (11.1)	33 (13.3)	45 (10.8)	75 (15.4)	67 (11.1)	64 (11.6)	62 (15.3)	44 (21.2)	10 (19.2)	0.01
Shanxi	HPV	516 (17.1)	2 (12.5)	13 (10.2)	23 (12.1)	46 (13.6)	71 (12.3)	101 (16.9)	110 (18.2)	109 (27.5)	41 (25.2)	0.00
	HPV16	101 (3.4)	0 (0.0)	4 (3.1)	4 (2.1)	10 (3.0)	20 (3.5)	17 (2.8)	13 (2.1)	26 (6.5)	7 (4.3)	0.02
	HPV18	48 (1.6)	0 (0.0)	1 (0.8)	1 (0.5)	5 (1.5)	5 (0.9)	5 (0.9)	8 (1.3)	14 (2.3)	10 (2.5)	0.32
	HPV16/18	147 (4.9)	0 (0)	5 (3.9)	5 (2.6)	15 (4.4)	25 (4.3)	25 (4.2)	26 (4.3)	36 (9.1)	10 (6.1)	0.00
	Other HPV	425 (14.1)	2 (12.5)	10 (7.9)	20 (10.5)	38 (11.2)	55 (9.5)	82 (13.7)	97 (16.0)	86 (21.7)	35 (21.5)	0.00
Zhejiang	HPV	462 (14.8)	1 (9.1)	16 (15.0)	27 (11.1)	59 (12.3)	75 (11.2)	104 (14.7)	103 (18.4)	54 (21.0)	23 (25.6)	0.00
	HPV16	65 (2.1)	0 (0.0)	1 (0.9)	4 (1.6)	7 (1.5)	13 (1.9)	14 (2.0)	13 (2.3)	6 (2.3)	7 (7.8)	0.03
	HPV18	37 (1.2)	0 (0.0)	1 (0.9)	2 (0.8)	6 (1.2)	7 (1.0)	7 (1.0)	10 (1.8)	2 (0.8)	2 (2.2)	0.00
	HPV16/18	98 (3.1)	0 (0.0)	2 (1.9)	6 (2.5)	12 (2.5)	19 (2.8)	21 (3.0)	21 (3.8)	8 (3.1)	9 (10.0)	0.03
	Other hrHPV	394 (12.6)	1 (9.1)	14 (13.1)	22 (9.0)	49 (10.2)	61 (9.1)	88 (12.4)	93 (16.6)	50 (19.5)	16 (17.8)	0.00

HPV, including HPV 16, 18, Other HPV types (31,33,35,39,45,51,52,56,58,59,66 and 68) infection.

3–4 times, had 3–4 live births, had disease history, had ≥ 2 sexual partners, and used other method of contraception (including external ejaculation, vaginal medication, and fallopian tube blockage) (**Table 3**).

Logistic Regression Analysis of Factors Associated With HrHPV Infection

Seven factors were candidate predictors that were associated with hrHPV infection on univariate analyses. HrHPV infection rates differed significantly according to age [odds ratio (OR) = 1.124, $P < 0.0001$], education level (OR = 1.068, $P = 0.025$), number of births (OR = 0.601, $P = 0.039$), marital status (OR = 1.476, $P < 0.0001$), number of live births (OR = 1.751, $P = 0.032$), age at first delivery (OR = 0.815, $P = 0.001$), and alcohol consumption history (OR = 1.164, $P = 0.024$).

Multivariate analysis confirmed that five variables were independently associated with hrHPV infection, including age, marital status, number of live births, education level, and alcohol consumption history (**Table 4**; **Supplementary Table 1**).

Detection Rates of Cytological Abnormalities in Different Age Groups

The cytological results for the 9,217 women included in the study were as follows: NILM ($n = 8,020$), inconclusive ($n = 45$), ASCUS ($n = 771$, 8.4%), LSIL ($n = 207$, 2.2%), HSIL ($n = 77$, 0.8%), AGC ($n = 23$, 0.2%), ASC-H ($n = 66$, 0.7%), and cervical cancer ($n = 8$, 0.1%). ASCUS or above was not detected in the 21–25 year-old age group, and the detection rate of abnormal cells differed significantly among age groups ($P < 0.05$), with the highest in women aged > 56 years (**Table 5**).

Detection Rates of Histological Abnormalities in Different Age Groups

Of the 9,217 women who underwent cervical cancer screening, 711 were referred for colposcopy, of whom 250 had abnormal histological findings. We found 108 cases of CIN1 (including 18 cases in Ordos City, 48 cases in Xiangyuan County, and 42 cases in Jinyun County, and Jingning County), 66 cases of CIN2 (including 25 cases in Ordos City, 28 cases in Xiangyuan County, and 15 cases in Jinyun County and Jingning County), 68 cases of CIN3 (including 21 cases in Ordos City, 24 cases in Xiangyuan County, and 23 cases in Jinyun County, and Jingning County), 3 cases of cervical cancer, and 3 cases of vulvar intraepithelial neoplasia among those women with abnormal histological findings. The overall CIN2+ detection rate was 1.45%, of which 0.04%, 0.33%, 0.48%, 0.24%, 0.22%, and 0.17% were in the 21–30, 31–40, 41–45, 46–50, 51–55, and > 56 years age groups, respectively; there was an overall CIN3+ detection rate of 0.77%, with 0.02%, 0.12%, 0.26%, 0.26%, 0.26%, and 0.12% in each age group, respectively. CIN 2/3+ was not detected in women aged 21–25 years, and the highest CIN 2/3+ detection rates were found in the 41–45 years age group, accounting for 32.12% and 17.51% of all cases respectively. The detection rate of abnormal cervical histology differed significantly among the different age groups ($P < 0.05$) (**Table 6**).

DISCUSSION

HrHPV infection is closely associated with genital warts and penile, anal, oropharyngeal, and cervical cancers. The elimination of HPV-related cancers, particularly cervical cancer, has attracted global attention as a public health problem (12). The WHO launched the "Global Strategy for accelerating the Elimination of Cervical Cancer as a Public Health Problem" on November 17, 2020, and 194 countries, including China, committed to eliminating cervical cancer for the first time (13). There remains much to achieve to reach the goal of eliminating cervical cancer in China (14). A major problem was low coverage of cervical cancer screening and vaccination with the HPV vaccine; however, some regions, including rural areas, of China, have taken effective measures to prevent and control HPV, such as Ordos City of Inner Mongolia Autonomous Region, Xiangyuan County of Shanxi Province, Jinyun County, and Jingning County of Zhejiang Province. Ordos was the first city in China to implement the national screening plan for women aged 35–64 years and HPV vaccine immunization for girls aged 13–18 years. Based on their experience and study findings, two "National Demonstration Base for Early Diagnosis and Treatment of Cervical Cancer" programs were set up in Xiangyuan County Maternal and Child Health Hospital (rural type) in Shanxi Province in February 2005 (15). Furthermore, Xiangyuan and the counties of Jinyun and Jingning) were the sites for clinical trials of the HPV vaccine and HPV testing kit. Compared with other regions, these areas could be expected to have superior outcomes in terms of prevention and control of cervical cancer, due to the implementation of screening. A 10-year cohort study cervical cancer screening reported reduced rates of HPV infection, particularly infection with HPV16 (16). To assess how the HPV infection rate, the rate of cervical lesion detection, and risk factors influencing the HPV infection rate have changed in these rural areas, we conducted this multicenter, population-based study focused on rural areas, including Ordos, Xiangyuan, Jinyun, and Jingning County, to provide theoretical guidance to further the realization of the plan for the elimination of cervical cancer in rural areas.

In our study, we found that the hrHPV infection rate was 16.3% in the screened population, which was consistent with the findings of Zhao et al. regarding the national screened population but lower than rates reported in other parts of the world, such as Africa (20.9%–23.4%) (17, 18). Combined with our results regarding risk factors, the observed differences may be related to poor health status, early age of marriage, and higher numbers of births, among other factors, associated with hrHPV infection. The HPV 16 infection rate was 3.0%, which was consistent with the findings of the ATHENA study in the USA (2.8%), but it was lower than that reported by the ICO (19, 20). The HPV 18 infection rate was 1.5%, higher than that reported by the ATHENA study (1.0%) (21). The infection rates with HPV 16/18 and the other 12 hrHPV types were 4.3 and 13.6%, respectively. Overall, infection rates with hrHPV, HPV16, 18, 16/18, and the other 12 hrHPV types were consistent with the findings from the national screening population, indicating declining infection rates in these rural areas (Ordos, Xiangyuan,

TABLE 3 | Analysis of factors associated with high-risk HPV infections.

Factor		Amount	HPV infection, *N* (%)	OR (95% CI)
Education level	Uneducated	641	122 (19.03)	1
	Primary school	1,885	318 (16.87)	0.86 (0.68, 1.09)
	Junior school	3,706	583 (15.73)	0.79 (0.64, 0.99)
	High school	1,398	232 (16.59)	0.85 (0.66, 1.08)
	Undergraduate and above	1,587	249 (15.69)	0.79 (0.62, 1.01)
Age at menarche (years)	10–13	1,814	267 (14.71)	1
	14–17	6,600	1,100 (16.67)	1.15 (0.99, 1.33)
	≥ 18	744	135 (18.14)	1.28 (1.02, 1.61)
	Unclear	9	2 (22.22)	1.66 (0.34, 8.01)
Age at first pregnancy (years)	≤ 18	230	45 (19.56)	1
	19–21	2,978	536 (18.00)	0.90 (0.64, 1.27)
	22–24	3,542	553 (15.61)	0.76 (0.54, 1.07)
	25–27	1,806	273 (15.11)	0.73 (0.52, 1.04)
	≥ 28	574	79 (13.76)	0.66 (0.44, 0.98)
	No pregnancy	79	17 (21.51)	1.13 (0.60, 1.78)
	Refuse to answer	8	1 (12.50)	0.59 (0.07, 4.89)
Age at first delivery (years)	No delivery	106	24 (22.64)	1.11 (0.69, 1.80)
	≤ 20	1,052	219 (20.82)	1
	21–25	5,609	918 (16.37)	0.74 (0.63, 0.88)
	26–30	2,244	314 (13.99)	0.62 (0.51, 0.75)
	≥ 31	198	28 (14.14)	0.63 (0.41, 0.96)
	Refused to answer	8	1 (12.5)	0.54 (0.07, 4.44)
Number of pregnancies	≤ 2	4,278	625 (15.21)	1
	3–4	4,208	735 (17.47)	1.18 (1.05, 1.33)
	≥ 5	731	117 (16.01)	1.07 (0.86, 1.32)
Number of births	1–2	8,037	1,264 (15.73)	0.73 (0.48, 1.12)
	3–4	963	204 (21.18)	1.06 (0.67, 1.66)
	≥ 5	84	9 (10.71)	0.47 (0.21, 1.06)
	None	133	27 (20.30)	1
Number of live births	None	134	27 (20.14)	1
	1–2	8,134	1,275 (15.67)	0.74 (0.48, 1.13)
	3–4	918	199 (21.68)	1.10 (0.70, 1.72)
	≥ 5	31	3 (9.68)	0.43 (0.12, 1.50)
Method of contraception	None	2,261	411 (18.18)	1
	Condom	1,424	178 (12.5)	0.64 (0.53, 0.78)
	Acyeterion	53	9 (16.98)	0.92 (0.45, 1.91)
	IUD	1,975	305 (15.44)	0.82 (0.70, 0.97)
	Sterilization	3,497	599 (17.13)	0.93 (0.81, 1.07)
	Other	28	6 (21.43)	1.23 (0.50, 3.05)
Menopause Status	Yes	27	6 (22.22)	1.47 (0.59, 3.64)
	No	9,190	1,498 (16.30)	1
Disease history	Yes	9	4 (44.44)	4.11 (1.10, 15.33)
	No	9,208	1,500 (16.29)	1
Smoking history	Yes	9,044	1,472 (16.28)	1
	No	220	32 (14.54)	0.97 (0.28, 3.31)
Alcohol consumption history	No	7,440	1,194 (16.05)	1
	Occasionally	1,708	294 (17.21)	1.09 (0.95, 1.25)
	Often	69	16 (23.19)	1.579 (0.90, 2.77)
Sexual partners	≤ 1	6,024	1,026 (17.0)	1
	≥ 2	68	16 (23.5)	1.49 (1.10,2.65)

OR, odd ration; HPV infection: including: HPV16, 18, Other HPV types (31,33,35,39,45,51,52,56,58,59,66 and 68) infection; IUD, intrauterine device, Disease history including Gynecological diseases, Vaginal infection, vaginitis.

TABLE 4 | Multivariate logistic regression analysis of factors associated with high-risk HPV infection.

Variable	B Value	Wald value	Sig value	Exp (B)	Exp (B) 95% CI	
					Lower	Upper
Age (years)	0.117	39.793	0.000	1.124	1.084	1.165
Education level	0.066	5.042	0.025	1.068	1.008	1.131
Age at menarche	0.054	0.893	0.345	1.055	0.944	1.18
Number of pregnancies	0.054	1.234	0.267	1.056	0.959	1.161
Number of births	−0.509	4.268	0.039	0.601	0.371	0.974
Number of live births	0.56	4.582	0.032	1.751	1.048	2.924
Smoking history	−0.18	3.055	0.080	0.836	0.683	1.022
Alcohol consumption history	0.152	5.114	0.024	1.164	1.02	1.328
Disease history	1.259	3.420	0.065	3.523	0.924	13.437
Marital status	0.389	16.998	0.000	1.476	1.226	1.775
Method of contraception	−0.013	0.577	0.448	0.987	0.954	1.021
Age at first pregnancy	0.003	0.005	0.946	1.003	0.916	1.099
Age at first delivery	−0.204	10.733	0.001	0.815	0.722	0.921

TABLE 5 | Detection of cytological abnormalities according to age group, *N* (%).

Age (years)	NILM	ASCUS	LSIL	HSIL	AGC	ASC-H	CC	Inconclusive	*P*-Value
21–30	479 (90.9)	35 (6.6)	9 (1.7)	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	$P < 0.0001$
31–40	1,960 (87.1)	187 (8.3)	50 (2.2)	17 (0.8)	10 (0.4)	18 (0.8)	0 (0.0)	7 (0.3)	$P < 0.0001$
41–45	1,610 (87.3)	135 (7.3)	54 (2.9)	19 (1.0)	4 (0.2)	11 (0.6)	0 (0.0)	11 (0.6)	$P < 0.0001$
46–50	1,640 (88.2)	145 (7.8)	38 (2.0)	16 (0.9)	1 (0.1)	13 (0.7)	1 (0.1)	6 (0.3)	$P < 0.0001$
51–55	1,340 (85.4)	159 (10.1)	31 (2.0)	12 (0.8)	4 (0.3)	11 (0.7)	3 (0.2)	10 (0.6)	$P < 0.0001$
56–65	991 (84.9)	110 (9.4)	25 (2.1)	10 (0.9)	4 (0.3)	12 (1.0)	4 (0.3)	11 (0.9)	$P < 0.0001$
Total	8,020 (87.0)	771 (8.4)	207 (2.2)	77 (0.8)	23 (0.2)	66 (0.7)	8 (0.1)	45 (0.5)	$P < 0.0001$

ASCUS, atypical squamous cells of undetermined significance; ASC-H, higher (including low-grade squamous cell-cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cell; NILM, negative for intraepithelial lesion or malignancy; CC, cervical cancer.

Jinyun, and Jingning County). Except for the infection rates of HPV18, the infection rates of hrHPV, HPV16, 16/18 and other 12 hrHPV types in Inner Mongolia and Shanxi Province were higher than those of in Zhejiang Province, which was indicated that the distribution of hrHPV, HPV16, 16/18 and the other 12 hrHPV types were regional. This may be related to the fact that the women living in pastoral areas of Inner Mongolia or rural areas in Shanxi Province had poor sanitary conditions and premarital sexual behavior (19). In our study, the infection rates of hrHPV, HPV16, 16/18 were higher in Inner Mongolia, Shanxi Province and Zhejiang Province than that in the western region (18) and ICO (20), which may be related to the research subjects coming from the areas with high incidence and mortality of cervical cancer in China. The change in the HPV18 infection rate was not obvious, which may be related to the low infection rate in China. It was suggested that the government should pay attention to the prevention and control of high incidence cervical cancer areas.

Infection rates with hrHPV, HPV16, 18, 16/18, and the other 12 hrHPV types differed significantly according to age ($P < 0.05$), with the peak age of infection at 56–65-years-old in the total mount, Inner Mongolia, Shanxi Province and Zhejiang Province. These findings are inconsistent with the double peak HPV infection rate phenomenon previously reported in rural areas of China (22), which described two peak HPV infection rates in the 25–29 years (14.2%) and 55–59 years (19.3%) age groups. This can likely be attributed to the fact that, in these rural areas (which were clinical trial sites for the HPV vaccine and HPV testing kit), women in the 25–35 years age group underwent HPV vaccine injection, while those aged 35–64 were screened for cervical cancer. Furthermore, the 21–24 years age

TABLE 6 | Rate of detection of histological abnormalities according to age group, *N* (%).

Age (years)	CIN1	CIN2	CIN3	CC	*P*-value
21–30	7 (1.3)	2 (0.4)	2 (0.4)	0 (0.0)	0.00
31–40	23 (1.0)	20 (0.9)	11 (0.5)	0 (0.0)	0.00
41–45	13 (0.7)	20 (1.1)	23 (1.2)	1 (0.1)	0.00
46–50	21 (1.1)	11 (0.6)	11 (0.6)	0 (0.0)	0.00
51–55	20 (1.3)	7 (0.4)	13 (0.8)	0 (0.0)	0.00
56–65	24 (2.1)	6 (0.5)	8 (0.7)	2 (0.2)	0.00
Amount	108 (1.2)	66 (0.7)	68 (0.7)	3 (0.0)	0.00

CIN 1, cervical intraepitelial neoplasia grade 1; CIN 2, cervical intraepitelial neoplasia grade 2; CIN3, cervical intraepitelial neoplasia grade 3; CC, cervical cancer.

group was relatively small in our rural population and women tended to marry earlier in rural areas, which may have led to an earlier peak in the HPV infection rate; however, HPV infection in this age group was transient and had no clinical significance. It is established that infection rates exhibit one peak in women aged 21–24 years, which was the highest rate (30.5%) in the ATHENA and ARTISTIC (39.9%) studies (23, 24), subsequently decreasing in women aged ≥ 55 years. Our findings differ from those reports mentioned above; we found that women aged 56–65 years had the highest rate of HPV infection, possibly associated with decreased immunity, a lower natural rate of HPV clearance, and an increased possibility of hrHPV infection in women experiencing menopause or perimenopause (25). Therefore, it is more clinically meaningful to conduct HPV testing for older than younger women, aiming for cervical cancer prevention and treatment in these rural areas (Ordos, Xiangyuan, Jinyun, and Jingning County).

We found that risk factors for hrHPV infection in our population were age, marital status, number of live births, education level, disease history, and alcohol consumption history, consistent with the findings of numerous domestic studies (26, 27). To date, studies conducted in China have unanimously recognized that many sexual partners, more pregnancies, more births, reproductive system diseases, and other factors can increase the risk of infection with hrHPV (28).

In this study, we found that a high number of live births is a risk factor for hrHPV infection, likely due to stimulation and damage of the cervical mucosa, resulting in cervical cell metaplasia or abnormal hyperplasia and changes in estrogen and progesterone levels in the body leading to reduced immunity and increased risk of HPV infection (29, 30). We found that a history of reproductive system infection and gynecological diseases were major risk factors for hrHPV infection, which may be related to the destruction of the cervical mucosal barrier by reproductive system infection, making it easier for HPV to invade and infect the epithelial basal layer, and reducing local immunity in the vagina, causing abnormal differentiation or proliferation of cervical cells (31). Reproductive tract infection with hrHPV is necessary for the development of cervical cancer and CIN; therefore, a key step in cervical cancer prevention is to prevent reproductive tract infections with hrHPV. Menopause was a risk factor for HPV infection in our study, consistent with a report from Smith et al. (32) on postmenopausal women with 7 years of follow-up observation. The proportion of women aged 46–65 years (per-menopause or menopause) in our study was high, and hormone levels in women of this age are relatively disordered, while physiological immunity begins to decline. We found an association between contraceptive methods with HPV infection, which was inconsistent with published literature reports (33). These results suggest that women in our study were insufficiently knowledgeable about contraceptive measures, such as condoms and intrauterine devices, leading to misunderstandings and making it impossible to determine the relationship between contraception and HPV infection rate.

Our data confirm that women with higher education levels had lower hrHPV infection rates, likely because women with higher education levels pay more attention to their health and maintain good personal life and hygiene habits. Previous reports indicate that drinking alcohol is not associated with increased HPV infection rates (34). The women in our study came from areas with large ethnic minority populations. In particular, people with Mongolian ethnicity drink alcohol more frequently than those from other regions. We found that drinking alcohol was a risk factor for hrHPV infection, which warrants further research.

HPV infection rates are higher in married, divorced, and widowed women, which may be related to the number of sexual partners of women in these groups. The HPV infection rate was higher in younger women, consistent with the literature (35). Women aged <20 years may be more likely to be infected with HPV due to immature cervical epithelium repair function and imperfect immune function, as well as early age of initial sexual behavior, which increases the opportunity for HPV infection (36). Due to decreased immune system function and weakened virus clearance ability, the HPV infection rate was higher in older women. Furthermore, women who had ≥ 2 sexual partners had more opportunities to be infected with HPV, consistent with a previous report (37).

We found that the total detection rate of ≥ASCUS was 12.98%, which was higher than those reported by the national "two cancers" screening report (3.93%) (38) and the national special industry project report (5.63%) (39). The detection rates of ASCUS, LSIL, HSIL, AGC, ASC-H, and cervical cancer were 8.4, 2.2, 0.8, 0.2, 0.7, and 0.1%, respectively. Further, the rate of detection of abnormal cytology was high in this study, which may have had several possible causes. First, the cytological diagnoses were all made by doctors with professional training in cytology working at grade A hospitals. Second, the population came from agricultural and pastoral areas, with relatively concentrated ethnic minority populations, or from rural areas that are economically underdeveloped. There were differences rates of abnormal cytology detection among age groups, with the highest rate found in the 56–65 years old group. These data suggest that screening for cervical cancer in older women in rural China should be strengthened. As no abnormal cervical cells were detected in the 21–25 years old group, cervical cancer screening is not advisable for this group. The rate of abnormal cytology detection in the 25–30 years old group was 0.4%, and these women may decide whether to carry out cervical cancer screening according to their economic status.

We found three cases of vulvar intraepithelial neoplasia, which were not analyzed according to age group; however, rates of abnormal cervical tissue differed among age groups. The detection rates of CIN2+ and CIN3+ were 1.45 and 0.77%, respectively, which were lower than those previously published in the literature for rural areas (40, 41). The highest CIN2+ and CIN3+ detection rates were in the 41–45-year-old group, which was similar to the peak age group (40–49 years old). This may be related to differences in geographical regions, methods for cervical cancer screening (liquid-based cytology, HPV detection), tools for screening, population characteristics, age structure, study design, classification used in cytology, and pathology and principles of biopsy sampling, as these factors influence the results of studies of the prevalence of CIN (42). It is clear that the prevalence of cervical lesions is lower in populations with higher

rates of screening than in those with lower rates of screening (43). Our study indicates that programs for the prevention and treatment of cervical cancer in these areas are generating initial results. No CIN2+ cases were found in the 21–30 years age group, indicating that cervical cancer screening is not suitable for women in this age group. The detection rates of CIN2+ and CIN3+ were 0.8 and 0.4%, respectively, among women aged 25–30 years, and were highest (32.12 and 17.51%) in women aged 41–50 years. These findings are broadly consistent with the literature (44, 45) and indicate that there should be more focus on cervical cancer screening for middle-aged and older women in rural areas of China.

Strengths and Limitations

This study has some strengths. The study population was large and a multicenter design was applied, using HPV genotype testing for cervical cancer screening in minority or rural areas of mainland China. To confirm the effects of HPV infection, we chose doctors at local hospitals to perform all screenings, permitting assessment by a superior hospital. Cervical cancer screening has been implemented in rural areas of China for more than ten years; however, the associated risk factors, HPV infection rates, rates of abnormal cervical cytology, and rates of abnormal histology and precancerous lesions in these areas are unclear, and elimination of cervical cancer by screening and prevention programs is expected. Second, our data provide a reference for real-world assessment of the effects of prevention and treatment programs for cervical cancer in rural areas of China.

The study also has some limitations. There was an inevitable loss to follow-up, with a rate of 18.74% in this study; however, analysis of the basic characteristics, main risk factors, and main outcome indicators of the lost population demonstrated that it is unlikely to have influenced our analyses. Furthermore, differences in the cytology, histology, and diagnosis findings of gynecologists in different regions may have had certain impacts on our results.

CONCLUSIONS

The rates of hrHPV and HPV16 infections and cervical lesions in the screened population included in this study were lower than the mean rates in rural China. The infection rates of hrHPV, HPV16, 18, and 16/18 showed a single-peak infection pattern, with a peak infection age of 56–65 years. Risk factors associated with hrHPV infection were: age, history of alcohol consumption, marital status, reproductive diseases, education level, and number of live births. Cervical cancer screening is not recommended for women aged 21–25 years in rural areas, while women aged 26–30 years may decide to undergo screening, according to their economic status. Older women (>30 years old), particularly those aged 41–45 years, are recommended to undergo cervical cancer screening.

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.

ETHICS STATEMENT

Central Ethics Approval was obtained from the Cancer Hospital, Chinese Academy of Medical Sciences (No. 16-013/1092). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-QY, M-YJ, R-MF, MB, WC, and Y-LQ participated in study design, data analysis and visualization, validation of the entire study, and preparation of the manuscript. Y-QY and M-YJ conducted data collection and supervision. Y-QY analyzed the data and write the article. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.911367/full#supplementary-material

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Cervical cancer screening, treatment and prophylaxis in Brazil: Current and future perspectives for cervical cancer elimination

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As a middle-income country, Brazil has one of the largest public health systems worldwide, which deals with free and universal access to health care. Regarding cervical cancer, the country possesses a large infrastructure for the screening of premalignant and malignant lesions, but yet based on old technology, having Papanicolaou as the major screening method, followed by colposcopy and treatment. Also, large disparities in access are present, which makes effectiveness of screening and treatment in different regions of the country highly unequal. In this review, we describe and evaluate the current screening, treatment and prophylactic (HPV vaccination) strategies to combat cervical cancer in Brazil, and discuss potential incorporation of more recent technologies in these areas in the country to pave its way toward cervical cancer elimination.

KEYWORDS

cervical cancer, LMICs, Brazil, HPV, HPV vaccine

Introduction

The history of actions for cervical cancer (CC) control in Brazil begins in the 1940's, with the introduction of colposcopy and cytology. During the following decade, those methods were disseminated throughout the country, albeit restricted to opportunistic assessment of women visiting health services for other reasons. In the 1960's, the first CC detection campaigns using the Papanicolaou test were launched, expanding in the following decades (1).

Public policies aimed at CC control were just developed from the second half of the 1970's onward, when the disease was finally recognized as a public health problem. In the 1980's, during the country's return to democracy, the healthcare reform and the growing force of women's movements enabled the

Comprehensive Women's Health Program development by the Brazilian Ministry of Health (BMoH). In 1995, the BMoH acknowledged the need of a nationwide program targeting CC control. Thus, the *Viva Mulher* (Live Woman) Program was created: the pilot project, the Cervical Cancer Information System (SISCOLO) implementation, and the program intensification phases one and two took place in 1996, 1998, 1999, and 2002, respectively. In 2005/2006, with the National Oncology Care Policy and the Health Pact launched, CC control also became part of state and municipal healthcare plans, encompassing the three government domains (1, 2).

