

Stemming the Tide of Cervical Cancer through Human Papillomavirus Vaccinations

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ABSTRACT

The trail of repeated bouts of HPV infections on the heel of Cervical Cancer is akin to the relationship between risky behavior and sexual activities. The causal relationship between HPV and Cervical Cancer has been consistently buttressed by overwhelming evidence from various studies all over the world. However, while the advanced nations of the world have made tremendous progress in the fight against Cervical Cancer and HPV infections, a cruel testament to the failure of governments and leaderships in taking ownership and responsibility for National Health Initiatives is attested by the high and increasing mortality rate arising from Cervical Cancer in the low- and middle-income countries. The gross disparity and inequities in healthcare services, access and outcomes has remained the stark reality of the low- and middle-income countries of the world. The low level of knowledge and misconceptions about Cervical Cancer, HPV, and the HPV vaccine are among several factors confounding the outcome of Cervical Cancers in the developing countries of the world. Cervical Cancer is preventable, and its associated morbidity, economic cost, and mortality are all avoidable only if proactive steps at mitigating infections with HPV are taken. In addition, appropriate initiatives aimed at screening and vaccinating vulnerable populations need to be duly implemented by governments and all stakeholders. Cervical Cancer can be prevented with an effective Cervical Cancer screening program, diagnosis of pre-malignant lesions and their treatment, and a well-structured HPV Vaccination Programs.

Key Words: Cervical Cancer, HPV, Vaccination, Sub-Saharan Africa, Health inequalities

1.0 INTRODUCTION

Cancer is one the leading causes of death globally. According to data reports by Globocan (2018), ^[1] there were over 18 million reported cases of cancer and well over 9.5 million reported deaths resulting from cancer in 2018 alone. Cancer as a disease can affect different parts of the body, causing cells at the affected parts to grow in an abnormal manner. ^[2] Certain cancer types such as breast cancer, colorectal cancer, endometrial cancer, lung cancer, cervical cancer, skin cancer, and ovarian cancers are usually found in women. ^[3] According to the WHO (2019), ^[4] Cervical Cancer is the fourth most common form of cancer in women with an estimated 570,000 incidence cases reported in 2018. This number represents about 6.6% of all cancer cases reported in women in 2018 with about 90% of all cervical cancer deaths recorded at low to middle-income countries of the world. ^[4] Cervical Cancer usually starts at the uterine cervix, the lower end of the uterus (the womb) which connects with the upper part of the vagina. ^[5] Very sensitive cells called the squamo-columnar cells are located at this end sometimes called the squamo-columnar junction. Malignant transformations usually arise from these cells especially when oncogenic agents such as the Human Papillomavirus (HPV) are constantly assaulting them. Almost all (99%) Cervical Cancer cases are associated with HPV infection, ^[6-7] and unlike the Human Immunodeficiency Virus (HIV) and Herpes Simplex Virus (HSV); HPV is the most common Sexually Transmitted Infection

(STI) among men and women. [8-9] There are over 100 strains of HPVs, with at least 13 strains able to cause cervical and other anorectal and oropharynx cancers. [9-10] Certain risk factors such as HIV infection, immune system suppression, tobacco smoking, chlamydia infection, obesity, long-term oral contraception use, multiple sexual partners, high parity rate, and early age at sex can all contribute significantly to the development of Cervical Cancer. [5]

Cervical Cancer is a global disease, but while the advanced nations of the world have made significant improvement in mitigating the impact and reducing the incidence of Cervical Cancer cases among their populations, the developing nations of the world in Africa, Asia, Latin America and the Caribbean still carries the largest burden of this disease. [11] While other regions of the world are also making steady improvement at reducing the incidence rates of cervical cancer among their populations, the rate of Cervical Cancer incidence on the African continent is still very high especially in Sub-Saharan Africa (SSA). [1,9,11] The relatively conservative sexual behavior of the Muslim dominated North African countries may not be unconnected to the low incidence rate of Cervical Cancer being reported from this region of Africa. [12] Cervical Cancer has been noted to be the leading cause of cancer related deaths among women in SSA. [13, 14] According to an estimate by the WHO, by the year 2030, nearly 90% of the global Cervical Cancer deaths will be in SSA. [14] The burden of Cervical Cancer in SSA is greatest in East and Southern Africa regions and the Western and Middle African regions respectively closely follow this in incidence rate. The region of Africa with the least burden of Cervical Cancer is Northern Africa. [1] The questions to be asked is why Cervical Cancer is still killing so much women in the world, especially in SSA, and what can we do to stem or mitigate the incidences of these disease? This article aims at emphasizing the need for the HPV Vaccination Initiatives towards mitigating

