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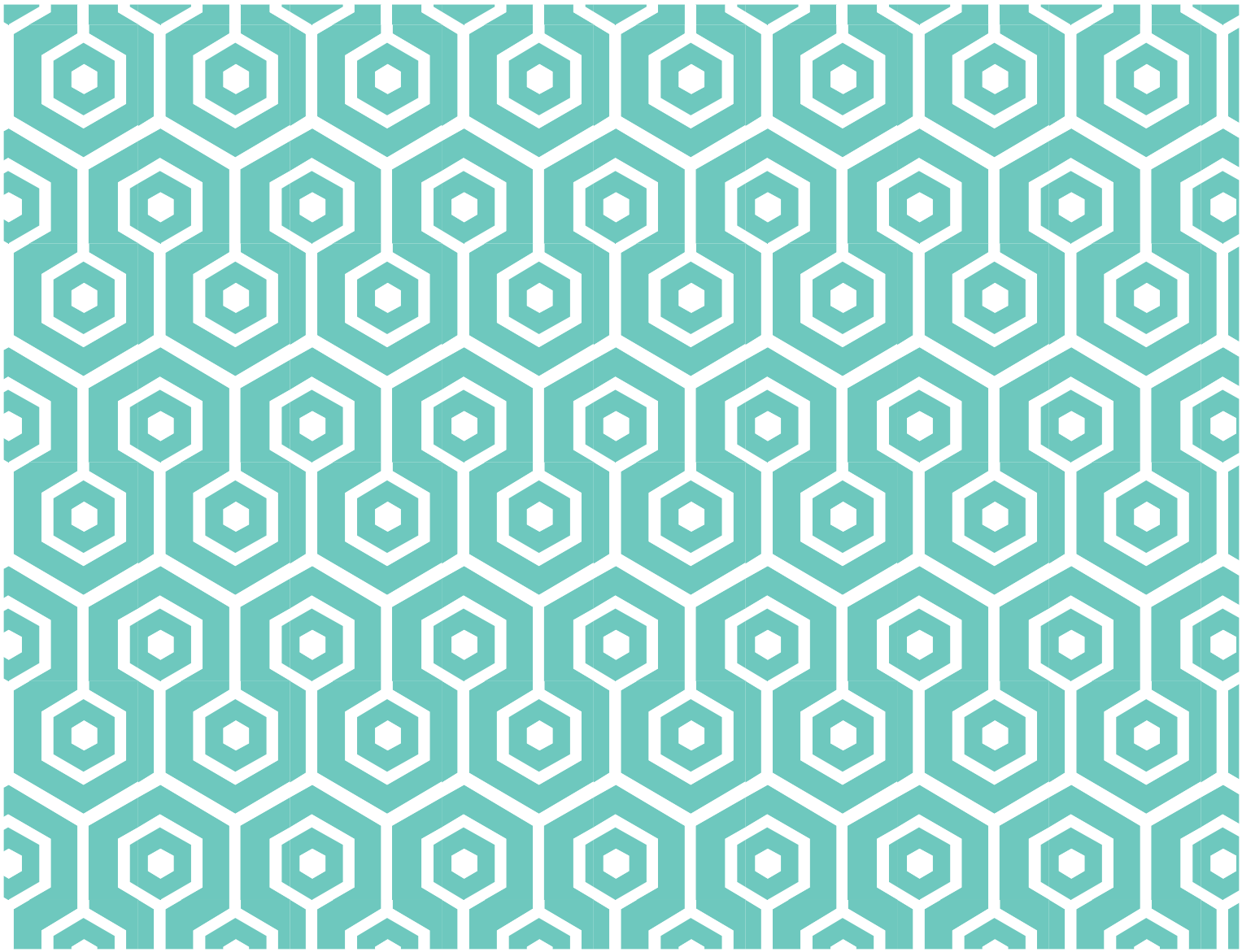
HPV, HIV and cervical cancer

Leveraging synergies to save women's lives



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Foreword

Cervical cancer diagnosed in a woman living with HIV is an AIDS-defining illness. Yet it is largely preventable if the human papillomavirus (HPV) vaccine is provided to girls and generally curable if diagnosed and treated early. Similarly, the unacceptably high rates of new HIV infections among women, particularly adolescent girls and young women living in sub-Saharan Africa, are preventable. These examples starkly expose the links between gender inequality, poverty, non-realization of rights and poor access to essential health services. Every year, more than 260 000 women—almost 90% from low- and middle-income countries—die, needlessly, from cervical cancer because of where they were born, because they were poor and because of inadequate health systems. With access to screening and treatment, rates of cervical cancer have steadily declined in many high-income countries. However, the benefits of these life-saving advances are not reaching all women and girls equally or equitably, particularly those living in the poorest regions of the world, which are worst affected by HIV, cervical cancer and noncommunicable diseases.

After more than three decades of the AIDS response there is encouraging progress. More people living with HIV than ever before are accessing life-saving antiretroviral treatment. The number of AIDS-related deaths has declined and fewer babies are being born with HIV. However, in a number of settings HIV continues to disproportionately affect women and adolescent girls. In 2015, 65% of new HIV infections among adolescents occurred among adolescent girls.

Globally, many adolescent girls and young women are unaware of their HIV status and health services are not designed to meet their health needs or to protect and promote their rights. In addition, cervical cancer is up to five times more likely to develop among women living with HIV compared with women who are HIV-negative.

The United Nations Sustainable Development Goals (SDGs) recognize the centrality to global development of women's empowerment, gender equality and equal rights to health and education. The SDGs, in addition to including the achievement of gender equality as a stand-alone goal—Goal 5—also address gender equality across the health, education, social and economic domains. These 2030 global goals are ambitious but achievable if women and girls are recognized as powerful agents of change for their own health and well-being. When women and girls are meaningfully engaged and their needs central to developing policies and programmes, their lives will improve. Women and girls must be able to protect themselves from HIV, to access quality services which meet their sexual and reproductive health needs and to live free from violence and coercion. Furthermore, recognizing that achieving gender equality requires partnerships between women and men, men and boys must be engaged in advancing the rights, health and empowerment of women.

An integrated programmatic response incorporating HIV, child and adolescent health, sexual and reproductive health and rights, gender equality, cancer and primary health-care services is most likely to address the interrelated factors that place women and girls at risk of HPV, cervical cancer and HIV, reducing new infections and saving lives. Against this backdrop, and reaffirming the need for collaboration and partnerships across agencies, sectors and movements, the Global Coalition on Women and AIDS, UNAIDS and the World Health Organization are calling for the scale-up of integrated and comprehensive sexual and reproductive health services, including for the prevention, screening and treatment of cervical cancer, and of HIV services, as reflected in the adoption of the 2016 United Nations Political Declaration on Ending AIDS.

Preventing unnecessary cervical cancer deaths and ending the AIDS epidemic by 2030 will require much more integrated service delivery that promotes not just better health outcomes but also gender equality and the realization of rights. This will require political commitment, investment, innovation and social change. Gender equality is not only a human rights obligation, it is a smart investment and a strategic imperative that will ensure progress in many areas of development, not just for the health and well-being of women and girls, but also for their families, communities, economies and countries.