Considering CC relevance persistence in Brazil, the BMoH elaborated and implemented a national plan to strengthen the prevention, diagnosis, and treatment network between 2010 and 2014. That included several actions such as the publication of the new National Cancer Prevention and Control Policy and the Brazilian Guidelines for the Cervical Cancer Screening update; the launch of the Cancer Information System (SISCAN) new web-based version dedicated to national screening programs; the redefinition of National Qualification in Cytopathology standards; the implementation of the Reference Services for Cervical Cancer Precursor Lesions Diagnosis and Treatment; and the human papillomavirus (HPV) vaccine incorporation into the National Immunization Program (PNI in the Portuguese acronym) (2).

Although all these efforts, cervical cancer still represents a major public health concern in Brazil. It is the third most common cancer in women and the fourth leading cancer death cause (3). In 2022, 16,710 new cases are estimated, with a rate of 16.35 cases/100,000 women (3). In 2020, there were 6,627 deaths from CC in the country, with a mortality rate of 5.33/100,000 women (4). In 2019, 160.8 disability-adjusted life-years (DALYs)/100,000 inhabitants were lost due to CC (5).

Despite the availability of HPV vaccination and CC screening free of charge in the Public Health System (SUS in the Portuguese acronym), the impact on disease magnitude has been minor, as vaccination coverage is low (6) and its effect on incidence and mortality occurs only in the long run. Consequently, screening remains an essential strategy as unvaccinated cohorts have a higher risk of developing CC and rely exclusively on early detection. However, screening remains opportunistic and cytology-based in Brazil, with challenges yet unmet to improve adherence and quality (7).

In 2018, the World Health Organization (WHO) made a global call to eliminate CC as a public health problem, and in 2020 it launched strategies to promote and accelerate this purpose (8, 9). One of the actions listed was the WHO Guideline for Screening and Treatment of Cervical Pre-cancer Lesions for Cervical Cancer Prevention review. The update process was based on Health Technology Assessment (HTA) and built from systematic literature reviews and cost-effectiveness analyses, focused on evaluating the benefits and harms associated with different alternatives, and conducted with extreme methodological rigor. The second edition of the guideline was published in July, 2021 (10).

Although CC elimination is a WHO priority, the impact of the new coronavirus disease (SARS-CoV-2/covid-19) pandemic may compromise the achievement of the proposed goals, as elective care was momentarily interrupted, causing a backlog (11). In Brazil, almost all cancer screening, diagnostic investigation and treatment related procedures decreased in 2020 compared to those recorded in 2019. Cervical cytopathological exams dropped 42% (12). However, the pandemic can be considered an opportunity to reassess CC control actions, increasing HPV vaccination coverage, promote screening organization and incorporation of novel technologies (13).

A timeline of cervical cancer prevention actions in Brazil is summarized in Figure 1.

Cervical cancer mitigation through vaccination, screening, and treatment

Prophylactic HPV vaccination in Brazil

HPV vaccines have been approved for distribution in Brazil through the SUS in late 2013. By March 2014, the first doses were distributed free of charge for young girls aged 11–13 yrs-old. One year later (2015), girls aged 9–10 yrs-old were also included in the PNI. Currently, the BMoH offers vaccination to girls aged 9–14 yrs-old (14). Women living with HIV (WLWH), solid-organ and bone marrow transplant recipients and cancer patients aged 9–45 yrs-old are also offered HPV vaccination (15). Since 2017, the distribution of the vaccine for young boys has also been approved, firstly for the 12–13 yrs-old range, and then expanded from 11 to 14 yrs-old (14). Likewise, young men living with HIV or under immunosuppression conditions from 9 to 26 yrs-old are also eligible for HPV vaccination (14).

Two vaccines have been initially approved in the country, the quadrivalent (qHPV, Gardasil®), protecting against HPV types 6, 11, 16, and 18; and the bivalent (bHPV, Cervarix®), protecting only against the high-risk oncogenic HPV types 16 and 18. These vaccines have been approved by the FDA in 2006 and 2009, respectively, denoting a significant delay in implementing HPV vaccination in large scale in Brazil. The BMoH adopted mostly the quadrivalent HPV vaccine for distribution within SUS, as it also includes protection against the development of anogenital warts in women and men induced by the low-risk HPV types 6 and 11. For girls and boys, two doses (0 and 6 months) are recommended; for those immunosuppressed (9–45 yrs-old), three doses are prescribed (0, 2 and 6 months). A third HPV vaccine, the non-avalent one (encompassing the HPV types 6, 11, 16, 18

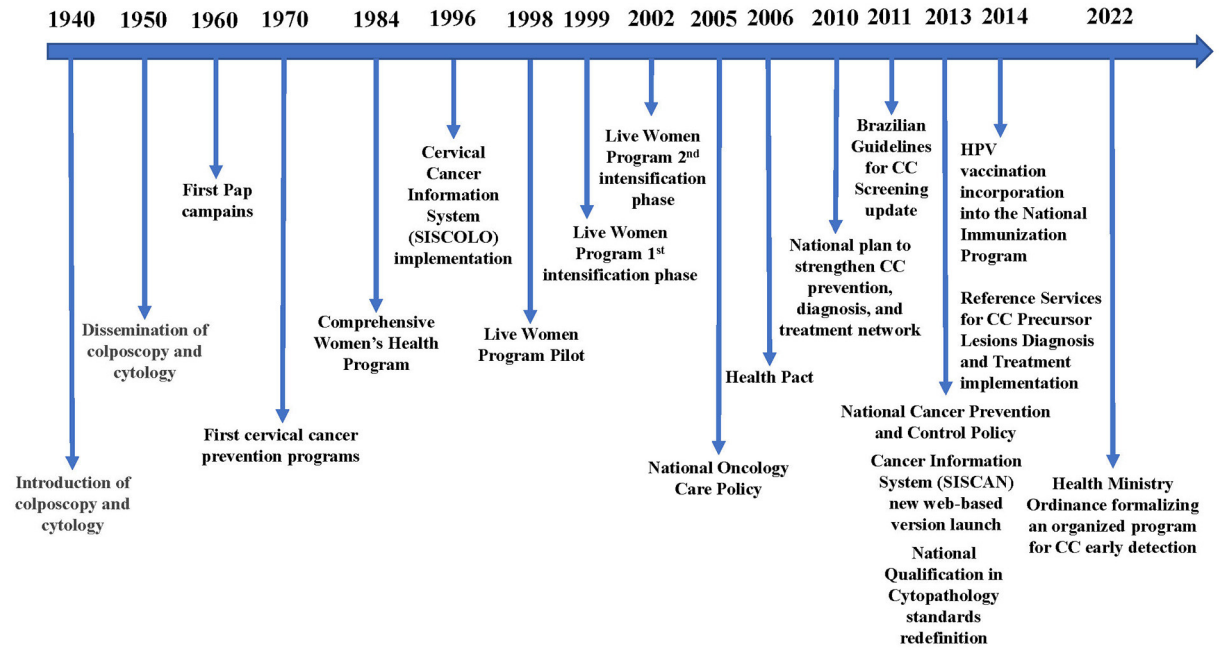

FIGURE 1
Timeline of cervical cancer prevention actions in Brazil.

present in the qHPV and additionally the types 31, 33, 45, 52, and 58; nHPV, Gardasil-9®), has also been developed, but is not incorporated into the Brazilian SUS free of charge. The additional HPV types covered by this vaccine protect for an additional 20% of cervical cancer cases induced by infection with those HPV types, and its adoption by the Brazilian government would be desirable, pending cost-effectiveness and budget impact analyses.

Maintaining HPV vaccination coverage constitutes a major challenge for most developing countries, and Brazil is no different in that regard. When comparing the two 1st years after the introduction of the HPV vaccine in Brazil (2014 vs. 2015), a reduction of 22% in coverage of the first dose has been observed (92 vs. 70%). In the 1st year of vaccination for boys (2017), the coverage of the first dose in that group was only 44% (16). Despite the fact that men can, in principle, benefit from the herd immunity provided by vaccination of women, this concept does not apply to men who have sex with men, who are not reachable by herd immunity and must rely on good vaccination coverage among boys (17).

As a country with continental dimensions, Brazil has also been impacted by socio-demographic and spacio-geographic factors that promoted low coverage HPV vaccination. In the 1st year of vaccination (2014), 87% of the Brazilian municipalities had achieved the goal target of 80% coverage for the first dose among eligible girls; this number dropped to 32% of the cities for the second dose (18). Numerous individual factors have been described as associated with low HPV vaccine coverage, including low educational level, low income, countryside residence and low access to information and health services (19–22). At a population level, social/structural determinants are paramount, such as living conditions, presence of sewage, piped water, garbage collection, etc. Along those lines, a study conducted with data from 2014 to 2017 across three cohorts of girls under eligibility for vaccination in that period showed Brazilian micro-regions of low coverage for the first dose in the North region of the country, particularly in the state of Amazonas and in some parts of Pará state (23). Coverage for the second dose followed the same socio-economic patterns, but with generalized lower percentages across the country compared to the first dose, as expected. In summary, a great impact of the social inequality across Brazil was seen on the spatial heterogeneity of the HPV vaccine coverage, urging for specific planning of strategies for each territory by state health authorities, including the expansion for a school-based program (23, 24).

Recently, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization reviewed real-world evidence on the efficacy of a single dose HPV vaccine schedule and advised that countries may adopt it for 9–14-year-old girls (25). This alternative schedule is less resource-intensive and easier to implement from the public health prospect, and could be evaluated in the Brazilian context.

Cervical cancer screening

Strategies aimed at increasing vaccination coverage would have minimal impact on cervical cancer incidence by 2030. As the impact of vaccination is long-term, it is essential to combine this strategy with screening if the WHO targets are to be achieved. Scaling up twice-lifetime cancer screening and treatment in addition to vaccination would result in a 34.2% mortality reduction by 2030 in low- and middle-income countries (LMICs) (26). A modeling study estimated that with 20–45% vaccination coverage and 25–70% once-per-lifetime screening coverage by 2030, followed by an increase in vaccination coverage to 40–90% and in once-per-lifetime screening coverage to 90% by 2050, the average cervical cancer incidence rates would decline to 1.3 per 100,000 for high-human development index (HDI) countries like Brazil (27). According to this modeling study, assuming a minimum twice in lifetime (at 35 and 45 years) CC screening in Brazil, the target incidence rates of 4 per 100,000 would be reached between the years 2070 and 2075. However, the baseline screening coverage considered for Brazil in the model was 82% and several other relevant issues were not considered, like timely access to the diagnostic confirmation and subsequent treatment of pre-malignant lesions or cervical cancer.

Although the results of the last national pre-pandemic health survey indicated that 81.3% of Brazilian women aged between 25 and 64 years underwent cervical cytopathological examination in the last 3 years, these are self-reported values that probably reflect some degree of overestimation (28). Moreover, this coverage is heterogeneous in the country, with lower coverage in regions with higher incidence and mortality rates and even lower coverage in socioeconomically disadvantaged groups in these regions (28). Another problem is the challenge of maintaining the quality of screening throughout the national territory. Although, in general, the percentage of unsatisfactory exams or with inconclusive results is within the expected parameters, indicators such as the positivity index and the proportion of high-grade intraepithelial lesion (HSIL) among the satisfactory exams indicate that the sensitivity of the screening is still below the desired level in some regions and in some cases the positivity index is inflated by inconclusive results such as atypical squamous cells (28, 29). Thus, the real impact of effective screening strategies in these regions and among women never screened will probably be higher than predicted by the models.

HPV detection tests were recommended by WHO as the primary screening method for both the general population of women and WLWH (9), as they are more effective than cytology in reducing CC incidence and mortality, due to higher sensitivity, negative predictive value (NPV) and reproducibility (30, 31). Although HPV detection tests have not yet been incorporated into SUS, recommendations to guide professionals working in scenarios in which these tests are available have already been published, so they can be used based on scientific evidence and according to best practices (32). Additionally, studies investigating the molecular approach shift in CC screening in the Brazilian context have been conducted and published (33–37).

Incorporating molecular tests into screening would bring some interesting perspectives such as automation and increasing the age of onset from 25 to 30 years and the interval between screening tests from triennial to quinquennial, due to high NPV and high sensitivity. For this to occur, the change in technology must be linked to the change in the organizational model, with the migration from opportunistic to population-based screening. In the current model of opportunistic screening, a significant lack of adherence to target population and screening interval recommendations persists. In the SUS, around 20% of screening cytopathological exams are performed outside the target population and 73% are performed outside the recommended interval, usually annually (29, 38). This inadequacy results in a screening model less efficient than it should be, even with the current technology. Several barriers to the implementation of the current guidelines for cervical cancer screening in Brazil, as seen from the public health manager perspective, have already been identified recently, of which the main ones were the low adherence of health professionals to the guidelines in the context of the opportunistic screening and the disorganization of the health services (39). Switching to molecular methods without organizational change would remove some of the key benefits of the new technology and could exacerbate overscreening.

An interesting perspective of the new screening methods is the possibility of incorporating self-sampling, which can reduce geographic access barriers, minimize cultural resistance to being examined by a health professional and favor the active search of women who do not regularly attend health services. Several strategies for implementing self-sampling are being studied (40), but their effectiveness may be impacted by local issues like educational level, health literacy and other cultural and socioeconomic issues.

SUS primary care covers 76% of the country's population (41). The Family Health Strategy is organized by geographic regions and composed by multi-professional healthcare teams, including community health workers. There is evidence on the impact of this strategy on mortality of adults aged 25–64 years (42). Family health teams register the population assigned to their territory and community health workers carry out periodic home visits, which could be used for active individual invitations to population-based screening.

Another improvement needed is the integration of SISCAN with the primary care information system (Sisab). This linkage between systems will allow the identification of the target-population and the organization of individual invitations for screening in primary care settings throughout the country. Moreover, the new mobile application of the Ministry of Health, called "ConecteSUS," allows the direct interaction of health

services with women and could also be used to invite the target-population for screening at the correct intervals and also for recall in case of positive exams.

Remuneration per procedure is the logic still in force in the country, with publicly funded screening even when performed outside the target population or recommended interval. To induce a shift to an organized screening program, this funding model should be modified to be based on the needs of the entire line of care, involving screening, diagnostic confirmation and treatment. In this new financing model, coverage of the target population, the follow-up of women with positive screening and the achievement of quality indicator targets would be encouraged.

In Brazil, there are some pilot experiences with new screening methods and better organization of screening (33–37, 43). Since 2012 an organized CC screening has been established in the interior of the State of São Paulo (18 municipalities in Barreto's region) (43). A computerized system enables the institutions to send letters inviting all women within the target-population to liquid-based cytology screening. The system identifies each woman's last cytology test and automatically generates the date on which she must repeat the exam. Women receive the cytology result and the next appointment date at their home address. Women with abnormal screening tests requiring recall for further assessment are automatically listed and have the appointment scheduled. Additionally, the system identifies women who are not up to date with their screening tests, generating convocation letters. The system also records sociodemographic information; previously performed cervical cytology screening results; quality indicators for monitoring both sample collection and laboratory analysis; follow-up and additional tests, such as colposcopy and biopsies and respective results. The collected exams percentage increased from 54.6% in 2012 to 62.4% in 2013, to 68.4% in 2014, and to 71% in 2015. Only 5% of all carcinomas were detected at stages III/IV and 98% of women with abnormal results attended colposcopy. However, screening coverage has not reached the 70% target.

Another recent initiative is the "PREVENTIVO" program (PREvention of HPV Viruses in ENTire Indaiatuba by Vaccination and Organization of Screening), a pivotal demonstration study developed in a real-life scenario in a Brazilian city, comparing CC population-based screening using primary DNA-HPV testing with the traditional opportunistic cytology-based strategy in the public health system context (35). The program achieved high coverage (80%) and age compliance (99.2%, compared to 78% for cytology). The HPV-based screening detected 21 women with CC with a mean age of 39.6 years, and 67% of cancers were early-stage compared to 12 CC cases detected by cytology ($p = 0.0284$) with a mean age of 49.3 years ($p = 0.0158$), and one case of early-stage ($p = 0.0014$). Furthermore, Indaiatuba's new program has proven more cost-effective than the conventional cytology-based screening (44).

The country has 5,570 municipalities and the great challenge is how to scale up organized screening programs. An innovative approach could be to link the use of new technologies to the change in the organization model and national and state managers to enable municipal managers to adhere to the new model based on eligibility criteria. A new ordinance by the Brazilian Ministry of Health, which formalized an organized program for the early detection of cervical cancer, could be an initial step toward this new model (45), although a general environment of encouraging the performance of screening tests outside the target population persists.

Other major barriers to the effectiveness of screening in Brazil are the access bottlenecks to diagnostic confirmation and treatment of precursor lesions. National pre-pandemic SUS data showed a deficit of 7.3% for colposcopy, 20.4% for biopsies, and 74.8% for type 1 and 2 excision of the transformation zone (ETZ) on an outpatient basis and 67.6% for type 2 ETZ and type 3 ETZ in hospitals (46). A recent study, carried out in a municipality with a high incidence of cervical cancer in the North of the country, showed 27.1% without evidence of any follow-up and 74.3% without complete work-up 10 months after screening among women with HSIL+ screening results (47). The entire process is very fragmented, and a woman who needs diagnostic work-up and treatment will generally require nine visits to health services, with an average time between cytology screening and colposcopy of 105 days, 40 days between biopsy and the histopathological report and additional 150 days until a high-grade lesion treatment (48). Therefore, the change in technology should also be considered in conjunction with protocols that reduce the number of steps in this process, in order to increase adherence. Furthermore, the switch to screening by HPV tests needs to be carried out in an organized program and complemented by a triage test because HPV infection is commonly found, so that there is no risk of aggravating the bottleneck in accessing diagnostic confirmation.

WHO guideline suggests triage of HPV DNA-positive women using cytology, partial genotyping, colposcopy or visual inspection with acetic acid (VIA). As the benefits, harms and programmatic costs of these triage methods are similar, the choice depends on feasibility, training, program quality assurance and resources (9). From the Brazilian perspective a recent review suggests that reflex liquid-based cytology or partial genotyping should be performed after a positive HPV test to avoid unnecessary colposcopies and follow-up losses (32). Other triage options under investigation are mRNA-HPV, extended genotyping, dual staining, and methylation (49).

Even if effective and efficient triage of HPV DNA-positive women is available, in certain settings of the country colposcopy and biopsy will remain a burden, and a screen-and-treat approach could be considered (9). Furthermore, new promising optical techniques/imaging methods are in development, such as low cost portable digital colposcopes, high resolution microendoscopes, and the use of smartphone technology and

artificial intelligence/deep learning algorithms for automated interpretation of cervical images (50, 51).

Treatment

Therapeutic HPV vaccination and the Brazilian perspective

All currently approved prophylactic HPV vaccines induce anti-HPV immunity through recombinant viral capsid proteins, L1 and L2 (52, 53). However, these viral proteins are not or are very rarely expressed in cells transformed with HPV. Therefore, subjects with persistent oncogenic HPV infection or HPV-associated established cancers do not benefit from vaccination with the current products (54, 55).

Therapeutic HPV vaccines should be based on viral products that are expressed in malignant cells, such as the viral oncogenic proteins E6 and E7, the major drivers of HPV-mediated oncogenesis (56, 57). Yet no product has been yet approved for clinical use anywhere in the world, research on therapeutic HPV vaccines are increasing over time, and over a 100 initiatives have already been registered at ClinicalTrials.gov (58), being most of them DNA vaccine products encoding the abovementioned viral oncoproteins or capsid proteins and using different delivery strategies. DNA vaccines are able to induce cytotoxic T-lymphocyte (CTL) responses that specifically target epitopes of these proteins expressed in HPV-transformed cells, leading to their elimination (59).

So far, two DNA vaccine candidates against HSIL have reached phase III clinical trials in Mexico and U.S. One of them, MVA E2, has been designed to induce cross-protective immunity to HPV using bovine papillomavirus (BHV)-specific E2 antigen inserted into a modified vaccinia Ankara (MVA) virus. The largest phase III trial enrolled over 1,300 subjects (mostly women) who received six injections of the immunogen in the malignant tissue. Almost 90% of the vaccinated women eliminated their lesions, and 80% cleared the oncogenic HPV associated with the disease (60). The other vaccine candidate (VGX-3100), using a completely distinct strategy, is based on naked plasmid DNA molecules carrying the genes that encode E6 and E7 from high-risk HPV types 16 and 18 and a delivery system using electroporation (61). In a modified intent-to-treat analysis with 193 patients recently publicized (62), 23.7% of patients in the vaccinee group responded with HSIL regression and HPV clearance at week 36, compared to only 11.3% of patients in the placebo group. Noteworthy, this vaccine has already shown efficacy against anal and vulvar displasia associated with HPV infection during phase II trials (63, 64).

Brazil has also developed anti-HPV therapeutic vaccine candidates in the latest decade. The most promising candidate has just been publicized by researchers from the University of São Paulo and other centers (65). The use of a recombinant fusion protein between HPV16 E7 and the herpes simplex virus 1 glycoprotein D (gD), either in the form of purified protein or recombinant DNA encoding this fusion, together with cisplatin treatment (the standard-of-care treatment for cervical cancer stages IB through IV) resulted in a synergistic control of HPV-associated advanced-stage tumors with reduced toxic effects in C57BL/6 mice. Moreover, the combined use of cisplatin and gDE7 protein induced tumor infiltration of immunomodulatory cell subsets and E7-specific CD8+ T-cells, and reduced the frequency of myeloid suppressor cells. Finally, such combination also induced synergistic therapeutic effects in advanced tumors as well as immunological memory responses and long-term protection from tumor relapses at different anatomical sites (65). The "chemo-vaccination" strategy proposed by the authors is a promising approach for the treatment of cervical cancer and likely to be further evaluated in early-phase clinical trials.

Precancerous lesions

CC precursor lesions treatment options include ablation with cryotherapy or thermal ablation, and excisional methods as loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC). Meta-analyses comparing the efficacy of these treatments showed similar performance (66, 67). Consequently, the method of choice should be based on available resources.

Ablative therapy is cheaper, safer, and simpler to use, can be performed by non-medical providers without anesthesia, but requires cervical visual assessment because it is recommended just if the cervical lesion is entirely visible, does not extend to the endocervix or the vaginal wall, and is totally covered by the probe tip. Cryotherapy relies on gas (carbon dioxide or nitrous oxygen) supply, which is difficult to procure and transport, although portable devices with built-in gas systems have already been developed. Thermal ablation is recommended by WHO in LMICs because it is technically easier to deliver than cryotherapy as the devices can be battery-operated, are lightweight, and have a shorter treatment time. Ablation is ideal for point of care treatments at the primary care level or for a screen-and-treat approach, and could be considered in some Brazilian settings (50, 51).

Excision is recommended if there is a contraindication for ablation, and is often preferred in high-resource settings because it allows histopathologic diagnosis. However, adverse events such as bleeding, infection, and obstetric complications (preterm delivery and perinatal mortality) are more frequent. Additionally, LEEP and CKC require medical training, anesthesia, hemostatic agents, electrical supply, diathermy machine, and loop electrodes (50, 51).

Cervical cancer

The advances in oncological care in the SUS in recent decades are undeniable (68). However, barriers to timely access to treatment still persist. In 2019, 48.3% of women had

TABLE 1 Existing barriers in cervical cancer control in Brazil and pertaining approaches.

Key steps	Barriers	Approaches	Action needed
HPV vaccination	Low coverage	Single dose	National Immunization Program, Primary health care, and Ministry of Education articulation
		School-based program	
		Non-adherent target-population active recruitment	
		Target-population, parents, and teachers IEC	KAP studies
		Health professionals training	
	New technology availability	nHPV incorporation	CEA, BIA
Screening	Opportunistic	Populational-based organized screening	Primary and Specialized health care articulation, including information systems
		Call and recall	
		Quality assurance	
		Precursor lesions timely follow-up and treatment	
	New technologies availability	DNA-HPV, mRNA-HPV, HPV genotyping, self-sampling, dual staining, methylation, portable devices and automated visual evaluation, thermal ablation incorporation	Regulatory approval, CEA, BIA, guidelines update
	Heterogeneous settings	Resource-oriented	Guidelines update with implementation of screen and treat protocols for some clinical settings
Diagnosis	Timely access	Improvement of the integration of different health services; active follow-up of women with positive screening; decrease in the number of consultations and unnecessary visits by women to health services	Release of a new module for follow-up in SISCAN (in progress); improve the implementation of clinical regulation; guidelines update
Treatment	Timely access	General population IEC and health professional training on early diagnosis;	KAP studies;
		Reduce shortfall in oncology services	Specialized health care capacity building
	New technologies availability	Anti-HPV therapeutic vaccine development	R&D
		Target therapy and immunotherapy	Regulatory approval, CEA, BIA, guidelines update

IEC, information, education, and communication; KAP, knowledge, attitudes, and practices; nHPV, human papillomavirus ninevalent vaccine; CEA, cost-effectiveness analysis; BIA, budget impact analysis; SISCAN, Cancer Information System; R&D, research and development.

more than 60 days between the diagnosis of cervical cancer and the start of treatment in the SUS and 22.8% had no information on treatment (69). During the pandemic, there was, paradoxically, some improvement with a drop in this percentage to 45.7% treated after 60 days (69), which may be related to the lower demand due reduction of diagnosed cases and less treatments (12).

A prospective cohort study of newly diagnosed patients with CC recruited at 16 Brazilian sites representing the five Brazilian regions found that most patients were diagnosed with locally advanced or metastatic disease (FIGO clinical stage II-IV in 81.8%, stage II in 35.2%, stage III in 36.1%, and stage IV in 10.5%) (70).

Early stage cancers (FIGO stages IA1, IA2, IB1), and in some selected cases stages IB2 and IIA1 may be treated by surgery alone or by a combination of surgery and adjuvant therapy. Locally advanced disease (FIGO IB2-IVA) requires chemoradiation plus high-dose-rate (HDR) brachytherapy. For metastatic and recurrent disease angiogenesis blockade and immunotherapy with checkpoint inhibitors and other agents are currently available in high resource settings. First-line treatment for patients with recurrent and/or metastatic CC includes the association of bevacizumab with chemotherapy. Important advances have been demonstrated in the last decade for second-line treatment with immunotherapy (71–73).

Notwithstanding, in 2016 the Brazilian health technology assessment (HTA) agency (Conitec in the Portuguese acronym) recommended against incorporating bevacizumab for the treatment of persistent, recurrent or metastatic CC in SUS, as the treatment was not considered cost-effective (74). Immunotherapy is not available as well. And aggravating this bottleneck regarding advanced disease, there is a shortfall in public radiotherapy services for cancer treatment in Brazil (75).

Table 1 summarizes the existing barriers to CC control in the country and lists pertaining approaches.

Conclusion

The effort to eliminate CC as a public health problem in Brazil requires a combination of multiple steps and strategies regarding primary prevention, screening, diagnosis, and treatment. The incorporation of novel technologies and approaches in those fronts is expected to help driving the country toward an elimination target. New approaches include single dose HPV vaccination—recently preconized by the WHO –; the adoption of the non-avalent vaccine, accounting for an additional 20% of the CC cases; an organized screening based on a populational basis, with assured quality, timely follow-up and treatment; novel technologies of screening and triage (DNA-HPV, mRNA-HPV, HPV genotyping, dual staining, methylation); and novel methods diagnosis and treatment of precancerous lesions (pocket colposcope, automated visual evaluation, and thermal ablation). Nevertheless, the incorporation of new technologies is not enough to impact cervical cancer incidence and mortality in a continental country with heterogeneous settings ravaged by profound inequities. Programmatic changes and resource-oriented approaches at national, regional and local levels are paramount to honor the commitment made with the WHO global call.

