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HPV AND CERVICAL CANCER: INSIGHTS INTO PREVENTION, DIAGNOSIS, AND TREATMENT

P. Naina Varshini[1*], MD. Amatul Haq Kubra[2], K. Kavyasri[3]

[1,2,3]B. Pharmacy 4th year Students, Anurag Pharmacy Collage, Kodad, Telangana.

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***Corresponding Author: P. Naina Varshini**
B. Pharmacy 4th year Students, Anurag Pharmacy Collage, Kodad, Telangana.
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ABSTRACT

Background: This review examines the potential impact of HPV-16/18 vaccination on age-specific cervical cancer incidence in India. It considers conflicting risks, decreasing immunity, and vaccine coverage and efficacy. The study aims to understand the heterogeneity of vaccine responses, type-specific effects on other HPV types, and the duration of vaccination effects. **Objective:** The main objective of this review is to learn more about human papillomavirus-related cervical cancer by investigating its basic causes, diagnosis, therapy, prevention and analyzing women's across worldwide. **Methods:** The review, spanning 2013-2024, analyzed 14 articles published in electronic health sciences databases, specifically focusing on "India," "understanding," and "cervical cancer assessment." **Discussion:** The study found that 58.26% of women were aware of cervical cancer, with early sexual activity and marriage increasing the risk. Symptoms included intermenstrual bleeding and foul-smelling discharge. HPV infection significantly influenced cervical malignancies. Lack of knowledge in rural and urban areas suggests the need for programs to increase awareness. **Conclusion:** Every year, over 1.5 million Indian women receive cervical precancer therapy, with cervix screening for HPV. Adolescent HPV vaccination prevents over 90% of cervical malignancies and precancers.

KEYWORDS: Cervical Cancer, Oncology, Human Papilloma Virus, Preventive Strategies, Early Detection.

INTRODUTION

In the world, cervical cancer ranks fourth in terms of incidence and is the fourth biggest cause of cancer-related deaths among women, accounting for 341,831 fatalities and 604,127 new cases per year. Each year, it causes 77,348 fatalities and 1,23,907 new cases, making it the second most frequent cancer in India. A call to action to eradicate cervical cancer as a public health issue was issued by the World Health Organisation's (WHO) Director-General in May 2018. In 2019, a draft global strategy was created that included triple-intervention targets for scaling up screening, vaccination,

precancer treatment, and invasive cancer treatment in every nation.[1] The disease posing one of the leading causes of global deaths cancer will be responsible for taking 10 million lives during 2020. The global cancer numbers will increase in the coming years yet low- and middle-income countries (LMICs) will experience the most significant rise because these nations are currently struggling most in their cancer burden response.[2] Chronic infection with some oncogenic human papillomavirus (HPV) infections is the cause of the disease; high-risk strains 16 and 18 are typically involved.[3] Since cervical cancer has a lengthy pre-invasive phase, it is curable. Reducing mortality rates from cervical cancer in women requires early detection and treatment. Thankfully, cervical cancer has a protracted premalignant phase that allows for screening and treatment before the disease progresses to invasive cervical cancer.[4] Geographic variations in cervical cancer occurrences stem from disparities in healthcare facilities combined with risk factor prevalence and social economic influences in HIV rates and gender bias and poverty factors.[5]

Etiology of cervical cancer

The primary cause of cervical cancer originates from persistent infection with high-risk HPV types that result in almost all instances of the disease. Research suggests that women who use the contraceptive pill during five years or longer have an increased risk of cervical cancer especially when they carry HPV. The danger remains low even though pill use effectively lessens the probability of developing ovarian and uterine malignancies. The habit of cigarette smoking serves as a major cervical cancer risk factor for women.[6]

Contraceptive pill: Cervical cancer risk is marginally increased by the contraceptive pill.

Cervical cancer risk increases if the tablet is used for more than five years. As soon as you quit taking it, the elevated risk starts to decrease.

The danger is the same as for those who had never taken it after ten years.

