JIMKI : JURNAL ILMIAH MAHASISWA KEDOKTERAN INDONESIA

TINJAUAN PUSTAKA

THE ROLE OF IMPLEMENTING AN HPV VACCINATION PROGRAM WITH OPTIMIZING CERVICAL CANCER SCREENING AND TREATMENT AS AN AMBITIOUS STRATEGY TO REDUCE CERVICAL CANCER PREVALENCE IN DEVELOPING COUNTRIES: A LITERATURE REVIEW

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Riwayat Artikel

Diterima: 17-07-2024
Selesai revisi: 31-03-2025

DOI :

10.53366/jimki.v11i3.780

ABSTRACT

Background: Cervical cancer is the fourth most common type of cancer in women in the world, with 94% of total deaths worldwide occurring in developing countries in 2022. In response to this problem, WHO initiated a movement to eliminate cervical cancer, known as the 90-90 strategy, through implementing vaccination programs and optimizing screening and treatment for cervical cancer cases. This literature review aims to describe the role of these strategies in eliminating cervical cancer, especially in developing countries. **Methods:** Literature was searched using search sites such as Google Scholar, Science Direct, ResearchGate, and NCBI. Inclusion and exclusion criteria were used to eliminate unrelated literature to obtain 36 literatures. **Discussions**: HPV vaccination has been proven to provide protective benefits in reducing the incidence of neoplastic lesions and shows a relatively decreasing trend in the group receiving the vaccine. Modelling studies show that successful implementation of the WHO 90-70-90 intervention by 2030 will reduce the incidence of cervical cancer to 0.7 per 100,000 women and the death rate to 0.2 per 100,000 women in all developing countries. **Conclusion**: The implementation of the HPV vaccination program with the optimization of cervical cancer screening and treatment is believed to be a solution modality to reduce morbidity and mortality rates due to cervical cancer in the world, especially in developing countries.

Keywords: “Cervical cancer [MeSH]”, “Cervical cancer screening”, “Cervical cancer treatment”, and “HPV vaccine”.

e-ISSN : 2721-1924
ISSN : 2302-6391

1. INTRODUCTION

Cervical cancer is cancer cause by human papillomavirus (HPV) infection. According to data from the World Health Organization (WHO), cervical cancer is the fourth most common type of cancer in women in the world with around 600,000 new cases and around 350,000 deaths in 2022. Not only that, of the 350,000 deaths due to cervical cancer in 2022, around 94% occur in low and middle-income countries. This occurs due to gaps in access to vaccination, screening and treatment services, risk factors including HIV prevalence, as well as social and economic determinants[1].

HPV infection is a common sexually transmitted infection that can affect the skin, genital area, and throat. Typically, it takes 15–20 years for abnormal cells formed from exposure to infection to become cancer cells, and can occur more quickly (5–10 years) in women with weakened immune systems, such as HIV[2]. Therefore, there is a need for a prophylactic agent to reduce the rate of infection transmission as well as an early diagnosis strategy that can speed up treatment to reduce the death rate due to cervical cancer.

Lei et al.'s study stated that the cumulative incidence of cervical cancer occurred at 47 cases per 100,000 women who had received vaccination and 94 cases per 100,000 women who had not received vaccination[3]. Another study states that screening every 3 years can reduce the incidence of cervical cancer by 51-55% while screening every 5 years can reduce the incidence of cervical cancer by 4.2-4.8% lower than screening every 3 years[4].

Eliminating cervical cancer as a public health problem is a WHO global strategy, which is defined as reducing the number of new cases each year to <4 per 100.000 women. This figure was achieved by setting three targets by 2030 for all countries in the world, namely 90% of girls receiving the HPV vaccine at the age of 15 years, 70% of women having high-quality screening tests at the ages of 35 and 45 years, and 90% of women with the disease cervix receiving treatment[1].

Referring to the problem of the high number of cases and deaths due to cervical cancer as well as the potential for vaccination and early screening to reduce the burden of this number, therefore, this literature review will discuss the role of implementing the HPV vaccination program by optimizing cervical cancer screening and treatment as an ambitious strategy to reduce the prevalence of cervical cancer.