Margaret Chan
Director-General, WHO

Michel Sidibé
Executive Director, UNAIDS

Executive summary

AIDS-related illnesses are the leading cause of death of women of reproductive age (15–44 years) *(1)*. Women living with HIV are at 4–5 times greater risk of developing cervical cancer, which is the second most common cancer in women living in low- and middle- income countries. In 2012, 528 000 new cases of cervical cancer were diagnosed, and 266 000 women died of the disease, nearly 90% of them in low- and middle-income countries *(2)*. These deaths are unnecessary, because cervical cancer is preventable and curable if detected and treated early. The human papillomavirus (HPV) is a major contributor to global morbidity and mortality each year, causing diseases that range from benign lesions to invasive cancers.

The burden that HIV places on women, particularly adolescent girls and young women from low- and middle-income countries, is compounded by the global burden of HPV infections and cervical cancer. Invasive cervical cancer is an AIDS-defining illness,[1] and rates of cervical cancer are estimated to be four to five times higher among women who are living with HIV than they are among HIV-negative women *(3)*.

Given the association between HPV and HIV, synergies must be leveraged, and a focused and integrated approach to saving women's lives must be taken. Synergies between the HIV response and efforts to prevent, diagnose and treat cervical cancer through HPV vaccination, education, screening and treatment must be maximized.

[1] Certain serious and life-threatening diseases that occur among people living with HIV are called "AIDS-defining" illnesses.

Existing HIV prevention and treatment programmes can play a strategic role in expanding primary and secondary cervical cancer prevention services. Thus, as governments, civil society and the international community move forward with important decision-making to address noncommunicable diseases (NCDs), it is vital that the prevention and treatment of cervical cancer becomes a priority.

To make the most of the synergies, this report was commissioned by UNAIDS—in collaboration with the World Health Organization (WHO) and the Global Coalition on Women and AIDS (GCWA)—as part of the work of the United Nations Interagency Task Force on the Prevention and Control of NCDs. It is intended to guide and inform global, regional and national advocacy and decision-making, and to improve investments pertaining to HIV, HPV and cervical cancer in the context of the WHO Global Action Plan for the Prevention and Control of NCDs, United Nations Secretary-General's Global Strategy for Women's and Children's Health, the 2016 Political Declaration on Ending AIDS and the UNAIDS 2016-2021 Strategy.

This report presents recent scientific evidence about the links between HIV, HPV and cervical cancer, and it supplies relevant epidemiological, screening, vaccination and innovation data. Ultimately, its goal is to (a) promote synergies between HIV and cervical cancer prevention programmes, (b) make the case for integrating cervical cancer prevention into existing HIV treatment and prevention programmes, (c) explain the opportunities for women's health that exist in coordinating HIV and cervical cancer prevention, and (d) advance prevention and treatment literacy among affected populations.

The target audience are ministries of health, policymakers, nongovernmental organizations and communities, activists, people living with HIV and potential private sector and civil society partners.

Key messages

"Today women are surviving an HIV diagnosis only to succumb to avoidable cervical cancer. The need for concerted efforts in responding to the "double burden" of HIV and cervical cancer is warranted now more than ever! We need to increase the coverage of cervical cancer screening services, especially for women living with HIV, link eligible women to early treatment, and make the HPV vaccine accessible to all eligible girls. Let us all do our part and humanity will thrive."

Gertrude Mutharika, First Lady of Malawi and Vice-President of the Organisation of African First Ladies Against HIV/AIDS

Cervical cancer is preventable

Cervical cancer is preventable with the HPV vaccine, and it is curable if detected and treated early. Each year, however, more than 500 000 women will develop cervical cancer and over 250 000 women will die of the disease. Most of these women live in low- and middle-income countries, particularly in Africa, parts of Asia, and Latin America and the Caribbean.

Women living with HIV are more at risk of cervical cancer

Cervical cancer is considered to be an AIDS-defining illness. While HPV infections are very common in the general population and most women with healthy immune systems will clear these infections over time, women with compromised immune systems (such as women living with HIV) are far less likely to clear an HPV infection. This means that once they have been infected with HPV, women living with HIV are more likely to develop pre-invasive lesions that can, if left untreated, quickly progress to invasive, life-threatening cervical cancer. The World Health Organization (WHO) recommends screening and providing adequate treatment to all women living with HIV as soon as they know their status and if they have started sexual relations.

Women's access to prevention, treatment and care for cervical cancer is a human rights issue

International norms and standards require Member States to ensure that women have access to comprehensive sexual and reproductive health

services and information, including services related to HPV and cervical cancer.

Cervical cancer programme coverage is insufficient in low- and middle-income countries, where rates of HIV and HPV are highest

Most low- and middle-income countries with a high prevalence of HIV have limited programmes for cervical cancer prevention and control. In high HIV-prevalence countries, every woman who has started her sexual life and has had a positive HIV test should be informed about HPV and offered cervical cancer screening and treatment (when necessary), regardless of her age.

Reducing preventable deaths from cervical cancer requires a comprehensive approach, as recommended by WHO, that delivers effective programmes to communities in a culturally appropriate way. This includes programmes in the following areas:

- Health education (including age-appropriate comprehensive sexuality education).
- HPV vaccination for adolescent girls,[2] as well as information and counselling.
- Screening, where all women at risk of developing cervical cancer are screened using visual inspection with acetic acid (VIA) and/or HPV DNA testing, if available *(4)*.
- Cervical cancer screening programmes should include HIV counselling, testing and treatment, as well as other sexual and reproductive health services, treatment of precancerous cervical lesions and invasive and advanced cervical cancer, including through chemotherapy and/or radiotherapy.
- Ensuring access to palliative care when needed.

Case study

The Cervical Cancer Prevention Program in Zambia has demonstrated that linking cervical cancer screening and HIV services is a cost-effective way of improving cervical cancer screening and treatment. This programme, which integrated a national cervical cancer prevention programme into an existing HIV programme, led to an expansion of cervical cancer screening to more than 100 000 women (28% of whom were living with HIV) over a period of five years *(5)*.

Research and development are crucial

Strengthening research capacity in countries is essential for helping policy-makers make evidence-informed decisions. National programmes need more capacity in order to improve the planning, delivery, and monitoring and evaluation of cervical cancer programmes, and to enable changes to be made (such as the introduction of new technologies and evidence-informed guidance).

[2] In order for girls aged 9 to 13 years to be fully protected, national authorities must ensure they receive vaccination independent of their HIV status (which is in keeping with WHO recommendations).

Case study

A large community-based trial in India, which included 151 538 women aged 35 to 64 years, assessed whether having trained primary health workers perform screening tests using visual inspection with acetic acid could lead to a reduction in cervical cancer mortality. After 12 years of follow-up, the programme has resulted in a significant 31% reduction in cervical cancer mortality *(6)*.

Political commitment for long-term resourcing of national priorities is essential

National programmes can only succeed with the support of governments, which should have clear strategies and adequate funding to promote access to sexual and reproductive health services for women, including HIV and cervical cancer prevention and treatment.