Author contributions

All authors collected and analyzed the regulatory, guideline, experimental data and information, prepared the first draft of the manuscript, contributed to manuscript revision, read, 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.

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Piloting a systems level intervention to improve cervical cancer screening, treatment and follow up in Kenya

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Although preventable, Cervical Cancer (CC) is the leading cause of cancer deaths among women in Sub-Saharan Africa with the highest incidence in East Africa. Kenyan guidelines recommend an immediate screen and treat approach using either Pap smear or visual screening methods. However, system (e.g., inadequate infrastructure, weak treatment, referral and tracking systems) and patient (e.g., stigma, limited accessibility, finance) barriers to comprehensive country wide screening continue to exist creating gaps in the pathways of care. These gaps result in low rates of eligible women being screened for CC and a high loss to follow up rate for treatment. The long-term goal of 70% CC screening and treatment coverage can partly be achieved by leveraging electronic health (eHealth, defined here as systems using Internet, computer, or mobile applications to support the provision of health services) to support service efficiency and client retention. To help address system level barriers to CC screening treatment and follow up, our team developed an eHealth tool—the Cancer Tracking System (CATSystem), to support CC screening, treatment, and on-site and external referrals for reproductive age women in Kenya. Preliminary data showed a higher proportion of women enrolled in the CATSystem receiving clinically adequate (patients tested positive were treated or rescreened to confirm negative within 3 months) follow up after a positive/suspicious screening, compared to women in the retrospective arm.

KEYWORDS

eHealth (mobile Health), system—level, cervical cancer screening, cervical cancer treatment, Kenya, cervical cancer tracking

Introduction

Cervical Cancer (CC) is preventable through HPV vaccination and screening to detect precancerous lesions; yet in 2018, an estimated 570,000 cases were diagnosed and 311,000 deaths occurred globally (1). In Kenya, CC is the second leading cancer in women, and the leading cancer-related death in women. Around 5,250 new cases of CC are diagnosed annually, and 3,200 women die of CC every year in Kenya (2).

Early detection and treatment of abnormalities and precancers that are likely to progress to invasive carcinoma (3) not only improves overall patient outcomes (5 year survival is 95.7 vs. 9.9% for CC diagnosed at stage 1a1 vs. stage IVb (4, 5) but also reduces the cost of treatment to the patient and health system (USD $85 for stage 0 vs. $1575 for stage III curative) (6). In most cases, CC is due to human papillomavirus infection (7). When HPV infection persists, the time from initial infection to development of high-grade cervical intraepithelial neoplasia and, finally, invasive cancer takes an average of 15 years. This combined with the system and patient screening barriers experienced in resource limited settings highlights the importance of frequent screening to detect intraepithelial disease, for prompt management. To achieve population level health gains, the WHO recommends countries reach 70% coverage with screening and 90% of those needing it receiving treatment (8).

Although awareness of the importance of CC screening is increasing (9), only 16–19% of eligible Kenyan women 18–69 years old are screened for CC (10). These low rates of screening contribute to 50–80% of cases identified in advanced stages of CC (11–13). Due to low cost, Visual inspection with acetic acid (VIA) and Visual inspection with Lugol's iodine (VILI) techniques are the most used screening methods in a low resource settings like Kenya. Kenyan guidelines call for a "screen and treat" protocol for women with pre-cancerous lesions identified by VIA/VILI (when PAP or HPV testing is unavailable), in which treatment is administered on the same clinic visit as diagnosis to minimize patient burden, treatment delay, and loss to follow-up (LTFU) (14). However, in a survey of 12 hospitals across 7 counties, only 25% of facilities had a functional cryotherapy machine (9), allowing them to offer services compliant with these guidelines. Even amongst those who offer same day services, supply stock outs, C02 shortages for the cryotherapy machine, and lack of trained providers available to perform the procedure can delay treatment and cause increased burden on patients (15, 16). Of those who do not receive same day services, only 20–53% of those diagnosed returned for cryotherapy (15, 16). Indeed, in a multinational study in sub-Saharan African capitals, only 15.8% of CC patients received care with curative potential (17). Individual and social barriers to treatment include concerns about side effects, treatment—related fear and stigma, fear of marital discord, religious and cultural beliefs, geographical location (rural vs. urban), and limited knowledge (18, 19). Financial constraints and long distances to travel for available services also pose substantial challenges to treatment access (20).

eHealth and eHealth interventions have been widely implemented in the past decade to support a range of health-related outcomes and have the potential to improve CC screening and follow up care. In Kenya, eHealth interventions have increased maternal retention in guideline-adherent PMTCT services and on-time testing of infants exposed to HIV (21, 22), and have improved postoperative circumcision follow up (23). In Kenya, patients who received CC rescreening reminders *via* SMS were eight times more likely to adhere to scheduled rescreening than those who did not (24). In a study evaluating the impact of sending CC screening results *via* SMS or phone call, women found both options acceptable and effective and resulted in higher treatment follow up than relying on patient clinic visits to relay results (25). Adapting proven eHealth strategies offers countries low cost strategies to address persistent gaps in the continuum of CC care.

Materials and methods

This study presents the findings from a pilot study utilizing an eHealth tool—the Cancer Tracking System (CATSystem), an adaptation of a web-based eHealth intervention called the HIV Infant Tracking System (HITSystem) (21). Designed for use in low to middle income settings, the primary goals of the CATSystem are to (a) increase rates of CC screening, (b) improve the treatment, referral (internal and external), and follow up rates of women screened positive with precancerous and cancerous lesions and c) identify missed re-screening and treatment opportunities. Using algorithm driven alerts for providers and SMS to patients, the CATSystem is designed to support CC screening, treatment, and referrals for reproductive age women (HIV + and HIV–) in Kenya. The system accesses satellite broadband *via* modems, generates a provider dashboard linking to patients who are overdue for a service or in need of patient outreach, and sends automated customized text messages to women to support screening and treatment follow-up per national Kenyan Ministry of Health guidelines (14). Decentralized for data entry, authorized providers (mentor mothers, data clerks, or clinicians) enter data in real-time at implementing hospitals, allowing the generation of timely alerts and provider follow up (patient tracing, phone calls, or SMS); however, as a web-based intervention, centralized updates to the programming of the system are automatically applied across sites as they become available.

Study overview

This study was an observational study with historical controls to evaluate an 11-month pilot of the CATSystem at one provincial level hospital in Rift Valley, Kenya. The standard of

care at the facility includes paper-based record keeping for CC screening (VILLI/VIA, pap smear and colposcopy) and on-site treatment with cryotherapy and loop electrosurgical excision procedure (LEEP). Patients needing chemotherapy or radiation treatment are referred to Kenyatta National Hospital, in Nairobi, which is approximately 160 km (3–4 h drive one-way) from the study hospital.

Cancer tracking system intervention

Adapted from the HITSystem, which is an eHealth intervention that has proven effective in improving maternal and infant HIV care in Kenya (21, 22), the CATSystem is an eHealth intervention that aims to improve follow up after an abnormal CC screen and increase rescreening rates per Kenya Ministry of health Guidelines (see **Figure 1**). Women are enrolled in the CATSystem through the comprehensive HIV care centers (CCC) and maternal and child health/Family Planning (MCH/FP) department. Demographic and contact information are captured at the time of enrollment. The patient is assessed for risk factors of CC including HIV status, age of onset of sexual activity, number of sexual partners, history of sexually transmitted infections, prior positive screenings, or history of *in situ* carcinoma of the vulvar or vaginal epithelium. Women are screened and those who have an abnormal CC screen are ideally treated on the same day. If the patient is unable to undergo same day treatment after a positive screen, the system sends an automated SMS alerts prior to the scheduled appointment and alerts in case of a missed appointment. They are tracked until they complete clinically indicated care based on their unique clinical presentation. After completing appropriate management for suspicious malignancy/*in situ* carcinoma or invasive malignancy, the patient continues to get automated alerts for follow up care based on national guidelines. Women who have a normal screen are prompted for rescreening at the indicated interval. Algorithm-driven electronic alerts notify clinical providers when patients are overdue or missing key services (treatment, labs, follow up care, missed appointments). The system also keeps a record of clinical findings, visual images of the cervix and lab results from each encounter.

The CATSystem was piloted in the Comprehensive Care Center (CCC, where HIV services are provided) and Maternal and Child Health Departments (MCH) from October 22nd, 2019, to January 26th, 2021. These departments are the two main points where CC screening occurs. The inclusion of the CCC also allowed us recruit women living with HIV who are vulnerable to CC due to the associated risk between HIV and contracting the Human Papilloma Virus (HPV) (26, 27). Each department had one or two nurses or clinical officers to conduct screenings and cryotherapy treatments. The facility had two gyno-oncologists to perform complicated procedures [biopsies, loop electrosurgical excision procedure (LEEP)]. Treatments for invasive CC (chemotherapy, radiation, radical hysterectomy) were referred to the highest tier referral hospitals. During this time, hospital operations across the country were limited or shut down due to multiple healthcare worker strikes (2019, Dec 2020–Feb 2021) and COVID-19 mitigation strategies (May–June 2020) affecting daily hospital operations and pilot study data collection. Data from enrolled participants were compared to data from historical controls who were screened for CC in the 6 months prior to CATSystem implementation April 2019–October 2019.

Study participants

All women ages 18–50 years who received CC screening in CCC or MCH during the study period were eligible. Due to the CATSystem's use of SMS text messages, women also needed cell phone access to participate in the study. All participants provided written informed consent prior to study participation.

During the historical control period, paper CC screening registries from CCC and MCH were reviewed. Data were entered in an Excel spreadsheet by study staff. Although the registries followed the required ministry of health format, the data quality was highly variable regarding consistency, completeness, and evidence of follow up. Where paper records were incomplete, study staff followed up with providers to fill in gaps as much as was possible and ensured that duplicate records were reconciled; however, in many cases retrospective data remained incomplete.

Study procedures

Clinic providers or study staff informed women presenting for CC screening about the purpose of the CATSystem and asked eligible women if they would like to participate in the study or would prefer to receive standard of care (paper-based record keeping without action alerts or communication). Participants' demographic and place/s of residence information were entered into the CATSystem upon enrollment. All subsequent counseling and clinical care data (including appointments, laboratory tests and results, treatment, rescreening) were entered into the CATSystem by a study research assistant. The CATSystem then used dates of services and other clinical criteria (i.e., screening results, appointment dates) to trigger electronic alerts to prompt providers when time-sensitive actions along the CC cascade of care were needed (see **Figure 2** for an image of the dashboard). Clicking on each alert name would bring up a list of patients requiring that service, allowing providers to easily identify and initiate follow up among patients with incomplete services. Alerts were only resolved once the indicated action had taken place and had been recorded in the CATSystem. Finally, an informal "lunch and learn" style group discussion was held with providers (CCC Nurse, MCH Nurse, MCH Clinical Officer, two Gyno-oncologists and Laboratory

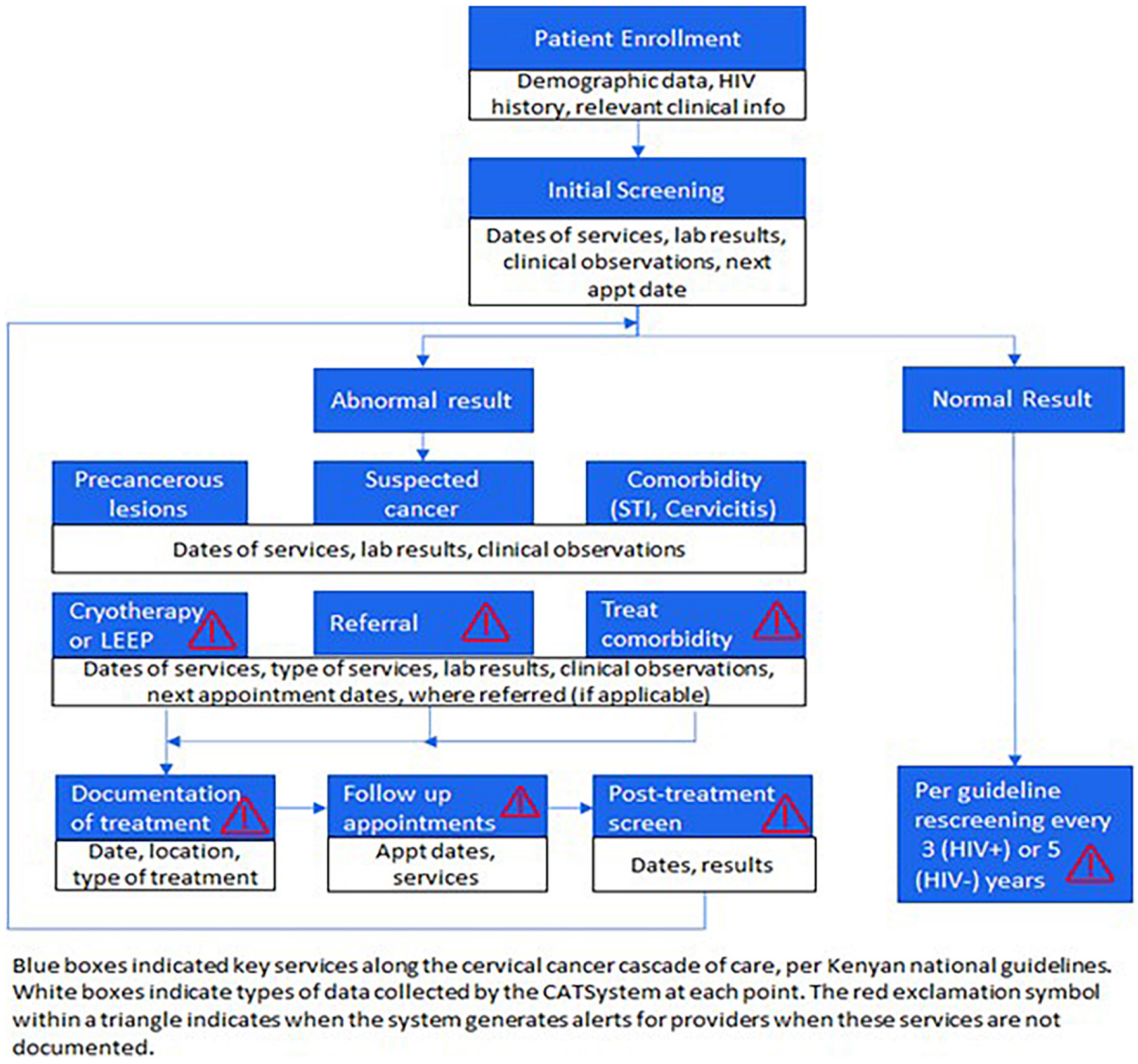

FIGURE 1
Kenya ministry of health national cervical cancer screening guidelines.

technician) where facilitators and challenges to utilization and identified modifications to the CATSystem that could improve its utility and implementation.

Outcomes

The primary outcome of our study was "clinically appropriate care" after an abnormal CC screen defined as completion of any of the following actions: (1) Onsite treatment for precancerous lesions, (2) onsite or referred LEEP treatment for more severe precancerous lesions, (3) referral to a treatment center if suspected of invasive cancer, or (4) treatment of coinfections (e.g., cervicitis or STI), followed by a re-screen with appropriate follow-up within 3 months. We compared the pilot data to a 6-month retrospective record review of all female patients seen in settings where CC screening should have been conducted prior to CATSystem implementation.

Analyses

Descriptive statistics were calculated for demographic variables and risk factors for CC. Continuous variables were expressed as mean ± SD where applicable. Due to limitation in availability of historical control data, output is only available for intervention arm demographic and risk factor variables. The primary outcome was proportion of patients with a positive screening obtaining clinically appropriate care. A chi-square analysis was done on the categorical outcome to determine significance. Data was analyzed using SPSS v27.

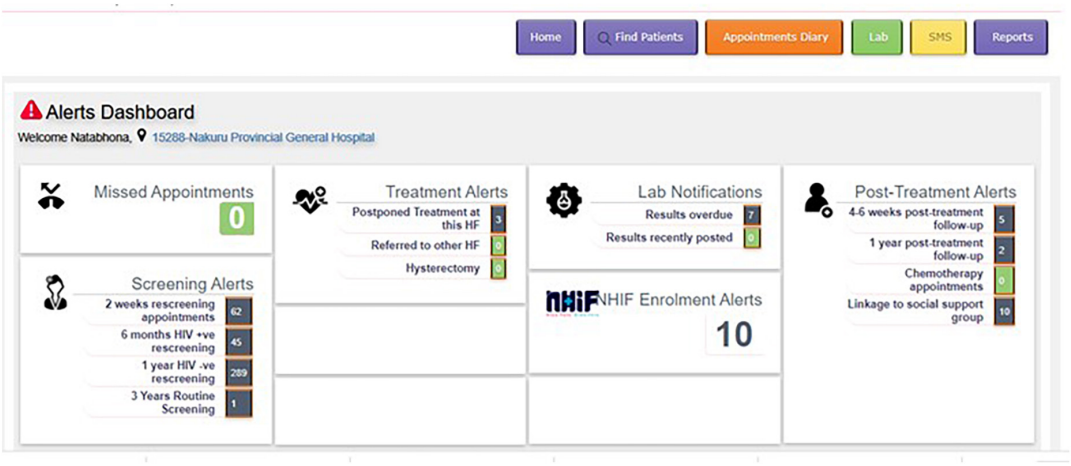

FIGURE 2
Cancer tracking system (CATSystem) dashboard.

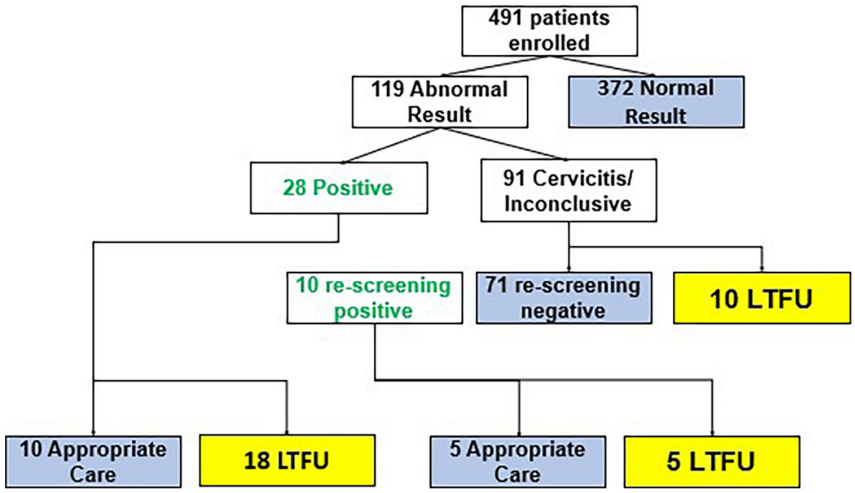

FIGURE 3
Flow of cancer tracking system (CATSystem) participants through cervical cancer care. Blue boxes indicate completion of care. Yellow boxes indicate loss to follow up prior to completion of care.

Results

A total of 491 patients were enrolled during the intervention period, and a total of 1,702 patient records were reviewed during the control period. Patient demographics are shown in Table 1. Due to lack of documentation in the CC registries, most demographic variables for control site participants were unavailable. The demographics collected through the CATSystem, however, indicate that the right target population were accessed during the pilot.

Among the 1,702 records screened in the control arm, 50 encounters had a documented positive screening test for CC, either VIA/VILI or PAP Smear or both. Among these 50 patients, 4 (8%) received further care in the form of clinically appropriate care that is, same day treatment by cryotherapy, or referral to a higher center for gynecology or oncology referral. Completion of referral treatment (i.e., surgery, radiation therapy, chemotherapy or other diagnostic or therapeutic interventions) could not be obtained, hence a documented referral for appropriate care was considered clinically appropriate follow up.

In the CATSystem arm, 119 patients had an initial abnormal screening result; of whom, 28 had a positive screen, of these, 10 received clinically appropriate care and 18 were lost to follow-up. Ninety-one patients had inconclusive results due to cervicitis and required rescreening. Of these 91, 10 were positive upon

TABLE 1 Cancer tracking system (CATSystem) patient demographics.

Demographic	Intervention $N = 491$	Control $N = 1,702$
Age	38.6 ± 10.7 years	39.5 ± 11.3 years
Education		
Primary education	180 (40.9%)	–
Secondary education	150 (34.1%)	–
University/college	110 (25.0%)	–
Weekly income		
Less than 500 KES	196 (47.0%)	–
500–750 KES	64 (15.3%)	–
750–1,000 KES	36 (8.6%)	–
1,000–2,500 KES	121 (29.0%)	–
History of vulvar or cervical intraepithelial neoplasm	9 (1.8%)	–
First sexual encounter 18 years of age or earlier	196 (46.8%)	–
History of sexually transmitted infection	28 (5.7%)	–
HIV positive at baseline	128 (26.1%)	–

rescreening, 71 were negative, and 10 were lost to follow up. Thus, a total of **38** patients had a documented positive screening test. Of these 38, 15 (39.5%) received appropriate treatment that is same day treatment by cryotherapy, thermocoagulation or referral to higher center for further management (see Figure 3). In the CATSystem arm, patients continued to receive SMS reminders for re-visit for treatment or visit to a tertiary care facility for continuation of care. Ultimately, the CATSystem intervention led to a fivefold increase in the number of patients receiving clinically appropriate care ($p < 0.01$), after a positive screening result. That is, 15/38 (39.5%) compared to 4/50 (8%) among standard of care participants enrolled prior to CATSystem implementation received clinically appropriate care.

Discussion

Preliminary evidence from this pilot study indicates that the CATSystem is a promising tool that can help clinicians improve rates of clinically appropriate treatment and follow up for suspected and invasive CC. The primary outcome of the study was the proportion of women with a positive screen result who received clinically appropriate care for precancerous lesions. With the CATSystem, we observed a fivefold improvement in receipt of clinically appropriate care after a positive screen: 15/38 (39.5%) among CATSystem participants compared to 4/50 (8%) among standard of care participants enrolled prior to CATSystem implementation. Despite these improvements, significant challenges in the provision of CC screening and care persisted at the system and patient level including: (1) Limited capacity of CC screening providers which meant missed screening, treatment and follow up opportunities, (2) a lack of clear linkage channels between screening and treatment points within the hospital, and (3) patient travel and treatment costs delaying their return for treatment. Informal conversations with providers confirmed the improvement in clinical care and reinforced many of the facilitators and challenges to utilization in the Kenyan context noted in the literature. Providers felt that the CATSystem features (dashboard alerts of missed screening and treatment appointments, pathology/lab results) gave them a more comprehensive picture of where their patients were in the cascade of care compared to the standard registers and allowed them to follow up with patients more easily.

Many of the system and patient-level challenges were outside the scope of the CATSystem and would need to be addressed at the system level through training and/or policy change. These challenges contributed to 61% of women not receiving clinically appropriate care, even with enhanced follow up through the CATSystem. While this is a drastic improvement from the 96% loss to follow up observed in the retrospective data, it highlights the urgent need for system and policy level changes to address remaining gaps. Such actions to improve could include: enhanced coverage for CC care through the National Hospital Insurance Fund (NHIF); training dedicated clinicians for CC screening and treatment services; prioritizing data and data systems, ensuring the availability of resources for CC screening and cryotherapy at all sub-county and higher hospitals; funding of more CC treatment centers; increased coordination between government, research, academic, and NGO stakeholders (28, 29).

Unlike in HIV, funding for CC prevention activities is not contingent on regular reporting, reducing the level of accountability. As such current data reporting levels are disjointed and incomplete contributing to the overall lack of monitoring data in Kenya. In pre-intervention data review of this study, the data quality was highly variable regarding consistency, completeness and follow up. Both CCC and MCH generally have one staff member tasked with carrying out the screening and record keeping, which on busy days affected data entry. Furthermore, for facility and county reporting purposes just noting the number of negative and positive screens is often adequate when reporting to county Ministries of Health. Once patients are referred, informal conversations with providers revealed that they are often too busy to follow up on the patient with other departments or the patient themselves resulting in a significant number of gaps in the paper registry. In addition, record overlaps were possible between registries as patients could be seen in both CCC and MCH departments. A way to fill in the gaps would have been to follow up with the patients, but due to limited staff and budget this was not possible. The need for improved data and data systems has been well noted (29, 30) and this is an area the National CC registry/board want to improve (28). In our study, the CATSystem significantly improved data quality and completeness and, indeed, was designed to help address this gap. Furthermore, the CATSystem

was programmed with the potential to interact with the National Center Registry, an ability that to our knowledge no other CC eHealth technology in Kenya is currently able to do. Linking these systems could contribute to a comprehensive database of CC care and outcomes, nationally. Systems such as CATSystem can be integral to addressing the noted gaps and improving the CC cascade of care.

Early investments in screening can not only improve outcomes for women, but also reduce costs associated with later care and save lives. Public sectors costs for CC diagnostic and treatment procedures are estimated at $180.00 and $85.00–$1,500 (depending on stage), respectively (6). Studies report that only about 9–20% of CC patients have NHIF (National Health Insurance Fund) coverage, and this coverage is limited in what it provides, leaving patients to foot a substantial financial cost for treatment. At the main referral hospital KNH, patients can pay as much as $100–$300 for MRI'S and CT scans, and $300 per chemotherapy course, costs that are prohibitive given the national income average of $641 per month (31). Ultimately a multifaceted approach that includes the scale up of both screening and treatment, investment in data systems, and training is needed to address the burden of CC in Kenya (31). However, ensuring timely screening and rescreening through the less expensive VIA//VILI approach can ultimately lead to early diagnosis and treatment leading to reduced morbidity/mortality and preclude the need for more expensive procedures. The CATSystem can help systemize documentation and strengthen referral pathways; maximize the existing investments in CC care.

Next steps

System-level and Intervention specific challenges, barriers/opportunities were identified in the pilot study that will be incorporated as we seek funding to conduct a rigorous evaluation (randomized control trial) of the system which will allow for longer follow up with more sites thus increasing the generalizability of findings. System level changes would include (1) working with facility, and local and national ministry of health to provide continuing education around CC screening, and (2) working with facility providers and administrators to develop clear in hospital linkage channels between screening and treatment points. Intervention-specific changes would include identifying specific personnel to enter data and based on informal conversations with providers the following additions to the system: (1) Sending SMS reminders not only to patients but to providers to remind when dashboard alerts come into the system, (2) sending post- operative SMS instructions after procedures such as colposcopy, LEEP and cryotherapy, (3) providing frequent supervision support and follow up training, and (4) setting up a data coordination system between involved departments. Finally, we will also include a cost analysis to assess the cost effectiveness of the CATSystem providing an argument for scaling up to other facilities.

Limitations

The COVID-19 pandemic and the fall out within the health system including health worker strikes and limited access affected implementation of the study, this could in part account for the discrepancies we saw in numbers pre and post the intervention (32). However, we contend that the improvements are still noteworthy, especially given increased challenges with accessing healthcare during the intervention period due to COVID-19 restrictions. The incomplete CC paper registries due to limited staffing and busy providers as well as documentation errors made it difficult to collect full patient CC screening records for comparison with the system and we have no additional information on control participants outside of what has been reported. With more funding the work of following up with patients and other sources can be feasible. However, these limitations in data represent the standard of care in Kenyan facilities and emphasize the need for improved system of data management. Furthermore, the CATSystem is a passive system and can only reach the population presenting for care at study hospitals and this study only enrolled women presenting in MCH and CCC care. We acknowledge this as a limitation in that women who do not access care in these settings are represented in our study and our data do not allow us to estimate the proportion of women who may have been missed. We also do not have any additional information on the number of characteristics of women who were eligible for participation but chose not to participate. While the women missed by our study may have greater challenges accessing care and may bias our results, we have no information on their characteristics to expand upon this hypothesis. Rates of refusal will be more comprehensively documented in the proposed R01 and a plan to conduct community outreach to expand the reach of CATSystem has been drafted.