2. METHODS

The method used in writing this literature review is a literature review using the keywords "Cervical cancer [MeSH]", "Cervical cancer screening", "Cervical cancer treatment", and "HPV vaccine". The literature search was carried out using search engines such as Google Scholar, Science Direct, ResearchGate, and NCBI. The inclusion criteria for this literature search were in vitro and in vivo experimental research journals, cohort studies, comparative comparative analysis studies, and review studies with publication requirements within the last 10 years. The exclusion criteria used were studies that had not been completed at the time of the literature search, studies that could not be accessed in full paper, and studies that used languages other than English and Indonesian. From the results of the literature search, the evaluation of inclusion and exclusion criteria was carried out by assessing the title and abstract as a first step, and then the full text was reviewed to see if there was a correlation between keywords in the journal so that it could support writing descriptions or analysis in this literature review. From the results of a literature search using inclusion and exclusion criteria, 36 journals were obtained, which were used in this work.

3. DISCUSSION

Cervical Cancer Epidemiology

Globally, cervical cancer continues to be one of the fourth-most common cancers in women. In 2020, the Global Cancer Observatory estimates the emergence of 604,000 new cases of cervical cancer worldwide and 342,000 deaths each year[5]. Most of the new cases and deaths (85% and 90%, respectively) occurred in low- to middle-income countries[6].

Regional differences in the cervical cancer burden are related to

inequalities in access to vaccination, screening and treatment services, risk factors including HIV prevalence, and social and economic determinants such as sex, gender biases and poverty. Women living with HIV are 6 times more likely to develop cervical cancer compared to the general population, and an estimated 5% of all cervical cancer cases are attributable to HIV. Cervical cancer disproportionately affects younger women, and as a result, 20% of children who lose their mother to cancer do so due to cervical cancer. Meta-analysis in 2021 of 24 studies shows that women living with HIV have a six-fold higher risk of developing cervical cancer relative to their counterparts without HIV. Globally, an estimated 6% of new cervical cancer cases in 2018 were diagnosed among women living with HIV and 5% of all cases were attributable to HIV infection. In both relative and absolute terms, the southern and eastern Africa UN subregions bear the largest share of this burden, with a respective 64% and 27% of women with cervical cancer living with HIV in these regions[7].

Cervical Cancer Pathophysiology

HPV infection begins when the virus enters through a wound or microabrasion in the mucosa and infects the basal cells of the squamous epithelium[8,9]. HPV will enter the cell and will integrate its genome into the host cell, which causes destabilization of the host cell genome and induces epigenetic programming that triggers excessive expression of the E6 and E7 genes[10]. Expression of E6 will trigger degradation of p53, which results in loss of control of cell apoptosis, inhibition of angiogenesis, and loss of the cell's ability to enter the resting phase, or G0 phase[9,11]. Meanwhile, E7 expression will cause the degradation of retinoblastoma (PRB), which functions in response to DNA damage and binds to cyclin-dependent kinase inhibitors so that cells enter the S cycle out of control[9,11,12]. This mechanism induces epithelial cell dysplasia[13].

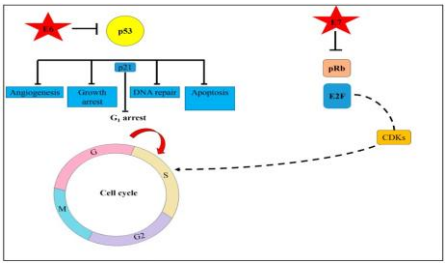

Figure 1. Schematic diagram illustrating the role of HPV oncoproteins in cervical carcinogenesis [11].