Case study

The Cervical Cancer Prevention in El Salvador HPV screening programme, which was launched in 2012, was led by the El Salvador Ministry of Health in partnership with Basic Health International (a non-profit organization) and a medical technology company. The programme's goal was to initiate HPV-based screening among approximately 30 000 women by the end of 2015. It also aimed to identify lessons learned in order to inform the incorporation of HPV screening and management into El Salvador's cervical cancer prevention programme.

El Salvador was the first country in Latin America and the Caribbean to receive a donation of HPV tests, and thanks to government commitment, it was one of the first countries to provide its female population with this updated screening approach to improve the detection and prevention of cervical cancer *(7)*.

Partnerships are necessary to support government efforts

Mobilizing the commitment and support of partners from diverse sectors (including the private sector) is an important method of strengthening the response to HPV and HIV.

The newly formed Joint UN Programme on Cervical Cancer Prevention and Control, which has the vision to eliminate cervical cancer as a public health issue across the world, will support governments in developing and implementing, sustainable high-quality national comprehensive cervical cancer control programmes that will allow equitable access to cervical cancer services for women. This strategic partnership is formed by the following United Nations (UN) entities, United Nations Population Fund (UNFPA), WHO, United Nations Children's Fund (UNICEF), UNAIDS, UN Women, International Agency for Research on Cancer and International Atomic Energy Agency.

Cervical Cancer Action is a global partnership that was founded in 2007 to reduce cervical cancer in high-burden, low-income countries. In 2015, Cervical Cancer Action launched a global five-year initiative called Taking Cervical Cancer

Prevention to Scale: Protecting All Women and Girls. This initiative is focused on expanding and aligning global efforts to ensure that all girls are vaccinated against HPV, the virus that causes cervical cancer, and that all women receive screening and preventive treatment of cervical precancer, especially in low- and middle-income countries *(8)*.

Extending the reach across other programmes

Existing sexual and reproductive health programmes—particularly those providing HIV and family planning services—present a valuable opportunity to integrate primary and secondary cervical cancer prevention services.[3] Youth-friendly sexual and reproductive health services can be used to integrate primary prevention, especially for girls out of school; and HIV and family planning services can integrate secondary prevention for women and girls.

Case study

Low- and middle-income countries offer several examples of programmatic synergies through the simultaneous delivery of programmes targeting adolescence with HPV vaccination. In 2011, Rwanda introduced a national cervical cancer prevention programme as part of school health days. This campaign resulted in high coverage rates and three-dose HPV vaccine coverage rates of 93.2% and 96.6% in 2011 and 2012, respectively. These coverage rates were made possible by enlisting teachers and village leaders in sensitization efforts, and by mobilizing the country's 45 000 community health workers to make the vaccine available to out-of-school girls *(9)*.

Action for policy-makers

There are a number of actions that policy-makers at all levels can take to address HPV, HIV and cervical cancer:

- Improve education (including age-appropriate comprehensive sexuality education) and communication regarding HPV and cervical cancer.
- Use existing health-care delivery systems as a platform to expand cervical cancer prevention screening and treatment and to take HPV vaccination to scale.
- Offer screening for cervical precancer and cancer to women and girls who have initiated sexual activity and tested positive for HIV, regardless of their age.
- Rescreen women living with HIV whose screening results are negative (no precancer) within three years.
- Provide counselling to women living in countries with high HIV prevalence who are diagnosed with cervical precancer or cancer, and offer them HIV testing.

[3] Primary prevention is ensured through vaccination against sexually transmitted HPV infection, as well as behaviour changes mediated by health education and information. Secondary prevention is done through screening and treatment of precancer.

- Intensify efforts to empower adolescent girls and young women by making comprehensive information on HIV, HPV and sexual and reproductive health available, to support their ability to make decisions over their own health, and to ensure the fulfilment of sexual and reproductive health and rights of all women.

A global opportunity

Implementing cervical cancer prevention and control programmes is a global opportunity to improve women's health, and this supports *The Global Strategy for Women's, Children's and Adolescents' Health (2016-2030) (10)*. The prevention and treatment of cervical cancer has been identified in the WHO's Global Action Plan for the Prevention and Control of NCDs, 2013–2020, as one of the available programmes that should be implemented in order to realize the goal of reducing the preventable and avoidable burden of morbidity, mortality and disability due to NCDs *(11)*.

Global epidemiology

Globally, approximately half of all people living with HIV in 2015 were women, but adolescent girls and young women in sub-Saharan Africa (where approximately two thirds of all new HIV infections occur) bear a disproportionate burden of HIV infection: young women aged 15 to 24 years in that region have HIV prevalence rates up to eight times higher than their male peers, and in southern Africa they acquire HIV at least five to seven years earlier *(12–13)*. In 2015, almost 390 000 new HIV infections occurred among young women aged 15 to 24 years, accounting for almost 60% of all new HIV infections worldwide in this age group *(14)*.

A complex interplay of biology, gender disparities and social, political and economic factors contribute to the heightened vulnerability of young women to HIV *(15)*. For instance, early sexual debut, partnering with older men and intimate partner violence all have been shown to be associated with an increased risk of acquiring HIV among women *(16–22)*. Sexual debut also marks initial exposure to a number of sexually transmitted pathogens, including viruses such as genital herpes (HSV-2) and HPV.

HPV is one of the most common sexually transmitted infections (STIs) worldwide. It is transmitted via skin-to-skin and sexual contact (including vaginal, anal and oral penetrative and non-penetrative sex), and approximately half of all sexually active men and women will be infected with a type of HPV at some point during their lives *(23)*. Some may be repeatedly infected. HPV infection occurs rapidly following sexual debut, with per-coital transmission rates estimated at 40% *(24)*.

Prevalence of HPV varies widely between regions. Overall, sub-Saharan Africa (24%), eastern Europe (21%) and Latin America (16%) have the highest rates of HPV *(25)*. Among women living with HIV, HPV prevalence rates are even higher, reaching levels as high as 80% in Zambia and 90–100% in Uganda *(26, 27)*. HPV prevalence typically peaks around age 25 in women, after which prevalence tends to decline, likely due to the natural clearance of the virus from the body.

More than 170 HPV genotypes, numbered sequentially, have been identified *(28)*. Fifteen types are recognized as high-risk or cancer-causing genital HPVs: types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. These types are strongly associated with anogenital cancers (particularly cervical cancer) and precursor lesions *(29, 30)*. Globally, HPV type 16 is the most prevalent type detected in HPV-associated cancers, followed by HPV type 18. Together, HPV 16 and 18 cause about 70% of cervical cancers worldwide *(31-33)*. The two most common low-risk mucosal HPV types are 6 and 11, which together cause about 90% of genital warts (*34)*.

HPV infection is the primary cause of cervical cancer, and it also is associated with cancers of the anus, penis, vagina and vulva, as well as a growing number of head and neck cancers *(35-37)*. Although the majority of HPV infections are usually benign and resolve naturally within one to two years without clinical signs or symptoms *(38)*, some infections persist and can progress to precancer—and, if left untreated, cancer *(37, 39-41)*.