Conclusion

There was a fivefold increase in the rate of clinically appropriate care after a positive screen among patients enrolled in the CATSystem, compared to pre-intervention data. Furthermore, it significantly improved data quality and completeness, which represents a priority among national stakeholders. Investing in systems to increase the rates of early detection and treatment of precancerious lesions can improve patients outcomes and ultimately reduce the costs associated with significantly more costly treatment of later-stage detection.

Data availability statement

The datasets presented in this article are not readily available because data is identifiable. Requests to access the datasets should be directed to corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Kansas Medical Human Research Protection Program. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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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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Case study of cervical cancer prevention in two sub-Saharan African countries: Rwanda and Sierra Leone

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Background: Cervical cancer is a public health issue of global concern. It is a preventable disease but continues to threaten the lives of women, especially in developing countries in sub-Saharan Africa.

Methods: We selected two African countries in sub-Saharan Africa (the Republic of Rwanda and the Republic of Sierra Leone) to show a good example of cervical cancer prevention and constrains hindering countries from effectively implementing cervical cancer programs. Secondary data were collected from the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the Global Burden of Cancer (GLOBOCAN), the United Nations Development Programme (UNDP), and the World Bank and from official websites of the selected countries. A descriptive analysis method was used to source data and compare variables such as the associated factors, disease burden, prevention programs, health workforce, success factors, and challenges.

Results: Rwanda achieved 93.3% human papillomavirus (HPV) vaccination of the three doses vaccinating girls in class 6, as a result of effective school-based platform delivery system and community partnership to identify girls who are out of school. Rwanda reduced the historical two-decade gap in vaccine introduction between high- and low-income countries. The country also introduced a nationwide cervical cancer screening and treatment program. An impressive decreased cervical cancer incidence rate in Rwanda in recent years was observed. Sierra Leone lags behind in terms of almost all cervical cancer prevention programs. Therefore, Sierra Leone needs more efforts to implement cervical cancer intervention programs at the national level, including HPV vaccination, and train and increase the number of health professionals, treatment, and palliative care services to accelerate cervical cancer activities.

Conclusion: The disease burden of cervical cancer for Rwanda and Sierra Leone is heavy. There remains huge room for improvement in preventing and controlling cervical cancer in these countries. The goal of cervical cancer elimination would not be feasible in countries without the awareness and will of the policymakers and the public, the compliance to fund cervical cancer programs, the prioritization of cervical cancer activities, the availability of resources, the adequate health workforce and infrastructure, the cross-sectional collaboration and planning, inter-sectorial, national, regional, and international partnerships.

KEYWORDS

cervical cancer, vaccination, screening, Rwanda, Sierra Leone

Introduction

Cervical cancer is a public health issue of global concern, with a projected number of 604,127 new cases and 341,831 deaths worldwide in the year 2020 (1). It is a preventable disease, but it continues to threaten the lives of women in their prime stage of life, especially in developing countries such as those in sub-Saharan Africa (2, 3). A recent study showed that cervical cancer accounts for 13% of female cancers. The study also illustrated Eastern and Western Africa as high-risk regions, with a cumulative risk of 3.8%, as well as (2.9%) Southern Africa (4). Many high-income countries decreased cervical cancer cases by more than 70% in the late 1950's to 1960's, by implementing cervical cancer screening programs (5). However, the situation is the opposite in developing countries, mainly in sub-Saharan Africa, due to the lack of screening, treatments of pre-cancerous lesions, limited resources, and other barriers; many sub-Saharan African countries have been unable to achieve cervical cancer rate reduction compared with many developed countries (6–10).

The World Health Organization (WHO) proposed an intermediate target toward elimination of cervical cancer by 2030, namely, 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by the age of 15 years, 70% of women screened using a high-performance test by the age of 35 years and again by the age of 45 years, and 90% of women with pre-cancer treated and 90% of women with invasive cancer managed. However, women in many sub-Saharan African countries face obstacles such as lack of funding and access to healthcare facilities due to geographic constrains. The challenges to introduce cervical cancer screening and HPV vaccination in sub-Saharan Africa are related to the neglect to implement the prevention program, shortage of personnel, cost, weak infrastructure system, insufficient technical staff, and lack of prioritization and will to support cervical cancer programs (11).

Furthermore, many sub-Saharan African countries are constrained by limited resources, some of them are yet to get access to the HPV vaccine, and some are yet to start any HPV demonstration project at national and/or district pilot phase. Although some countries have vaccination programs, they are below the recommended vaccination coverage.

The aim of this analysis was to describe cervical cancer disease burden and trends, HPV vaccination, screening, and health-related resources in Rwanda and Sierra Leone, to provide information and suggestion for sub-Saharan Africa countries on elimination of cervical cancer.

Methods

Country selection

We selected two African countries in sub-Saharan Africa, the Republic of Rwanda (Rwanda) and the Republic of Sierra Leone (Sierra Leone), to describe the possibilities and challenges of carrying out cervical cancer prevention programs. We chose Rwanda for study because of its thriving cervical cancer prevention programs, such as the mass nationwide HPV vaccination program, the number of referral hospitals for cervical cancer management, the encouraging number of oncologists, physicians and nurses, palliative care services, vaccine platform delivery systems (community-based and private partnership), and cervical cancer mobile team outreach programs in remote areas. A decreased cervical cancer incidence rate in Rwanda in recent years was observed recently (Figure 1). In terms of communicable diseases, Rwanda has reduced the burden and has a strong public health system compared with other sub-Saharan African countries. On the contrary, Sierra Leone had only done pilot phase of cervical cancer demonstration at the district level since 2014 and has and/or among countries with the worse resources constrains in the subregion in terms of cervical cancer of cervical cancer program implementation. In addition, the first author, Bangura Mohamed S, who is from Sierra Leone, aims to make a difference in cervical cancer prevention and control in his country. In

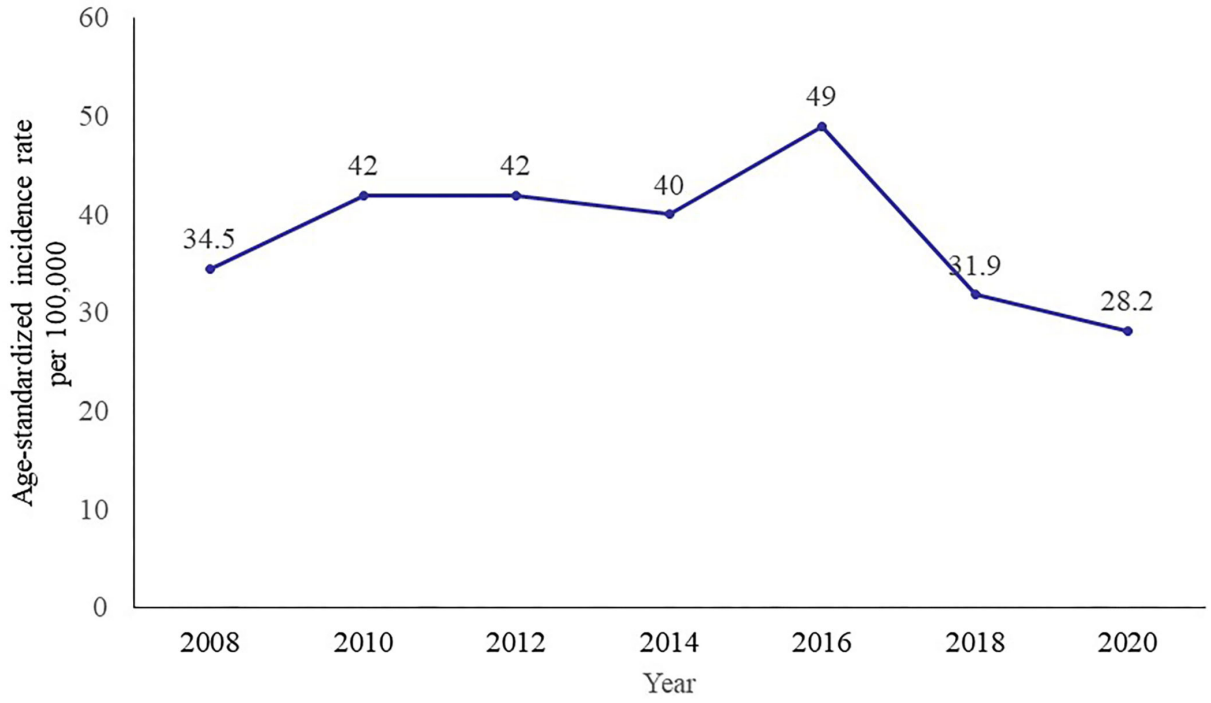

FIGURE 1
Trend of age-standardized incidence rate of cervical cancer in Rwanda, 2008–2020. Data source: IARC.

short, Rwanda and Sierra Leone represented the best and worst cervical cancer prevention program implementation among sub-Saharan Africa, respectively. Other sub-Saharan African countries mostly fall between these two countries.

Data collection

Secondary data were collected from the WHO, the International Agency for Research on Cancer (IARC), the Global Burden of Cancer (GLOBOCAN), the United Nations Development Programme (UNDP), and the World Bank, and official websites of the governments of the analyzed countries. The search and data collection was performed by two researchers (MSB and MJGM) independently and then were presented and discussed with the study team.

We used a descriptive analysis method to source data, describe the results, and list the variables such as the prevalence of known associated factors of cervical cancer, cervical cancer incidence and mortality rates, HPV vaccination coverage, cervical cancer screening, implementation programs, challenges and other indicators. The validity or trustworthiness of the organizations that managed and released the data enabled our team to reliably use the data for this study.

Data analysis

The indicators were divided into two category: general indicators and cervical cancer-specific indicators. General indicators included gross domestic product (GDP), health systems, the maternal mortality rate (MMR), health workforce, health expenditure, and infrastructure, which were compared with the international standard recommended number of physicians per 10,000 population, the number of gynecologists and oncologist nurses, and expenditure in healthcare services. The cervical cancer indicators included the prevalence of associated factors and cervical cancer incidence and mortality rates, cervical cancer nationwide screening activities implemented, and HPV vaccination coverage in these countries, which were compared with the WHO- and GAVI-recommended thresholds.

We used the descriptive method and direct comparative method to assess what are lacking and/or present and absent in the countries in terms of cervical cancer programs. We used direct observation and also compared the outcomes of these countries with international standard thresholds.

No human studies, animal studies, or potentially identifiable human images or data are presented. The study was approved by the Chinese Academy of Medical Sciences & Peking Union Medical College (No. DL2021194001L).

TABLE 1 General indicators of Rwanda and Sierra Leone.

Indicators	Country	
	Rwanda	Sierra Leone
GDP per capita ($)/year	797.9/2020	509.4/2020
Health expenditure (% of GDP)/year	6.41/2019	8.75/2019
MMR*/year	248/2017	1,120/2017
Doctors per 10,000/year	1.18/2019	0.74/2018
Number of oncologists (*N*)	5	1
Number of oncologist nurse (*N*)	19	ND
Number of palliative staff (*N*)	75,000	–
Number of referral hospitals (*N*)	100	–
Cervical cancer screening scale/year	Nationwide/ 2011-2012	Pilot stage /2014

*MMR, maternal mortality rate, per 100,000; ND, no data; -, unavailable.
Data source: the World Bank, Rwanda Biomedical Center, and UNDP.

Results

General description of the included countries

Rwanda

Rwanda is a landlocked country in sub-Saharan Africa (in Eastern Africa) with a population of 11 million comprising 2.72 million women, at the age of 15 years and older, who are at risk for developing cervical cancer (12). The country has robust record of tackling and curbing communicable and non-communicable diseases. The MMR of Rwanda has been reduced to an accelerating number from 1,071 per 100,000 women in 1992 to 203 in 2020, drawing closer to the Sustainable Development Goals commitment number of 70 by 2030 (13). The key indicators of the country are as follows: health financing, with the total health expenditure per capita was $58.31 in 2018 and out-of-pocket total expenditure on health in 2011 was 21%; the GDP per capita in 2011 and 2012 were $668.5 and $704.2, respectively (Table 1); the health workforce such as physicians per 100,000 population was 0.06 in 2010; the ratio of doctor to population was 1:16,001; the ratio of nurses and midwives per 100,000 per population was 1:1,291 in 2010; the antenatal care coverage population with at least four visits was 43.90% in 2021; the population with household spending on health >10% of the total household budget (SDG 3.8.2) was 1.15% in 2021; and the Human Development Index (HDI) was 0.43 (14).

Rwanda met the Global Alliances for Vaccines and Immunization (GAVI) criteria, with a DTP3 threshold of 70% national coverage, and a pilot demonstration was carried out to check the ability to deliver complete multi-dose series of vaccines to at least 50% of the target population in a district within the country to determine countries qualification for vaccination assistance (15). As a result of robust national health system of Rwanda, over 90% of all Rwandans infants within the age of 12–23 months received all the WHO-recommended basic immunization.

Sierra Leone

Sierra Leone is located in Western Africa. According to the World Bank, the life expectancy in Sierra Leone has increased from 39 to 54 years from 1990 to 2017, being the fourth lowest worldwide. The general government expenditure on health as a percentage of total of government was 10.84% in 2014. The per capita GDP of Sierra Leone in 2020 was 509.4$. The ratio of medical doctors per 10,000 people was 0.74. According to the Demographic Health Survey (DHS), the number of nurses and midwives personnel per 10,000 was 72.54 in 2018. The percentage of births by 15- to 19-year-olds attended by skilled health personnel in 2017 was 81.72% (78.28–84.72). According to the latest information, the antenatal care coverage (at least four visits) is 78.8% (16). Sierra Leone has the highest MMR in the world, at 717 maternal deaths per 100,000 live births in 2019 (17). Sierra Leone continues to experience outbreaks that have overwhelmed and added to the already fragile health system (16). In addition, the per capita total expenditure on health services is 95$, and 76% of health spending is from individual out-of-pocket expenditure, 16% is government-funded, and 13% is from donors' fund (18).

Rwanda indicators

Cervical cancer disease burden in Rwanda

Cervical cancer is common and fatal among women in Rwanda. Eastern Africa is one of the most affected cervical cancer burden region, with an incidence of 30 cases per 100,000 women per year (19). Before 10 years, the global cancer statistics showed that 1,000 women are diagnosed annually in Rwanda, and almost 700 women died of cervical cancer in the year of 2010 (4). The disease is the most commonly diagnosed condition among women aged 15–44 years (20). The estimated incidence of cervical cancer in Rwanda was 49 cases per 100,000 women per year, which is higher than the estimated cases for Eastern Africa and globally, with 34.5 and 16 new cases around 2010, respectively. Studies showed that the prevalence of pre-cancer and invasive cervical cancer (5.9%) and (1.7%) was high in Rwanda. The associated factors with the high prevalence were a result of the factors such as multiple sexual partners, high parity (over three kids born), tobacco use, and long-term contraceptive pill use (21, 22). Table 2 shows the data of the associated factors of cervical cancer by country.

Recent data showed that the current (2020) cervical cancer burden in Rwanda is still high (23). Approximately 1,229 new cervical cancer cases are diagnosed yearly, and the data showed that the crude incidence rate is higher in Rwanda (18.7 per 100,000) than the world crude incidence rate (15.6 per 100,000).

TABLE 2 Cervical cancer-associated factors among women in Rwanda and Sierra Leone.

Factors	Rwanda	Sierra Leone
Smoking		
Smoking of any tobacco adjusted prevalence (%) [95% UI]*	4.2 [2.5–6.3]	8.6 [5–13]
Parity		
Total facility rate per woman (*N*)	3.8	4.3
Hormonal contraception (%)	8.40	-
Oral contraceptive use among married women or in union (%)	-	5.30
Injectable contraception use among married women or in union (%)	-	11.9
Implant contraceptive use among women who are married or in union (%)	-	3.60
HIV		
Estimated percent of adults aged 15–49 living with HIV (%) [95% UI]	3.2 [2.6–3.6]	1.8 [1.5–2.3]
Estimated percent of young adults aged 15–24 living with HIV (%) [95% UI]	-	1.1 [0.5–1.8]
HIV prevalence among sex workers (%)	-	6.69
Estimated number of adults (15+ yrs) living with HIV (*N*) [95% UI]	-	38,000 [31,000–47,000]

-, no data available/not applicable.
*Smoking at the time of the survey, including both daily and occasional smoking.
Data source: the World Bank and WHO.

However, the age-standardized incidence rate is half the Eastern Africa age-standardized rate (28.2 vs. 40.1 per 100,000), although still higher than the world age-standardized rate (13.3 per 100,000). The cumulative risk (3.04%) for women in Rwanda at 75 years old is higher than the world cumulative risk (1.39%; Table 3) (24). Cervical cancer ranked the second most common cancer in Rwanda. In 2020, 829 cervical cancer deaths occurred, and it ranked the first leading cause of female cancer death in Rwanda. The crude mortality rate, age-standardized mortality rate, and cumulative risk at 75 years old are all higher than the world rates. While there are little differences in terms of rates between Rwanda and Eastern Africa (Table 3) (25).

Human resource training and infrastructure

As part of the human resource training to recruit competent personnel in the healthcare sector, the Rwanda National University of Medicine started a 4-year residency program in pathology; 12 pathologists have graduated and more had been trained in 2018. In 2013, community health workers engaged in doing mobile team work with one physician and four nurses engaged in visiting local health centers for free 3-day HPV screening (26). Rwanda initiated a policy to introduce 45,000 community health workers to provide essential services. In addition, the Ministry of Health of Rwanda has trained 30,000 new community health workers in palliative care at the community level for HIV and cancer and other chronic disorder management (27).

A comprehensive cancer center was set up at the district hospital level in 2012. A majority of the referral hospitals have maintained cancer registries. By 2013 to 2015, cervical cancer screening in Rwanda was decentralized into 30 public hospitals and nearly 100 health centers by 2015 (26).

Achievement of Rwanda in cervical cancer prevention

Rwanda was the first country in Africa to develop, introduce, and implement a nationwide strategies for cervical cancer prevention, control, and treatment. The country demonstrated effective cervical cancer program planning and introduction and serve as an ideal example of human resources for health personnel and healthcare settings in Africa or in developing regions.

Rwanda was recorded as the first developing country in the world to offer free universal HPV vaccination (28). A nationwide sensitization campaign preceded the delivery of the first dose. In 2011, the Ministry of Health of Rwanda partnered with international donors to offer HPV vaccines for free to girls under the required ages. This vaccination introduction was successful as a result of the Ministry of Health partnering with public–private and community collaboration to promote effective, efficient, and equal vaccine and vaccination delivery nationwide. This was as a result of effective school-based platform delivery system and community partnership to identify girls who are out of school (28). From 2011 to 2012, Rwanda recorded 227,246 vaccinated girls with three doses of the HPV vaccine with the three dose coverage rates of 93.2 and 96.6% achieved in 2011 and 2012, respectively (Table 4).

The country also introduced nationwide cervical cancer screening and treatment programs based on visual inspection with acetic acid (VIA), testing for HPV DNA, cryotherapy, loop electrosurgical excision procedure, and other advanced treatment options (26). As of 2021, Rwanda has screened 16,563 and 559 women treated for pre-cancerous lesions.

Rwanda reduced the historical two-decade gap in vaccine introduction between high- and low-income countries. High coverage rates were achieved due to a delivery strategy that built on Rwanda's robust vaccination system and human resource framework. Those great efforts and investments in healthcare and cervical cancer prevention led to great achievement. An impressive decrease in the cervical cancer incidence rate in Rwanda in recent years was observed (Figure 1) (24).

TABLE 3 Cervical cancer incidence and mortality in Rwanda, Sierra Leone, sub-Saharan Africa, and worldwide estimates for 2020.

Indicator	Rwanda	Eastern Africa	Sierra Leone	Western Africa	World
Incidence					
Annual number of new cancer cases (N)	1,229	54,560	504	27,806	604,127
Crude incidence rate*	18.7	24.3	12.6	13.9	15.6
Age-standardized incidence rate*	28.2	40.1	21.2	22.9	13.3
Cumulative risk at 75 years old** (%)	3.04	4.46	2.48	2.48	1.39
Mortality					
Annual number of new cancer deaths (N)	829	36,497	367	18,776	341,831
Crude mortality rate*	12.6	16.3	9.18	9.41	8.84
Age-standardized mortality rate*	20.1	28.6	16.4	16.6	7.25
Cumulative risk (%)at 75 years old**	2.27	3.36	1.99	1.88	0.82

*Rate per 100,000 women per year.
**Cumulative risk (incidence/mortality) is the probability or risk of individuals getting the disease in ages 0–74 years. For cancer, it is expressed as the % of newborn children who would be expected to develop or die of a particular cancer before the age of 75 years if they had the rates of cancer observed in the absence of competing causes.
Data source: the IARC.

TABLE 4 HPV vaccination coverage in Rwanda, 2011–2012.

	2011			2012		
	Round 1	Round 2	Round 3	Round 1	Round 2	Round 3
No. of girls vaccinated						
In school*	91,752	89,704	88,927	137,147	13,645	134,115
Outside school	2,136	3,066	3,180	1,162	845	1,024
Overall	93,888	92,770	92,107	138,309	135,490	135,139
Cumulative coverage (%)**	95.0	93.9	93.2	98.8	96.8	96.6

*Three rounds of vaccination in 2011 only covered girls who were in grade 6 of primary school, whereas the rounds in 2012 covered girls who were then in grade 6 of primary school or the 3rd year in secondary school.
**The denominator for 2011; 98,792 eligible girls; denominator for 2012:139,968 eligible girls.

Sierra Leone indicators

Cervical cancer disease burden in Sierra Leone

Sierra Leone has a female population of 2.23 million between the ages of 15 years and above who are at risk of developing cervical cancer. Data are yet to be available on HPV burden in the general population. However, in Western Africa region where Sierra Leone is located, an estimate of 4.3% of the women in the general population of the country harbor cervical HPV16 and18 infections, and 55.6% of invasive cervical cancers are attributed to HPV 16 and 18, respectively (29). An estimate of 504 new cervical cancer cases are diagnosed, and 367 cervical cancer deaths occur annually in Sierra Leone. According to estimation for 2020, the age-standardized incidence is estimated above 25.6 per 100,000 women. Cervical cancer ranks the second leading cause of female cancer occurrence and cancer death, and it is the second commonest female cancer and leading cause of cancer death among women aged 15 to 44 years. Table 3 shows the new cases and deaths of cervical cancer in Sierra Leone, Western Africa, and the world. According to recent data, there is no cancer registry available in Sierra Leone yet. The crude incidence rate, age-standardized rate, and cumulative rate among 75-year-old women are almost equal to those of Western Africa and, in some cases, higher than the world rates. This may be attributed or linked to the absence of cervical cancer screening and HPV vaccination programs (30).

Studies have shown some of the exact variables, such as sexual behavior, contraception use, parity, HIV, and smoking, as key behavior risk factors of cervical cancer among women (31–34). The study showed that the rate at which women smoke in the country is high, and parity and estimated HIV prevalence among women are also high.

Human resource training and infrastructure

Sierra Leone has a shortfall, unequal and maldistribution of its health workforce. An estimate of 92% of the doctors and 72% of the nurses reside in the urban settings, where only 18% of the population of the country is located. According to recent findings from the Global Disease Burden study, statistics showed that Sierra Leone is one of the countries with the least workforce in sub-Saharan Africa and probably in the world. Sierra

Leone has the highest workforce attrition, dropout, and health personnel switching rates compared with other public health sectors. If the country is to tackle this situation, it estimated to spend about $18.25 per capital to reach similar workforce retention in Guinea and Liberia, neighboring countries (35–37). In 2017, Sierra Leone had only 300 midwives to serve a population of seven million people (36); however, an increase of 987 midwives was recorded in 2019 (17). The health indicators such as the total number of oncologists, number of oncologist nurses, number of trained health staff to provide palliative services, and number of cervical cancer referral hospitals to manage the disease are presented in Table 1 (26, 27, 38, 39).

Cervical cancer prevention in Sierra Leone

The country has implemented the One Health approach at national and regional levels to enhance coordination of multi-sectorial response to health, but the One Health approach and/or national action plan did not capture specific policy for scaling up trainings, personnel, and education programs for cervical cancer activities (18). In addition, in 2021, the UNFPA-Sierra Leone and the University of Sierra Leone Teaching Hospitals Complex (USLTHC) established the Public–Private Partnership Pilot Program on Cervical Cancer Screening and developed 3 first ever national policy on cervical cancer, strategic plan, and clinical guidelines for the management of cervical cancer and refurbished reproductive health centers in seven health centers. In 2020, China and the UNFPA-Sierra Leone partnered on reducing maternal mortality support training of 50 healthcare providers on cervical cancer screening and management of cervical cancer pre-cancerous lesions (17), but the number is still low compared to the population (2.23 million) of women in Sierra Leone who are at high risk of HPV infection (29).

Sierra Leone is one of the countries eligible for GAVI funding to introduce HPV vaccination and cervical screening interventions in Africa. The burden of cervical cancer is high, although in August 2021, there was yet another national HPV vaccination program. The country has completed national demonstration projects in 2013–2014, supported by GAVI. Sierra Leone projected to add HPV vaccine into the routine immunization schedule after a national pilot phase in 2021, and GAVI projected to support HPV vaccine introduction in Sierra Leone by 2023 (40).

Some low-income countries and regions have used VIA as a method and other low-cost strategies in reducing the rate of cervical cancer (41). However, the situation in Sierra Leone is different. Previous findings showed that cervical cancer screening is unavailable in Sierra Leone, except demonstration projects conducted in a region using VIA in 2012–2014 (30). In general, Sierra Leone is lagging behind in terms of cervical cancer screening program.

Discussion

The primary purpose of comparing indicators from both countries was to analyze the significant and likelihood of reducing cervical cancer in these sub-Saharan African countries. Rwanda has performed remarkably well in implementing HPV vaccination and nationwide cervical cancer screening activities, and has increased the number of referral hospital health workforce to manage cervical cancer patients, which was as a result of developmental improvements such as health financing system, health policy, an increase in investments in the infrastructural system with good referral systems from remote areas to urban centers, mass training of medical staff, and high turnout of medical graduates (26). In sub-Saharan Africa, Sierra Leone is one of the countries with the lowest (0.2%) health workforce and shortage of healthcare personnel and encounters constraints of sanitation facilities and access to healthcare. Sierra Leone is lagging behind in terms of almost all cervical cancer prevention programs. In order to achieve health and development, reports showed that improving the GDP of a country is critical (42–47). Both Rwanda and Sierra Leone have huge potential to attain an incidence rate of <4 cases per 100,000 women per year, if cervical cancer programs in these countries, especially in Sierra Leone, are given attention to.

Strategies for preventing and controlling cervical cancer in Rwanda and Sierra Leone

The current cervical cancer situation in sub-Saharan Africa poses a challenging health outcome for these countries. To reduce cervical cancer disease burden, it would be necessary to implement the three WHO multiple spring pillar strategies, namely, 90% of girls fully vaccinated by age 15 years, 70% of women screened with a high-performance test by age 35 and 45 years, and 90% of women with pre-cancer treated and those with invasive cancer managed.

In countries with high coverage of HPV vaccination as in Rwanda, they should maintain the ongoing efforts to monitor cervical cancer incidence and mortality, assess the impact of HPV vaccination programs, and also optimize high service quality. In recent years, the WHO recommended a two-dose HPV vaccination schedule (48). In the year of 2022, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) evaluated evidence and recommends updating dose schedules for HPV that one- or two-dose schedules for the primary target of girls aged 9–14 years (49). The recommendation of the single-dose strategy could accelerate progress toward the goal of vaccinating 90% of girls younger than 15 years by 2030. Rwanda should closely follow the recommendations from the

WHO, saving its limited health resources, and, at the same time, take the advantage of its robust vaccination system to maintain sustainability of the high coverage of vaccination programs.

