

# Cervical cancer screening and prevention

KJ Mahlaba,<sup>1,2</sup> VV Nkwini,<sup>2,3</sup> RL Lebelo,<sup>2,3,4</sup> JC Meyer,<sup>1,2</sup> RJ Burnett<sup>2,3</sup>

<sup>1</sup> School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

<sup>2</sup> South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, South Africa

<sup>3</sup> Department of Virology, School of Medicine, Sefako Makgatho Health Sciences University, South Africa

<sup>4</sup> National Health Laboratory Service, South Africa

Corresponding author, email: hannelie.meyer@smu.ac.za

## Abstract

Despite cervical cancer being a vaccine-preventable disease, and being treatable if diagnosed in the early stages, it is the third most common cancer among women in terms of both global incidence and cause of cancer deaths, affecting mostly low- and middle-income countries. Persistent infection of the cervix with high-risk types of human papillomavirus (HPV) is the necessary (but not sufficient) cause of cervical cancer. These infections are sexually transmitted and can be prevented or reduced through vaccination before sexual debut, and managed if detected early through cervical cancer screening programmes. This review offers insight into the challenges faced in South Africa regarding the prevention of cervical cancer, and the role of pharmacists in addressing these challenges.

**Keywords:** human papillomavirus (HPV), human papillomavirus vaccine, cervical cancer

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## Introduction

Cervical cancer is a preventable and treatable disease, provided it is detected early and managed effectively.<sup>1</sup> Despite this, cervical cancer was the third most common cancer among women of all ages in terms of both global incidence (569 847 cases) and cause of cancer deaths (311 365 deaths) in 2018.<sup>2</sup> Amongst women aged 15–44 years, cervical cancer was the second most common female cancer and the second leading cause of female cancer deaths globally.<sup>2</sup> Low- and middle-income countries are disproportionately affected by cervical cancer, with approximately 84% of cervical cancer cases and 88% of deaths due to cervical cancer occurring in low-income countries.<sup>3</sup> Future projections of cervical cancer burden based on 2018 estimates indicate a 26.7% and 47.6% increase in cervical cancer deaths among women of all ages by 2030 and 2040 respectively.<sup>4,5</sup> In 2019, considering the huge burden of cervical cancer, the World Health Organization (WHO) drafted the first global strategy towards eliminating cervical cancer as a public health problem, to be presented to the World Health Assembly in 2020.<sup>1</sup> The global strategy, aligned with the Sustainable Development Goals of 2030, proposes a comprehensive approach towards prevention, screening and treatment of cervical cancer with global targets for 2030.<sup>1</sup>

## Burden of disease in Africa

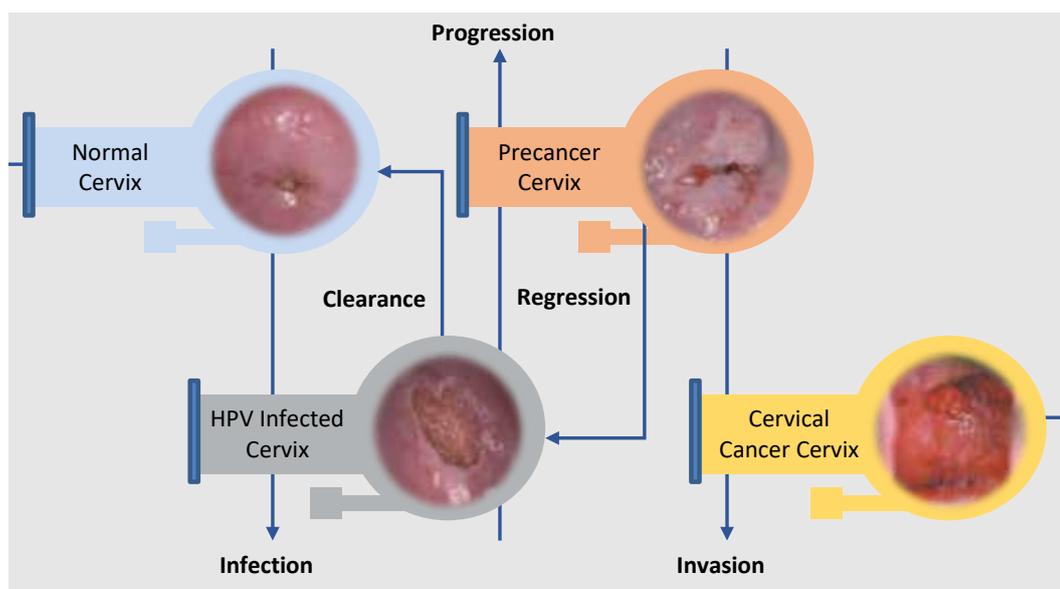
There are noteworthy disparities in cervical cancer disease burden between high-income and low-income countries, due to inequities in access to effective cervical cancer prevention and control services.<sup>1,6</sup> These inequities result in Africa having the highest age-standardised incidence (27.6) and mortality (20.0) rates per 100 000 women in the world, with the highest burden being in southern Africa.<sup>6</sup> In 2018, cervical cancer was the second most common female cancer in South African women of all ages with 12 983 new cases, and the leading cause of female cancer deaths, with 5 595 deaths. South Africa's cervical cancer age-standardised