and stemming the tide of the global Cervical Cancer burden especially in the low- and middle-income countries. A review of relevant literature will help shed more light on the importance of the use of the HPV Vaccines in stemming the tide of the global Cervical Cancer pandemic.

2.0 Cervical Cancer

Cervical Cancer is one of the four most commonly occurring cancers in women globally, [4] and it is the number one most commonly occurring cancer among women in developing countries. [15, 16] As at 2008, the incidence of Cervical Cancer was estimated to be about 6.6% of the global cancer cases reports among women. [4] In developing countries where Cervical Cancer screening programs and services are either not available, too erratic, or sometimes too expensive and hence not easily accessible, the incidence of Cervical Cancer is reported to be steadily rising. [13, 14, 17] An estimated annual global death from this disease is projected to rise to about 443,000 by the year 2030. [14] About 90% of these deaths is projected to be in Africa due to several conflicting factors. The pathogenesis of Cervical Cancers usually starts with the metaplastic transformations of cells at the cervical squamo-columnar junction. When this metaplastic cells are persistently infected by the cancer-causing HPV strains, these epithelial cells eventually transforms into Metaplastic cells and then into pre-malignant lesions. When these lesions are not detected early, they typically progress to invading the epithelium of the cervix within 5 to 10 years. [17] Invasion of the basal epithelium and full-blown malignancies are however developed over the course of decades at which point the cancer might have metastasize to other cells and organs of the body. The survival rate at late detection of Cervical Cancer is usually very low and this explains the large burden of mortality of this disease experienced at low and middle-income countries. Due to the unavailability of screening, diagnostic, treatment and palliative facilities at these low resource settings, many women with persistent

oncogenic HPV infections are not detected until it is too late.

Evidence of the causal relationship between high risk HPV and Cervical Cancer have been well documented. [10, 16-25] 70% of Cervical Cancer and Cervical Pre-malignant lesions are caused by two strains of the high-risk HPV (types 16 and 18). [6, 7] When adequate sample is taken for testing, the HPV DNA testing technique has been able to detect 95% to 100% HPV DNA in Cervical Cancer specimens, [15] thus increasing the odds ratio of the causal effects of HPV DNA in Cervical Cancer cases. Factors such as early age of sexual exposure, poverty, tobacco smoking, HIV infection, immune suppression, increased parity, long-term use of oral contraceptives, etc. [5] all contribute in no small way to the eventual development of Cervical Cancer.

Cervical Cancer usually arises from the cervix of the uterus and it's the fourth most common form of cancer found in women. [6, 7] It is a HPV-associated cancer, aside some other anorectal and oropharynx cancers also caused by HPV. [10] Cervical Cancer is a public health disease of global proportion, but while its incidence has steadily fallen in the developed nations of the world and while also steadily reducing in some developing nations of the world, the chances of increased incidence are steadily rising in SSA. [14] Cervical Cancer is primarily caused by repeated bouts of infection with the oncogenic HPV strains. [6-7, 10, 26] However, several factors such as early age of sexual exposure, poverty, tobacco smoking, HIV infection, immune suppression, etc. all contribute to the development of Cervical Cancer, the time lapse between HPV infection to the development of Cervical Cancer sometimes takes about 10 to 20 years. With a poor survival rate still being reported in SSA, Cervical Cancer related mortality among African women is still very high. [13] Cervical Cancer has long been thought to be a disease closely associated with poverty, but in recent times, the rate of Cervical Cancer deaths among high profiled and