Meanwhile, efforts on the cervical cancer screening program for early diagnosis and treatment are necessary. For example, a successful 5-year cervical cancer screening program in Inner Mongolia, China, screening over 40,000 women demonstrated a clear practical scenario of how to implement screening programs in low-resource settings as a way to reduce cases and promote women health and wellbeing in a developing country context (50). Furthermore, data from China showed that using low-resource screening methods (VIA/VILI and careHPV testing methods) is feasible, acceptable, and efficient in detecting cervical cancer and pre-cancerous lesions (41, 51). These strategies may be suitable for Rwanda to incorporate into its screening programs and healthcare system and to provide a lifetime screening service for adult women, rather than copying the high-resource intensive liquid-based cytology screening program, which is costly and impossible to sustain in resource-limited countries and regions. And if possible to source more in the area of knowledge and technology transfer to sub-Sahara African countries in the area of the screening material such as careHPV or Artificial Intelligence (AI) technologies from other countries; which will increase screening coverage of women and it works well in low resource settings with limited health infrastructure. In addition, limited data for pre-cancer and invasive cancer treatment and management were available; therefore, further investigation on this part should be noticed. Although there has been remarkable progress, substantial activities are still needed to further decrease cervical cancer burden in Rwanda (52).

Sierra Leone needs total commitment from the policymakers and public will to prioritize and fund cervical cancer activities in the country. Sierra Leone mainly needs to give attention to cervical cancer prevention activities. This attention can be in the form of providing sustainable funding and investment in primary healthcare facilities; training more health professionals; increasing the capacity of the health workforce and cancer registry; increasing funding for cervical cancer activities; creating local, regional, and international partnerships; increasing specialist training on oncology; and incorporating cervical cancer interventions into the already exiting health program in the primary healthcare setting. For low-resource settings like Sierra Leone, it is yet to vaccinate girls with the HPV vaccine as did Rwanda with over 93% vaccination coverage. The prioritization of HPV vaccination programs is needed to foster cervical cancer interventions in Sierra Leone as the first step. The recommendation of one-dose schedule is an opportunity for countries like Sierra Leone to meet the stage goal of vaccinating 90% girls for cervical cancer elimination. For cervical cancer screening in Sierra Leone, low-cost primary screening approaches, such as careHPV testing and VIA/VILI, may be feasible if the healthcare workforce improves, to provide the minimal screening service for 70% of women at 35 years of age and again by 45 years of age, as recommended by the WHO.

In general, to further accelerate the 90-70-90 target to eliminate cervical cancer, Rwanda needs to maintain the high HPV vaccination coverage for girls and increase screening coverage, and investigation of the cervical cancer treatment and management data for pre-cancer and invasive cancer are needed to assess the treatment rate. Sierra Leone needs to introduce nationwide cervical cancer prevention programs and increase and continue to scale up knowledge and awareness campaigns and HPV vaccination coverage, screening, and treatment.

Study implications and recommendations

The absence of adequate attention for women's health has posed as barriers for effective cervical cancer prevention programs. The unavailability of screening program such as cytology, HPV testing, VIA/VILI, and LBC due to the technical and financial constraints to organize and fund screenings in the country has posed as a challenge to preventing cervical cancer. Because of the financial and health resource constrains involved to run and maintain sophisticated screening tests such as cytology or to implement organized screening, VIA/VILI, and careHPV testing, other low-resource screening approaches are suggested to be introduced in order to decrease cervical cancer burden.

In addition, it would be necessary to integrate cervical cancer screening and vaccination into existing health programs. For example, Sierra Leone should try to follow Rwanda system in cervical cancer programs such as introducing nationwide HPV vaccination campaign, effective advocacy, and partnering with international and private sector organizations.

Rwanda stands out as a model country for effective cervical cancer prevention and controlling activities in sub-Saharan Africa and other developing countries worldwide. However, Rwanda should still continue increasing the screening coverage, and diagnostic and treatment investments to reach the elimination stage within the twenty-first century.

Conclusion

The disease burden of cervical cancer in Rwanda and Sierra Leone are heavy. There remains huge room for improvement in preventing and controlling cervical cancer in these countries. The goal of cervical cancer elimination would not be feasible in countries without the awareness and will of the policymakers and the public, the compliance to fund cervical cancer programs, the prioritization of cervical cancer activities, the availability of resources, the adequate health workforce and infrastructure, the cross-sectional collaboration and planning, and inter-sectorial, national, regional, and international partnerships. It is essential

to have national well-planned strategies backed by international support in place, then national coverage for HPV vaccination and screening for cervical cancer can be achieved within the shortest possible time in countries such as Sierra Leone and accelerate Rwanda's cervical cancer controlling and preventing progress to meet WHO's agenda and 2030 target to eliminate the disease.

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

MB: conceptualization, literature search, data collection and interpretation, data analysis, manuscript preparation, manuscript editing, and approval of the final draft. MG: conceptualization, literature search, data collection and interpretation, data analysis, manuscript editing, and approval of the final draft. YZ, YW, and SD: literature search, data collection, manuscript preparation, manuscript editing, and approval of the final draft. KX: literature search, data collection, data analysis, manuscript preparation, manuscript editing, and approval of the final draft. LM, RR, and Y-LQ: conceptualization, literature search, supervision, data collection and interpretation, data analysis, manuscript preparation, manuscript editing, and approval of the final draft. All authors contributed to the article and approved the submitted version.

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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.

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Changes in rate and socioeconomic inequality of cervical cancer screening in northeastern China from 2013 to 2018

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Objective: Cervical cancer, the fourth leading cancer diagnosed in women, has brought great attention to cervical cancer screening to eliminate cervical cancer. In this study, we analyzed two waves of provincially representative data from northeastern China's National Health Services Survey (NHSS) in 2013 and 2018, to investigate the temporal changes and socioeconomic inequalities in the cervical cancer screening rate in northeastern China.

Methods: Data from two waves (2013 and 2018) of the NHSS deployed in Jilin Province were analyzed. We included women aged 15–64 years old and considered the occurrence of any cervical screening in the past 12 months to measure the cervical cancer screening rate in correlation with the annual per-capita household income, educational attainment, health insurance, and other socioeconomic characteristics.

Results: A total of 11,616 women aged 15–64 years were eligible for inclusion. Among all participants, 7,069 participants (61.11%) were from rural areas. The rate of cervical cancer screening increased from 2013 to 2018 [odds ratio (OR): 1.06; 95% confidence interval (CI): 1.04–1.09, $p < 0.001$]. In total, the cervical cancer screening rate was higher among participants who lived in urban areas than rural areas (OR: 1.20; 95% CI: 1.03–1.39, $p = 0.020$). The rate was also higher among those with the highest household income per capita (OR: 1.30; 95% CI: 1.07–1.56, $p = 0.007$), with higher educational attainment ($p < 0.001$), and with health insurance ($p < 0.05$), respectively. The rate of cervical cancer screening was also significantly associated with parity (OR: 1.62; 95% CI: 1.23–2.41, $p = 0.001$) and marital status (OR: 1.45; 95% CI: 1.15–1.81, $p = 0.001$) but not ethnicity (OR: 1.41; 95% CI: 0.95–1.36, $p = 0.164$).

Conclusion: Cervical cancer screening coverage improved from 2013 to 2018 in northeastern China but remains far below the target 70% screening rate proposed by the World Health Organization. Although rural-urban inequality disappeared over time, other socioeconomic inequalities remained.

KEYWORDS

cervical cancer screening, inequalities, organized screening program, rural areas, China

Introduction

Cervical cancer is the fourth leading cancer diagnosed in women globally, being responsible for ∼311,000 deaths in 2018 alone worldwide (1), with >85% of the burden from cervical cancer existing in low-income and middle-income countries (2). Annually, China contributes ∼18.6% of new cervical cancer cases and 19.3% of the deaths caused by cervical cancer (3). However, some cases of cervical cancer may be preventable. Recently, the World Health Organization (WHO) proposed the "90–70–90 movement" toward 2030 (4)—that is, 90% coverage of human papillomavirus (HPV) vaccination, 70% coverage of screening twice in a lifetime, and 90% access to the pre-invasive lesion and invasive cancer treatments (2).

Worldwide, two major types of national-level cervical cancer screening programs, organized programs and opportunistic programs, have been implemented by various countries to eliminate cervical cancer (5). Organized programs are supported by the government and invite all eligible women to undergo cervical cancer screening delivered by trained physicians in appointed facilities (6, 7). In an organized program, cervical cancer screening is usually paid for by the government. In contrast, an opportunistic program provides cervical cancer screening when individuals request the screening or their health care providers recommend the screening (8). Previous research has suggested that organized programs may achieve greater coverage of cervical cancer screening and may be more effective than opportunistic screening programs (7). However, there is a lack of consistent conclusions about whether organized screening can eliminate the socioeconomic inequality of cervical cancer screening. Further, no studies have investigated the impact of organized programs and opportunistic programs in low-income or middle-income countries.

To reduce the health care burden brought on by cervical cancer, especially that among residents in rural areas, in 2009, China launched an organized program called the "National Cervical Cancer Screening Program in Rural Areas" (NCCSPRA) (9, 10) to provide cervical cancer screenings to rural women aged 35–59 years. The program was subsequently expanded to cover rural women aged 35–64 years in 2012 (11). The NCCSPRA program was the very first effort made by the Chinese government to improve access to cervical cancer screening for residents in rural areas and represented a step toward the nationwide provision of cervical cancer screening (11). Staff in township health care centers provides education and mobilization on cervical cancer screening for eligible women in their jurisdiction. Women who agree to undergo screening tests are organized and transported to the appointed health care center for the examination. Yet, such a program has remained unavailable in urban areas, although residents in an urban area who are formally employed may take uniform cervical cancer screening tests provided by their employers, while other women in urban areas without this type of access may take the tests ordered by their health care providers as needed. Despite the target coverage rate of 70% for cervical cancer screening, from 2009 to 2011, only 7% of rural women aged 35–59 years were covered by organized cervical cancer screening programs in China (10). The overall screening rate among women >18 years of age was only 19.7% in 2010 in China (12, 13). No study has investigated the impact of the NCCSPRA program on cervical cancer screening in China either in terms of the screening rate or socioeconomic inequality.

In this study, we analyzed two waves of provincially representative data from China's National Health Services Survey (NHSS) (14) in 2013 and 2018 collected in Jilin Province of China to identify the temporal changes and socioeconomic inequalities in cervical cancer screening in northeastern China.

Methods

Study design and data sources

In this study, we analyzed data from two waves of the NHSS of northeastern China collected from Jilin Province in China during the 2 years of 2013 and 2018, respectively. The NHSS of China is a survey administered every 5 years by the Center for Health Statistics and Information of the National Health Commission. The survey is designed to investigate the status of population health, health services demand and utilization, health insurance coverage, medical costs, expenditures, and their financial burden on Chinese residents. NHSS data were collected from a nationally representative sample of Chinese residents following a design of multi-stage stratified random cluster sampling *via* one-to-one interviews using a structured questionnaire. The overall response rate to the NHSS was >90% in both the 2013 and 2018 waves. This study included data from female participants aged 15–64 years old surveyed in the two waves of 2013 and 2018 in Jilin Province of northeastern China and excluded the participants who had any missing values in independent variables. The total sample size of this study, combining the participants surveyed in 2013 and 2018, was 11,616 people. After excluding participants with missing values, a total of 11,611 participants were eligible for inclusion in our data analysis.

Study procedures and variables

Dependent variable

The primary dependent variable in this study was the use of cervical cancer screening during the past 12 months by NHSS

participants. In the NHSS, female participants were asked about their use of cervical cancer screening by a question: "Have you received any cervical smear test in the past 12 months?" in 2013 and by a substitute question "Have you received cervical cancer screening (including cervical smear test, liquid-based cytology [LBC] test, or HPV DNA test) in the past 12 months?" in 2018. As mentioned, there are four cervical cancer screening tests: the conventional visual inspection with acetic acid, the pap smear test, the LBC test (15), and the newly introduced HPV deoxyribonucleic acid (DNA) test (2). LBC and HPV testing were introduced for cervical cancer screening in China in 1999 (16). Therefore, the slight difference between the questions between the 2 years was because of the availability of new cervical cancer testing technologies and changes in cervical cancer screening guidelines in China, in that LBC testing and HPV DNA testing were included in 2018 but not 2013 for cervical cancer screening.

Independent variables

In this study, we included the following variables as independent variables: residence (rural or urban), age (15–21, 22–29, 30–39, 40–49, 50–59, or 60–64 years old), educational attainment (primary school or below, secondary school, or college and above), travel time to health care facilities (<15, 15–30, or ≥30 mins), parity (0 or ≥1), ethnicity (Han majority or another minority), marital status (married, unmarried, or other), and health insurance (17, 18) [none, Urban Employee Basic Medical Insurance (UEBMI), Urban Resident Basic Medical Insurance (URBMI), New Rural Cooperative Medical Scheme (NRCMS), or other]. According to China's current insurance system (17, 18), the UEBMI scheme covers eligible urban employees and consists of a pooled fund for inpatient care and individual medical savings account for outpatient visits. The URBMI scheme covers the rest of the urban population who are not eligible for enrollment in the UEBMI. The NRCMS is designed to cover all rural populations, and it is financed by the premiums of those enrolled and generous subsidies from both central and local governments. We also included the annual per-capita household income as a proxy for the financial status of participants. We defined five household income categories based on quartiles of annual household income per capita [Q1, <US dollars (USD) $1,005.3; Q2, USD$1,005.3–$1,587.3; Q3, USD$1,587.3–$2,380.9; Q4, USD$2,380.9–$3,703.7; Q5, >USD$3,703.7]. Note that the average of the exchange rate during 2013 and 2018 was as follows: 1 USD = 6.3 yuan (CNY) or the people's renminbi (RMB). The annual per-capita household income in 2013 was adjusted by a cumulative consumer price index rate of 9.3% from 2013 to 2018, which was reported by China's National Bureau of Statistics (http://www.stats.gov.cn/).

Statistical analysis

A descriptive analysis was conducted to represent the socioeconomic and other characteristics of the study population. The results were also stratified by the year of the NHSS survey and by the participants who underwent cervical cancer screening. Pearson's chi-squared test was performed to compare the distribution of the participants across the categories defined by these characteristics. To compare two proportions between the two survey years, a z-test was performed. A multivariate logistic regression analysis was conducted to determine the factors associated with cervical cancer screening. Separate multivariate logistic regression analyses were performed to examine these associations in each of the two survey years. All statistical analyses were performed in Stata version 11.0 (StataCorp LLC, College Station, TX, USA).

Results

This study enrolled a total of 11,611 female participants aged 15–64 years old, including 5,490 surveyed in 2013 and 6,121 surveyed in 2018, respectively. Socioeconomic and other characteristics for all participants and those who underwent cervical cancer screening are presented in Table 1. Among all participants, 7,096 participants (61.11%) were from rural areas (3,413 in 2013, 3,683 in 2018), whereas 4,515 participants (38.89%) were from urban areas (2,077 in 2013, 2,438 in 2018). Significant improvements in annual household income per capita (χ^2 statistic = 292.87, $p < 0.001$) and educational attainment (χ^2 statistic = 30.06, $p < 0.001$) were observed among all survey participants from 2013 to 2018. The participants surveyed in 2018 tended to be older than those surveyed in 2013 (χ^2 statistic = 105.31, $p < 0.001$). Health insurance coverage distribution was different between 2013 and 2018 (χ^2 statistic = 347.64, $p < 0.001$), with the coverage rate increasing from 90.95% to 95.33%. Travel time to health care facilities decreased over time among the participants (χ^2 statistic = 235.47, $p < 0.001$), and <10% of participants required >15 minutes to reach their closest health care facility. There was a rise in parity over time (χ^2 statistic = 31.92, $p < 0.001$), but the marital status did not show a significant change from 2013 to 2018.

Among the participants who underwent cervical cancer screenings, 53.48% in total came from urban areas; more specifically, this percentage was 55.52% in 2013 and 52.17% in 2018, respectively, which did not show a significant difference (χ^2 statistic = 1.80, $p = 0.180$; Figure 1). The annual household income per capita increased from 2018 to 2013 (χ^2 statistic = 51.30, $p < 0.001$) among these participants. There was a significant difference in health insurance as well. Travel time to health care facilities decreased over time (χ^2 statistic = 76.53, $p < 0.001$), while parity, ethnicity, and marital status did not

TABLE 1 Socioeconomic and other characteristics of all study participants and those who underwent cervical cancer screening in 2013 and 2018.

Characteristic	All participants			Participants who underwent cervical cancer screening			Proportion of participants who underwent cervical cancer screening	
	2013, n (%)	2018, n (%)	*p*-value	2013, n (%)	2018, n (%)	*p*-value	2013, %	2018, %
Total	5,490	6,121		652	1,016		11.88%	16.60%
Residence			0.027			0.180		
Rural	3,413 (62.17%)	3,683 (60.17%)		290 (44.48%)	486 (47.83%)		8.50%	13.20%
Urban	2,077 (37.83%)	2,438 (39.83%)		362 (55.52%)	530 (52.17%)		17.43%	21.74%
Annual household income per capita (USD)			<0.001			<0.001		
Q1: <$1,005.3	1,026 (18.69%)	1,297 (21.19%)		81 (12.42%)	152 (14.96%)		7.89%	11.72%
Q2: $1,005.3–$1,587.3	1,069 (19.47%)	1,260 (20.58%)		98 (15.03%)	142 (13.98%)		9.17%	11.27%
Q3: $1,587.3–$2,380.9	1,396 (25.43%)	1,019 (16.65%)		144 (22.09%)	164 (16.14%)		10.32%	16.09%
Q4: $2380.9–$3703.7	1,198 (21.82%)	1,049 (17.14%)		174 (26.69%)	174 (17.13%)		14.52%	16.59%
Q5: ≥$3,703.7	801 (14.59%)	1,496 (24.44%)		155 (23.77%)	384 (37.80%)		19.35%	25.67%
Educational attainment			<0.001			0.005		
Primary school or below	1,493 (27.19%)	1,865 (30.47%)		90 (13.80%)	184 (18.11%)		6.03%	9.87%
Secondary school	3,269 (59.54%)	3,336 (54.50%)		403 (61.81%)	548 (53.94%)		12.33%	16.43%
College or above	728 (13.26%)	920 (15.03%)		159 (24.39%)	284 (27.95%)		21.84%	30.87%
Age (years)			<0.001			<0.001		
15–21	287 (5.23%)	260 (4.25%)		0 (0.00%)	3 (0.30%)		0.00%	1.15%
22–29	688 (12.53%)	474 (7.74%)		78 (11.96%)	58 (5.71%)		11.34%	12.24%
30–39	961 (17.50%)	1,127 (18.41%)		162 (24.85%)	281 (27.6%)		16.86%	24.93%
40–49	1,503 (27.38%)	1,593 (26.03%)		237 (36.35%)	337 (33.17%)		15.77%	21.16%
50–59	1,489 (27.12%)	1,882 (30.75%)		142 (21.78%)	274 (26.97%)		9.54%	14.56%
60–64	562 (10.24%)	785 (12.82%)		33 (5.06%)	63 (6.20%)		5.87%	8.03%
Health insurance			<0.001			<0.001		
None	497 (9.05%)	286 (4.67%)		42 (6.44%)	24 (2.36%)		8.45%	8.39%
UEBMI	1,064 (19.38%)	941 (15.37%)		223 (34.20%)	258 (25.39%)		20.96%	27.42%
URBMI	875 (15.94%)	897 (14.65%)		136 (20.86%)	123 (12.11%)		15.54%	13.71%
NRCMS	2,794 (50.89%)	3,175 (51.87%)		198 (30.37%)	392 (38.58%)		7.09%	12.35%
Other	260 (4.74%)	822 (13.43%)		53 (8.13%)	219 (21.56%)		20.38%	26.64%
Travel time to healthcare facilities			<0.001			<0.001		
<15 mins	4,408 (80.29%)	5,526 (90.26%)		525 (80.52%)	957 (94.19%)		11.91%	17.32%
15–30 mins	616 (11.22%)	365 (5.96%)		87 (13.34%)	46 (4.53%)		14.12%	12.60%
≥30 mins	466 (8.49%)	231 (3.77%)		40 (6.13%)	13 (1.28%)		8.58%	5.63%
Parity			<0.001			0.810		
0	771 (14.04%)	649 (10.60%)		43 (6.60%)	64 (6.30%)		5.58%	9.86%
≥1	4,719 (85.96%)	5,472 (89.40%)		609 (93.40%)	952 (93.70%)		12.91%	17.40%
Ethnicity			<0.001			0.492		
Han majority	4,961 (90.36%)	5,652 (92.34%)		579 (88.80%)	913 (89.86%)		11.67%	16.15%
Minority	529 (9.64%)	469 (7.66%)		73 (11.20%)	103 (10.14%)		13.80%	21.96%
Marital status			0.345			0.239		
Married	4,652 (84.74%)	5,225 (85.36%)		606 (92.94%)	928 (91.34%)		13.03%	17.76%
Unmarried or other	838 (15.26%)	896 (14.64%)		46 (7.06%)	88 (8.66%)		5.49%	9.82%

NRCMS, New Rural Cooperative Medical Scheme; other, government agency health insurance plan or private health insurance plan; UEBMI, Urban Employee Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance.

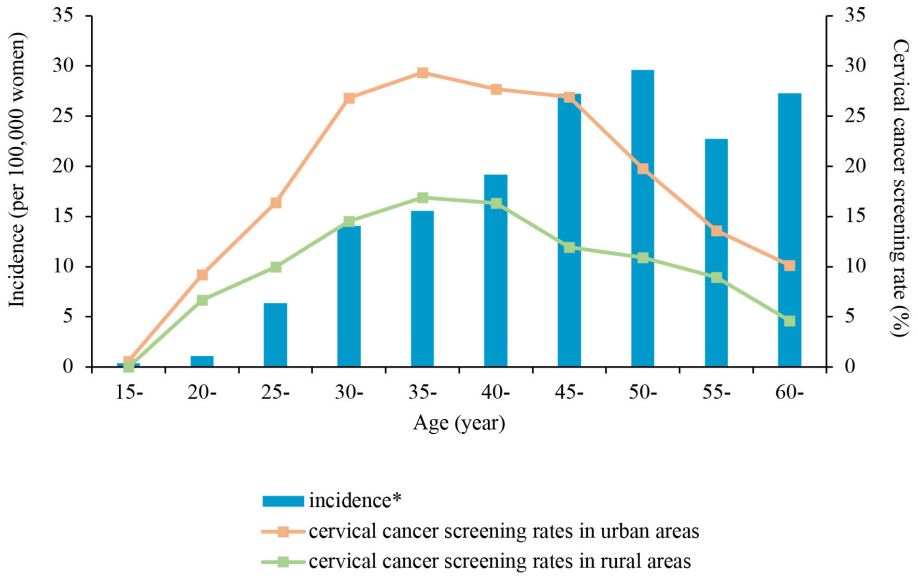

FIGURE 1
Incidence of cervical cancer reported by the Global Burden of Disease Study 2017 and the 2013 and 2018 total cervical cancer screening rate in Jilin Province of China by age groups and urban-rural areas. *The data of cervical cancer incidence reported by the Global Burden of Disease Study 2017 (33).

demonstrate any change from 2018 to 2013. The proportion of participants who underwent cervical cancer screening increased significantly from 11.88% in 2013 to 16.60% in 2018 (χ^2 statistic = 52.47, $p < 0.001$). This shows a significant increase in the use of cervical cancer screening by the population; moreover, the proportion significantly improved in both rural (χ^2 statistic = 40.16, $p < 0.001$) and urban (χ^2 statistic = 13.14, $p < 0.001$) areas.

Table 2 reports the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) along with p-values that were obtained from fitting the multivariate logistic regression of the use of cervical cancer screening on the socioeconomic and other factors for the years of 2013 and 2018, respectively, and for all participants taking the year of the survey as an independent variable. The rate of cervical cancer screening increased from 2013 to 2018 (OR: 1.06; 95% CI: 1.04–1.09, $p < 0.001$). Overall, participants from urban areas were more likely to undergo cervical cancer screening tests than those from urban areas (OR: 1.20; 95% CI: 1.03–1.39, $p = 0.020$) when participants in the two survey waves were analyzed as a whole group. However, though this rural-urban inequality was observed in 2013 (OR: 1.34; 95% CI: 1.04–1.73, $p = 0.022$), it disappeared in 2018 (OR: 1.08; 95% CI: 0.89–1.32, $p = 0.446$). The participants in the highest category of annual household income (Q5, >USD$3,703.7) had greater odds of undergoing cervical cancer screening compared to those in the lowest category of annual household income (Q1, <USD$1,005.3) (OR: 1.30; 95% CI: 1.07–1.56, $p = 0.007$); otherwise, there was no significant difference between the income categories.

Participants with greater educational attainment were more likely to undergo cervical cancer screening than those with lower educational attainment ($p < 0.001$ for the two categories of "secondary school" and "college and above"), and this trend existed in both 2013 and 2018. Participants who had any type of health insurance were also more likely than those who were not covered by any health insurance to undergo cervical cancer screening tests ($p < 0.001$ for UEBMI, URBMI, and others; $p = 0.031$ for NRCMS). However, exceptions were noted in the group of NRCMS (OR: 1.30; 95% CI: 0.69–1.54, $p = 0.887$) in 2013 and in the group of URBMI in 2018 (OR: 1.49; 95% CI: 0.92–2.40, $p = 0.104$), respectively. The impact of travel time to a health care facility on the rate of cervical cancer screening was insignificant overall (OR: 0.75; 95% CI: 0.56–1.01, $p = 0.056$) and inconsistent from 2013 to 2018.

In total, the rate of cervical cancer screening was higher among the four age groups of participants aged 22–59 years ($p < 0.001$) compared to the reference group of participants aged 60–64 years. However, the rate was lower among participants aged 15–21 years (OR: 0.16; 95% CI: 0.05–0.51, $p = 0.022$; Figure 1). The rate of cervical cancer screening was also significantly associated with parity (OR: 1.62; 95% CI: 1.23–2.41, $p = 0.001$) and marital status (OR: 1.45; 95% CI: 1.15–1.81, $p = 0.001$) but not ethnicity (OR: 1.41; 95% CI: 0.95–1.36, $p = 0.164$).

TABLE 2 Odds ratios, 95% confidence intervals, and *p* values obtained from multivariate logistic regression of the use of cervical cancer screening on the socioeconomic and other factors for 2013 and 2018 in China.