incidence and mortality rates in 2018 were 43.5 and 19.2 per 100 000 women respectively.<sup>7</sup> According to the Ekurhuleni Population-Based Cancer Registry in South Africa, 1 in 38 women are at risk of cervical cancer by the age of 75 years.<sup>8</sup>

## Causes of cervical cancer

There are more than 200 human papillomavirus (HPV) types infecting human mucosal and cutaneous epithelia, with low-risk HPV types causing benign lesions (e.g. genital warts), while persistent infection with high-risk HPV types cause several types of cancer.<sup>9</sup> Approximately 40 HPV types are sexually transmitted, infecting the anogenital tract.<sup>9</sup> Persistent high-risk HPV infection of the cervix is the necessary (but not sufficient) cause of cervical cancer.<sup>9,10</sup> HPV infection is common and will occur in up to 80% of women during their lifetime, with the vast majority of infections clearing spontaneously without any clinical signs and symptoms.<sup>10</sup> Over time, persistent high-risk HPV infection may progress from precancerous cervical lesions including low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) to invasive cervical cancer.<sup>2,9</sup> Progression from LSIL to invasive cervical cancer is slow and mostly asymptomatic, with a high case-fatality rate in women seeking treatment in the late stages of symptomatic disease.<sup>11</sup> Figure 1 illustrates the progression from precancerous cervical lesions to invasive cervical cancer.

Globally, high-risk HPV types 16 and 18 are prevalent in 69.4% of all cervical cancer cases, 51.9% of HSIL cases, 25.8% of LSIL cases and 3.9% of women with normal cervical cytology.<sup>2</sup> The same trend is observed in sub-Saharan Africa (cervical cancer: 62.7%; HSIL: 38.6%; LSIL: 25.2%; and normal cytology: 3.8%) and South Africa (cervical cancer: 64.2%; HSIL: 33.7%; LSIL: 21.1%; and normal cytology: 3.2%).<sup>6,7</sup> HPV type 16 has the highest prevalence (50.7%) in South African cervical cancer cases, followed by HPV 18 (13.5%), 33 (7.3%), 35 (6.0%), 45 (5.6%), 31 (2.9%), 52 (2.1%), 53 (1.6%), 58 (1.3%) and 68 (1.0%).<sup>7</sup>



**Figure 1:** Life cycle of cervical cancer from infection through progression to invasive cervical cancer

Adapted from: <http://www.coheahr.eu/background/cervical-cancer/>

## Cofactors and risk factors for cervical cancer

While persistent infection with high-risk HPV types is a necessary cause of cervical cancer, other cofactors for cervical cancer are important as not all persistent infections progress to cervical cancer.<sup>9,12</sup> Well-established cofactors are tobacco smoking, long-term use of oral contraceptives, high parity and human immunodeficiency virus (HIV) coinfection.<sup>2,9,12</sup> There is also some evidence that *Chlamydia trachomatis* coinfection, herpes simplex virus type-2 coinfection and immunosuppression may be cofactors.<sup>2</sup> In addition, because HPV infection is sexually transmitted, certain sexual behaviours that increase the chances of exposure to HPV, are risk factors for cervical cancer.<sup>9</sup> These include having multiple sex partners and sexual debut at a young age.<sup>9</sup>