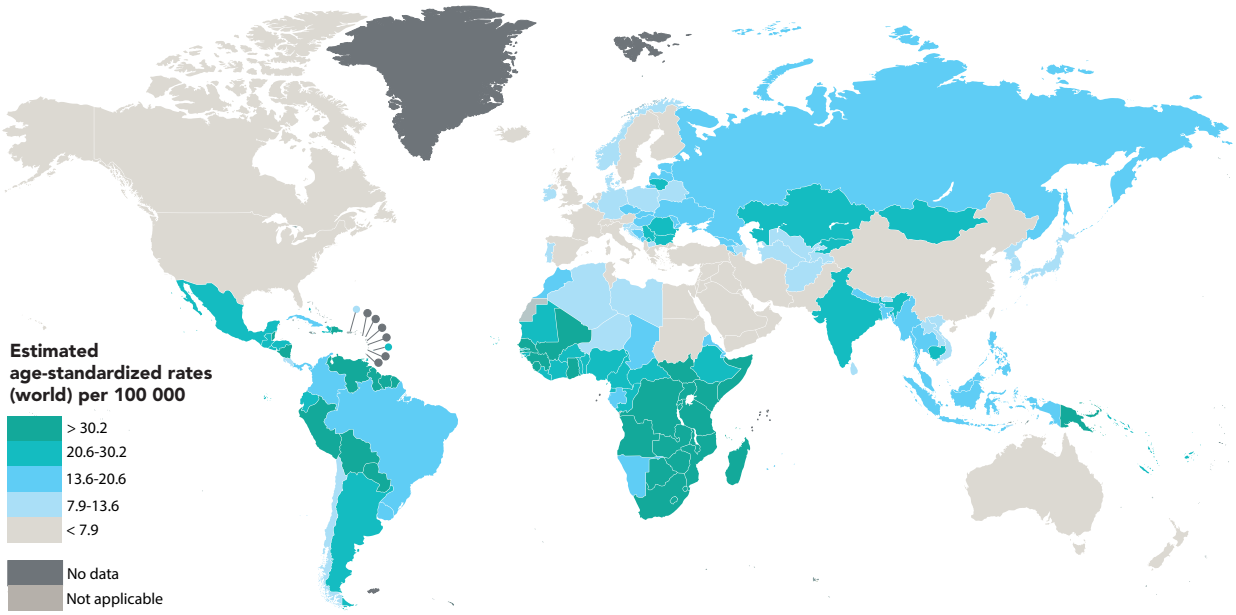
There were an estimated 528 000 new cases of cervical cancer worldwide in 2012. According to the WHO and the International Agency for Research on Cancer (IARC), cervical cancer is the fourth most common cancer in women worldwide, and the second most common cancer in women living in low- and middle -income countries.

The highest burden of cervical cancer occurs in less developed regions, particularly Africa, parts of Asia and Latin America and the Caribbean (Figure 1). Cervical cancer is the most common cancer in women in eastern and central Africa.

An estimated 266 000 women died from cervical cancer worldwide in 2012 (Figure 2), with 87% of these deaths occurring in less developed regions *(42)*. Without changes in prevention and control, global estimates of cervical cancer are projected to rise to 720 415 new cases and 394 905 deaths by 2025 *(43)*.

People living with HIV have been shown to have higher rates of HPV infection and to be more likely to be infected with high-risk HPV and multiple HPV types than HIV-negative individuals *(44, 45)*. Two large prospective studies—the Women's Interagency HIV Study (WIHS) and the HIV Epidemiology Research Study (HERS)—have shown that the prevalence of HPV 6 or 11 was 5.6 times (WIHS) and 3.6 times (HERS) higher among women living with HIV than it was among HIV-negative women *(46)*.

Figure 1
Estimated cervical cancer incidence worldwide in 2012



Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

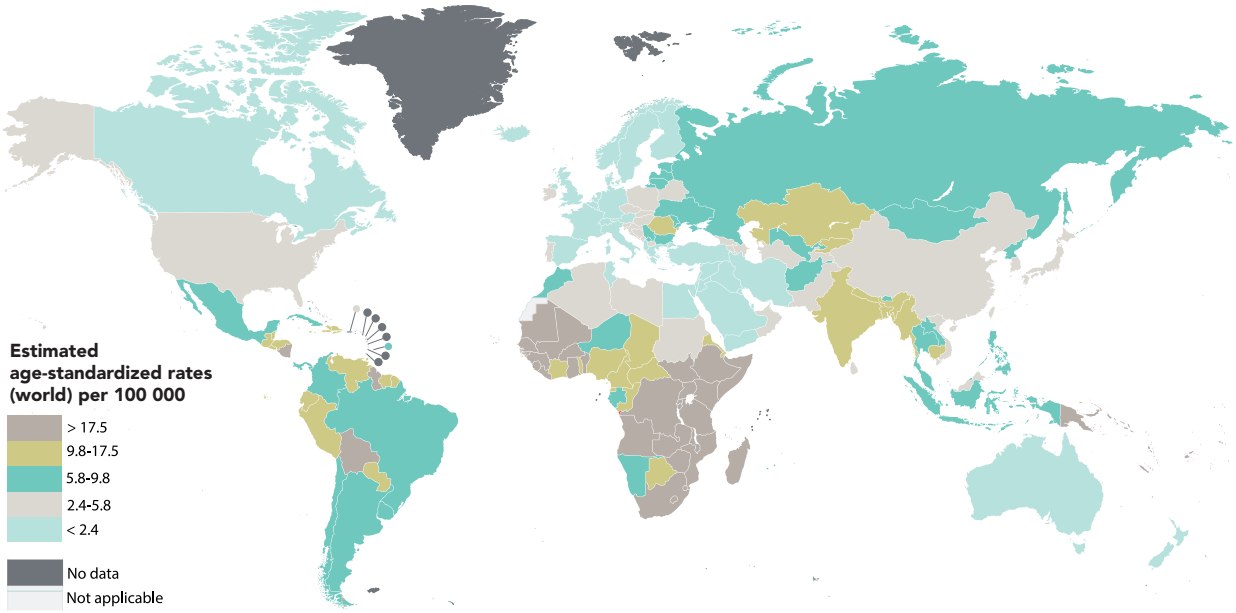
Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.1, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 (http://globocan.iarc.fr, accessed 15 September 2015).

Individuals living with HIV also experience higher frequencies of anal HPV infections and have higher HPV viral loads *(47)*. High HPV viral loads are associated with an increased risk of cervical abnormalities and enhanced HPV transmission with the presence of anal warts. Anal warts and HIV infection are independent risk factors for the development of anal intraepithelial neoplasia (AIN), a precursor for anal cancer *(48)*.