wealthy elites has shown that our assumptions as regarding this disease in SSA may not be correct. Clearly, other social-cultural, religious, and level of awareness may be some of the factors influencing the poor survival outcome of this disease in SSA. Majority of people with HPV infection will usually not be aware of it as the host's immune system will naturally fight the infection and clear it off the body within two years of exposure. [10] However, when the host's immune system is compromised, this infection can become a problem. According to the CDC in 2018, [10] at least four of five women would have been infected with the HPV by the time they are age 50. In essence, the host's immune system can resolve or ward off the HPV infection; however, this self-resolution may be ineffective if the host's immune system is suppressed or if the impact of the host's risk factors outweighs the palliative and remedial effects of the host's immune system.

3.0 Human Papilloma Virus (HPV) in the Etiology Cervical Cancer

The close relationships between risky behavior and sex have long been associated with the transmission of sexually transmitted diseases. [27] HPV is strongly implicated in the carcinogenesis of the cervix, with some studies alluding to the impossibility of Cervical Cancer in the absence of sexually transmitted HPV infection. [22-23] The involvement of HPV as a necessary precursor in the development of Cervical Cancer has both the HPV viral infection, persistence of infection, host genetics and behavioral factors at its etiologic basis. The most carcinogenic strains of HPV include HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, and HPV68. [27] While HPV16 causes about 50% of all Cervical Cancer cases, HPV18 is mostly implicated in the cases of Adenocarcinoma of the Cervix. [27] Major factors that have been implicated in the increased possibility of a woman developing Cervical Cancer includes the following:

long-term use of oral contraception, multiparity, smoking, multiple sexual partners, regular unprotected sexual intercourse, infections with HIV, Chlamydia infection, herpes simplex virus type-2 (HSV-2) infection and other genetic and immunologic host factors. [28-30] According to the WHO (2019), HPV infection is mostly transmitted through sexual contact with most people being infected as soon as they started having sexual encounters. [6-7] In addition, HPV types 16 and 18 causes about 70% of all Cervical Cancer and Precancerous Cervical Intraepithelial lesions. [7]

4.0 Signs and Symptoms of Cervical Cancer

The signs and symptoms of Cervical Cancer may include any or a combined observation of the followings: Vaginal bleeding after sex, bleeding or spotting between periods, abnormal vagina bleeding, vagina bleeding after menopause, longer or heavier menstrual flows, pain during sexual intercourse, and abnormal vaginal discharges. [6-7, 26] The presence of any or a combination of these signs and symptoms may not necessarily infer the presence of Cervical Cancer; however, these symptoms and signs are clear indications warranting immediate Hospital or Gynecologic visits.

5.0 Cervical Cancer Diagnosis

Because screening tests are not diagnostic in nature, the first clue as to the incidence of a Cervical Cancer case is usually through Pap smear (Cytology). When women presents with abnormal Pap smear results or with the classical signs and symptoms of Cervical Cancer, either or a combination of the following diagnostic tests can be requested: a colposcopic biopsy, an endocervical curettage or scraping, or a cone biopsy. All these methods involve the removal of a portion of the pre-cancerous or cancerous tissue for proper histological examination. Histological examinations help to diagnose and stage the extent of the cancer growth on the cervical epithelium. [31] In women with confirmed Cervical Cancer, the attendant Gynecologic Oncologist may further request for such

tests as Cystoscopy, which involves the examination of the bladder and urethra for any malignant growth. Proctoscopy may also be requested, which involves the medical examination of the rectum for any malignant growth. Further tests to confirm the extent of spread of the cancer cells beyond the cervix could include Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET scan), and Intravenous Urography. [31] Cervical Cancer when diagnosed is usually classified into stages, which defines the extent to which the cancer cells have spread in the body. The stages ranges from 0, I, II, III and IV. The lower the staging, the less the spread of the cancer cells and the better the chances of survival. Also the higher the staging, the more the spread of the cancer cells to other organs of the body and the lesser the chances of survival. However, the WHO has developed guidance for the assessment and referral of suspected cases of Cervical Cancer especially in low-resource settings. [32]