## Prevention of cervical cancer

The comprehensive global strategy for eliminating cervical cancer, drafted by the WHO, is based on evidence from primary, secondary and tertiary level prevention interventions.<sup>1</sup> This strategy (dubbed “90-70-90”) proposes that by 2030, countries should reach 90% full HPV vaccination coverage of girls aged  $\leq 15$  years; screen at least 70% of women aged  $\leq 35$  years (and again at 45 years) with a high-performance test; and treat or manage 90% of all women with precancerous or cancerous cervical lesions.<sup>1</sup> The WHO elimination strategy is aligned with South Africa’s overall cancer strategy of education and training, screening and treating/managing with an aim of rehabilitation and support.<sup>13</sup> Similarly, the South African Cervical Cancer Prevention and Control Policy (2017) aims to reduce high-risk HPV infection incidence and cervical cancer mortality, and improve quality of life, through vaccination, early screening and management, and supportive therapy.<sup>14</sup> Figure 2 shows a summary of an integrated approach to cervical cancer prevention and management at the various levels of care in South Africa, which will be discussed in more detail in the next sections.<sup>1,14,15</sup>

## Primary prevention: Vaccination

### Human papilloma virus (HPV) vaccines

Primary prevention of cervical cancer is through vaccination of adolescent girls, which is considered by the WHO as the most effective long-term prevention strategy.<sup>1</sup> Currently there are two HPV vaccines licenced in South Africa, both containing synthetic non-infectious L1 virus-like particles, produced by recombinant DNA technology.<sup>16-19</sup> The bivalent vaccine, Cervarix®, and the quadrivalent vaccine, Gardasil®, protect against new infections with high-risk HPV types 16 and 18, the most common types responsible for cervical cancer. In addition, Gardasil® also protects against two low-risk HPV types 6 and 11, responsible for genital warts.<sup>16-19</sup> A nonavalent vaccine, Gardasil9®, which is not yet available in South Africa, protects against a further five high-risk HPV types (31, 33, 45, 52 and 58).<sup>17,20,21</sup> Also, there is evidence that both the bivalent and quadrivalent vaccines may provide cross-protection against high-risk types 31, 33 and 45.<sup>21</sup>

All HPV vaccines contain adjuvants to increase their immunogenicity. The adjuvant used in Gardasil® and Gardasil9® is amorphous aluminium hydroxyphosphate sulfate, while Cervarix® uses an adjuvant system known as AS04, comprising 3-O-desacyl-4'-monophosphoryl lipid A and aluminium hydroxide.<sup>17,20,21</sup> All three vaccines are recommended by the WHO, having found their safety, efficacy and effectiveness profiles to be excellent with very slight non-significant differences between them.<sup>21</sup> The most common adverse reactions reported during HPV vaccine clinical trials were local reactions at the site of injection, including pain, redness or swelling.<sup>21</sup> Systemic adverse reactions are mostly mild and self-limiting, including fever (most common), nausea, dizziness, myalgia and malaise, with serious adverse events being very rarely reported.<sup>21</sup> Similar to other vaccines administered via injection to adolescents, the psychogenic response of syncope (fainting) has been reported following vaccination with all three vaccines.<sup>21,22</sup> The vaccinee should therefore be seated while being vaccinated and a 15-minute observation period is recommended after vaccination.<sup>21,22</sup>