Normally, when a viral infection occurs, the immune system will recognize and eliminate the virus, which is played by macrophages, dendritic cells, and NK cells by expressing Toll-like receptors (TLRs), which will then activate the transcription factor-like nuclear factor kappa B (NF-κB). and interferon response factor-3 (IRF3) to produce cytokines.[11] However, overexpression of E6 and E7 will inhibit Toll-like receptors (TLRs), which activate interferon response factor-3 (IRF3)[11,13]. E7 specifically inhibits the production of the cytokine IFN-ß, which plays a role in the antiviral mechanism, while E6 plays a role in inhibiting TLR through the YAP-1 mechanism[13]. Meanwhile, overexpression of E5 inhibits the formation of immunoproteasomes, which function in forming MHC I and inhibiting antigen presentation[14]. This mechanism causes HPV infection to become persistent and supports the development of cancer cells.

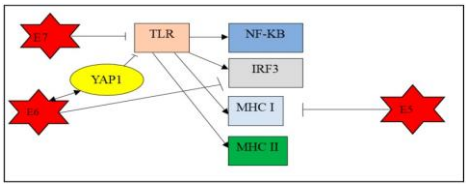

Figure 2. Molecular mechanisms involved in HPV infection[11].

Current Treatment for Cervical Cancer

The incidence of cervical cancer can be prevented by vaccination and screening for precursor lesions, followed by good therapy and evaluation. Screening aims to detect cancer early, so that patients receive faster therapy and reduce the risk of death from cervical cancer[1].

a. Promotive and Preventive

According to the WHO, a woman should be screened for cervical cancer every 5 – 10 years, starting at the age of 30, while women who suffer from HIV should start screening at the age of 25.[1] From 1900 to 2020, there have been many advances in cervical cancer screening following the rapid development of technology, as summarized in Figure 3[15].

Figure 3. Development of cervical cancer screening in general[15].

Currently, cervical cancer can be detected early. This can be done with several approaches for cervical cancer screening, namely conventional and liquid-based cytology (pap smear), visual inspection with acetic acid (VIA), and HPV nucleic acid testing (including HPV DNA and RNA testing). Cervical cancer screening using the cytology method is still considered effective and widely used. However, conventional cytology analysis has the possibility of obtaining unsatisfactory slide results, whereas liquid-based cytology is considered better in quality and provides the opportunity to perform molecular and cytological tests with one sample.[16] In addition, the VIA method is a cost-effective alternative by identifying color changes after the application of 3-5% acetic acid to the cervix. VIA is also the main choice because it is accurate and safe, especially in countries with limited access to health services[17].

In recent years, researchers have studied HPV testing as a primary screening modality. The advantage of using HPV testing as primary screening is that it can be carried out by patients through self-swabbing with sensitivity and specificity commensurate with sampling by medical experts. [17] In addition, several previous cohort studies concluded that HPV testing (including HPV DNA and RNA testing) is more effective in detecting pre-cancer and reducing the incidence of cervical cancer when compared with cytology analysis and/or VIA. In addition, the HPV mRNA test has been shown to have comparable cross-sectional sensitivity and higher specificity than the HPV DNA test to detect cervical cancer stage CIN3+[16].

One method of preventing cervical cancer is implementing the HPV vaccination program. There are three vaccines recognized by the Food and Drug Administration (FDA), namely Gardasil, Gardasil 9, and Cervarix. These three vaccines protect against HPV genotypes 16 and 18, which cause 70% of cervical cancer incidents. The Centers for Disease Control recommends vaccination for men and women at ages 9–26, while the FDA recently approved HPV vaccination up to age 45. In addition, recent research studying the carrageenan compound extracted from red algae is known to play a role in preventing the binding of HPV virions to body cells. Results from in vitro studies show that carrageenan actively fights various HPV genotypes that can cause cervical cancer and genital warts. Currently, current research is focused on developing therapeutic HPV vaccines to treat the large portion of the population suffering from high-risk HPV infections. A therapeutic HPV vaccine is needed to cover the shortcomings of the prophylactic HPV vaccine, which does not have a healing (therapeutic) effect on existing infections and lesions[17].

b. Currative and Rehabilitative

The treatment approach and prognosis of cervical cancer depend greatly on the stage of the disease when the patient is first diagnosed. Patients with cervical cancer have a life expectancy of up to 5 years, ranging from 90% if diagnosed immediately to 20% if the diagnosis is made late or metastases have occurred[18]. In early stages and without metastases, treatment options include radical hysterectomy or radical trachelectomy, pelvic lymphadenectomy, and concurrent chemotherapy and radiation therapy. For cancer that has metastasized, treatment focuses more on systemic therapy[19].

