1. Introduction

1.1 Background

Cervical cancer is a leading cause of mortality among women. In 2020, an estimated 604 000 women were diagnosed with cervical cancer worldwide and about 342 000 women died from the disease. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the leading cause of cancer death in 36 countries. The vast majority of these countries are in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia *(1)*.

In May 2018, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), issued a call to action for the elimination of cervical cancer. A WHO global strategy to accelerate the elimination of cervical cancer as a public health problem was presented and unanimously endorsed by the Seventy-third World Health Assembly in August 2020. Subsequently, WHO officially launched the Global strategy to accelerate the elimination of cervical cancer on 17 November 2020.[2]

The targets of the global strategy are, by 2030:

- **to vaccinate 90% of eligible girls against HPV;**
- **to screen 70% of eligible women at least twice in their lifetimes; and**
- **to effectively treat 90% of those with a positive screening test or a cervical lesion, including palliative care when needed** *(2)*.

In the context of this global strategy, countries are updating their protocols for the prevention of cervical cancer and for the care and treatment of affected women. Cervical cancer prevention also plays an integral role in reaching the Sustainable Development Goals (SDGs), both for health (SDG 3) and gender equality (SDG 5).

To prevent cervical cancer, women can be screened using various tests to identify those who have or are at risk of cervical pre-cancer (see *Table 1.1*). Cervical intraepithelial neoplasia (CIN) is characterized by cellular changes in the transformation zone of the cervix. CIN is typically caused by infections with human papillomavirus (HPV), especially the high-risk HPV types such as strains 16 and 18 (these two strains cause more than 70% of cervical cancers) *(3,4)*. CIN1 lesions – also referred to as low-grade squamous intraepithelial lesions– are morphological correlates of HPV infections. CIN2/3 lesions – also referred to as high-grade squamous intraepithelial lesions – are correlates of cervical pre-cancers that, if left untreated, may progress into cervical cancer (for further details, refer to Chapter 1 of WHO's *Comprehensive cervical cancer control* guidance *[5]*).

[2] Launch page: *https://www.who.int/news-room/events/detail/2020/11/17/default-calendar/launch-of-the-global-strategy-to-accelerate-the-elimination-of-cervical-cancer*

Table 1.1 Three approaches to cervical cancer screening and future tests

Molecular	Cytologic	Visual inspection
Nucleic acid amplification tests (NAAT)[a] » high-risk HPV DNA/ NAAT » mRNA **DNA methylation[b]** **Protein biomarkers[b]** » HPV antibodies » oncoproteins	**Conventional Pap smear[a]** **Liquid-based cytology (LBC)[a]** **Dual staining to identify p16 and Ki-67[a]**	**Visual inspection with acetic acid or with Lugol's iodine (VIA/VILI)[a]** » naked eye » magnified by colposcope or camera **Automated visual evaluation of digital images[b]**

[a] Current tests
[b] Tests under evaluation (future tests).

The traditional method to screen women for cervical cancer has been cytology (the Papanicolaou test, also known as the Pap smear or smear test). When cytology results are positive, the diagnosis is confirmed by colposcopy, and appropriate treatment is informed by biopsy of suspicious lesions for histological diagnosis. In countries with effective cytology-based cervical cancer screening and treatment programmes, the mortality from cervical cancer has been reduced fivefold over the past 50 years *(6)*. This screening approach has not been as successful in low- and middle-income countries *(7)*.

Newer screening tests introduced in the last 15 years include visual inspection with acetic acid (VIA), and molecular tests, mainly high-risk HPV DNA-based tests,[3] which are suitable for use in all settings (*Table 1.1*). More recently, even newer tests and techniques have been developed: (i) other molecular tests such as those based on HPV mRNA, oncoprotein detection or DNA methylation; (ii) more objective tests performed on cytological samples such as p16/Ki-67 dual staining; and (iii) more advanced visual inspection tests based on artificial intelligence/machine learning platforms (e.g. automated visual evaluation of digital images) *(8–11)*.

[3] In this guideline, "an HPV DNA test" refers to a high-risk HPV DNA test. An HPV DNA test is a nucleic acid amplification test (NAAT).

1.2 Approaches to screening and treatment

In this document, two approaches to screening and treatment are distinguished: the screen-and-treat approach and the screen, triage and treat approach.

Screening and treatment approaches

- In the **"screen-and-treat approach"**, the decision to treat is based on a positive primary screening test only.

- In the **"screen, triage and treat approach"**, the decision to treat is based on a positive primary screening test followed by a positive second test (a "triage" test), with or without histologically confirmed diagnosis.

In a **screen-and-treat approach**, treatment is provided based on a positive primary screening test alone, without triage (i.e. no second screening test and no histopathological diagnosis).

- When the patient is eligible for ablative treatment, this should ideally be done immediately, at the same visit as the screening test (the single-visit approach). At some facilities, this is not feasible and a second visit is needed (the multiple-visit approach).
- Women who are not eligible for ablation can have excisional treatment on the same day if the clinic has the capacity for large-loop excision of the transformation zone (LLETZ).[4] If LLETZ is not available on-site, women need to be referred for the excisional treatment or for further evaluation.