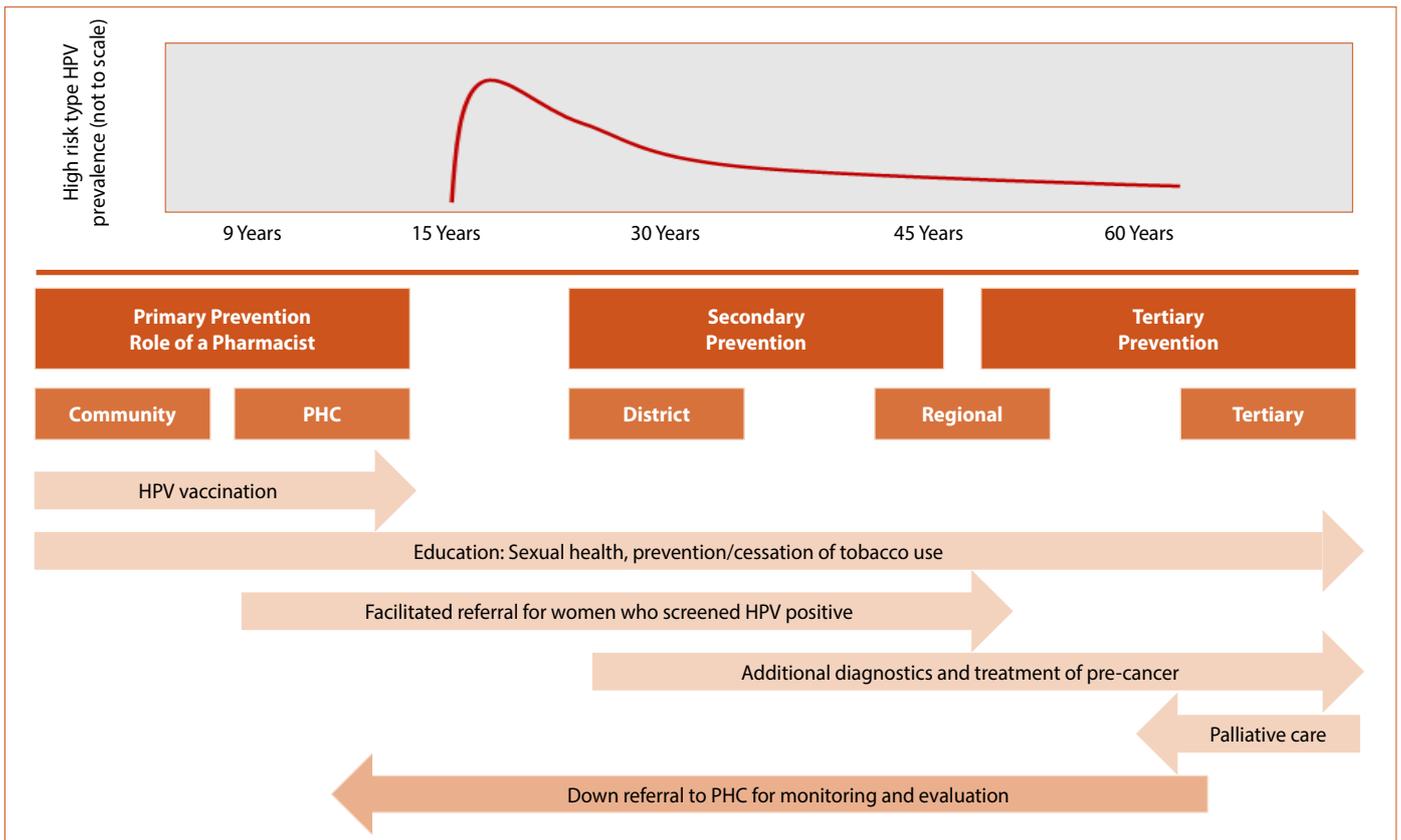


Figure 2: Integrated approach for cervical cancer prevention and management at various levels of care in South Africa<sup>1,14,15</sup>

**Vaccination strategies**

The majority of HPV vaccination strategies target young girls between the ages of 9 and 13 years, before they are sexually active and have high immune responses.<sup>23,24</sup> In the African region, 21 countries have a national HPV vaccination programme, with most, including South Africa, using a schools-based delivery platform targeting girls from the age of 9 years (see Table I).<sup>25</sup> Half of all countries with national HPV vaccination programmes (including South Africa), follow the two-dose schedule (prime-boost) using either the bivalent or the quadrivalent vaccine.<sup>14,26</sup> A third dose is recommended for older and immunocompromised women who received their second dose within five months after the first dose (see Table I).<sup>27</sup>

**HPV vaccination uptake**

South Africa introduced its national HPV vaccination programme in 2014 through the Integrated School Health Programme (National Department of Health [NDoH] and Department of Basic Education and Social Development), targeting girls in Grade 4 attending public sector schools.<sup>14,22</sup> During the 2014 campaign, 86.6% of eligible girls in public sector schools were successfully vaccinated free of charge.<sup>29,30</sup> Since then coverage has been reported in numbers only, with second dose numbers being more than 20% lower than first dose numbers in 2014 and 2016.<sup>29</sup>

Girls attending South African private sector schools are not covered by the national HPV vaccination programme, thus must be vaccinated at their own cost and convenience.<sup>29</sup> A recent national online survey found that only 19.4% (80/413) of age-eligible private sector school girls had received HPV vaccination.<sup>31</sup> Low uptake might be attributed to system-related factors, parental concerns and vaccine hesitancy, resulting in missed or incomplete HPV vaccine doses.<sup>29</sup> Vaccine hesitancy (i.e. a delay in acceptance or refusal of an available vaccine)<sup>32</sup> is a global problem associated with negative mainstream and social media coverage, with misinformation about HPV vaccine safety and adverse events following immunisation affecting HPV vaccination uptake in many countries.<sup>29</sup> Although South African data on HPV vaccine hesitancy are lacking,<sup>29</sup> the online survey found that reasons related to vaccine hesitancy were largely responsible for low HPV vaccination acceptance by caregivers of private sector school girls.<sup>31</sup>