6.0 Prevention of Cervical Cancer

The high morbidity and mortality rate of Cervical Cancer has made it a disease of global public health importance. Several initiatives from major world health bodies and national primary preventive programs have gone a long way in helping to reducing the scourge of the initial Cervical Cancer pandemic especially. The impacts of these initiatives are most evident in the drastic reduction in the incidence and mortality rate of Cervical Cancer cases especially in the advanced nations of the world. Aside taking basic steps such as avoiding risky sexual behaviors, avoiding smoking, avoiding the use of oral contraception for a long period of time, practicing safe sex, and eating nutritious food among many others, several measures can be taken at preventing Cervical Cancer; and in effect, reducing the incidence and mortality rates of Cervical Cancer among populations. These measures include:

6.1 Cervical Cancer Screenings

Because most women with Cervical Cancer could be without symptoms, it is most essential therefore, that all women at risk of developing Cervical Cancer be thoroughly screened for this disease. The primary purpose of screening is to detect the pre-malignant or pre-cancerous changes that may lead to the cancer stage if not detected and treated immediately. [32] The essence of screening is to provide an effective follow up for the treatment and possible management of any abnormality identified in the cervical cells. Cervical Cancer screening is done in either of four (4) ways that includes the traditional Pap smear (Cytology) which involves the collection of cervical cells and microscopically examining them for any malignant morphological changes. HPV DNA testing also involves the collection of cervical cells and testing those cells for high-risk HPV strains. Another screening method is the “Cotesting” which involves the use of the same cervical cells samples for both the Pap smear and HPV testing. The fourth screening method involves the use of “Visual Inspection with Acetic Acid (VIA)” and “Visual Inspection with Lugol’s Iodine (VILI)”. [18, 32] Usually after screening, women with abnormal screening results are followed up immediately with further confirmatory diagnostic tests and an appropriate treatment. The ultimate aim of Cervical Cancer screening is achieved when the largest population of at risk women are reached and screened with a high quality screening method. In order to avoiding the unnecessary physical and psychological stress caused to clients whose HPV infections would have been naturally resolved by their immune system without any intervention, the following screening intervals have been recommended for the at risk age groups: (1) Women between the ages of 21 and 29 should be screened with Pap Smear once every three years. (2) Women between the ages of 30 and 65 should be screened every five years with any of the available screening methods.

Women with high Cervical Cancer risk factors should screen more frequently. [26, 31]

6.2 HPV Vaccination

More than any other cancer diseases, Cervical Cancer has glaringly portrayed the persistent challenge of health inequalities in the world. [4, 9, 13] Because of the advantage of vaccination gives against most infectious diseases, and the proven efficacies recorded in the use of HPV vaccines at preventing Cervical Cancers in women, [33-34] concerted efforts must now be made by all governments at stemming the tide of Cervical Cancer through massive investment in the use of this primary preventive approach. With about 99% of all Cervical Cancer cases associated with HPV infections, the use of HPV vaccines such as Gardasil-9®, Gardasil®, and Cervarix® for the primary prevention of Cervical Cancers have become all too important. [35] In a bid to ensuring the universal coverage of the HPV Vaccination and building on the efforts at removing the limitations of health disparities and inequities among populations, much still needs to be done at ensuring the proper integration of HPV vaccinations into the various National Immunization Programs. The consolidated gains made in the Expanded Programs on Immunization (EPI) in various countries can be leveraged to making HPV vaccines available to children. [36] Getting adolescent and the adult populations vaccinated however might be a challenge as large HPV Screening exercises would need to be carried out before vaccinating the eligible candidates. Also, because the life-long efficacy of these vaccines have not been validated through large population-based Randomized Control Trials, much still needs to be done to determining the dosage of administration, route of administration, immunological response rates, duration of protection, and the need for booster doses especially in children. [36] For the adolescent and adult populations, the use of HPV testing should be largely encouraged as the primary screening test instead of the current use of cytology. Due to the narrowed and

limited Public Health budgets available, especially in developing countries, cytology screening should be reserved for clients with a positive HPV Testing results. [37] This approach is more cost-effective and could help create a longitudinal outcome tracking system for both vaccinated clients and those requiring immediate treatment. In 2018, the WHO made a global call towards the elimination of Cervical Cancer through HPV vaccination, Cervical Cancer screening and treatment of pre-malignant cervical lesions, and the management of Cervical Cancer cases. [7]