Lymph node metastasis is the single most important prognostic factor in clinically early-stage cervical cancer patients. In addition, the status of the lymph nodes is also important for planning additional treatment programs. Therefore, pelvic lymph node dissection (PLND) is one of the important procedures in radical surgery for cervical cancer[20]. However, PLND has the side effects of lower urinary tract dysfunction

(70%–85%) and sexual dysfunction (66.67%)[21,22]. Taking effective measures to prevent pelvic organ dysfunction is important to improve rehabilitation outcomes and patient quality of life.

Immunotherapy is a cancer treatment strategy that aims to modify and recruit the body's immune system to more effectively and specifically target cancer cells. The development of immunotherapy is one area that offers hope for improving treatment and survival for cervical cancer patients. Currently, the use of immunotherapy for the treatment of cervical cancer is still being actively investigated, although to date only one immunotherapy drug (pembrolizumab) has been approved by the FDA as an anti-cervical cancer immunotherapy drug[18].

An immunotherapy approach that can also be used is adaptive cell therapy (ACT). This strategy is generally tailored to the individual patient and involves eliminating both tumor-reactive and tumor-infiltrating lymphocytes. Then, in vitro engineering will be carried out to produce lymphocytes that are reactive to the tumor and will be multiplied in number so that they are much higher[23]. However, the efficacy of ACT is generally limited to solid tumors[24].

Impact of Implementing The HPV Vaccination Program

Vaccines are the most effective public health intervention in preventing morbidity and mortality due to infectious diseases. Vaccines are also the most cost-efficient health intervention[25]. HPV vaccination is the most efficient approach to preventing and reducing cervical cancer morbidity and mortality rates, especially in developing countries and regions with low cervical cancer screening rates[26].

The HPV vaccine is a non-infectious recombinant vaccine containing viral-like particles (VLP) obtained from the main capsid protein (L1), which is highly immunogenic[27,28]. The VLPs in the vaccine cause a stronger humoral reaction against L1 than natural HPV infection by inducing high-quality and sustained titers of specific serum antibodies (mostly IgG) against HPV L1 and inducing the production of specific serum antibodies (anti-L1 IgG) in large quantities. approximately 10 to 100-fold higher than natural infection within 1 month after the last dose, thereby

providing protection against persistent infection and pre-malignant neoplasia[27,29]. This is because adjuvant components in vaccines such as aluminum hydroxide and monophosphoryl lipid A (MPL) increase antibody production and also encourage the formation of memory B cells[29].

Based on the results of previous studies, it shows that, compared with women who received HPV vaccination, the risk of cervical cancer was much higher, ranging from two to twelve times greater in women who did not receive vaccination[30]. Another study states that the cumulative incidence of cervical cancer is 47 cases per 100,000 women who have received vaccination and 94 cases per 100,000 women who have not received vaccination. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51[3]. This shows that vaccination is quite effective in reducing the risk of cervical cancer incidence due to HPV virus infection.

Impact of Implementing Early Detection for Cervical Cancer

Cervical cancer screening plays an important role in the early detection and therapy of cervical pre-cancer so that it can reduce cervical cancer morbidity and mortality rates. A cohort study predicts that the incidence rate of cervical cancer is 104 cases per 100,000 people, while the mortality rate due to cervical cancer reaches 100 cases per 100,000 people. By screening every 3 years, you can reduce the incidence of cervical cancer cases by 51 – 55%, while screening every 5 years can reduce the incidence of cervical cancer cases by 4.2 – 4.8%, which is lower than screening every 3 years[4].

Previous research considered the impact of advancing screening initiation to age 20 and found that earlier screening would increase the number of lifetime cervical screening tests, reduce mortality by 4.3%, and improve pre-cancer treatment by 4.2–12.8% compared with starting screening at age 25 years[4].