**Secondary prevention: Screening**

*Cervical cancer screening*

Secondary cervical cancer prevention mainly aims to detect and treat precancerous cervical lesions before they become invasive.<sup>33</sup> Screening modalities include visual inspection with acetic acid

**Table I:** Recommended vaccination schedule for both bivalent and quadrivalent HPV vaccines<sup>14,18,19,25,27,28</sup>

Administration schedule	First dose	Second dose	Third dose
Grade 4–7 girls	9–13 years	6 months later	NA
Girls > 15–45 years and immunocompromised women	Person's first encounter with healthcare professional	1–2 months later	1–3 months after second dose and 5 months after the first dose

(VIA) or visual inspection with Lugol's iodine, Papanicolaou (Pap) smear and HPV DNA testing. Pap smear (conventional cytology) as a screening method for cervical cancer has been critical in decreasing the cervical cancer incidence and mortality rates in high-income countries.<sup>34</sup> The South African Cervical Cancer Prevention and Control Policy recommends Pap smear as the screening method of choice for all women over 30 years of age, once per decade, for three decades. Other screening modalities endorsed by the policy include liquid-based cytology (LBC), which is more sensitive than Pap smear, and VIA.<sup>14,34</sup> The WHO on the other hand, recommends HPV DNA testing, which is the most sensitive of all methods, as the ideal cervical cancer screening method.<sup>28</sup> In South Africa, HPV DNA testing has been endorsed and included in guidelines for cervical cancer screening, but is not yet available in the public sector.<sup>14</sup>

Table II shows a summary of the different cervical cancer screening methods, including the advantages and disadvantages of each method.<sup>14,28,34-37</sup>

### Cervical cancer screening uptake

South Africa has seen a steady increase in cervical cancer screening coverage in the past decade, from 50.3% in 2012/13 to 65.1% in 2018/19 for women aged  $\geq 30$  years, which is an overall increase of 14.8% over this period.<sup>14,38,39</sup> Low screening coverage is associated with a number of factors, including lack of trained providers, attitudes of healthcare professionals, overburdened healthcare facilities, insufficient supplies, non-adherence to treatment, high costs of testing, cultural beliefs, inadequate funding of the programme and women not being comfortable with having a sample taken for a Pap smear.<sup>40-42</sup> Factors such as being married, visiting healthcare professionals regularly, being knowledgeable