The tablet may also slightly increase the risk of breast cancer. But it's important to know that taking the pill can reduce the chance of womb and ovarian cancers.[7]

Having many sexual partners or becoming sexually active early: Sexual contact with an HPV-positive individual almost invariably leads in the spread of HPV strains that cause malignancy. A woman's chance of contracting HPV is typically increased if she has had numerous sexual partners. This raises their chance of getting cervical cancer.[8]

A weakened immune system: The immune system weakness makes HPV infection and cervical cancer more likely to occur in women. Immunosuppressive medication use to treat organ transplant patients alongside individuals who have HIV create the main factors that result in immune system deficiencies. Cancer cells become difficult to fight and spread within the body when a person has a weakened immune system which also increases their risk of HPV infection.[9]

Human Papillomavirus (HPV) Infection: HPV stands as the main cause which leads to cervical cancer development. Cervical cancer has two main high-risk viruses among over150 viruses in this group known as HPV. HPV-16 and HPV-18 show strong associations with cervical cancer disease. Sexual contact serves as the primary means for HPV transmission.[10]

METHODOLOGY

We explored through the electronic health sciences databases PubMed, Google Scholar and web of sciences to find reviews that was published between 2013 to 2024. The search phrases that were used - "India," "understanding," and "cervical cancer assessment." 14 articles were included in the review based on the qualifying criteria.

DISCUSSION

Clinical stages of cervical cancer

Stage 0: The cells are precancerous.

Stage 1: The cancer cells have spread from the surface into the cervix's deeper tissues, potentially reaching the uterus and adjacent lymph nodes.

Stage 2: Although the cancer has progressed past the uterus and cervix, it has not yet reached the pelvic walls or the lower vagina. It might or might not impact the lymph nodes in the area.

Stage 3: Cancer cells are seen in the pelvic walls or lower vaginal region, and they may be obstructing the ureters, which are tubes that convey urine from the bladder. It might or might not impact the lymph nodes in the area.

Stage 4: Grown from the pelvis, the cancer spreads to the bladder or rectum. The lymph nodes may be impacted or not. It will extend to distant organs such as the liver, bones, lungs, and lymph nodes later in stage 4. An individual's chances of survival can be improved by undergoing screening and getting medical aid if any symptoms appear.[11,12]

Diagnosis

Cervical cancer screening currently uses two diagnostic test types: the HPV test and the Papanikolaou test. In the first, precancerous and cancerous cell lesions are detected early for effective therapy; in the second, HPV infections that may lead to cancer are detected. Most HPV infections are self-curable and do not cause precancerous cell changes; only persistent infections by specific HPV types can cause abnormalities of cervical cells. Cervical cancer may develop from these anomalies (precancerous or high-grade lesions) if they are not addressed after many years.[13]

According to the most recent World Health Organisation guidelines, HPV testing, cytology (including liquid-based cytology smear and classic pap smear), and visual inspection with acetic acid (VIA) are the three screening techniques that are recommended for the early diagnosis of cervical cancer.[14] Since VIA is only utilised when the first two are unavailable, we concentrated on the first two techniques. Cervical cells that have been brushed/exfoliated are used as test samples for HPV testing and cytology. HPV testing identifies high-risk HPV infection in the cervix, while cytological examination looks for potential cervical cancer or precancerous lesions in cervix cells under a microscope.[15]

Prevention strategies

WHO introduced a worldwide strategy during 2020 to hasten the elimination of cervical cancer which focused on reducing worldwide disease occurrence rates while decreasing financial weight. The method evaluates the existing differences in healthcare system capabilities among nations.[16] The strategy contains three quantitative targets called objective indicators also known as 90-70-90 targets which state that 90% of female schoolchildren should receive HPV vaccination before age 15 and 70% of adult women must get screening at age 35 or 45 as well as 90% of women with precancerous disease and 90% of women with invasive cancer need immediate medical attention. HPV testing includes the Pap test as a form of screening that World Health Organisation and other groups endorse through their guidelines.[17]

