

Worldwide initiatives to eliminate cervical cancer

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Abstract

In 2020, more than 600 000 women were diagnosed with cervical cancer and 342 000 women died worldwide. Without comprehensive control, rates of cervical cancer incidence and mortality are expected to worsen. In 2020, the World Health Organization adopted the global strategy to eliminate cervical cancer to the threshold of four cases per 100 000 women within the 21st century, using a triple pillar intervention strategy comprising 90% of girls fully vaccinated by the age of 15 years, 70% of women screened by the age of 35 years and again by 45 years, and 90% of women with pre-cancer treated and 90% of women with invasive cancer managed. In countries with high cervical cancer incidence, a tremendous effort will be needed to overcome the challenges. This article discusses the efforts in place to accelerate achievement of this ambitious goal.

KEYWORDS

cervical cancer, elimination initiatives, FIGO Cancer Report, prevention, screening, treatment

1 | EPIDEMIOLOGY OF CERVICAL CANCER WORLDWIDE

Cervical cancer is the fourth most diagnosed cancer and the fourth leading cause of cancer death in women worldwide. In 2020, GLOBOCAN estimated that 604 000 women were diagnosed with cervical cancer and 342 000 women died from the disease.¹ Over the past decades, incidence and mortality rates of cervical cancer have declined in most regions of the world. However, large geographic variation in morbidity and mortality rates are observed. Globally, the estimated age-standardized incidence rate of cervical cancer was 13.1 per 100 000 women and varied among countries (from less than 2 to 75 per 100 000 women).² Despite the primary prevention of novel vaccination and secondary prevention of cancer screening, cervical cancer remains the most common female cancer and

the leading cause of death in Sub-Saharan Africa, Melanesia, South America, and Southeast Asia.² In addition, an increasing incidence rate was reported in many areas across Africa (Eastern, Southern, and Middle Africa), with the highest incidence in Eswatini.² In a populous country such as India, approximately 100 000 new cases are diagnosed and 60 000 women die from cervical cancer annually, accounting for nearly one-third of all cervical cancer deaths globally.³

2 | CERVICAL CANCER RISK FACTORS

The two major histologic types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Several studies have demonstrated that these histologies share common risk factors.⁴⁻⁶ The fundamental risk factor for developing cervical cancer is persistent oncogenic HPV infection, with approximately 99.7% of cervical cancer

tumors associated with oncogenic HPV infection. HPV 16 and HPV 18 account for two-thirds of cervical carcinoma in all continents.⁵ Additional oncogenic HPV genotypes are 31, 33, 35, 45, 52, 58, and 59, which lead to cancer at several sites, such as the cervix, vulva, vagina, and anus.⁵

HPV transmits primarily through sexual contact and most people are infected shortly after the onset of sexual activity.⁷ HPV infection can be transmitted not only by penetrative sexual intercourse but also skin-to-skin genital contact.⁷ In general, early HPV infection can cause clinically detectable low-grade cervical cell abnormalities. However, these usually spontaneously resolve within 12–24 months.⁵ When infection with oncogenic HPV genotypes is persistent, the risk of developing high-grade cervical cell abnormalities increases and can proceed to cancer within 10–15 years if left untreated.^{5,8} Additional cofactors for cervical cancer are early onset of sexual activity, multiple sexual partners, high-risk sexual partner, history of sexually transmitted infections, history of vulval or vaginal precancerous and cancerous lesions, smoking, oral contraceptive pills, and immunocompromise.^{9,10}

Scientists and researchers have developed novel tools for both prevention and treatment of cervical cancer. Furthermore, high-grade precancerous and early-stage cervical cancer can be treated effectively.⁸ Consequently, cervical cancer should be considered the most preventable cancer in our lifetime.

3 | OBSTACLES TO CERVICAL CANCER SCREENING

Cervical cancer screening based on Pap smear or conventional cytology was introduced in the 1940s by Dr George Papanicolaou. Fifty years later, this screening test had been widely implemented in national cervical cancer screening programs and was developed into liquid-based cytology in the early 2000s.¹¹ Although it has similar sensitivity to conventional cytology, liquid-based cytology reduces the rate of inadequate samples, increases screening capacity by partially automated analysis, and offers HPV testing.¹¹