**Table II:** Cervical cancer screening methods<sup>14,28,34-37</sup>

Method	Procedures	National Department of Health recommendations	Advantages	Disadvantages
<b>Pap smear (conventional cytology)</b>	Exfoliated cells collected from the transformation zone of the cervical face and endocervix, are spread on a glass slide, Pap stained and examined microscopically for cervical premalignant and malignant cells	<ul style="list-style-type: none"> <li>In the short term, method of choice</li> <li>HIV-negative women aged <math>\geq 30</math> years should have three free Pap smears during their lifetime</li> <li>Interval for low-risk women: 10 years; 3 years when abnormality detected and treated</li> <li>Interval for high-risk women*: Screen at diagnosis, then every 3 years if negative, or annually when abnormality detected</li> </ul>	<ul style="list-style-type: none"> <li>Affordable</li> </ul>	<ul style="list-style-type: none"> <li>Resource intensive</li> <li>Laboratory-based</li> <li>Requires trained personnel to prepare, stain, and analyse the slides</li> <li>Multiple clinic visits before commencement of treatment</li> <li>Low to moderate sensitivity</li> </ul>
<b>Liquid based cytology (LBC)</b>	Cells collected in a liquid medium to make a suspension producing a thin layer of cells, are transferred to a glass slide, Pap stained and examined microscopically	<ul style="list-style-type: none"> <li>In the longer term, preferred over Pap smear</li> <li>Not yet phased in due to limited resources</li> <li>Interval: As for Pap smear</li> </ul>	<ul style="list-style-type: none"> <li>The sample can be used to perform primary HPV test and triage tests</li> <li>Likely to reduce the number of false-negative test results</li> </ul>	<ul style="list-style-type: none"> <li>There might be blood, and inflammation due to the collection method</li> <li>Endocervical part of the combi brush can be covered with mucous, thus hindering the pick-up of endocervical cells</li> </ul>
<b>Visual inspection with acetic acid (VIA)</b>	Acetic acid (5% diluted) is applied directly to the cervix and visually inspected for colour change (whitening)	<ul style="list-style-type: none"> <li>For use in low-income settings pending the national scale up of LBC and roll-out of HPV DNA testing</li> <li>Interval: As for Pap smear</li> </ul>	<ul style="list-style-type: none"> <li>Can be offered at primary healthcare level by non-physician health workers</li> <li>Uses minimal commodities and supplies, making it affordable</li> <li>Laboratory support not required</li> <li>Results are available immediately</li> <li>Treatment can be offered during the same visit</li> </ul>	<ul style="list-style-type: none"> <li>Requires well trained personnel, results are subjective in nature</li> <li>Reliability and validity are concerns</li> <li>Lower sensitivity (more specially in postmenopausal women) as compared to HPV test</li> </ul>
<b>HPV DNA testing</b>	Cells of the cervix are collected by a healthcare worker or by the woman herself using a brush or a swab and cells are analysed for HPV DNA using polymerase chain reaction assays in the laboratory (GeneXpert technology used in South Africa)	<ul style="list-style-type: none"> <li>Point-of-care testing highly recommended by the NDoH using GeneXpert when available</li> <li>Cells can be transported to laboratories with GeneXpert machines</li> <li>Interval: As for Pap smear</li> </ul>	<ul style="list-style-type: none"> <li>High sensitivity compared to Pap smear</li> <li>Allows self-sampling</li> </ul>	<ul style="list-style-type: none"> <li>Only routinely offered in the private sector</li> <li>Not yet widely available in the public sector as part of the national screening programme</li> <li>Specialised equipment needed (only 250 GeneXpert machines available in South Africa in 2017)</li> </ul>

\*High-risk women: HIV-positive women regardless of whether or not they are receiving antiretroviral treatment; organ transplant recipients; those with immunocompromising diseases or on chronic immunosuppressive treatment.

about cervical cancer and having low perceived barriers to cervical cancer screening, predicted better screening uptake.<sup>43</sup>

## Role of the pharmacist in cervical cancer prevention

Pharmacists are trusted healthcare professionals who are well positioned within communities to play a significant role at primary healthcare level to improve HPV vaccination and cervical cancer screening uptake. They can become partners in cervical cancer prevention by introducing prevention measures such as education and communication, to dispel myths and address concerns regarding HPV vaccines, provide access to HPV vaccination services and coordinate the completion of HPV vaccination series.<sup>44</sup> For example, pharmacists can establish caregivers' current knowledge regarding cervical cancer prevention and HPV vaccination, create a shared interest and use various media to provide short health promotion sessions and to address barriers such as culture, literacy and hesitancy.<sup>22,45</sup> This is of particular importance for community pharmacies, considering that free HPV vaccination is not offered to girls attending private sector schools in South Africa. Should these girls not be vaccinated and subsequently contract HPV at a later stage, which could lead to cervical cancer, it will result in an additional burden to the South African healthcare system, particularly with the future National Health Insurance implementation. According to Good Pharmacy Practice in South Africa, vaccine services form part of the scope of practice of pharmacists and can be offered in pharmacies.<sup>46</sup> Research is also underway in the United States of America to evaluate how best pharmacists can further be integrated in HPV vaccination strategies.<sup>47</sup>

## Conclusion

Cervical cancer remains one of the biggest global public health threats, being one of the most common cancers amongst women, with low- and middle-income countries bearing the highest burden of incident cases and deaths. The WHO has drafted a comprehensive global strategy built upon three main pillars: improving HPV vaccination coverage, cervical cancer screening coverage and treating precancerous lesions. Much must still be accomplished to enable South Africa to reach the 90-70-90 goals by 2030 set by the WHO (90% full HPV vaccination coverage of girls aged  $\leq 15$  years; screen at least 70% of women aged  $\leq 35$  years [and again at 45 years] with a high-performance test; and treat or manage 90% of all women with precancerous or cancerous cervical lesions).

Pharmacists can play an important role in assisting the country to reach these goals, since they are trusted healthcare professionals in direct contact with patients in communities. They are thus well positioned to improve access to vaccination services and address patients'/caregivers' concerns that might result in vaccine hesitancy and fear of cervical cancer screening, in order to improve uptake of primary and secondary cervical cancer prevention interventions.

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