The HPV-DNA test procedure includes colposcopy to determine suitability and tissue sampling by biopsy when results show HPV or abnormalities. Urinalysis to detect HPV-DNA should be measured a year afterward for women with negative results while those with positive outcomes need to undergo colposcopy immediately. When a patient receives a CIN2 histological diagnosis surgical treatment should be offered and focused follow-up monitoring should continue over time.[18]

Prevention-cervical screening, precancer treatment

However, in different settings where HPV DNA testing is not available, visual inspection after acetic acid (VIA) and Papanicolaou (Pap) tests may still be used in accordance with local guidelines.[19,20] For women between the ages of 30 and 49, these guidelines advise screening based on HPV testing every 5 to 10 years.[21]

Cancer prevention programs are to be administered as a complete and included into an all-encompassing health care delivery system.[22] Efforts should be made to ensure that women have access to the cervical cancer prevention techniques of cervical cancer vaccination, precancerous lesion screening, and treatment.[23]

Treatment for cervical cancer

Cervical cancer remains a substantial health danger to global populations although it can be prevented and successfully treated. In 2020 cervical cancer ranked as the fourth deadliest cancer relating to female mortality and it was also the fourth most diagnosed type of cancer in women. The healthcare burden of disease from cervical cancer primarily affects low- and middle-income countries where Africa together with Melanesia and South America and Southeast Asia and South-Central Asia exhibit the worst incidence and mortality levels (age-standardised rate per 100,000: incidence, 15.3–40.1; mortality, 7.8–28.6).[24]

According to estimates, the death rate in LMICs could drop by up to 92% by 2070 if screening, HPV vaccination, and treatment facility expansion are implemented successfully.[25] In the majority of affluent nations, cervical cancer incidence has decreased due to screening and vaccination (notably, Japan discontinued the advice of HPV vaccination in 2013 and resumed it in 2022 and patients are frequently treated at an early stage with great survival rates.[26]

Radiotherapy

The primary research trial for cervical cancer treatment must use intensity-modulated radiotherapy along with customised MRI-guided brachytherapy or image-guided adaptive brachytherapy (IGABIT); this technique provides optimal protection for surrounding tissue through its ability to minimize both acute and late treatment side effects and intestine and urinary symptoms.[27]

Medical Therapy

The cervical cancer treatment standard now involves primary simultaneous RCT with cisplatin combined with radiotherapy as well as management through these treatment approaches. According to patient circumstances along with tumour features healthcare providers provide targeted therapies combined with immunotherapy treatments. surgical and radiologic (lymph node) staging.[28] The recommendation for recurrent or persistent or metastatic cervical cancer patients involves administration of cisplatin/topotecan or cisplatin/paclitaxel together with bevacizumab. Research conducted in the phase II CECILIA trial suggests that using carboplatin together with paclitaxel and bevacizumab yields similar treatment effectiveness with improved tolerance between side effects. Irinotecan along with vinorelbine and topotecan as well as pemetrexed and ifosfamide and nap-paclitaxel are treatment options for second-line therapy.[29]

Chemotherapy

The typical cervical cancer management incorporates chemotherapy as an essential element through three main therapeutic strategies: primary use for locally advanced conditions and combined radiotherapy treatment and post-

surgical supplement following surgery because of unfavorable tumor characteristics. For the past thirty years cisplatin has maintained the status of being the most successful clinical drug in treating cervical cancer.[30]

Human Papilloma Virus (HPV)

The human papillomavirus (HPV) functions as a widespread sexually transmitted infection (STI) because it generates genital warts and leads to cancer development mainly of the cervix and secondarily within anal, vulvar, vaginal, penile, and oropharyngeal regions.