HPV infections also are more likely to persist in women living with HIV *(49–52)*. As a consequence, women living with HIV develop cervical

Figure 2

Estimated cervical cancer mortality worldwide in 2012



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intraepithelial neoplasia (CIN) and cervical cancer more frequently than HIV-negative women *(40, 51, 53, 54)*. In fact, rates of cervical cancer are estimated to be four to five times higher in women living with HIV than they are among HIV-negative women *(3)*. Despite the increased risk, however, women living with HIV often do not receive regular screening or treatment for cervical cancer.

Associations between HPV and HIV

"I was advised by my doctor to go for cervical cancer screening. It took less than 15 minutes to be told I had cervical cancer. I was later referred to treatment and assured of potential positive outcomes as my cervical cancer was in early stages. The treatment wasn't painful at all and I started feeling well after a couple of days. I want women to learn from me. I am a survivor. I implore organizations to help women prevent and fight cervical cancer, especially in the face of HIV which increases the likelihood of cervical cancer for those of us living with the virus."

Agnes Phakameya,
cervical cancer survivor in Malawi

The presence of STIs, particularly those that cause genital ulceration or inflammation, has been shown to play an important role in the transmission of HIV by increasing both the risk of transmission by people living with HIV and the susceptibility of HIV-negative individuals *(55–57)*. Genital herpes, for example, has been shown to be associated with increased risk of HIV acquisition in men and women (increases of 2.8 times and 3.4 times, respectively) *(58)*.

Accumulated data indicate that HPV also may be an important co-factor in HIV acquisition among men and women. A systematic review and analysis in 2012 showed that the overall risk of HIV acquisition in women doubled when they had a prevalent HPV infection with any genotype *(21)*, while a 2013 review and analysis showed that HIV acquisition was significantly associated with any HPV infection and infection with high-risk HPV types *(59)*.

Two studies involving men also were reviewed: one in heterosexual men and one in a cohort of men who have sex with men. Both studies showed an association between HPV infection and HIV acquisition. In the cohort of men who have sex with men, the presence of two or more HPV types was associated with a significantly increased risk of HIV acquisition *(60)*, while in heterosexual men, the presence of any HPV in the penis was associated with increased HIV risk *(61)*.

Given the growing evidence of the association between HPV infection and HIV acquisition, HIV surveillance during the implementation of HPV vaccine programmes is warranted.

HPV vaccination

Two prophylactic vaccines are currently available and marketed in many countries worldwide for the prevention of HPV-related disease: a quadrivalent vaccine and a bivalent vaccine, both of which are directed against oncogenic genotypes.

The HPV4 vaccine is currently approved in 129 countries, and over 183 million doses have been distributed. The safety of these vaccines is being closely monitored, and thus far, the results are very reassuring *(62)*. A detailed analysis of post Licensure data, accumulated between 2006 and 2015, shows that the HPV4 vaccine continues to have a favourable safety profile *(63)*.

Both vaccines exhibit excellent safety and immunogenicity profiles *(64, 65)*, with long-term protection against infection with vaccine types and a moderate degree of cross-protection against some non-vaccine types (including HPV types 31, 45 and 52) *(66-68)*. Soon after licensure in 2006, developed countries rapidly introduced HPV vaccines into their routine immunization programmes. Scale-up of HPV vaccinations in some of these developed countries has already resulted in a significant reduction among vaccinated women of both HPV prevalence and cervical abnormalities *(69, 70)*.

In the United States of America, population-based surveillance data show that the prevalence of HPV types 16 and 18 in CIN2+ lesions decreased significantly among women who received at least one dose of the HPV vaccine, declining from 53.6% in 2008 to 28.4% in 2012 *(71)*. Substantial decreases in cases of genital warts also have been

observed in countries such as Australia, Denmark, Sweden and the United States of America following the introduction of a national HPV vaccination programme using a quadrivalent vaccine *(72)*.

Given that HPV incidence rises rapidly following sexual debut and that the current HPV vaccines are not therapeutic vaccines but prophylactic, the vaccine is most effective when implemented before sexual exposure. WHO recommends that the vaccine be administered to young adolescent girls between the ages of 9 and 13 years. Some countries also have started to vaccinate boys aged 11 or 12 years, as the HPV4 vaccine also prevents genital cancers in males.

The Advisory Committee on Immunization Practices (ACIP) in the United States recommends vaccination for females aged 13 through 26 years and for males aged 13 through 21 years who have not been previously vaccinated. The vaccine also is recommended for gay men and other men who have sex with men and immunocompromised persons, including people living with HIV up to the age of 26 years if they have not previously been vaccinated *(62)*. A two-dose schedule at zero and six months is recommended for young women below the age of 15 years; a three-dose schedule at zero, one to two months and six months is recommended for immunocompromised individuals, including people living with HIV and all young women 15 years and older. HPV vaccination is safe and best given to young girls and boys before sexual debut.

Misconceptions about vaccine safety and its potential to promote sexual promiscuity among young adolescents are several reasons reported for low vaccine uptake in some countries. A study of recently vaccinated young women aged 13 to 21 years (n = 339) showed that risk perceptions after HPV vaccination were not associated with riskier sexual behaviours: vaccination was not associated with subsequent sexual initiation among sexually inexperienced young women (42.5%), and it did not result in an increase in the number of sexual partners or alter condom use among sexually experienced participants (57.5%) *(73)*. Such misconceptions about HPV vaccination underscore that addressing knowledge gaps among adolescents and parents—and increasing how frequently clinicians recommend HPV vaccination—are critical to protecting adolescents against HPV-associated cancers and genital warts *(74)*.

Prevention, screening, diagnosis and care

Although HPV vaccination has the potential to significantly reduce the burden of cervical cancer, it does not replace the need for cervical cancer screening. Even in countries where the HPV vaccine is introduced, screening programmes will need to be developed or strengthened, particularly for women who are already infected with HPV or those who have not yet been vaccinated.

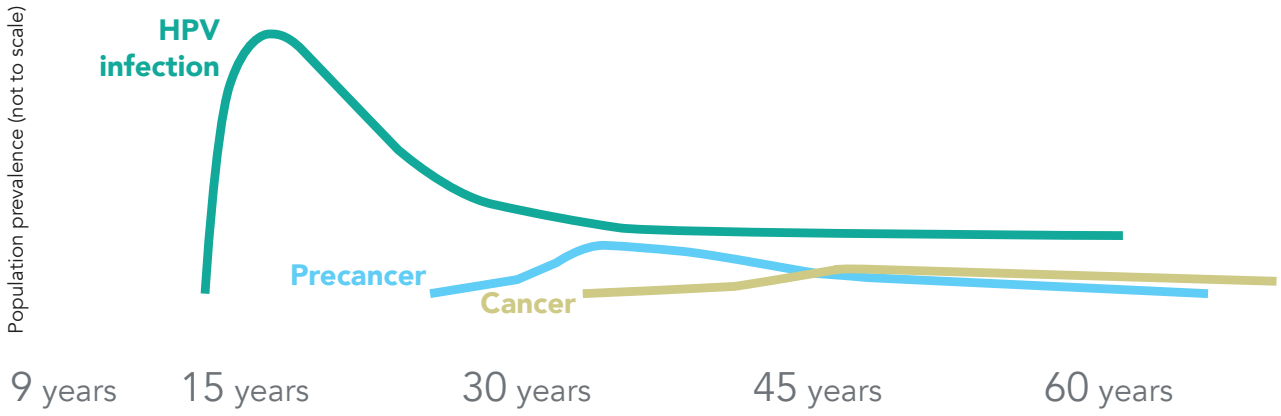
Minimizing deaths from cervical cancer requires a comprehensive approach, and it should be based on a multipronged approach, delivering effective programmes throughout the life of the individual (Figure 2) *(75)*. This involves primary prevention (HPV vaccinations) in girls aged 9 to 13 years before their sexual debut, secondary prevention (screening and treatment) for women aged 30 to 49 years, and tertiary prevention (treatment of invasive cervical cancer) for affected women.