Characteristic	2013		2018		Total	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Year						
2013	–	–	–	–	Reference	
2018	–	–	–	–	1.06 (1.04–1.09)	<0.001
Residence						
Rural	Reference		Reference		Reference	
Urban	1.34 (1.04–1.73)	0.022	1.08 (0.89–1.32)	0.446	1.20 (1.03–1.39)	0.020
Annual household income per capita (USD)						
Q1: <$1,005.3	Reference		Reference		Reference	
Q2: $1,005.3–$1,587.3	0.92 (0.66–1.27)	0.599	0.81 (0.63–1.04)	0.099	0.86 (0.70–1.04)	0.124
Q3: $1,587.3–$2,380.9	0.98 (0.72–1.32)	0.872	1.10 (0.85–1.41)	0.472	1.00 (0.82–1.20)	0.961
Q4: $2,380.9–$3,703.7	1.25 (0.93–1.68)	0.145	0.97 (0.75–1.26)	0.816	1.04 (0.86–1.25)	0.714
Q5: ≥$3,703.7	1.44 (1.05–1.98)	0.026	1.33 (1.04–1.69)	0.021	1.30 (1.07–1.56)	0.007
Educational attainment						
Primary school or below	Reference		Reference		Reference	
Secondary school	1.38 (1.06–1.80)	0.019	1.49 (1.22–1.81)	<0.001	1.45 (1.23–1.70)	<0.001
College or above	1.83 (1.27–2.64)	0.001	2.40 (1.82–3.17)	<0.001	2.16 (1.73–2.69)	<0.001
Age (years)						
15–21	–	–	0.21 (0.06–0.72)	0.013	0.16 (0.05–0.51)	0.002
22–29	3.76 (2.28–6.18)	<0.001	1.43 (0.94–2.17)	0.098	2.17 (1.59–2.97)	<0.001
30–39	3.90 (2.54–5.98)	<0.001	2.98 (2.19–4.06)	<0.001	3.24 (2.53–4.16)	<0.001
40–49	3.91 (2.61–5.86)	<0.001	2.72 (2.02–3.65)	<0.001	3.09 (2.43–3.92)	<0.001
50–59	1.86 (1.24–2.80)	<0.001	1.97 (1.47–2.64)	<0.001	1.94 (1.53–2.45)	<0.001
60–64	Reference		Reference		Reference	
Health insurance						
None	Reference		Reference		Reference	
UEBMI	2.49 (1.71–3.60)	<0.001	2.60 (1.63–4.16)	<0.001	2.42 (1.82–3.23)	<0.001
URBMI	1.95 (1.34–2.84)	0.001	1.49 (0.92–2.40)	0.104	1.63 (1.21–2.19)	0.001
NRCMS	1.03 (0.69–1.54)	0.887	1.78 (1.14–2.78)	0.011	1.37 (1.03–1.82)	0.031
Other	2.78 (1.76–4.39)	<0.001	2.88 (1.82–4.58)	<0.001	2.63 (1.95–3.55)	<0.001
Travel time to healthcare facilities						
<15 mins	Reference		Reference		Reference	
15–30 mins	1.51 (1.17–1.99)	0.002	0.83 (0.60–1.14)	0.242	1.17 (0.96–1.42)	0.130
≥30 mins	1.08 (0.76–1.53)	0.656	0.43 (0.24–0.77)	0.005	0.75 (0.56–1.01)	0.056
Parity						
0	Reference		Reference		Reference	
≥1	1.89 (1.20–2.98)	0.006	1.41 (1.00–2.01)	0.053	1.62 (1.23–2.14)	0.001
Ethnicity						
Han majority	Reference		Reference		Reference	
Minority	1.13 (0.86–1.49)	0.388	1.12 (0.88–1.43)	0.345	1.14 (0.95–1.36)	0.164
Marital status						
Married	1.62 (1.10–2.38)	0.015	1.35 (1.02–1.80)	0.034	1.45 (1.15–1.81)	0.001
Unmarried or other	Reference		Reference		Reference	

CI, confidence interval; NRCMS, New Rural Cooperative Medical Scheme; OR, odds ratio; other, government agency health insurance plan or private health insurance plan; UEBMI, Urban Employee Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance.

Discussion

Using two waves of provincially representative data from China's NHSS in 2013 and 2018 collected in Jilin Province of China, we investigated the temporal changes and socioeconomic inequalities in cervical cancer screening in northeastern China. Our analysis showed that the cervical cancer screening coverage rate improved between 2013 and 2018 in both rural and urban areas, but the overall screening rate in Jilin Province remained far below the target 70% screening rate proposed by the WHO. Although the screening rate in rural areas was still lower than that in urban areas, the rural–urban inequality that was observed in 2013 disappeared in 2018. However, socioeconomic inequality still existed between the highest and the lowest income categories. Women with greater educational attainment or with health insurance were more likely to undergo cervical cancer screening. Our findings suggest that the use of cervical cancer screening still has a big gap to cross before achieving the target and that inequality persists especially socioeconomic inequality.

The WHO set the 70% goal of cervical cancer screening coverage, while the outline of "Healthy China 2030" proposed that the cervical cancer screening rate should reach 80% in 2030 (19). We found that the current screening coverage in China is far below both targets, which may be due to the different definitions of utilization. The WHO goal focuses on the coverage of twice-lifetime screening, while the target in "Healthy China 2030" focuses on screening utilization in the past 5 years. However, our study focused on utilization in the past 12 months, which may underestimate the use of cervical cancer screening.

Comparing the coverage of cervical cancer screening in Jilin Province to that of other provinces in China, we found that the overall screening rate was similar among women older than 18 years old reported in 2010 (12, 13). However, a study by You et al. (20) in Jiangsu Province using data from the NHSS reported that, in 2013, coverage of cervical cancer screening was 35.57%. Coverage in Jiangsu Province was higher in the study of You et al. maybe because only women aged 36–65 years old were included, while our study enrolled women older than 15 years old. In some developed countries, such as Norway (6), the coverage rate may reach >70% after the nationwide screening program is carried out. In South Africa and Turkey, the rates of cervical cancer screening were found to be 52.0% (21) and 22.0% (22), respectively. The coverage of cervical cancer screening in our study is lower than the target and lower than the level in some developed countries.

The use of cervical cancer screening increased from 2013 to 2018 in both rural and urban areas. Although the cervical cancer screening rate was lower in rural areas, the rural-urban inequality that existed in 2013 disappeared in 2018. This result may be explained using different screening strategies in urban and rural areas. Organized screening programs provide free screening services to all eligible women in rural areas so that, no matter a woman's household income or type of social health insurance, she can receive free service equally (11). However, in urban areas, women who cannot obtain organized screening need to search for services at a hospital. Under this circumstance, vulnerable women in urban areas are more likely to be influenced by socioeconomic factors, and, finally, the rural-urban inequality vanished.

We found that people with the highest income status had the greatest rate of cervical cancer screening in 2013 and 2018. This finding might be partly due to the low capacity to pay despite the service provided by the NCCSPRA being free. Socioeconomic inequalities attributed to a low capacity to pay were widely reported as barriers to universal coverage (20, 23). Income-related inequality is common all over the world and is documented in 67 countries (24). A study also found that a 20% increase in outpatient reimbursement could increase the rate of cervical cancer screening by 2.3% (25). A previous study in Korea found that, after Korea's National Cancer Screening Program expanded free cancer screening to people in the lower 50% of household income bracket in 2005, the disparity in Korea was improved and only the highest income group showed a significant difference compared to the lowest income group (26). Our result might reflect the importance of an organized program in eliminating income inequality.

Apart from the low capacity to pay, a reduced willingness to undergo screening and less health awareness was also associated with the utilization of screening services (27) in our study. The coverage showed an increasing trend as the level of educational attainment increased from 2013 to 2018. Women with greater educational attainment were more likely to undergo cervical cancer screening, which may be attributed to women with lower educational attainment not realizing the importance of cervical cancer screening (28). This finding was in concordance with those of studies from both developing and developed countries documenting that the screening rate of cervical cancer among women with greater educational attainment was higher (22, 26, 27, 29, 30). Studies reported that organized programs implemented in Denmark and Sweden did not eliminate the inequalities associated with educational attainment (31, 32), matching with our result. We found that organized screening programs in rural areas could not eliminate the inequalities caused by educational attainment, even though coverage among women with lower educational attainment grew faster.

Besides socioeconomic inequality, age also is an important indicator that caused inequality in screening rates. The latest data from the Global Burden of Disease study (33) showed that, with advancing age, the risk of cervical cancer increases (Figure 1). The incidence of cervical cancer was highest among women aged >45 years old, while the cervical cancer screening rate was highest among women aged 30–49 years and dropped significantly after 50 years of age. The demand for cervical cancer screening differed greatly from its actual utilization

(33). This phenomenon may be due to the misunderstanding of menopause, in that older women believe menopause can reduce the risk of cervical cancer (34). Instead, the capability of menopause to reduce the risk of cervical cancer is a misconception, which had a negative impact on screening participation (35). Based on the available evidence, the incidence of cancer among women aged 50–64 years with adequate screening was 1/6 that among those not screened (36). In implementing an organized screening program, special attention should be paid and targeted policies should be designed for elderly women in response to the growing disease burden.

The cervical cancer incidence in China in 2017 was 15.8 per 100,000 women, and the WHO's goal of reducing the cervical cancer incidence was set to <4 per 100,000 women. These study findings indicate that, to reach the 70% target put forward by the WHO and eliminate the inequalities, the effectiveness of organized screening programs in rural areas should be continually improved. Moreover, organized screening programs should also be implemented in urban areas and carried out using a multi-sector strategy to cover the whole process, including mobilization and monitoring.

Well-run organized screening programs should integrate health education, service provision, staff training, and effective monitoring. Before providing services, physicians and communities should mobilize women to improve their health awareness and therefore enhance their willingness to undergo screening. The efficacy of organized screening in rural areas still requires monitoring and enhancement to ensure an increase in coverage and the effectiveness of screening programs. It is important to include the whole process, from mobilization to effect monitoring, into an organized screening program. Based on the current disease burden, organized screening programs should involve policies targeting older women and should pay special attention to vulnerable populations (e.g., those with less educational achievements and a lower socioeconomic status).

Our study has inherited limitations from the design of the NHSS survey. First, the language of the survey question on whether or not the participant underwent any cervical cancer screening tests in 2013 and 2018 was not consistent. While it is possible to have underestimated the use of cervical cancer screening services in 2013, we thought that the difference in questions was mainly due to the use of new technologies and changes in cervical cancer screening guidelines, as mentioned above. Thus, it would have little effect on our conclusion. In addition, the cervical cancer screening utilization indicator in the NHSS survey was self-reported, and this may introduce a certain degree of recall bias. Another limitation of our research is that the socioeconomic characteristics in our analysis only included a limited number of subject-level factors: residence, annual household income, education, health insurance status, access to healthcare facilities, ethnicity, and marital status. Therefore, our investigation does not cover all aspects of socioeconomic domains and therefore is not comprehensive. Further studies are needed to conduct a comprehensive study on cervical cancer screening.

Conclusions

Cervical cancer screening coverage was improved from 2013 to 2018 in northeastern China but remained far below the target screening rate of 70% proposed by the WHO. Although the rural-urban inequality disappeared, other socioeconomic inequalities remained. Our findings suggest that an organized program may help to increase equality. However, the use of cervical cancer screening alone may not resolve the issues in achieving a high targeted rate and reducing the socioeconomic inequality of cervical cancer screening.

Data availability statement

The data that support the findings of this study are available from the National Health Services Survey of the Chinese Center for Disease Control and Prevention, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request from the corresponding author and with permission of the Chinese Center for Disease Control and Prevention.

Author contributions

The authors confirm contribution to the article as follows: study conception and design and draft manuscript preparation: YL, JG, GZ, BZ, and XF. Analysis and interpretation of results: YL, JG, BZ, and XF. All authors reviewed the results and approved the final version of the 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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Cervical cancer in Nepal: Current screening strategies and challenges

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Nepal has a high burden of cervical cancer primarily due to a limited screening program. Most present with advanced cervical disease. Despite no national cervical cancer control program, Nepal's Ministry of Health and Population has taken many initiatives with various international collaborations in screening, vaccination, and treating pre-invasive and invasive cancer. However, the existing prevention and treatment modalities are dismally inadequate to meet the targets of WHO's cervical cancer eliminative initiative by 2030. We provide an overview of the Ministry of Health and Population, Nepal's efforts to tackle the growing cervical cancer burden in the country. We discuss the challenges and potential solutions that could be practical and augment screening uptakes, such as single-dose vaccination and HPV DNA tests. The screen-and-treat approach on the same day could potentially address treatment delays and follow-up loss after testing positive. Our narrative summary highlights existing and innovative strategies, unmet needs, and collaborations required to achieve elimination across implementation contexts.

KEYWORDS

cervical cancer, Nepal, screening, prevention, HPV

Introduction

Nepal is a South Asian landlocked country located between India and Tibet Autonomous Region of China, with an approximate population of 29 million (1). The country is administratively divided into seven provinces which in turn into 77 districts. Nepal's health care providers without robust and effective primary, secondary, and tertiary health referral systems are the public and private health sectors unequally spread across the nation's hilly to low plain regions. The gross domestic product per capita stands at USD 1,222.9 in 2022, 12.7% higher than in 2017 (2). In 2019, 17.4% of Nepalese were multi-dimensionally poor—just under five million persons (3). The estimated life expectancy at birth is 71 years as of 2017 (4), 2 years more than neighboring India. These numbers point toward Nepal's relentless pursuit of progress guided by the overarching national aspiration of "Prosperous Nepal, Happy Nepali" by 2030 (5).

Cervical cancer was the leading cause of death in women in most countries in the middle of the 20th century. Since the introduction of the Papanicolaou (Pap) test, cervical cancer has dramatically reduced in high-income countries over the last five decades (6). In contrast, cervical cancer remains and is rising among women in low- and middle-income countries (LMICs), with an estimated 531,631 (88%) of 604,127 new cases yearly. Within Nepal, Cervical cancer continues to be the leading cancer among women, with an annual incidence of 2,244 new cases and 1,493 deaths. Nepal has a cervical cancer incidence of 16.4 per 100,000 women, in contrast to the WHO's desired target of 4 per 100,000 women, nearly four times the target to eliminate the public health issue of cervical cancer (7). In Nepal, cervical cancer kills almost 11 women for every 100,000, even though cervical cancer is preventable with time-tested screening strategies (1). In addition to the toll on health and mortality, cervical cancer imposes a significant social and economic burden in LMICs like Nepal. The WHO estimates that by investing in cervical cancer prevention and control, nations can empower an estimated 250,000 women to contribute to the world's economy, which is estimated to be $28 billion through 2050 (8).

The WHO recognizes the enormous cervical cancer burden on women living in impoverished low middle-income countries. Hence, to address this global health burden, the WHO launched "The Global Strategy for the Elimination of Cervical Cancer," with an intermediate 2030 triple-intervention strategy known as the 90–70–90 targets in 2019. The triple targets to achieve are 1-vaccination of 90% of girls with the HPV vaccine by age 15, 2-screening of 70% of women by 35 and 45 years of age, 3-Treatment and management of 90% of women identified with the cervical pre-invasive and invasive cancer respectively. The successful implementation and scaling-up of the triple intervention would reduce mortality attributed to cervical cancer by 33.9% (24.4–37.9 per 100,000 women) by 2030 and almost 99% by 2120 (mortality) among women aged between 30 and 69 years (8).

Globally, as nations embrace the WHO's call to action on the cervical cancer elimination initiative, we sought to summarize the current status of various screening strategies and treatments available for cervical cancer in Nepal and the challenges to surpass the WHO's 90–70–90 targets.

Screening strategies

Cervical cancer development is a multistep carcinogenic process and starts with HPV infection. Dr. Hausen, in 1975 hypothesized the link between cervical cancer and Human Papillomavirus (HPV) (9). The following decades witnessed rapid progress in understanding the pathogenesis of HPV-driven cervical cancer. More than 200 HPV genotypes have been identified, subdivided into low-risk and high-risk categories based on their pathogenicity to cause cancer. Once HPV infection occurs, it can regress, persist or progress (10). Persistent high-risk HPV infections, most commonly 16 and 18 genotypes, are responsible for nearly all invasive cervical cancer (11). High-risk HPV 16 and 18 elaborate oncoproteins E6 and E7 implicated in carcinogenesis: E6 binds to p53, accelerating its degradation, while E7 binds to pRB, releasing E2F, which allows cells to progress in the cell cycle with genomic instability (12–14). In addition, the integration of viral genes in the host genome facilitates the further expression of E6 and E7, with subsequent lethal genetic changes contributing to neoplastic transformation. It takes 10–20 years, or even longer, for HPV-infected cells to progress from normal to pre-invasive to invasive cancer. This long interval provides a window to detect early pre-invasive neoplastic lesions and prevent cancer development by screening. There are three methods of cervical cancer screening. They are:

i) Cytology-based screening: conventional pap smear and liquid-based cytology.
ii) Visual inspection by acetic acid examination.
iii) HPV DNA testing concurrent with pap smear (co-testing) or primary screening technique.

Cytology-based screening

The Pap smear test was developed in the early 1940s by George Papanicolaou. The test involves taking the sample from the cervix and smeared on the glass slide with subsequent staining for microscope examination by a trained cytotechnologist or pathologist. It is the earliest screening technique that became widespread by the 1960s, chiefly in high-income countries with 70–80% sensitivity (15–17). The specimen adequacy is crucial for the Pap test's accuracy (18). The cellular changes are reported according to "The Bethesda System for Reporting Cervical Cytology," which provides consistent and reproducible criteria for diagnosing pre-invasive and invasive cancer (19). The most important advantage of a conventional pap smear is its low cost (20). A significant advance in cytology-based screening happened when US FDA approved a new liquid-based cytology technique (LBC: Thin prep and SurePath) to enhance further the sensitivity to detect various pre-invasive lesions and improve specimen adequacy (21).

In contrast to a conventional pap smear, the collected sample is placed inside a preservative liquid in a small bottle of LBC. At the laboratory, mucus and blood were removed, and cells were placed on a glass slide for microscopic examination. The distinct advantages of LBC are fewer unsatisfactory smears, high sensitivity, less obscuring materials such as blood, mucous, and inflammatory cells in smears, and residual cell suspension for testing human papillomavirus (HPV) DNA (22). Though liquid-based cytology is available in the selected private laboratories, it is not a common technique used in the public sector in

Nepal. A recent systematic review and meta-analysis by Shrestha et al., which included 17 studies from Nepal, reported that liquid-based cytology is not a screening method in Nepal (7).

High-income countries witnessed the impact of cytology-based screening, which is the most successful screening technique for cancer prevention ever designed. Nearly 90% of women were screened at least once in their lifetime in these countries, attributed to organized quality-assured screening programs and widespread public awareness (23). Because of the successful national cervical cancer screening programs, high-income countries are on the verge of cervical cancer elimination (24). Without such a screening program, only 2.8% of Nepali women were screened when the population at risk is 11.4 million women aged 15 years and older (25). The most vulnerable are women (>80%) living in rural areas. Screened women were mainly from urban areas highlighting the further inequality in accessing the available health services (25). There is no data available on whether these screened women were asymptomatic or symptomatic such as irregular and postcoital bleeding and vaginal discharge, which could guide us in the screening uptake behavior among urban women.

The cytology-based screening process is a highly skilled personnel-intensive program. Major limitations are the low sensitivity to detect early pre-invasive lesions, the complex logistical and care network to implement quality control and subsequent appropriate clinical management (e.g., colposcopy, biopsy, endocervical curettage) of women with positive screening. These reasons precluded low- and middle-income countries, including Nepal, from rolling out population-based screening, where screening occurs opportunistically in health camps (26–28). Therefore, implementing cytology-based screening to enhance the coverage from the current 2.8% to the WHO target of 70% by 2030 seems remote in Nepal. However, the Ministry of Health and Population, Nepal, must continue investing in cytology which is of immense value for triaging women who test hrHPV positive by any other techniques.

See and treat approach

An alternative cost-effective screening technique is a visual inspection of the cervix by applying 3–5% acetic acid (VIA). The application of acetic acid highlights the cervical dysplastic areas with immediate color changes visible to the naked eye. Any modification in the color is categorized as positive for pre-invasive cervical cancer. VIA is a simple, easy-to-use technique that has been used since the 1990s, especially in LMICs, including Nepal. The distinct advantages of the VIA technique are that healthcare personnel can perform without requiring high technology or infrastructure and the same-day "Screen and Treat" (SAT) strategy. Previous studies have shown that a single-visit approach effectively reduces high cervical precancerous lesions (29). Low and middle-income countries have implemented SAT strategy in pilot programs and sporadically with much success (30–32). Several studies have found the sensitivity of VIA for detecting high-grade cervical pre-invasive lesions ranges from 73 to 85% and a specificity of 81–89% (33–35). The VIA technique's drawbacks are provider-dependent and subjectivity and have lower sensitivity for women older than 40. However, the benefits outweigh these drawbacks in the current situation.

The cervical cancer burden in Nepal has not gone unnoticed by the Government of Nepal. In 2010 The Ministry of Health and Population, Nepal developed "national guidelines for cervical cancer screening." The guidelines envisioned screening 50% of the target population, women in the age range of 30–60 years, by 2015 based on the VIA technique. However, the screening program did not gain momentum resulting in dismally low coverage owing to implementation difficulties. Recently, a pilot study was initiated to investigate the Effect of a "community-based intervention for cervical cancer screening uptake in a semi-urban area of Pokhara Metropolitan, Nepal" (COBIN-C) (36). This study is based on trained female community health volunteers (FCHVs), important last-mile connectivity to the community (37) who deliver home-based health education to enhance the cervical cancer uptake by VIA technique among eligible women. The study results are crucial and expected to shed light on the social and cultural barriers, community health practices, and how the intervention results in overcoming the obstacles to a positive attitude toward cervical cancer screening.

The Ministry of Health and Population, Nepal, issued "The national guideline for Cervical Cancer Screening and Prevention (CCSP)" in 2010. The goal was to screen at least half of women in the age group of 30–60 years, which was revised to 70% in 2017. By 2019, only 8.2% of women aged 30–49 years were screened.

HPV/DNA-based molecular test as a primary screening assay

Human papillomavirus (HPV) is a small, non-enveloped deoxyribonucleic acid (DNA) virus belonging to the Papillomavirus family and the most common sexually transmitted infection. HPV is highly transmissible, with peak incidence soon after the onset of sexual activity, and most persons acquire infection at some time in their lives. A deep understanding of HPV biology led to the development of HPV-based diagnostic tests and HPV vaccines (38). Among 200 HPV genotypes, 40 are known to infect the genital tract determining cervical carcinogenicity. The genotypes with greatest risk are HPV 16, 18 followed by 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. HPV types 16 and 18 account for 73% of cervical cancers globally (39). The studies have shown regional differences in the prevalence of HPV genotypes associated with cervical cancer (40). The reliable data on the prevalence of HPV genotype in

Nepal would greatly help to consider the scope of HPV DNA testing and HPV vaccination tailored to its locoregional needs. To this end, two studies in Nepal demonstrated that overall HPV prevalence was 8.6%, and 90% of examined cervical samples showed high-risk genotypes HPV 16 and 18. HPV 16 and 18 infection is 2% among Nepalese women and is responsible for 80.3% of invasive cervical cancers (41, 42).

In 2002, the American Cancer Society (ASC) guidelines incorporated HPV DNA testing in screening pre-invasive cervical cancer in tandem with cytology (43). Further research with accumulating data showed that primary cervical cancer screening by HPV DNA testing was comparable to cytology alone or co-testing in addition to longer screening intervals (44–47). In 2014, HPV DNA testing became a primary screening test in addition to cytology when the US FDA approved the Cobas HPV test as a first-line screening test for 25 years and older women (48). Recent studies across the globe, including LMICs, have shown that HPV testing is a reliable, reproducible, and cost-effective screening compared to cytology screening for cervical neoplasia (49–53).

WHO recommends screening should start at the age of 30 years with regular testing every 5–10 years for women. In contrast, women with HIV should begin screening at 25 years, with regular screening every 3–5 years.

HPV DNA-based screening tests

Initial HPV DNA tests were polymerase chain reaction (PCR) based nucleic acid amplification tests (NAAT) or signal amplification techniques, such as the Digene Hybrid Capture® II assay (38). A recent study from Srilanka successfully demonstrated that HPV-DNA testing using Cobas 4800 HPV/DNA automated PCR machine can be implemented as a primary screening method in low-resource settings (49). In recent years, the development of rapid molecular-based point-of-care tests for detecting HPV DNA (e.g., care HPV® –Qiagen, GeneXpert® –Cepheid) has outperformed the earlier expensive, time-consuming, and laboratory-intensive techniques (54). In a study in a rural Chinese population, the authors found primary HPV DNA Qiagen testing compares favorably to VIA cost-effectively (55). These accurate and affordable rapid tests provide new options to roll out mass cervical cancer screening programs in Nepal (52).

Advantages and limitations of HPV DNA-based screening tests

The distinct advantages are cost effectiveness, suitability for all settings, reduced investment in health workforces and infrastructure, and prolonging the screening interval. DNA-based tests also leave no space for human errors, such as subjective and interobserver variability associated with pap smear and visual inspection methods (56). For these reasons, WHO recommends hrHPV testing as a preferred screening strategy wherever feasible (57, 58). The flip side of this argument is that HPV-DNA test as a primary screening could potentially detect clinically insignificant diseases than the women at risk of developing cervical cancer because it is highly sensitive but less specific than cytology alone (38). Therefore, triaging to determine the optimal management of HPV-DNA test-positive women is essential to avoid unnecessary diagnostic and treatment burdens on the health system, outweighing the benefits of HPV DNA testing.

Barriers to cervical cancer screening programs in Nepal

Barriers are not significantly different across low and middle-income countries. However, there are many locoregional specifics, such as hilly regions of Nepal rendering the accessibility to the health facility. In general, we can break down barriers into three major categories.

Clinic and laboratory

Setup is a bare minimum for any of the three screening methods to succeed. According to a recent report by Nepal's Ministry of Health and Population, the laboratory testing capacity in Nepal is that only 12% of facilities can perform basic tests like hemoglobin, malaria testing, and stool microscopy (4). Despite sparse physical infrastructure, there are stories of sporadic success when planned well.

Cultural and social factors

Besides the economic sustainability, numerous studies have highlighted the challenges for nationwide cervical cancer screening in Nepal. Institutional research at a tertiary care center in Kathmandu showed varying knowledge of cervical cancer among participants; 37% had an average, and 16.5% had good knowledge. Further, 70% of the participants had a positive outlook toward cervical cancer screening. Surprisingly, the cervical cancer screening uptake among those with a positive outlook was <25%. The significant barriers to screening were, in descending order, embarrassment (72%), pain (71%), lack of privacy (65.9%) (59), and misconceptions about the screening. Additional obstacles were social issues, cultural barriers, healthcare workers' behavior, and geographical challenges in seeking screening center services.

Financial sustainability

Economic assessment of any screening strategy has enormous implications for the success in the context of LMICs, including Nepal. Each country should develop its economic

evaluation. In addition, on behalf of LMICs, WHO must negotiate global pricing of HPV testing with the manufacturers. The prices should be competitive for the LMICs so the governments can pay. Innovative and sustainable financial models for procuring HPV tests should be developed to enable those most in need to access the tests.

Steps to be taken and emerging techniques to overcome the known barriers

For LMICs like Nepal, the most feasible screening technique is the hrHPV molecular assay. hrHPV testing can be done on a self-collected sample. Self-sampling for HPV is an innovative technique to collect the specimen in privacy with many advantages: women can decide their time, place, and comfort level. It can potentially overcome the fear and stigma associated with visiting the clinic, a trained clinician, and a pelvic examination (60–62). In addition, the self-sampling specimens are comparable with the provider-taken specimen, and samples can be stored for up to 32 weeks for later transportation without compromising specimen quality (63). Thus, the self-sampling technique offers critical advantages in successfully overcoming the known barriers and implementing Nepal's cervical cancer screening program.

A meta-analysis by Arbyn (64) found that participants' acceptance of self-sampling for HPV screening was two times more than women without. The acceptance rate went further high when women received the HPV self-sampling kits at home either by mail or from a health worker. Shrestha et al. (65) explored the concept of self-sampling for HPV DNA testing among Nepali women in Kathmandu Valley, mostly limited to urban areas, demonstrating that 56.7% of the participants were willing to accept the self-sampling technique. Because of the disparity between urban and rural Nepal, the results cannot be generalized. In a recent study in rural, southwestern Uganda, authors studied the challenges associated with "implementing community-based human papillomavirus self-sampling with SMS text follow-up for cervical cancer screening." 82% of eligible women underwent self-sampling hrHPV testing. Most women rated self-sampling highly and confidence in test results was higher for self-screening than VIA. Despite good acceptability, only 35% hrHPV positive women returned for follow-up despite SMS texts. This study identified the gap in the cervical cancer screening cascade and linkage to care (66).