A significant reduction in the incidence of cervical cancer has been reported in many countries, mainly in high-income nations, for example the UK, USA, and European countries.¹¹ Differences in incidence and mortality rates reflect disparities in access to screening and treatment across and within countries^{12,13}; for example, the Human Development Index (HDI) and poverty rates accounted for over 50% of the global difference in mortality.¹³ The failure of cervical cancer screening in low HDI countries is mainly the result of unorganized public health policy and lack of resources, infrastructure, and community awareness¹⁴; in contrast, in high HDI countries, failure results from nonparticipation, under-screening, and loss to follow-up of abnormal results.^{15,16} Recent data demonstrated that only 44% of women in low- and middle-income countries (LMICs) have ever been screened for cervical cancer and the lowest screening rate (16.9%) was reported among women in Sub-Saharan Africa.¹⁶

Knaul et al.¹⁷ described similar characteristics between cervical cancer and neglected tropical diseases in that: (1) they commonly affect poor people; (2) the population at risk is overlooked by policy makers; (3) they are associated with stigma and discrimination; (4) they impact female morbidity and mortality; (5) they are neglected in clinical research; and (6) they can be controlled and prevented. The authors state that “cervical cancer is not a disease of the past, it is a disease of the poor”.¹⁷

If left uncontrolled, cervical cancer rates are expected to worsen. The estimated annual number of cervical cancer cases is expected to increase from 570 000 to 700 000 between 2018 and 2030, while the annual number of deaths is projected to rise from 311 000 to 400 000 and the vast majority of women in LMICs will suffer without the ability to seek a healthcare provider.¹² This inequality is no longer acceptable in our globalized era, and it must be promptly regulated.

In May 2018, World Health Organization (WHO) Director-General, Dr Tedros Adhanom Ghebreyesus, brought cervical cancer back to global attention when he called for the elimination of cervical cancer to the threshold of four cases per 100 000 women. In 2020, WHO adopted a global strategy for eliminating cervical cancer through a triple pillar intervention strategy: 90% of girls fully vaccinated by the age of 15 years, 70% of women screened by the age of 35 years and again by 45 years, and 90% of women with pre-cancer treated and 90% of women with invasive cancer managed.¹⁸ Comprehensive cooperation between organizations and health policy makers is crucial, especially in countries with a high incidence of cervical cancer.

4 | STRATEGY TO SCALE UP COVERAGE OF HPV VACCINATION

Primary prevention via HPV vaccination is one of the major challenges for low HDI countries. In fact, less than 30% of LMICs have implemented national HPV vaccination programs, while this has been accomplished in over 80% of high-income countries.¹²

Three HPV vaccines are currently prequalified by WHO: a bivalent vaccine targeting HPV 16 and HPV 18; a quadrivalent vaccine targeting HPV types 6, 11, 16, and 18; and a nonavalent vaccine targeting HPV types 31, 33, 45, 52, and 58, in addition to HPV 6, 11, 16, and 18. In 2009, WHO recommended implementation of HPV vaccination into national immunization programs. WHO also recommends two vaccine doses for girls aged 9–14 years, as this is the most cost-effective public health strategy against cervical cancer.¹⁹ However, obstacles to achieving this are evident: (1) lack of an existing service platform to deliver the vaccine in this age group in some countries; (2) strong social communication and movement are required to ensure acceptance and compliance with a two-dose schedule (a survey in India by Hull et al.²⁰ reported that only 40% of parents accepted HPV vaccination prior to health counselling, with safety of the vaccine followed by the perception that it could be seen as permission to engage in sexual activity given as the most common concerns);

and (3) HPV vaccines and their operational costs are relatively expensive. However, successful models in different countries are continuously being reported.

Following approval by the European Medicines Agency in 2006, bivalent and quadrivalent vaccines are now widely used in European countries. In 2007, Switzerland implemented HPV vaccines into the national vaccination program, beginning in the canton of Geneva. The program used school services, a public hospital, and private physicians as vaccination providers. Four years later, HPV vaccination coverage was 72.6% and 74.8% in targeted cohorts for three and two doses, respectively. The authors suggested that the high coverage of this vaccination program in Geneva was likely related to free vaccination and easy access to the vaccine. The combination of delivery services including schools, health services, a public hospital, and private physicians enabled coverage of most eligible 11–19-year-old girls.²¹

In 2007, Thailand recommended HPV vaccination for girls and women who could afford to pay for the vaccine. After 10 years of tremendous effort, in 2017 Thailand had successfully implemented HPV vaccines into its national immunization program. Two free doses of HPV vaccine are delivered through a school-based service for girls aged 11–12 years nationwide. After 3 years of implementation, coverage had reached 95% of the target population.²²