Apart from that, other research compares the benefits and harms obtained from each screening method (table 1)[16].

Table 1. Comparative Effectiveness of the Established Cervical Cancer Screening Methods[16].
*The symbol >> indicates that the benefits of testing clearly outweigh the harms, the symbol > that the benefits outweigh the harms, and the symbol ≥ that are benefits do not outweigh the harms. VIA denotes visual inspection with acetic acid.
*Cotesting involves screening and cytologic analysis combined

Methods Compared	Comparison of angesBenefit-to-Harm Balances
HPV DNA testing vs. VIA	HPV DNA testing >> VIA
HPV DNA testing vs. cytology	HPV DNA testing > cytology
HPV DNA testing vs. cotesting*	HPV DNA testing ≥ cotesting

Based on table 1, it can be seen that HPV DNA testing has a significant positive impact compared to VIA, cytology, and cotesting[16]. In addition, WHO initiated the implementation of the '90–70–90' strategy, which is targeted at 2030 for all countries, so that it is hoped that the annual incidence of cervical cancer cases can fall to 4 cases per 100,000 people. The targets to be achieved using this strategy are vaccination with the HPV vaccine on 90% of girls aged 15 years, screening with a high-performance test on 70% of women aged 35 years and when the woman is 45 years old, and 90% of women identified as being infected with pre-cervical cancer having access to adequate therapy and care[4].

The Correlations Between Implementing the HPV Vaccination Program and Optimizing Cervical Cancer Screening and Treatment in Reducing Cervical Cancer Morbidity and Mortality Rates

HPV vaccination has been shown to provide protective benefits in reducing the incidence of neoplastic lesions. Pei et al.'s cohort study stated that the incidence of cervical adenocarcinoma increased from 1975 to 2019, but the increasing trend only occurred in the group that did not receive the HPV vaccine, while the trend was stable and relatively decreased in the group that received the vaccine[32]. A comparative modeling analysis study in 78 low- and lower-middle-income countries estimates that there will be a median reduction in cervical cancer incidence after a consistent focus on age-specific female-specific HPV interpretation from 19.8 to 2.1 cases per 100,000 women per year in the next century, preventing 61.0 million cases over the period[33].

Cervical screening for early detection of cancerous lesions has been proven to have a positive impact on morbidity and mortality due to invasive cervical cancer[34]. Landy et al.'s study proved that screening within 3 years reduced the likelihood of non-local cancer by 83% and stage I cancer by 48% compared to women who did not undergo screening within 5 years[35]. A previous modeling study estimated that implementation of twice-lifetime HPV-based screening in women aged 35 years and 45 years in developing countries would prevent 12.5–13.4 million cases in the next 50 years[36].

Based on existing data, it is proven that HPV vaccination and cervical screening are important parts in the management of reducing morbidity and mortality rates due to cervical cancer. Meanwhile, early screening can make treatment steps timely and effective for precancerous lesions and cervical cancer. Therefore a modeling study shows successful implementation of the WHO 90-70-90 intervention by 2030 will reduce the incidence of cervical cancer to 0.7 per 100,000 women and the mortality rate to 0.2 per 100,000 women in all developing countries[34].

4. CONCLUSION

The existence of the WHO 90-70-90 three-intervention strategy through the implementation of the HPV vaccination program with the

optimization of screening and treatment for cervical cancer is believed to be a solution modality for reducing morbidity and mortality rates due to cervical cancer in the world, especially in developing countries. Several cohort studies have shown stable and relatively decreasing rates of cervical cancer cases and deaths in groups receiving HPV vaccination. Other cohort studies also show the positive impact of cervical screening in increasing the discovery of precancerous lesions and cervical cancer so that it can speed up treatment and improve the prognosis of this group. In addition, recent modeling analysis studies also show positive estimates for the implementation of the elimination program. The findings in this literature review can be a strong reason for WHO to accelerate and strengthen cervical cancer elimination strategies and overcome compliance challenges from countries around the world that have committed.

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