Successful implementation of HPV self-sampling screening programs in Nepal depends on how we address the above challenges, such as identifying the target population, educating them about the technique, and removing the fear from their mind and immediate family. WHO has created a great resource highlighting the factors to consider while introducing HPV self-sampling. The success of self-sampling-driven HPV DNA testing in Nepal largely depends on the active participation of the Female Community Health Volunteers (FCHV). They have a strong presence in all 77 districts of the country. According to the family health division under the Ministry of Health and Population, Government of Nepal, there are 47,328 FCHVs at the rural level and 4,142 at the urban level establishing last-mile community connectivity (4). Currently, FCHVs are actively involved in advocacy, promotion, and service delivery with an overall aim to support maternal and child health, family planning, and other community-based health activities. Expanding and involving FCHVs in cervical cancer elimination initiatives is imminent if we need to succeed in our efforts to reach out to all eligible women for screening by 2030. The Nepal government should support the FCHV by empowering them with knowledge, skills, and training to increase awareness of cervical cancer screening among community members. The other significant challenges to address while implementing the self-sampling technique are; options for returning the sample and; receiving the test results. The next big challenge is triaging women with positive results. The system should not allow positive cases to slip out of the radar for clinical assessment and treatment of cervical lesions. We are optimistic that the study results of the COBIN-C trial will address this challenge.

In the future, screening by cost-effective HPV testing alternative to cytology and VIA will auger well in LMICs. Policymakers should consider HPV testing with self-collection samples as it gains traction among the population (51).

Cytology has been the mainstay for cervical cancer screening for decades and has been largely successful in reducing cervical cancer in high-income countries. However, screening strategies are changing, with many different options available now. Current risk-based management is largely based on established practice from cytology-based screening programs. Hence, evaluating the different cervical cancer prevention options in risk-based management is critical moving forward.

HPV vaccination status, success, and challenges

The tremendous progress in understanding HPV and cervical cancer's natural history has allowed primary prevention by vaccination against HPV to become a reality. The vaccine is primarily used to avoid an HPV infection; thus, its administration before the onset of sexual activity gives the best chance of preventing the disease. The first milestone in that direction was in 2006 when GlaxoSmithKline produced an AS04-adjuvanted HPV-16/18 bivalent vaccine (Cervarix) that has proven effective in preventing HPV-16/18-related persistent infections and cervical intraepithelial neoplasia grade 2 and above (67).

Subsequently, Merck produced Gardasil, a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (68); and Gardasil-9, a non-avalent vaccine for HPV types 31, 33, 45, 52, and 58, in addition to the coverage of quadrivalent vaccine (69). All three HPV vaccines when administered intramuscularly, have resulted in good immunogenicity with persistent high anti-HPV antibody titers in adolescents (aged 9–15 years, two doses) and young women (16–26 years, three doses). All the vaccines were well tolerated, without any major vaccine-related adverse events.

The HPV infection among sexually active women is almost two-thirds, and hrHPV 16 and 18 genotypes are responsible for more than two-thirds of cervical cancer cases (70, 71). HPV vaccines have been approved for women in developed countries since 2006. In contrast, access to new vaccines in developing nations has historically been a decade late; however, HPV vaccines are now available in at least 124 countries, including Nepal. Only 15% of girls in the target age for HPV vaccination are globally fully protected (72). For complete protection against cervical cancer, WHO recommends two doses of HPV vaccine for 9 and 14 years, aged girls. However, only about 15% of eligible girls worldwide have been fully vaccinated (71). Several studies highlighted common factors across low–middle-income countries that led to such low coverage; high cost, supply chain hurdles, and lack of national HPV vaccination programs.

Current vaccination status in Nepal

The median age range of first sexual activity is 16.5–17.9 for women in Nepal (73, 74).

The first attempt at HPV vaccination in Nepal was carried out in 2008 using 3,300 vials of Gardasil with the assistance of the Australian Cervical Cancer Foundation (ACCF) (75). Seventeen schools were selected; 1,096 school girls aged 10–26 were vaccinated; 90% were 12–16. Only five and two girls missed their second and third doses, respectively, making it a highly successful vaccination drive. The success of this collaboration also led to the establishment of the Nepal Australian Cervical Cancer Foundation (NACCF), which has been a strong advocate of public awareness at the community level and provides free-of-cost vaccines. In addition, collaboration with GAVI led to the HPV vaccine demonstration project in 2016–2017, launched in Chitwan (8,243 girls) and Kaski (6,500 girls) districts. This project incorporated the two doses of Cervarix vaccine into the annual regular immunization program for girls between 11 and 13 years at school and 10 years old out-of-school girls at the health facility. Encouraged by the success of the pilot projects, the Nepal Government launched an HPV vaccination drive in nine districts across the country. Regrettably, the prevailing political scenario and lack of funds derailed the vaccination drive and halted it indefinitely (76). Currently, Nepal does not have a national HPV vaccination program; hence no vaccination coverage data in the country.

Barriers to HPV vaccination and strategies to roll out a national HPV vaccination program

Previous vaccination programs in Nepal have demonstrated that HPV vaccination acceptance was high among school-going girls despite less knowledge of HPV; only 13.9% knew of an HPV vaccine. In one study, 96% of parents expressed willingness to have their child HPV vaccinated if it is free of cost. The high vaccine cost seems to be the most significant barrier to achieving WHO's target of 90% by 2030. Financial sustainability is crucial for introducing and scaling up an HPV vaccination program. Recently approved "the quadrivalent Cervavac vaccine" in India costs ~400–500 Nepali rupees (USD 5) per dose compared to the currently available vaccines for USD 46 per vaccinated person (76). Another bivalent vaccine, Cecolin, which has been licensed in China, is presently under an active prequalification process by WHO making them promising more affordable vaccines than existing licensed HPV vaccines (77). Another encouraging piece of information is the New England Journal of Medicine data, which could further reduce the cost and vaccine affordability (78). Additionally, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) concluded that a single-dose Human Papillomavirus (HPV) vaccine is comparable to 2-dose schedules in its efficacy (79). Single-dose HPV vaccine administration simplifies the system, which is logistically less expensive, easy to administer with broader coverage rates, and ideally suited for LMICs like Nepal.

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.
- Two doses with a 6-month interval for women older than 21.

There is limited evidence regarding the efficacy of a single dose in immunocompromised individuals, including those with HIV, who should receive three doses if feasible, and, if not, at least two doses.

In addition, social and cultural factors like ethnic variations, public awareness, reaching out to non-school-going girls, consent issues, and strong political commitment are the major hurdles to launching and implementing the vaccination program in Nepal (59, 80). Vaccine hesitancy in the pilot programs is a non-factor in the vaccination uptake among school-going girls in Nepal. These data will provide relevant

evidence to plan Nepal's following cervical cancer prevention programs. Cervical cancer will remain problematic unless an effective HPV vaccine program is rolled out to all adolescent girls, irrespective of social and economic status. Concerted and well-coordinated efforts between the ministry of health, Nepal, its partners, and the private sector are essential to overcome seemingly possible hurdles. One shining example of these efforts is a Sub-Saharan African nation: Rwanda has rolled out the comprehensive cervical cancer program and had incredible success in the HPV vaccination coverage across the nation. The coverage rate is comparable to the high-income countries and is on the verge of eradication (81). A robust vaccination strategy and human resource framework led to this spectacular success in Rwanda.

The recent Covid-19 pandemic has shown that the governments in low-middle-income countries have the ability and political will to administer an enormous number of vaccines to their public. Ministry of Health and Population, Nepal must reach out to the neighboring countries to procure the Cervavac and Cecolin vaccines at a negotiated price as it did to get the Covid-19 vaccine. Nepal government must change the protocol to a school-based immunization program incorporating the HPV vaccine ensuring high coverage among young girls aged 9–14. Additionally, the inclusion of HPV vaccination and cervical cancer screening within community-based immunization programs that provide sexual and reproductive health, human immunodeficiency virus (HIV)/sexually transmitted infection (STI) screening, and management is feasible.

Cervical cancer treatment

In Nepal, 2,244 new cases of cervical cancer are diagnosed annually, and 1,493 women die of cervical cancer (74). Notwithstanding the prevention interventions, these new cervical cancer cases will impact the next 10–20 years. Hence, priority must be on early detection of precancerous and treatment of invasive cancer. Mostly, women with cervical cancer have locally advanced disease at diagnosis, requiring radiation and cisplatin-based chemotherapy rather than surgery (82). Nepal's healthcare personnel trained to manage such cases is severely limited. Specialized physicians are few: estimated to be 20 gynecologic oncologists and 35 radiation oncologists in the country, catering to 29 million populations. They are mainly concentrated in urban centers. The total strength of healthcare providers trained to manage cervical pre-invasive lesions is unknown.

A historical city Banepa saw the first women's clinic, constructed by NACCF with the support of ACCF. It is a model health center in Nepal, providing care for VIA+ women and offering general screening and examination facilities. Skilled human personnel specialized in performing VIA, colposcopy and cervical biopsy, thermal ablation, and loop excision are acutely short in Nepal. Though infrequent, a recent visit by a team of experts from the USA comprising the members of The American Society of Clinical Oncology (ASCO) and The University of Texas MD Anderson Cancer Center trained 42 personnel in essential skills for the diagnostic procedure and management of cervical cancer (83). Appropriate cancer care requires a multidisciplinary approach with a team of experts consisting of oncologists, surgeons, pathologists, radiologists, oncology/radiation nurses, medical physicists, radiation therapy technicians, and trained social health workers. Local governments have partnered with various domestic and international stakeholders such as the Bill and Melinda Gates Foundation, PATH (a global health organization), Global Alliance for Vaccine and Immunization, and ASCO to recruit, train and retain health care personnel to mitigate the effects of health care personnel shortage.

Integration of the lessons learned into the existing health infrastructure

A lack of medical knowledge and reluctance to seek timely healthcare contribute to the cervical cancer burden in Nepal. However, the enthusiasm from participants for sporadic attempts at screening and vaccination in Nepal is encouraging. With the growing Mobile health (mHealth) technology, the Ministry of Health and Population, Nepal, can reach out to every corner of the country with health campaigns. Recent experience with MANTRA, a mobile game app in rural Nepal, developed to tackle maternal and child health issues, demonstrated positive engagement with rural women despite limited educational level (84). It enabled them to identify the early danger signs and make informed health decisions. FCHVs were encouraged by the participant's responses, and they acknowledged that MANTRA intervention amplified the impact of their efforts in rural Nepal.

Nepal has higher mobile subscriptions than most countries in South Asia, with ∼110 subscriptions per 100 people, according to World Bank's 2016 data (85). This should enable mHealth interventions to be easily incorporated into Nepal's existing national health infrastructure, which begins with health posts. Health posts are Nepal's first institutional contact point for basic health services. These bottom-level health facilities monitor the activities of female community health volunteers (FCHVs). Primary health care outreach clinics (PHC-ORCs) and Expanded Program on Immunization (EPI) are additional basic health services. Each level above the health post level is a referral point in a network ranging from primary health care centers (PHCCs) to primary- and secondary level hospitals and, finally, tertiary-level hospitals. Community health units are gradually increasing at the ward level. In addition, Nepal has established urban health centers (UHCs) to ensure that the urban poor can receive treatment.

In summary, Nepal's efforts to eliminate cervical cancer must be sustainable and continuous. Widespread single-dose HPV

vaccination and point-of-care (POC) HPV testing with self-sampling should form the basis for Nepal's national cervical cancer screening program. Pro-active involvement of FCHVs, in the above strategy, must be initiated. Follow-up care for women who tested positive should be provided in the designated clinics backed by a robust reflex communication system for recall reminders. Further, the knowledge and evidence from the previous and ongoing efforts should guide the Nepal government's policymakers about the necessary domestic and international collaborations, which will augment the capacity secondary prevention and management of cervical cancer with a reliable infrastructure to treat HPV-driven pre-invasive and invasive cancer.

Author contributions

MN: conceived, literature search and review, and manuscript writing. SK: manuscript review and extensive input on-ground facts. 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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Implementing HPV testing in 9 Latin American countries: The laboratory perspective as observed in the ESTAMPA study

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Background: Replacement of cytology screening with HPV testing is recommended and essential for cervical cancer elimination. HPV testing for primary screening was implemented in 12 laboratories within 9 Latin American countries, as part of the ESTAMPA cervical cancer screening study.

Our observations provide information on critical operational aspects for HPV testing implementation in diverse resource settings.

Methods: We describe the implementation process of HPV testing in ESTAMPA, focusing on laboratory aspects. We assess the *readiness* of 12 laboratories to start HPV testing and their *continuity capacity* to maintain good quality HPV testing until end of recruitment or up to December 2021. *Readiness* was based on a checklist. Information from the study database; regular meetings and monitoring visits; and a questionnaire on laboratory operational aspects sent in May 2020 were used to assess *continuity capacity*. Compliance with seven basic requirements (readiness) and eight continuity requirements (continuity capacity) was scored (1 = compliant, 0 = not compliant) and totaled to classify *readiness* and *continuity capacity* as very limited, limited, moderate or high. Experiences, challenges, and enablers of the implementation process are also described.

Results: Seven of 12 laboratories had *high readiness*, three *moderate readiness*, and of two laboratories new to HPV testing, one had *limited readiness* and the other *very limited readiness*. Two of seven laboratories with *high readiness* also showed *high continuity capacity*, one *moderate continuity capacity*, and the other four showed *limited continuity capacity* since they could not maintain good quality HPV testing over time. Among three laboratories with *moderate readiness*, one kept *moderate continuity capacity* and two reached *high continuity capacity.* The two laboratories new to HPV testing achieved *high continuity capacity*. Based on gained expertise, five laboratories have become part of national screening programs.

Conclusion: *High readiness* of laboratories is an essential part of effective implementation of HPV testing. However, *high readiness* is insufficient to guarantee HPV testing *high continuity capacity,* for which a "culture of quality" should be established with regular training, robust monitoring and quality assurance systems tailored to local context. All efforts to strengthen HPV laboratories are valuable and crucial to guarantee effective implementation of HPV-based cervical screening.

KEYWORDS

HPV testing, HPV testing implementation, readiness and continuity capacity, ESTAMPA study, cervical cancer screening, Latin America

Introduction

More than 600,000 new cases and 300,000 cervical cancer deaths occur every year; over 90% of these are in low-income and middle-income countries (LMIC) (1).

Cytology-based screening has successfully reduced cervical cancer rates in places where it has been systematically implemented (2). However, cytology has limited and variable sensitivity, requiring frequent repetition to reach an acceptable level of precancerous lesions detection (3, 4). Frequent cytology screening has not been feasible in most LMIC, where coverage is generally low, and follow-up of women with abnormal cytology and treatment of detected lesions is very limited (3, 5).

Persistent infection with high-risk HPV is the leading cause of cervical cancer (6). Several molecular techniques are available to detect HPV DNA and can be used in primary screening (7, 8). There is overwhelming worldwide evidence that HPV testing is more effective than cytology in identifying women at greater risk of precancerous cervical lesions (9–13). HPV testing is objective, can be automated, and can be done using self-collected samples with potential to increase screening coverage (14–17). In addition, the high negative predictive value of HPV testing allows extension of the screening interval (in comparison to the 3 years interval when using cytology) (18, 19), facilitating screening and treatment coverage in limited-resource settings.

In the World Health Assembly (20) adopted a global strategy for eliminating cervical cancer as a public health problem. In order to reach elimination by the end of the century, countries should achieve full vaccination of 90% of girls by age 15, screening of 70% of women twice by age 35 and 45 with a high-performance test, and treatment of 90% of women with cervical disease (precancer or invasive cervical cancer) (21). In 2021, WHO published cervical cancer screening and treatment guidelines recommending the use of HPV DNA detection in a screen and treat approach or a screen, triage and treat approach starting at age 30 every 5 to 10 years for the general population, and using HPV DNA detection in a screening, triage and treat approach starting at age 25 every 3 to 5 years for women living with HIV (22). As evidence-based cervical cancer screening and treatment interventions are available, it is time for country-driven implementation research to understand how to implement and scale-up HPV-based cervical screening (23, 24). In fact, reports from countries in Latin America that are replacing cytology with HPV testing at the national level or in pilots suggest that HPV-based cervical screening implementation is very challenging, and demands extensive planning of activities across the screening care continuum including preparation of laboratory facilities and training of personnel for HPV testing before scaling-up (25–29).

Several tools are available to support countries with the implementation of HPV testing within cervical cancer screening (30–33). In particular, the step-by-step guide on introducing and scaling up HPV within a comprehensive program of prevention and control of cervical cancer (33), intends to offer practical guidance to program managers once the decision to introduce HPV testing in their national cervical cancer prevention program has been made. Guidance covers three main domains: planning, implementation, and monitoring/scaling up of HPV testing in primary screening. Once planning is completed, the preparation of an implementation roadmap is recommended, to establish or strengthen quality management systems in laboratories, to define the procurement process and to use indicators to monitor the progress of the implementation. This is key to consolidate a screening platform for scaling up and final adoption of the screening strategy at national level. Using several features of this step-by-step guide, here we describe the HPV testing implementation process, including monitoring and evaluation of HPV testing performance over time of 12 laboratories in Latin America participating in the ESTAMPA study (NCT01881659) (34).

Materials and methods

ESTAMPA is a multicentric study of cervical cancer screening with HPV testing conducted in 12 study centers' laboratories (SC1-12) in nine countries in Latin America. The study aims to evaluate the performance of different techniques and approaches to triage HPV positive women and to inform on how best to implement affordable and sustainable HPV-based screening programs in LMIC.

The study protocol has been previously published (34). Briefly, women aged 30 to 64 years old were invited for cervical cancer screening with HPV testing and, following country guidelines, also cytology. Women who consented to participate underwent pelvic examination, and samples were collected using Cervex brushes (Papette, Wallach, USA) that were washed in PreservCyt medium (PC) (Hologic, USA) for HPV testing and cytology.

Samples were tested for HPV DNA detection using either *Digene* HC2 HPV DNA test (QIAGEN, USA) or COBAS HPV test (Roche, Switzerland). After HPV testing, aliquots of PC were prepared for future molecular triage. *Digene* HC2 sample conversion kit was used for conversion of samples collected on PC before HC2 HPV testing. HPV (HC2 or COBAS) was done following manufacturer instructions and ESTAMPA standard operating procedures (SOPs). For quality control (QC) of HPV testing, in some laboratories, about 10% of samples tested with HC2 or COBAS were retested either at the same laboratory using a different HPV technique or at and international hub with COBAS. In one center, samples from the first 900 recruited women were stored in the Digene Standard Transport Medium (STM) and subsequently tested with HC2. In this center, a sub-study evaluating the impact of operational factors on HPV positivity of HPV assays including HC2, COBAS and APTIMA (Hologic, USA) was conducted and COBAS results were assumed as QC of HC2 and APTIMA (35).

Women with abnormal cytology or positive HPV results (including QC HPV test) were referred to colposcopy, 2-3 biopsies were collected from any observed lesions, and women diagnosed with cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2 +) were treated with LLETZ. At this colposcopy visit, a cervical sample was collected for HPV testing and other molecular triage tests. Women with negative colposcopy or histology showing lesions less severe than CIN2 (< CIN2) were invited for a follow-up visit at 18 months for a second HPV screen to complete ascertainment of disease. Women positive for HPV at this visit were referred to colposcopy and clinically managed as needed.

Overall, women could have one, two, three or four HPV tests during the study, depending on their screening results and associated study visits (initial screening, colposcopy and 18months follow-up) and on the sample being selected for QC.

Steps to implement HPV testing in 12 ESTAMPA laboratories

The main steps carried out to implement HPV testing in ESTAMPA laboratories (**Figure 1**) are described as follows.

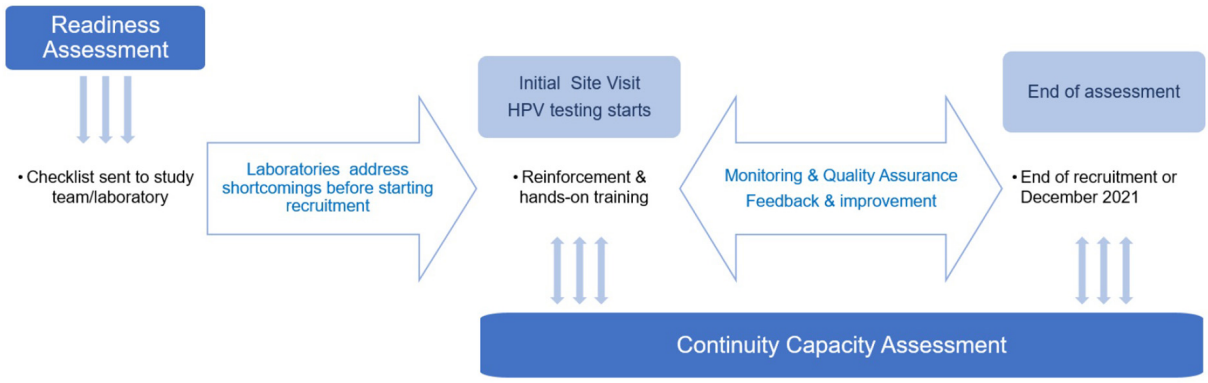

FIGURE 1
Steps followed in ESTAMPA for HPV testing implementation.

(1) Assessment of *readiness* for HPV testing implementation in the laboratory. Before launching the study, local principal investigators willing to take part, were asked to identify a laboratory with adequate facilities as to carry out HPV testing for primary screening. Laboratory-based investigators could propose their own facilities or others thought more suitable for future participation in national HPV-based cervical screening program.

Next, a checklist (**Supplementary Material 1**) was used to assess the existing installed capacity of each laboratory. As the study was launched early on in the introduction of HPV testing in primary screening (December 2012), laboratories were asked about the availability of HPV equipment in the laboratory; whether collection medium and HPV reagents were registered in the country and if not, whether investigators had experience with importing and customs; and whether additional HPV testing consumables specifically selected for the study were available in the laboratory or the country.

Laboratories were also asked whether they had personnel to perform the test; and whether they had established logistics for transport and storage of samples, management of reagents validity and delivery of results. We did not request specific arrangements for external quality assurance (EQA) in this checklist, but we proposed different QA measures as the study progressed.

Based on this initial assessment, each study center developed a road map to address limitations and joined the project when ready to launch recruitment.

(2) Initial site visit to start recruitment and HPV testing. The study covered the cost of HPV reagents and additional consumables where needed. Procurement was done internationally or in-country, depending on availability of local distributors and registration of products. Once consumables were in place (usually for the first 500-1,000 tests) and laboratories were ready, a site visit by IARC researchers to launch the ESTAMPA study was organized.

During this initial visit, training on the study protocol, study's SOPs and good clinical practices was given to all study personnel over 1-2 days, followed by real-life recruitment. In parallel, the selected HPV testing laboratory was visited to verify that conditions were ready to start testing. When enough samples for a full- or a half-testing batch (3-7 days depending on local arrangements) had been collected, additional training on the study protocol, laboratory SOPs and overall sample handling from reception at the laboratory to delivery of results, was provided to all laboratory personnel.

Next, using recently collected samples, hands-on training was given to 1-2 technicians on: (i) Running HPV testing if no previous experience, (ii) Performing conversion of samples collected in PC if HC2 testing was used, (iii) Preparing aliquots from PC vials, and (iv) Recording results on the study database. Lead investigators at each center made arrangements to repeat this training as needed when new laboratory personnel joined the study.

As the study progressed initial and monitoring site visits were done by a team mostly composed by local researchers selected from study centers already recruiting with support from ESTAMPA researchers.

(3) Assessment of *continuity capacity* of laboratories to perform good quality HPV testing. Laboratories' continuity capacity was assessed throughout the study. Sources of information used for the assessment included: minutes from meetings with local investigators and laboratory managers, reports from monitoring visits, data provided by the study centralized web-system, and from a questionnaire on laboratory operational aspects (**Supplementary Material 2**) sent to laboratory managers in May 2020.

As laboratories joined the study, implementation of quality assurance processes was recommended, such as providing regular training to technicians on HPV testing and study's SOPs, retesting of a subset of samples and annual subscription to EQA. The study covered the first year EQA fees for new

laboratories which were encouraged to ensure funding for next subscriptions.

The centralized web-system specifically developed for the study allowed regular checking on the progress of recruitment, the number of HPV tests carried out (at enrolment, colposcopy, and 18 months), the speed of uploading results, and statistics on clinical activities. Thus, the web-system provided effective indicators of the HPV testing capacity of laboratories, such as the volume of HPV testing and the HPV positivity over time. As over 75% of samples tested in each laboratory were collected at the initial screening visit, the number of recruited women per study center was used as a proxy of HPV testing volume, and the positivity of HPV testing at the time of enrolment was used as a proxy of overall HPV positivity, independently of the HPV detection technique used (HC2, COBAS). Based on previously reported HPV prevalence among Latin American women (36–38), we assumed that HPV positivity values reported by laboratories should be between 12.5 and 15%. HPV positivity was regularly tabulated by center and was graphically assessed by plotting the HPV positivity with 95% confidence intervals (using exact binominal distribution and the R statistical package for computations). If any laboratory showed HPV positivity below 10% or above 16% in two consecutive runs, on any assessment, a full data inspection across the screening process (i.e., sample collection, HPV testing and laboratory activities, clinical management, data management) was done and whenever necessary was followed by a site visit to offer refresher training or suggest corrective measures.

The questionnaire sent to laboratory managers requested current details on HPV equipment status, annual subscriptions to EQA, training on HPV testing for current and new technicians, preparedness for procurement process of HPV and related laboratory supplies, availability of tracking systems for HPV reagents and laboratory supplies and for samples transport and storage and turnaround time of HPV results.

As recruitment progressed, many logistic activities were smoothly handled over to local investigators, including procurement of reagents and consumables if they became available in the country, and responsibility for maintaining adequate stocks. This transition facilitated implementation or expansion of HPV-based cervical screening programs.

All collected data were used to assess whether laboratories were able to continue performing good quality HPV testing over time, from the first batch of testing up until end of recruitment or December 2021.

Evaluation of laboratories' readiness and continuity capacity for HPV testing implementation

Collected data from the readiness and continuity capacity assessments were summarized in six main domains: characteristics of the laboratory facility, personnel, procurement of reagents and consumables, tracking systems for reagents expiry and supplies, logistics for transport and storage and delivery of testing results. Responses to the initial checklist were classified into seven basic requirements (within the above six domains) and were used to assess the laboratory *readiness* for HPV implementation. Monitoring, and operational questionnaires classifying eight continuity requirements (within the six domains), were used to assess the *continuity capacity* of laboratories to perform good quality HPV testing over time.

Each requirement was scored as compliant (value = 1) or non-compliant (value = 0), and values were summed up to generate a total score (range = 0-7 for readiness and 0-8 for continuity capacity). Using the scores, the readiness of laboratories to start HPV testing at the time of initial assessment was classified as *very limited* (score $\leq$ 3), *limited* (score = 4-5), *moderate* (score = 6) and *high* (score = 7). Similarly, the continuity capacity of laboratories to perform HPV testing over time was classified as *very limited* (score $\leq$ 3), *limited* (score = 4-5), *moderate* (score = 6-7) and *high* (score = 8) (**Tables 1**, **2**).