Although cervical cancer screening does not prevent HPV infection, it has the potential to prevent most cervical cancer cases and deaths if precancerous lesions are detected early and treated appropriately. In many developed countries, organized, population-based screening of adult women, and prompt treatment for precancerous lesions of the cervix, have significantly decreased the incidence of (and mortality from) cervical cancer *(77-79)*.

Screening coverage in low- and middle-income countries is generally suboptimal, and women at the highest risk of developing cervical cancer (especially women living with HIV) are among the least likely to be screened *(77)*. Screening rates are low in developing countries in part because of limited

Figure 3

Overview of programmes throughout the life of individuals in order to prevent HPV infection and cervical cancer



PRIMARY PREVENTION

Girls 9-13 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warning about tobacco use*
- Sexuality information tailored to age and culture
- Condom promotion/ provision for those engaged in sexual activity
- Voluntary medical male circumcision

* Tobacco use is an additional risk factor for cervical cancer.

SECONDARY PREVENTION

Women >30 years of age

Screening and treatment as needed

- "Screen and treat" with low cost technology VIA followed by cryotherapy
- HPV testing for high risk HPV types (e.g. types 16, 18 and others)

TERTIARY PREVENTION

All women as needed

Treatment of invasive cancer at any age

- Ablative surgery
- Radiotherapy
- Chemotherapy

Source: World Health Organization. Comprehensive Cervical Cancer Control A guide to essential practice Second edition a, Switzerland: World Health Organization; 2014.

resources and weak health infrastructure, including a shortage of health professionals to perform screening. Furthermore, many women—including those who are living with HIV—have low levels of knowledge about HPV and the risk for cervical cancer.

There are three safe and cost-effective tests available for cervical cancer screening: the Papanicolaou (Pap) test and/or liquid-based cytology (LBC), VIA, and HPV nucleic acid detection (DNA and RNA tests). Pap tests have lower sensitivity than HPV-based testing, and about 12% of women globally who have normal cytological findings are actually infected with HPV *(80)*. Although new tests for the molecular biomarkers of infection and disease have greatly improved sensitivity and reliability *(81)*, VIA and/or Lugol's iodine (VILI) have been shown to have a similar sensitivity (although lower specificity) in a number of cross-sectional research and demonstration projects *(82)*. Visual inspection methods also require minimal resources, are technologically accessible and feasible for use in screening for precancerous lesions, and have been shown in clinical trials to reduce cervical cancer mortality. However, scaling-up of VIA progammes has been more challenging than anticipated.

Despite the importance of cervical cancer screening, many women do not consistently receive cervical cancer screening that is in accordance with the most appropriate guidelines *(83)*. To address that, innovative strategies have been investigated in several countries to improve cervical cancer screening uptake *(76, 84, 85)*. A trial in Argentina, for instance, showed that cervical screening coverage could be increased fourfold by using an existing network of trained community health workers to implement self-collection of samples for high-risk HPV detection *(86)*.

If precancerous changes are discovered during cervical cancer screening, women could be treated immediately or undergo further tissue evaluation (colposcopy and biopsy) and then be treated. WHO recommends a screen and treat—or a screen, diagnose and treat—approach *(75)*. The size, location and stage of a precancerous or cancerous lesion determine the choice of treatment.

Treatment options include cryotherapy, loop electrosurgical excision procedures (LEEP), laser surgery, hysterectomy, chemotherapy and radiation therapy. Cervical precancer can be successfully treated with cryotherapy or LEEP.

- Cryotherapy involves using a cryoprobe[4] to freeze precancerous lesions on the cervix. This procedure can generally be performed within 15 minutes by a trained physician, nurse or midwife at a health centre. Linking screening to treatment with cryotherapy may enable screening and treatment to take place during one visit, but it also may result in large numbers of women being subjected to unnecessary treatment. A number of studies, however, have shown that cryotherapy is not associated with significant side-effects or complications, and that it is well-tolerated *(87)*.
- LEEP is primarily used to remove large lesions that cannot be covered with a cryoprobe, or to remove lesions that involve the endocervical

canal. The procedure is performed by physicians in hospital settings, who use a thin, electrically heated wire to remove lesions and any transformed tissue after the patient has been given local anaesthesia.

- Early invasive cervical cancer is ideally treated by radiotherapy (with a combination of external beam radiation and brachytherapy, insertion into the cervix of a radiation source); or alternatively by a radical hysterectomy (with or without pre-operative chemotherapy), which is curative in most cases *(88)*.
- The standard therapy for locally advanced cervical cancer is a combination of radiotherapy and cisplatin-based chemotherapy. It has an overall five-year survival of less than 50% *(89)*. Locally advanced cancers are characterized by high recurrence rates and a poor prognosis, with a median survival of less than one year *(89)*.
- In the case of stage IV metastatic cervical cancer, palliative care can be provided, which is not only end-of-life care but also includes care to reduce pain and improve the quality of life for cancer patients.
- A number of therapeutic vaccines also are being evaluated as an alternative to invasive surgery, and they may provide an opportunity to control cervical cancer in the future.

[4] An instrument used to apply extreme cold during cryosurgery. A variety of different freezing methods can be used, including liquid nitrogen, carbon dioxide or nitrous oxide.

Key alliances and partnerships

The HIV response has leveraged multisectoral partnerships that engage government and civil society organizations alongside people living with HIV, the private sector, the scientific community, faith-based communities, and academia, and it offers strong examples of intersectoral partnerships and provides many valuable lessons. Strategic and innovative partnerships and alliances between organizations—including the private and public sectors—present a significant opportunity to strengthen a comprehensive approach to addressing HPV, cervical cancer and HIV. Examples of successful partnerships and alliances include the following:

- **The Joint UN Programme on Cervical Cancer Prevention and Control**, which was launched in May 2016, will support governments in developing and implementing functioning and sustainable high-quality national comprehensive cervical cancer control programmes that allow women to access services equitably. The vision of the programme is the elimination of cervical cancer as a public health issue across the world, and it pursues this through action to support the WHO voluntary global target of a 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases by 2025, as through the Sustainable Development Goal target to reduce premature mortality from noncommunicable diseases by one third by 2030. This is in line with the UNAIDS 2016–2021 Strategy, which emphasizes that prevention, treatment, care and support services should be integrated with services that address coinfections and comorbidities, and with sexual and reproductive health services such as

prevention, screening and treatment for STIs and cervical cancer.