In a **screen, triage and treat approach**, the triage test is done if the primary screening test is positive, and the decision to treat is made when both the primary test and the triage test are positive.

- A positive triage test can lead to colposcopy with biopsy and histopathological examination for diagnosis to determine the appropriate treatment. The implementation of colposcopy and biopsy can be challenging, however, so this guideline also considers triage strategies that are not dependent on the availability of colposcopy.
- When the primary screening test is positive, and the triage test is negative, women need appropriate follow-up evaluation at a specified date according to the recommendations.

[4] In this guideline, the term LLETZ is used to refer to excision of the transformation zone. In some countries, this terminology was changed to LEEP (loop electrosurgical excision procedure), and the two terms are often used interchangeably.

1.3 Rationale for this new edition of recommendations

Recommendations for screening and treatment to prevent cervical cancer, including for women living with HIV, can be found in four existing WHO guidelines – on screening and treatment of pre-cancer lesions, treatment for CIN2/3 and AIS, cryotherapy for CIN, and thermal ablation for pre-cancer lesions (12–15). These recommendations (except for those on thermal ablation, published later in 2019) were consolidated in the 2014 second edition of *Comprehensive cervical cancer control: a guide to essential practice* (5), which also includes the WHO recommendations for HPV vaccination, treatment of cervical cancer and palliative care. In 2020, WHO published guidance documents to support the introduction and scale-up of screening and treatment interventions, specifically relating to HPV testing and relevant medical devices (16,17).

Guidelines should be updated when new knowledge or developments could materially influence existing recommendations. They should also be updated when the publication date, presentation, background text, evidence synthesis methods, or evidence-to-decision (EtD) considerations might threaten their credibility. In addition, end-user feedback might highlight recommendations that are conflicting, ambiguous, out-of-date or difficult to implement, thus also necessitating an update.

The overwhelming approval of the WHO global strategy to accelerate the elimination of cervical cancer by Member States during the World Health Assembly in 2020 underlined the urgent need to provide up-to-date WHO guidance on screening and treatment to prevent cervical cancer. The WHO guidance on the recommended algorithms and treatments for use in screening and treatment programmes for cervical cancer prevention, previously published in 2013, was assessed as in need of an update, to effectively guide and facilitate country-level decision-making for starting and scaling up programmes. The updating of this guideline began in 2019 and was informed by implementation experience and research findings, while ensuring that the new and updated recommendations are feasible and acceptable for both the health workers providing the screening and treatment services, and for the end-users of those services (see *Chapter 2: Methods*). This guideline will support efforts to reach the 2030 targets of the global strategy.

Guideline objective:

To improve national strategies for screening and treatment to prevent cervical cancer in all women, including women living with HIV.

Since the publication of the previous edition of this guideline in 2013 (12), HPV screening tests have been pre-qualified by WHO, and thermal ablation and cryotherapy have been added as recommended ablative treatment methods. Some interventions described in the 2013 guideline, such as cytology or the need for histological diagnosis, may no longer be relevant or commonly used in the screening and treatment protocols of many countries. Several high-quality studies have been published in the intervening years evaluating new tests, comparative recurrence rates after treatments and appropriate screening intervals. New information is also available concerning women living with HIV, on the type of screening and treatment and the age at which to start screening. This guideline also aims to clarify the optimal number of lifetime screens and, for countries with routine screening programmes, the recommended age for the first screening and the recommended frequency of subsequent screening following negative screening results and following treatment for signs of pre-cancer lesions.

1.4 Phased approach for the development of the recommendations

The following are the four phases of the updates to WHO's cervical cancer screening and treatment recommendations. This guideline delivers the output of Phase 1.

Phase 1	Update the recommendations on screening and treatment and the clinical algorithms for the most commonly used screening and triage strategies for both women in general and those living with HIV.
Phase 2	Evaluate the evidence for the clinical algorithms that were not prioritized in Phase 1.
Phase 3	Develop recommendations for the implementation of these screening and treatment strategies.
Phase 4	Establish a "living guideline" for screening and treatment tests and algorithms which will allow the recommendations to be updated as new evidence becomes available and is evaluated.

1.5 Target audience

This document is intended primarily for policy-makers, programme managers, programme officers and other professionals in the health sector who have responsibility for choosing strategies for cervical cancer prevention, at country, regional and district levels. Health-care professionals – such as doctors, nurses and community health workers working in reproductive health programmes, antenatal and postnatal services, family planning services, HIV/AIDS control programmes and in clinics that care for women at the district and primary health care levels – may also consult this document to understand how recommendations are developed and why it is vitally important to select and implement evidence-based strategies to prevent cervical cancer.

This document will also be informative in an adapted form for women, girls and their families in making decisions about cervical cancer screening and treatment.

All individuals have the right to equality and non-discrimination in sexual and reproductive health care. In this guideline, we recognize that most of the available evidence on cervical cancer is based on study populations of cisgender women, and we also recognize that cisgender women, transgender men, non-binary, gender fluid and intersex individuals born with a female reproductive system require cervical cancer prevention services. However, to be concise and facilitate readability, we use the term "women" to refer to all gender diverse people at risk for cervical cancer. Sexual and reproductive health service providers and cervical cancer prevention services must consider the needs of – and provide equal care to – all individuals independently of gender identity or its expression.