HPV vaccination is currently the cornerstone of long-term cervical cancer control. Numerous studies have confirmed the safety, efficacy, and cost-effectiveness of these vaccines^{20,23,24} and the number of cervical cancer cases is predicted to decrease after five decades of comprehensive vaccination.²⁰ However, considerable financial support is vital to overcome the many barriers. Fortunately, Gavi, the vaccine alliance, has been supporting pilot projects of HPV vaccines in many LMICs, mainly in Sub-Saharan Africa, since 2013, and by 2020 more than 30 million girls had been vaccinated in over 40 countries with the organization's support.²⁵ Although introduction of HPV vaccination is challenging, it also provides many opportunities to strengthen adolescent health through implementation of other vaccinations (such as hepatitis B, tetanus), reproductive health education, HIV prevention, and nutritional support programs.

HPV vaccination can be successfully implemented in national immunization programs in different settings. Encouragingly, the number of LMICs with national HPV vaccination programs is gradually increasing.

Furthermore, a strategy to scale up vaccination coverage using a single-dose vaccination schedule is being studied. This strategy aims to address concerns over vaccine shortages and enhance the potential induction of vaccination to limited-resource settings. However, evidence for the effectiveness of a single-dose vaccination program remains unclear.²⁴ Currently, comprehensive cooperation between researchers, partner organizations, countries, and vaccine manufacturers is essential to equally distribute two-dose HPV vaccine schedules to the target populations in neglected areas and to prevent shortages of vaccines in the future.

It is important to note that women who are outside the WHO recommended vaccination group, such as women aged 16–26 years

and older who have never been exposed to HPV, are recommended to have three vaccination doses for cervical cancer prevention.²⁶

Although HPV vaccination of the target population plays a leading role in primary prevention, other supporting interventions are also crucial to maximize efficacy. It is important to implement healthy sex education programs for boys and girls to raise their awareness of sexually transmitted infections by encouraging delay in sexual initiation, reducing high-risk sexual behaviors, promoting condom use, smoking cessation, and male circumcision in countries where it is relevant. However, these interventions should be adapted, as appropriate, depending on age and culture.²⁷

5 | PARADIGM SHIFTS IN CERVICAL CANCER SCREENING

Secondary prevention including a high coverage screening program, health promotion, and early precancerous treatment are essential actions to inhibit the development of cervical cancer, especially in unvaccinated women and women infected with subtypes other than HPV 16 and HPV 18. In general, high sensitivity screening tools are the key element of effective screening.²⁸ However, cytology-based testing has been the gold standard for cervical cancer screening for over 50 years, primarily due to its high specificity. Nevertheless, several limitations have been reported, including low sensitivity, poor reproducibility, and imperfect fixation. Moreover, it requires well-trained personnel and expensive infrastructure that are the fundamental obstacles in low-resource settings. Despite alternative methods such as liquid-based cytology and visual inspection using acetic acid (VIA) or Lugol iodine, their sensitivities remain suboptimal.^{29,30}

Cumulative evidence supports primary HPV-based testing as the most favorable candidate for cervical cancer screening. High-risk HPV-based testing has higher sensitivity to detect high-grade cervical abnormality and cancer, and a higher negative predictive value compared with cytology-based testing.^{28,29,31} Consequently, in settings where screening intervals are long or disorganized, screening with HPV-based testing may be a reasonable alternative to cytology-based screening.³⁰

In addition, HPV-based testing can be performed using self-collection, which has the potential to overcome the barriers encountered with clinician-based screening methods.³² Several studies on HPV self-collection testing have shown increased screening coverage in remote areas or those with high levels of nonattendance.^{28,32} However, HPV self-collection should be implemented with careful consideration based on local context and with continuous evaluation.²⁸