- **Gavi, the Vaccine Alliance** is a public–private partnership that has brought about significant reductions in the cost of HPV vaccines, which are now available in developing countries for about US$ 4.50 per dose (compared to US$ 100 in developed countries). Gavi have planned to support more than 20 countries to vaccinate approximately one million girls with HPV vaccines through demonstration projects by 2015. By 2020, more than 30 million girls are expected to have been vaccinated in more than 40 countries through Gavi support.
- **Cervical Cancer Action (CCA).** The CCA is a global partnership that was founded in 2007 to reduce cervical cancer in high-burden, low-income countries. In 2015, the CCA launched a global five-year initiative called Taking Cervical Cancer Prevention to Scale: Protecting All Women and Girls. This initiative is focused on expanding and aligning global efforts to ensure that all girls are vaccinated against HPV, and that all women receive screening and preventive treatment of cervical precancer, especially in low- and middle-income countries *(8)*.
- **Pink Ribbon Red Ribbon (PRRR)** was launched in 2011 by President George W. Bush, Secretary Hillary Clinton, the Komen Foundation, UNAIDS and Merck to bring together public, private and multisectoral actors to address HPV and HIV. A public–private partnership, its donors and partners include Becton, Dickinson, and company, the Bill & Melinda Gates Foundation, the Bristol-Myers Squibb Foundation, the Caris Foundation, GlaxoSmithKline, IBM, Merck, QIAGEN, the National Breast Cancer Foundation, the LiveStrong Foundation, GE Healthcare and the American Cancer Society. With the engagement of national governments, nongovernmental organizations, and key local leadership, the partnership results in country-owned, sustainable programmes that allow women and girls to access the care they need to have the opportunity to thrive. During its first year, PRRR implemented cervical and breast cancer control activities in select countries in sub-Saharan Africa and Latin America. Since then, it has screened nearly 200 000 women for cervical cancer and more than 6000 women for breast cancer, and it has vaccinated over 42 000 girls against HPV.
- **The UN Interagency Task Force on the Prevention and Control of Noncommunicable Diseases**, which was established in 2013, coordinates the activities of relevant UN funds, programmes, specialized agencies and other intergovernmental organizations to support the realization of the commitments made in the 2011 *Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non communicable Diseases*. In particular, it attempts to do this by implementing the WHO Global NCD Action Plan 2013–2020. An objective of the collaboration facilitated by the UN Interagency Task Force is the effective coordination of UN agencies to increase access to cervical cancer prevention and control services as an entry point for other types of cancer in low- and middle-income countries.

Programmatic integration

"HPV and cervical cancer are just a few of the many reasons why it is imperative that sexual and reproductive health and rights are a reality for all women and adolescent girls globally. We must abandon the notions that limit access to quality and comprehensive services and sexuality education. We have the prevention and screening tools, now we must be committed to making them accessible, affordable and prioritized to keep women and adolescents healthy, aware, pro-active and free from cervical cancer."

Ebony Johnson, gender equality & public health consultant SRHR and Policy Focal Point Athena Network

A number of health care programmes have been identified as being suitable for joint delivery with HPV vaccination and addressing cervical cancer, including service integration and health system strengthening to address both HIV and cervical cancer.

A review of existing health programmes for girls and boys aged 9 to 15 identified 14 effective programmes that could potentially be appropriate for integration with HPV vaccination *(90)*. Selecting which programmes should be added to HPV vaccine delivery, however, will depend on individual countries and communities.

Community outreach and mobilization lessons from the HIV experience are highly relevant to HPV services, especially the provision of preventive services where stigma and denial may be a factor (such as HIV testing services).

Introducing a vaccine to adolescent girls for the prevention of an STI faces several challenges. For the vaccine to be acceptable, parents need a better understanding of cervical cancer and why it is important to vaccinate young girls in order to prevent an infection that can lead to a disease decades later. Since HPV is sexually transmitted, culturally appropriate information including age-appropriate comprehensive sexuality education must be developed to avoid a negative reaction against vaccination or sexual and reproductive health services, particularly since young girls are the primary vaccine recipients. Even if only women and girls receive the vaccine, information must be provided to men and boys about cervical, anal,

penile and oral cancers *(91)*. Using appropriate channels where parents receive information, often from a trusted source like a health worker or teacher, is even more important when young adolescents are involved, and it may enhance the effectiveness of existing community awareness activities related to HIV prevention *(92)*. Preparing and using materials (which often are generated through previous formative research) to answer potential questions from parents can help focus key messages for informed decision-making.

Delivering multiple programmes along with the HPV vaccine is an opportunity to increase access to health care and services among adolescents. This is especially the case when it comes to reaching adolescents for preventive health care (especially in low- and middle-income countries), because their contact with health facilities between early childhood and sexual debut is generally low *(90)*.

There are a number of examples of successful vaccination strategies:

- In Uganda, linking HPV vaccine delivery with the semi-annual "child health days"—when vitamin A, deworming and supplemental vaccinations are provided in the community—was shown to be beneficial and cost-effective. If the same health staff are involved in all the services, there is some overlap (if not an exact match) among the groups receiving services, and the amount of time needed for the new programme did not significantly affect the other activities *(93)*. Other examples of integrated programmes include combined HPV vaccination and deworming treatment in Bhutan and the integration of the HPV vaccine into the routine school health programme for adolescents in Malaysia and Panama.
- HPV vaccination demonstration projects have used various delivery strategies and platforms to reach adolescent girls, including school-based programmes, campaign-style delivery, health facility-based on-demand delivery, and community-based outreach *(94)*. A combination of school and health facility-based options also have been used to vaccinate girls who missed school vaccination days and to girls who were not enrolled or attending school at the time *(92)*.
- In 2006, Zambia used its HIV programme infrastructure to introduce the Cervical Cancer Prevention Program in Zambia, a nurse-driven cervical cancer screening and treatment programme that was integrated into public sector clinics as a routine health-care service *(95)*. The programme initially focused on women living with HIV; it later recruited and trained women from the community to promote the service and inform other women about cervical cancer screening and treatment. Nurses were trained to perform cervical cancer screening and offer HIV testing services to women undergoing cervical cancer screening who did not know their HIV status. Newly diagnosed women living with HIV were referred to nearby clinics for HIV treatment, care and support. Within five years, the programme provided services to over 58 000 women *(95)*.

Existing sexual and reproductive health programmes—particularly family planning services— also could be used to integrate primary and secondary cervical cancer prevention services, especially for young girls who are out of school *(91)*. Most sexual and reproductive health programmes already offer programmes addressing STIs, including HIV testing services and cervical cancer screening *(91)*.

In order to reach young girls, particularly those who are out of school, programmes must become more accessible and youth-friendly. Unmarried teenagers often encounter societal disapproval and are reluctant to seek sexual and reproductive health services because of negative attitudes among health service providers, or because they face other obstacles in accessing services (such as inconvenient locations or operating hours, or insufficient funds to pay for services or transportation). Furthermore, health providers often lack adequate training and skills to deliver youth-friendly sexual and reproductive health and HIV services that respond to the diverse realities of young women.