Results

Twelve study centers with corresponding HPV laboratories, located in nine Latin American countries (Argentina, Bolivia, Colombia, Costa Rica, Honduras, Mexico, Paraguay, Peru and Uruguay) participated in the ESTAMPA study. Eleven laboratories were part of public systems (4 were based in general hospitals, 2 were national-referral laboratories, 5 were university-based), and one offered service under a private system. Six laboratories had staff with experience in detecting HPV for clinical diagnosis and research at the initial assessment. Two of the remaining laboratories had experience in detecting HPV for research only, and two had experience in HPV detection for diagnosis but not for research. One laboratory was set up in a regional hospital, but the study team was based on a high-level expertise (diagnostics and research) HPV reference laboratory. Finally, one laboratory did not have previous experience in HPV detection or any other molecular diagnostics (**Figure 2**).

Despite differences in recruitment targets (ranging from 500 to 10,000) and year when recruitment and HPV testing started (2012 to 2017), among 42,502 women with valid HPV results recruited until December 2021, the overall yearly HPV positivity consistently ranged between 12 and 16% over time (mean HPV positivity: 14.1%, 95CI: 13.8-14.4) (**Supplementary Figure 1**).

Compliance with readiness requirements

Table 1 summarizes the compliance with the seven readiness requirements per laboratory. Nine of the twelve laboratories had equipment for HPV detection (8 used

TABLE 1 *Readiness* of laboratories based on compliance (1 = complied, 0 = not complied) to 7 essential requirements.

Study center/ Laboratory (SC)	Laboratory facility	Personnel	Procurement		Tracking systems	Transport and storage	Delivery of results	Classification	
	HPV testing equipment available in the laboratory (HC2 or COBAS)	Personnel designated to perform HPV testing	Collection medium, HPV reagents registration in the country. If not, experience with importing/customs	Additional HPV testing consumables available in the laboratory or in the country*	Laboratory management of reagents validity logistics	Logistics for transport and storage of samples	Logistics for delivery of results (standard report template, time and route to reach women)	Total score of HPV testing requirements implemented	Readiness level
SC1	1	1	1	1	1	1	1	**7**	High
SC2	1	1	1	1	1	1	0	**6**	Moderate
SC3	1	1	1	1	1	1	0	**6**	Moderate
SC4	0	1	1	1	1	1	1	**6**	Moderate
SC5	1	1	1	1	1	1	1	**7**	High
SC6	1	1	1	1	1	1	1	**7**	High
SC7	0	0	1	1	1	1	1	**5**	Limited
SC8	1	1	1	1	1	1	1	**7**	High
SC9	1	1	1	1	1	1	1	**7**	High
SC10	1	1	1	1	1	1	1	**7**	High
SC11	1	1	1	1	1	1	1	**7**	High
SC12	0	0	1	1	0	1	0	**3**	Very limited

*Other laboratory consumables specific and standard for the study. Readiness classification according to scores: 7 = high readiness, 6 = moderate readiness, 4-5 = limited readiness, ≤ 3 = very limited.

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TABLE 2 *Continuity capacity* of laboratories based on compliance (1 = complied, 0 = not complied) to 8 continuity requirements.

Study center/ Laboratory (SC)	Laboratory facility		Personnel	Procurement		Tracking systems	Transport and storage	Delivery of results	Classification	
	Maintenance of HPV equipment (regular inspection, calibration)	Regular subscription to external quality assurance for HPV testing	Regular training on HPV testing & laboratory SOPs	Procurement ability for timely purchase of consumables	Appropriate coordination for importation of supplies	Tracking system for HPV reagents and other consumables	Tracking system for transport and storage of samples and aliquots	Turnaround of HPV testing results within one month	Total score of HPV testing requirements sustained over time	Continuity capacity level
SC1	1	1	1	1	1	1	1	1	**8**	High
SC2	1	1	1	1	1	1	1	0	**7**	Moderate
SC3	1	1	1	1	1	1	1	1	**8**	High
SC4	1	1	1	1	1	1	1	1	**8**	High
SC5	1	1	1	1	1	1	1	1	**8**	High
SC6	1	1	1	1	1	1	1	0	**7**	Moderate
SC7	1	1	1	1	1	1	1	1	**8**	High
SC8	1	0	1	1	0	1	1	0	**5**	Limited
SC9	1	0	1	1	1	0	1	0	**5**	Limited
SC10	1	1	1	1	0	0	1	0	**5**	Limited
SC11	0	1	1	1	1	0	1	0	**5**	Limited
SC12	1	1	1	1	1	1	1	1	**8**	High

Continuity capacity classification according to scores: 8 = high, 6-7 = moderate, 4-5 = limited and ≤ 3 = very limited.

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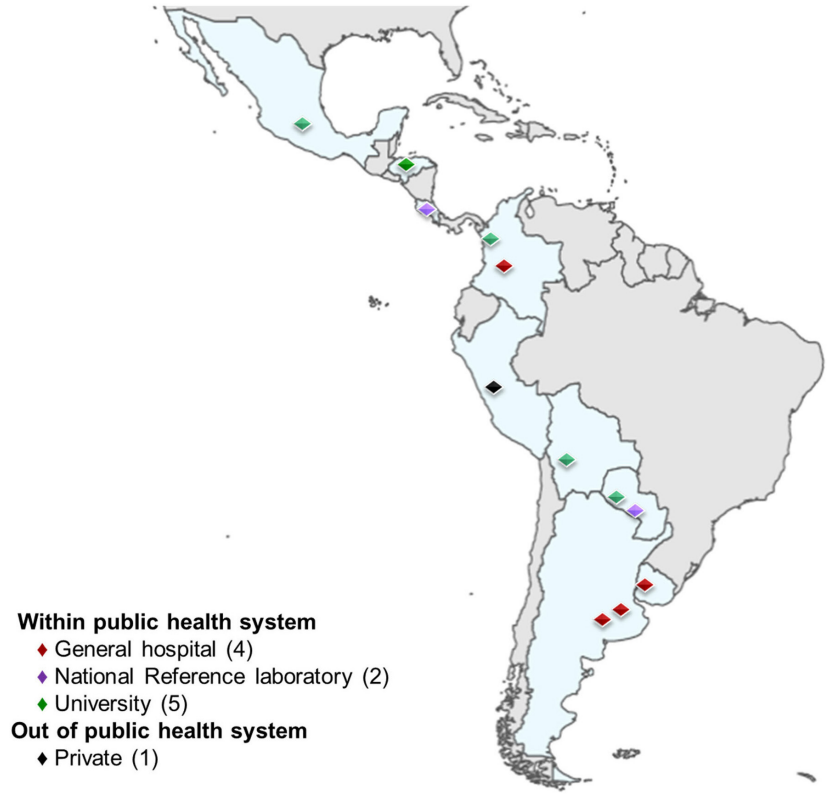

FIGURE 2
Laboratory location and health system affiliation.

HC2, 1 used Cobas). Procurement of equipment for the remaining three laboratories was dependent on when the local team agreed to participated in ESTAMPA and the availability of local funding. In study center 7 (SC7), the principal investigator who led an international reference HPV laboratory, obtained a Cobas machine under a loan for study purposes, which was installed in a regional hospital, as the national cervical screening program had plans to implement HPV testing there. The SC7 team trained, supervised, and supported the newly laboratory throughout the study. HC2 equipment was procured by the central team in 2014 for the laboratory working with study center 4 (SC4), while study center 12 (SC12) secured local funding for HC2 equipment, although political and administrative complexities meant final procurement did not happen until 2018. Regardless of previous experience on HPV detection techniques, all laboratories except the new ones, SC7 and SC12, had personnel allocated to perform HPV testing at the time of initial assessment.

As the study provided all relevant consumables at the start, centers did not need to engage in direct procurement activities. However, all teams and particularly laboratory leads demonstrated awareness of current local regulations for purchasing in-country, and the ability to deal with importation of non-registered in-country consumables or to negotiate prices of testing kits and machine loaning as SC7.

All laboratories had established logistics for transporting and storage samples (as per protocol), only (SC12) did not have a system to control the validity of laboratory reagents, and in addition to SC2 and SC3 did not have a system in place to return results to women, did not have a standard report template nor instructions on how to share results with participants.

In summary, seven laboratories (SC1, SC5, SC6, SC8, SC9, SC10, and SC11) had *high readiness* at initial assessment and three (SC2, SC3 and SC4) had *moderate readiness* with only one essential requirement not fulfilled. Of two laboratories totally new to HPV testing, the one (SC7) supported by a high-level laboratory had *limited readiness* and the other one (SC12) *very limited readiness*.

Compliance with continuity capacity requirements

Table 2 summarizes the compliance with the eight continuity capacity requirements per laboratory. All laboratories had regular maintenance including cleaning and calibration of their HPV testing equipment except for SC11 which was not

serviced on time and testing had to stop, leading to severe delays in processing samples. Six laboratories (SC1, SC2, SC5, SC6, SC7, and SC10) that were already performing HPV testing (mainly for research) at initial assessment, had established EQA systems and maintained regular participation in either the College of Pathologists (CAP) scheme or the Quality Control for Molecular Diagnostics (QCMD). The study covered the first subscription payment for other four laboratories (SC3, SC4, SC11, and SC12), but only one (SC11) maintained the subscription using their own funds afterward, and two laboratories (SC8 and SC9) never subscribed to EQA during the assessment period. In parallel to these schemes, all laboratories were encouraged to repeat testing of 10% of samples, preferably with a different HPV detection platform or in a different laboratory.

All laboratories offered appropriate training in HPV testing and laboratory study SOPs to new laboratory personnel, even if they were not assigned to HPV testing and gained or improved the ability to ensure timely procurement of HPV reagents and other consumables.

Laboratories developed procurement plans, independently of whether the planning only involved preparing paperwork for customs clearance in advance or dealing with local distributors or purchasing the consumables (with study's funds, health authorities funds or research granted competitive funds). However, two laboratories (SC8, SC10) had difficulties coordinating supplies' importation all over recruitment.

Laboratory management systems (manual or digital) for tracking of reagents expiry and handling of samples (transport and storage) were incorporated or improved by all laboratories. However, three laboratories (SC9, SC10, and SC11) needed the central team to send regular reminders to verify expiration dates throughout the study.

Six laboratories struggled to consistently deliver results within one month. Four of them (SC8, SC9, SC10, and SC11) had additional challenges linked to procurement of consumables, while the delays for the other two laboratories (SC2 and SC6) were largely related to the study setting. SC2 recruited in a remote location, and samples were shipped by air only 1-2 times per month. SC6 recruited in several centers concurrently in order to reach its recruitment target of 10,000 women. This meant that samples arrived at both laboratories in large batches and accumulated, causing delays with processing and turnaround of HPV results. In such cases, different measures were applied when to guarantee adequate follow-up of screen-positives (e.g., testing in another laboratories, using cytology results for referral to or offering colposcopy to those with delayed results).

Overall, six laboratories (SC1, SC3, SC4, SC5, SC7, and SC12) showed *high continuity capacity* as they fulfilled all criteria; two (SC2 and SC6) had *moderate continuity capacity* having only not fulfilled one requirement and four (SC8, SC9, SC10 and SC11) showed *limited continuity capacity*.

Relation between readiness and continuity capacity

Figure 3 further depicts the relation between readiness and continuity capacity for HPV testing. Two (SC1, SC5) of seven laboratories (SC1, SC5, SC6, SC8, SC9, SC10, and SC11) with *high readiness* also showed *high continuity capacity*, one (SC6) showed *moderate continuity capacity*, and the other four (SC8, SC9, SC10, and SC11) were not able to maintain good-quality HPV testing over time after an excellent start and showed *limited continuity capacity*. Among three laboratories with *moderate readiness*, one (SC2) kept *moderate continuity capacity* and two (SC3 and SC4) reached *high continuity capacity*. The two laboratories new to molecular testing (SC7, SC12) with subsequent *limited* and *very limited readiness*, respectively, achieved *high continuity capacity*.

Recruitment targets and laboratories' participation in national screening programs by level of continuity capacity

Table 3 details the recruitment targets and their attainment status at the end of the assessment period, as proxy of HPV testing volume over the study, and whether laboratories is currently part or is considered to become part of the national screening program by level of continuity capacity. Among six study centers whose HPV laboratories showed high continuity capacity, SC5 reached its recruitment target, SC12, that is still recruiting, has achieved 64% of the target, SC4 and SC7 did not reach their targets, and SC1 and SC3 exceeded them. SC4 stopped after recruiting 88% of its target because of difficulties with the uptake of screening for several months, while SC7 stopped at 67% mainly due to termination of the loan of the COBAS machine to the study team and emerging priorities of the clinical team. Both SC2 and SC6 with moderate continuity capacity achieved their targets. SC9 only targeted 500 women and stopped at 82% after a slow recruitment pace over time which worsened with COVID pandemic restrictions. The SC8 team experienced sudden change of political and organization authorities who caused important disruptions to screening activities with unexpected disassembling of the study clinic. The SC10 highly experienced research laboratory faced study leadership instability leading to poor coordination of screening and laboratory activities. In view of these political and leadership issues, recruitment stopped at 14 and 17% attainment for SC8 and SC10 respectively. The only laboratory with direct HPV testing problems was SC11, where inadequate maintenance of the HPV equipment led to 31% of screened women (n = 497) having invalid HPV results. Immediate correcting measures to guarantee the safety of participants (e.g., multiple attempts to

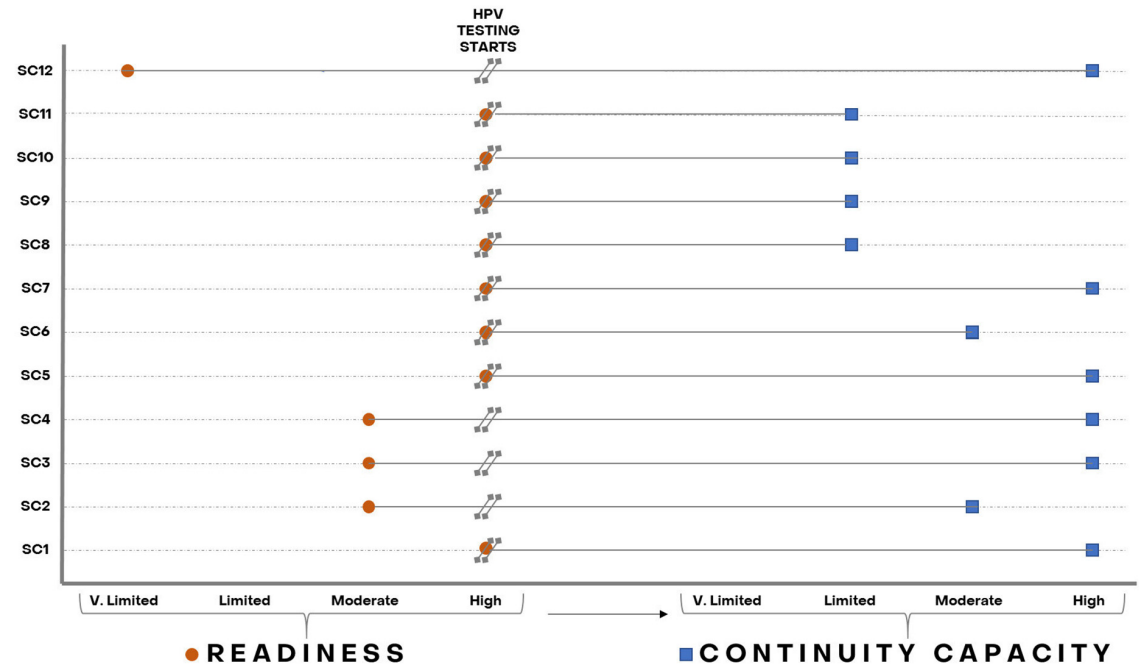

FIGURE 3
Laboratories' readiness and continuity capacity to perform HPV testing throughout recruitment in the ESTAMPA study. Orange circles represent laboratories' readiness and blue squares laboratories' continuity capacity as assessed from the start of HPV testing up to December 2021.

TABLE 3 Recruitment targets per study center (as proxy of HPV testing volume) and inclusion of laboratories in national screening programs by level of continuity capacity.

Continuity capacity	SC/ Laboratory	Recruitment up to December 2021		Laboratory in the national screening program?
		Target	Target attainment	
High	SC1	10,000	Target exceeded (110%)	Yes
	SC3	5,000	Target exceeded (127%)	No
	SC4	5,000	Stopped due to COVID. Target not attained (88%)	No
	SC5	2,000*	Target attained (> 99%)	No
	SC7	5,000	Stopped. Other clinical team priorities. Target not attained (67%)	Yes
	SC12	5,000*	Recruitment ongoing until December 2022, 64% of target attained.	No
Moderate	SC2	1,250*	Target attained	No
	SC6	10,000**	Target attained	Yes
Limited	SC8	5,000	Stopped. Multiple political issues affected screening and research activities including laboratory procedures. Target not attained (14%)	No
	SC9	500	Stopped due to COVID. Target not attained (82%)	Yes
	SC10	5,000	Stopped. Multiple leadership and coordination issues affected screening and research activities including laboratory procedures. Target not attained (17%)	Yes
	SC11	500	Recruited 497 women but 154 (31%) had invalid results. Target not attained (69%)	No

SC: study center. SC/Laboratory: laboratory performing HPV testing for each SC.
*Started with pilot targeting 500 women.
**Initial target of 5,000 increased to 10,000 due to strong local health authorities' endorsement.

repeat sampling, recalling women directly to colposcopy) were implemented in these three SCs.

Five of the 12 laboratories are now or soon will be part of their national HPV-based screening program, including SC1 and SC7 with high continuity capacity, SC6 (moderate) and despite challenges during the study, SC9 and SC10 with limited continuity capacity based on their nature (national referral public health, highly experience research) and on the experience, increased installed capacity and lessons learnt throughout the study.

Discussion

The WHO recommends screening women with a high-performance test, such as HPV DNA testing, twice by age 35 and 45, and encourages countries to move from cytology- or VIA- to HPV-based cervical screening programs. However, most cervical screening worldwide is done with cytology and transition to HPV-based cervical screening should be carefully planned. There are several important factors to consider, such as the size of target population, the screening approach, women's acceptance and participation in HPV testing, local availability of HPV testing platforms (equipment, consumables), laboratory installed capacity, availability of trained personnel, quality assurance, and other operational aspects.

In our study, two main factors enabled successful performance of HPV laboratories as part of HPV introduction: the initial assessment of existing laboratory capacity and the regular support offered to participating laboratories throughout the study. The initial assessment identified limitations in the laboratory's ability to perform HPV testing and helped laboratory teams to develop a road map (staff training, equipment, procurement plan) to address shortcomings before launching the study. In all laboratories, rapid training of new technicians, regardless of their role, was provided in order to minimize disruption of activities. The simple hands-on processing of both HPV tests used in the study (HC2 and COBAS) also helped train new personnel. The training was usually completed within a week, even where staff had no previous HPV testing experience.

The ESTAMPA study aims to evaluate triage techniques for HPV positive women and contribute to the implementation of HPV-based cervical cancer screening in Latin America. Two baseline cervical samples were collected using a cytobrush washed in vials containing PreservCyt medium (PC) to assess the performance of different molecular triage techniques. HC2 testing is incompatible with PC and uses its own collection medium (Digene sample collection medium, STM). This meant that study centers using HC2 had to prepare samples for testing using a conversion kit, adding on average 1.5 full working days per testing batch of 88 samples. Additionally, all laboratories (independently of the HPV test used) were requested to produce aliquots from both PC vials for future evaluation of molecular triage techniques. This process could take up to one full working day. Additionally, screened positives attended a colposcopy visit at which another sample for HPV testing was collected, and those not receiving treatment based on colposcopy and histology results were recalled at 18 months and had another HPV test, and aliquots were produced from samples once HPV tested. In real-life settings, laboratories may have more capacity for HPV testing as these extra research activities will not be required.

The average HPV positivity over time was 14.1%, with some fluctuations related to debut and end of recruitment and testing at each center along the study. We detected HPV positivity values below 10% or above 16% (the inspection threshold) in some centers over time. This triggered an immediate evaluation of the entire screening process by using the study centralized web-system, followed by a site visit to reinforce training and ensure safety of participants as needed. In most cases, low or high HPV positivity was usually associated with characteristics of the included study population. For instance, one center reported a consistently high positivity (>16%), most likely due to the recruitment of a referral population (women with previous abnormal smears attending colposcopy) (data not shown). Assessments suggested HPV testing problems only in one laboratory, where immediate evaluation of the HPV equipment and a plan to maintain good cleaning and calibration of laboratory equipment were requested. This laboratory could not comply with these measures and the study had to stop before reaching the recruitment target.

Readiness for HPV testing was measured ahead of starting recruitment, and study teams whose laboratories were not fully ready to start, took several months (up to 3 years) to deal with shortcomings and they only started recruitment and testing once they fulfilled *high readiness* requirements. Once testing started, laboratories faced challenges in achieving *high continuity capacity* for HPV testing. In some study centers, the recruitment rate was unexpectedly low at times, leading to several weeks of delay before enough samples for a whole testing batch were collected, sometimes leading to expiry of reagents before HPV testing and impacting the turnaround of HPV results. Corrective measures such as testing half batches were introduced; however, sometimes, even half-batch testing was not achievable, particularly during the COVID pandemic, and inevitably led to wastage of reagents. In addition, as HPV testing had not been rolled out in almost all participating countries during the study, collection medium and HPV testing reagents needed to be imported as local procurement was not possible. Local principal investigators had to quickly learn regulations to import unregistered products, logistics associated with

customs clearance, and different aspects of the procurement process, including price negotiation and management of expiry and stock levels of consumables. Laboratories managers were encouraged to subscribe to international EQA schemes. Six laboratories had yearly subscription to EQA schemes before the start of the study as required by local policies. The study covered the first-year fees for other four laboratories, but only one of them managed to continue with subscriptions afterward. Fees for the remaining two laboratories were not provided by the study nor covered by the laboratory. The main reason for not ensuring funds for EQA, in addition to limited resources, was the lack of a "culture of quality", as managers did not understand the importance of maintaining regular EQA not only for HPV testing but for other laboratory activities.

We did not observe any relationship between laboratory high continuity capacity and attainment and size of recruitment goals. Of six laboratories with high continuity capacity, two exceeded their original recruitment targets of 10,000 and 5,000 by 10% and 27%, one reached its target (2,000), one is still recruiting (already 64% attained) and two aiming to recruit 5,000 had to stop at 67% and 88% attainment. The two with moderate continuity capacity reached their targets (1,250 and 10,000); and none of the four showing limited continuity capacity completed recruitment, two originally targeted 500 and the other two 5,000 women. Of importance, independently of the level of continuity capacity, five laboratories will become or are already part of their national screening program. For instance, one laboratory with high continuity capacity that stopped recruitment because the HPV testing platform loan ended, and the equipment was retrieved by the manufacturer company is now part of the national program though using a different HPV testing platform but maintaining the laboratory staff trained on HPV testing for the study. The incorporation of these five laboratories into national programs demonstrates that all efforts in training, continued support, and engagement with and between local and regional stakeholders during the study, are certainly contributing to the implementation of HPV-based screening programs in Latin America.

Most difficulties faced by laboratories reflect the early days of the HPV testing market. Currently, more than 250 HPV tests are available on the market, although most of them are not yet adequately validated (14, 39). It is important that manufacturers invest in validating their tests in line with consensus requirements that ensure safe use in clinical settings (40, 41). Notably, several adequately validated tests can be run in small batches or even individual samples and include internal (per sample) controls that can facilitate monitoring testing accuracy (14). Such tests are ideal for scenarios where the target screening population is small, or reaching screening coverage will take a long time, or where access to care is difficult and screening uptake is limited.

The main strengths of our results are: (1) The diversity of laboratories where HPV testing was performed, contributing with valuable information on the multiple challenges that countries may face during transition to, implementation and scale-up of HPV testing in primary screening; (2) The use of regular feedback given by the central coordinating team and most importantly through exchange of experiences and lessons through the strong ESTAMPA study network, which facilitated installing a "culture of quality" in laboratories, and (3) The demonstration that readiness and continuity capacity are good indicators of how HPV implementation is ongoing in terms of laboratory management and quality of HPV testing, and can be assessed using simple checklists and questionnaires. On the other hand, two limitations of our study are related to these simple tools. First, information provided by laboratory researchers or managers may be prone to reporting bias, and second, continuity capacity was assessed based on responses to a single-time questionnaire. Nevertheless, in our study, these limitations were mitigated by completing and verifying information through monitoring visits to all teams and their participating laboratories over time. However, it should be noted that in the context of a screening program, regular monitoring visits may not be feasible and other strategies may be needed to complete implementation assessment.

The 12 laboratories participating in ESTAMPA were essential for study centers screening and overall study achievements, despite several of them being new to HPV testing or to its use in cervical screening and having faced challenges to adopt the technique into daily activities. The strong support provided by the study network facilitated overcoming most difficulties leading to 42,502 HPV screened women across 12 study centers. We have described here the process of introducing HPV testing in 12 laboratories across Latin America, we further plan to use data per HPV testing batch to evaluate and compare HPV performance across laboratories, over study visits (enrolment, colposcopy, 18-months follow-up) and over time.

Conclusion

In summary, our assessments confirm that as *high readiness* is essential for successfully implementing HPV testing in laboratories; however, *high readiness* is not sufficient to guarantee HPV testing *high continuity capacity*. Several aspects to achieve this *high continuity capacity* should be considered:

(1) A "culture of quality" in laboratories and across the cervical cancer screening spectrum should be established, including regular training on SOPs, robust monitoring and quality assurance systems (with internal and external quality control measures) tailored to the installed capacity and local resources

(2) Using a friendly and tailored to local context database, if possible centralized and web-based, to allow regular monitoring of the overall screening process, including laboratory and clinical activities, and feedback for improvement
(3) Training on preparation of appropriate plans for HPV supplies procurement and stocking and on local regulations on products registration and importation of laboratory supplies should be provided to laboratory managers and leaders of cervical screening programs
(4) Strategies to guarantee reasonable turnaround of HPV results to women should be in place to ensure that any screened woman receives her HPV results and that screened positives receive adequate and timely treatment and follow-up
(5) Exchange of experiences and lessons learnt between multidisciplinary implementers from different settings and countries should be encouraged to apply most suitable implementation strategies according to context and define additional implementation research needs.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the International Agency for Research on Cancer (IEC Project 12-27-A7), the Pan American Health Organization (PAHO) Ethics Committee and Ethical Committees in each of the study participating centers. The informed consent include details on the background, procedures of the study, risks and benefits, statement of confidentiality, specimen use and study staff to contact. The study is considered minimal risk as the procedures are standard practice in cervical cancer screening programs. The patients/participants provided their written informed consent to participate in this study.

Authors contributions

MA and RH conceived the ESTAMPA study and are the principal investigators responsible for its overall conduction. MAP, AF, GS, LM, CT, LF, VV, GV, AC-V, GR, AC, and CW are the local principal investigators responsible for recruitment, clinical management, and data collection. MAP, AF, and GS conceptualized the laboratory aspects of the study and together with MLR, MH, LM, MRP, CT, PH-N, FD, JA-S, MZ, and VV coordinated all laboratory activities including training of new technicians as needed. JL, AP, MB, LM, PM, YC, RC, DC, LG, AR, MR, MLB, and LC performed HPV testing. JV and AB provided statistical support and together with MA, MH, MLR, EL, and AR centrally coordinated the study. MA, RH, NB, and SL contributed to the funding acquisition and local capacity building. MLR and MA wrote the manuscript. MH, AB, JV, SL, NB, and RH contributed to the finalization of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

Author MH was employed by SMS-Oncology, Amsterdam, Netherlands. Author FD was employed by Laboratorio de Patología Oncológica, SAC, Peru.

The remaining 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1006038/full#supplementary-material

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