In 2020, the American Cancer Society recommended cervical cancer screening with HPV test alone every 5 years for every woman with a cervix from the age of 25–65 years. Alternative methods are co-testing using HPV and cytology testing every 5 years or cytology testing every 3 years. In general, when an abnormal screening result is found, the patient will be referred for colposcopy and tissue biopsy for histological confirmation, with treatment given for

patients with high-grade cervical intraepithelial neoplasia (CIN 2 or higher).³³ These multiple evaluation steps require skilled personnel and resources, which are limited in low-resource countries. Instead, WHO has recommended a screen-and-treat method over the standard process, especially in countries with geographic barriers and limited resources.³⁴ This strategy aims to ensure that treatment is provided soon or ideally immediately after a positive screening result. The difference between these protocols is that the treatment decision for the standard protocol is based on histology, while for the screen-and-treat method it is based on screening result. WHO expert panels also recommend an HPV test-and-treat approach over VIA and treat.³⁵ Nevertheless, if HPV testing is not available, VIA and treat is suggested. However, in countries with an existing appropriate screening strategy, either an HPV test or cytology test followed by colposcopy could be used. Regardless of screening method, all women with a positive result should be evaluated with VIA to assess the size of the lesion and to rule out gross malignancy. Cryotherapy is the most preferable treatment in the protocol. However, if the patient is not eligible for ablative treatment in the case of a large lesion, large loop excision of the transformation zone (LLETZ) is recommended. Women who test negative on VIA or cytology are recommended to repeat screening at 3–5 years, whereas a minimum screening interval of 5 years is recommended for women with a negative HPV test result. Women who undergo treatment should receive post-treatment follow up at 1 year.³⁵

Of note, in areas of high endemic HIV infection, women should receive counselling for HIV testing. Women living with HIV are at higher risk of persistent HPV infection. Cervical cancer screening is recommended as soon as they become sexually active, regardless of age. Women in endemic areas commonly develop precancerous lesions at a young age and progress to cancerous lesions in a short period of time. As a result, they are advised to follow a 3-yearly screening schedule.³⁶

6 | TERTIARY PREVENTION: TREATMENT OF INVASIVE CERVICAL CANCER

Cervical cancer is preventable and curable. However, the cure rate depends on the stage at diagnosis and efficiency of treatment. The goal of tertiary prevention is to improve the patient's quality of life and reduce disability through effective treatment and rehabilitation. Multidisciplinary teams are encouraged to work together to analyze and prepare fundamental health factors such as infrastructure, financial resources, and human resources. Recommended factors for effective tertiary prevention are: (1) provision of a practical referral mechanism to facilitate timely diagnosis and treatment; (2) provision of the most appropriate available treatment based on the diagnosis; and (3) provision of a palliative care facility for advanced stage cancer patients.³⁷ Currently, 85% of cervical cancer deaths are among women in LMICs. A major barrier for these women is inability to access medical treatment. As a result, country leaders must close the gap by ensuring that cervical cancer prevention and control program

costs are included in a country's budget and health services such as universal coverage are affordable for everyone.³⁷

Provision of personal education on cervical cancer screening and treatment is an important factor to catalyze the public health system. A systematic review showed that the implementation of multifaceted roles of health providers was associated with improvement of cervical cancer control.³⁸ Community health leaders work closely with the community to raise health awareness and encourage social movement and acceptance of cancer prevention strategies. Primary care providers are trained personnel who perform the screening test, follow-up, counselling, and refer patients to higher facilities for diagnosis and treatment. Secondary care (district) providers are doctors and teams who perform all diagnostic and treatment services and refer patients to both higher and lower levels of care. Finally, tertiary care providers are doctors and teams who manage patients with invasive and advanced disease and refer them back to primary or secondary care facilities as appropriate.³⁷

Australia is one of the world leaders in cervical cancer prevention; it was the first country to implement the HPV vaccine into national immunization programs and one of the earliest to change national screening programs to HPV-based testing. It is estimated that Australia will eliminate cervical cancer by 2035.³⁹ Australia and other countries with successful strategies are working closely together with partnership countries by sharing knowledge, experiences, resources, and innovative low-cost technology to accelerate the elimination of cervical cancer globally.³⁹

In summary, elimination of cervical cancer is an ambitious global movement that will improve women's rights. It is time for comprehensive cooperation between countries, partnership, and external multinational agencies to overcome the inequities. The triple pillar intervention strategy covers vaccination, screening, and treatment and its implementation will not only save lives and enhance quality of life for millions of women, but also provide a great opportunity for countries to build strong and sustainable healthcare systems. Although it will take an enormous effort to overcome the barriers, we believe that every nation will soon reach this goal within the lifetime of today's youngest girls.

AUTHOR CONTRIBUTIONS

All authors contributed to concept, research, manuscript writing, review, and revision. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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How to cite this article: Wilailak S, Kengsakul M, Kehoe S. Worldwide initiatives to eliminate cervical cancer. *Int J Gynecol Obstet.* 2021;155(Suppl. 1):102-106. <https://doi.org/10.1002/ijgo.13879>