7.0 Challenges with HPV Vaccinations

Cervical Cancer poses a very critical Public Health challenge to Sub-Saharan African (SSA) countries, where it is the number one cause of female cancer deaths. [38] However, implementing HPV vaccination at this region has being met with stiff challenges ranging from socio-cultural belief, logistical difficulties and lack of proper financing. [38] It is of note that while most developed countries have a high uptake of the HPV vaccine, countries like the United States still have many challenges associated with the low uptake of the HPV vaccine. [39] This challenges ranges from misconceptions about HPV and the HPV vaccine and socio-economic status. [35] Myriads of challenges hampering the implementation of HPV vaccination also abounds in the Middle East and North Africa, where there are no organized Cervical Cancer screening systems in place; [40] thus resulting in most Cervical Cancer cases being diagnosed at advanced stages of the diseases. Other factors hampering the implementation of HPV vaccination include cultural and religious sensitivities, weak health systems and infrastructures, political instability and financial constraints, and limited Public Health funding amid competing priorities. [40] In Europe, challenges with HPV vaccination uptake were associated with concerns about the long-term effectiveness and possible side effects of the vaccine. [41] Despite these

myriads of issues and challenges, studies have shown that education can be used as a tool towards influencing the acceptance of the HPV vaccine. [35] In addition, the provision of the right information to clients by healthcare workers would go a long way in helping to improving the acceptance of HPV vaccination. [42] Massive Public Health education on issues relating to Cervical Cancer and its causal relationship with HPV is needed towards the successful implementation of the HPV Vaccination programs among all age groups. Governments needs to invest more into this primary preventive initiative, and donor agencies and supporting partners all need to forge a formidable front at combating the menace of this deadly disease especially in Low and Middle-income countries. International efforts at mitigating the impact of this disease through the Global Alliance for Vaccine and Immunization (GAVI Alliance) are also strongly encouraged. Large Pharmaceutical companies producing these vaccines could also be supported towards subsidizing the price of these vaccines to making them more affordable to poorer countries. The involvement of the men folks as active partners in the advocacy for HPV vaccination initiatives is also strongly advocated. [43]

8.0 CONCLUSION

The high mortality rate occasioned by Cervical Cancer especially in developing countries of the SSA and other low- and middle-income countries is a stark testament to the global health disparities found in the world today. The unavailability of adequate infrastructures at mitigating the impact of this disease in some parts of the world is also well known. [40] Tremendous gains has however being made especially in the developed nations of the world towards a drastic reduction in the number of mortality occasioned by Cervical Cancer. [44] These gains were made through the availability of adequate screening, testing, and diagnostics infrastructures. Early detection of this disease saves life; however, in low-and

middle-income countries with poor screening, testing, and diagnostics infrastructures, cases present late after the Cervical Cancer has metastasized to other parts of the body, which leads to low survival rate. [40,45] In the midst of this varied outcomes however, some governments in the developing countries are now taking responsibility and full ownership of the HPV Vaccination Initiative towards safeguarding the health of their populations. Countries, such as Rwanda has successfully implemented the HPV Vaccination Program through social mobilization, school-based delivery models, and developing initiatives at reaching out-of-school girls. [38] Quite a number of SSA countries are now becoming eligible for the GAVI Alliance support for the introduction of vaccines. Hence, with the successes in Rwanda serving as a pointer to the possibility of attaining success in this initiative even at low- and middle-income countries, it is high time governments and all stakeholders forge a common front in the fight against Cervical Cancer.

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