There is, however, growing recognition of the importance of adapting health services to the needs of young people. Adolescent health programmes are developing user-friendly services that aim to provide counselling on sexual health that focuses on the prevention of pregnancy and STIs (including HIV). Including a new programme (such as an HPV vaccine) into these services could extend their scope and help integrate other programmes, thereby making them more attractive to young people *(91)*.

Guidance for policy-makers

Scale up HPV vaccination as a public health priority

Opportunities to prevent and control cervical cancer occur at multiple stages during a woman's lifetime. Opportunities for primary prevention occur early in life (before exposure), and the best chance to prevent infection with HPV is during adolescence, prior to sexual debut. Scaling up HPV vaccinations for adolescent girls aged 9 to 13 years therefore should be a priority. In resource-constrained settings, the two-dose schedule—which has been shown to be as effective as the current three-dose schedule *(72)*—may be easier and more cost-effective to administer. Organizations such as Gavi, PATH and PRRR have successfully reduced the cost of HPV vaccines, making the expansion of routine administration of the HPV vaccine in low- and middle-income countries a reality.

Expand screening for and treatment of cervical cancer

Opportunities to reduce morbidity and mortality associated with HPV infection extend into adulthood. WHO recommends that, given the significant increase of cervical cancer risk after the age of 30, every woman should be screened for cervical cancer at least once between the ages of 30 and 49 years, receiving the necessary treatment when required. The recommended screening interval is three to five years for women who test negative when screened using VIA or cytology (Pap smear); for women who test negative when screened using HPV testing, the interval should not be less than five years. Women who have received treatment should receive post-treatment follow-up

screening at one year to ensure effectiveness of treatment *(75)*.

Screening is not recommended for women younger than 30 years of age unless they are known to be living with HIV or living in a high HIV prevalence area. Despite the importance of cervical cancer screening, many women do not consistently receive cervical cancer screening according to WHO guidelines *(83)*.

The implementation of innovative strategies like self-screening with a tampon-like device has been shown to improve screening uptake in a number of settings *(76, 84, 86)*. Where possible, the so-called screen and treat option should be implemented for women identified with precancerous lesions. This approach reduces loss to follow-up, and it can reduce delays for women who need treatment.

Intensify efforts to advance gender equality and the sexual and reproductive health and rights of women

The enjoyment of the highest attainable standard of health is a fundamental right of every human being. Unfortunately, there are large inequalities in access to sexual and reproductive health services, and women who have limited access to those services also have limited information about (and access to) effective cervical cancer screening and treatment. They also experience higher rates of invasive cervical cancer. In particular, young women, women living with HIV and women from key populations frequently experience multiple barriers to care, including age discrimination and lack of youth-inclusive providers. This limits their access to quality screening, prevention and treatment, and it essentially results in negative health and rights outcomes.

Governments, civil society and the international community can dramatically reduce the burden of diseases by prioritizing sexual and reproductive health and rights for young women; such a focus also will improve sexual and reproductive health and increase gender equality. This, in turn, will result in healthier women, workforces and economies.

Expand collaborations and resources

While policy strategies will play a critical role in cervical cancer screening and prevention, resources and global support (via organizations such as the UN Interagency Task Force on the Prevention and Control of Noncommunicable Diseases, Gavi, PATH, Jhpiego and PRRR) must be secured to augment a multipronged approach to preventing and treating cervical cancer.

Collaboration between multiple sectors is necessary for cervical cancer prevention to be a success. Country-specific policy strategies to increase the uptake of HPV vaccines likely will involve multiple stakeholders, including the following:

- Departments of health and education.
- School health teams.
- Primary health-care nurses.
- Hospital doctors and nurses.
- Private practitioners.

- School principals, teachers and governing bodies.
- Parents.
- Civil society organizations including networks of women living with HIV and the women's rights movement.
- Community and traditional leaders.
- Community-based organizations.
- Media.

Long-term investments in training, bio-medical infrastructure, research and human resources also are needed for the successful implementation of cervical cancer prevention and control programmes.

Leverage HPV programmes to expand access to other health care programmes

The scale-up of HPV vaccinations provides an opportunity to increase synergies between cancer prevention and control programmes and other health priorities. Delivering multiple programmes along with the HPV vaccine is an opportunity to increase access to health care and services among adolescents *(90)*.

Health-care programmes that have been identified as potentially suitable for joint delivery with HPV vaccination include the following:

- Screening (e.g. for schistosomiasis and defects in vision).
- Health education (e.g. on mosquito-borne diseases, the benefits of exercise, accessing health care, and sexual and reproductive health).
- Skills building (e.g. improving condom usage).
- Delivery of commodities (e.g. anthelminthic drugs, vitamin A supplements, soap and bed nets) *(90, 94)*.

Improve education and communication about HPV and cervical cancer, including through synergies with HIV infrastructure

Outreach, community mobilization, health education (including comprehensive sexuality education) and counselling are essential components of an effective cervical cancer prevention and control programme that ensures high vaccination and screening coverage and high adherence to treatment *(75)*. Community outreach, mobilization and engagement also are essential components of the HIV response. Use of HIV infrastructure can ensure optimization of resources and additional efficiencies for both programmes.

Reducing cervical cancer morbidity and mortality requires improved education and communication. Community knowledge of cervical cancer and the causal relationship between HPV and cervical cancer is generally poor, making the need for continued education around the importance of HPV prevention and regular cervical screening a priority *(83, 96, 97)*. Communication about cervical cancer needs to reach adolescents, women living with HIV, parents, educators, leaders and people working at all levels of the health system. Community outreach and mobilization lessons from the HIV experience are highly relevant to HPV services, especially providing services where stigma and denial may be at play (such as HIV testing services). In addition,

community mobilization and the methods used for the delivery of HIV services has relevance for HPV vaccinations.

Use existing health-care delivery systems as a platform to expand cervical cancer prevention and treatment

The infrastructure developed for HIV prevention, testing and treatment could be used as an opportunity to affect morbidity and mortality associated with cervical cancer. For people living with HIV, infection with HPV introduces unique challenges that require heightened prevention, screening and treatment efforts. The high prevalence of high-risk HPV infection, STIs and cervical lesions among women living with HIV makes regular screening of these women particularly important *(98)*. WHO recommends that women and girls who test positive for HIV should be screened for cervical cancer and undergo annual screening *(75)*.

Several countries in Africa are implementing voluntary medical male circumcision programmes for HIV prevention. Since 2008, over 11 million voluntary medical male circumcisions had been performed for HIV prevention in the 14 priority countries of east and southern Africa *(99)*. Circumcision of HIV-negative men has been associated with a decreased risk of acquiring HPV *(100)*, reduction in the incidence of penile cancer *(101)* and reductions in the transmission of HPV to female partners *(41, 102)*. In countries and specific communities with high HIV and HPV incidence, existing male circumcision programmes therefore could potentially be used as a resource to expand HPV campaigns for boys and girls.

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