During the 1980s PhD scientist Harald zur Hausen discovered the HPV-cervical cancer connection which led to his joint Nobel Prize win in Physiology or Medicine in 2008 because HPV stands as a leading cancer-causing agent after Helicobacter pylori affects five percent of all cancer types related to infection.[31] His research on HPV 16 and 18 from biopsies of cervical carcinoma.[32] There are currently more than 170 HPV genotypes known, which are separated into low-risk and high-risk groups.[33] The majority of HPV-causing malignancies are caused by at least 12 high-risk strains, with HPV 16, 18, 31, and 45 being the most common.[34] Although they seldom cause cancer, low-risk strains of HPV, such 6 and 11, can cause warts of the mouth, throat, anus, and genitalia. The precise mechanism of HPV infection is unknown. The most widely accepted explanation claims that HPV penetrates cells by moving to the nucleus for transcription and genome replication after endocytosing micro lesions in the epithelial basement membrane.[35] Sexual contact, usually through skin-to-skin or skin-mucosal contact, is how HPV is spread.[36] Over 80% of persons who engage in sexual activity will come into contact with HPV at some point in their lives. It is far less likely to spread vertically throughout the perinatal period. There have also been isolated reports of autoinoculation or indirect infection in non-sexually active individuals.[37]

Mechanism of action

The cervical cancer development from HPV infection results from HPV's expansion of its E6 and E7 reading frames that disable host cell p53 and Rb proteins. A host cell produces no infectious viruses following HPV infection because E6 and E7 manufacturing goes beyond normal levels and disrupts viral genome control.[38]

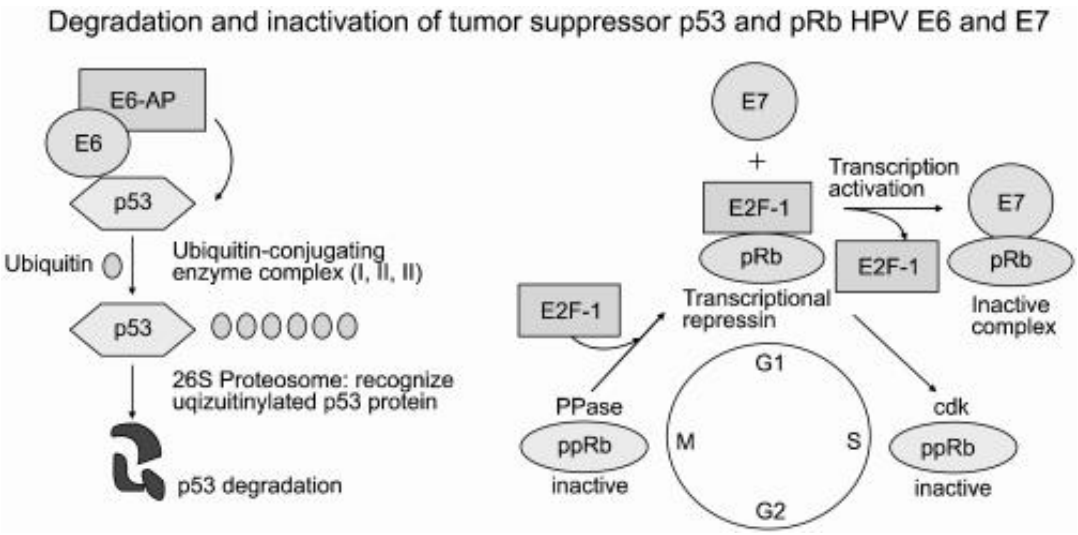

Fig 2: Mechanism of Action of HPV.

- HPV infections can cause productive infections which enable the efficient viral life cycle function. The position where HPV infects a person determines the exact steps which lead to cancer formation.
- Cervical cancer develops primarily in the area known as the transformation zone that bridges the two epithelial types of stratified squamous and columnar epithelium.
- After HPV enters the body it controls viral gene expression unpredictably thus causing tissue metaplasia until cancer forms. Reserve cells experience an increase in abortive infections rather than productive infections as the disruption of viral life cycle occurs. People with infection-caused anal cancer develop symptoms in a way similar to cervical cancer because HPV mostly attacks the anal transformation zone.[39]

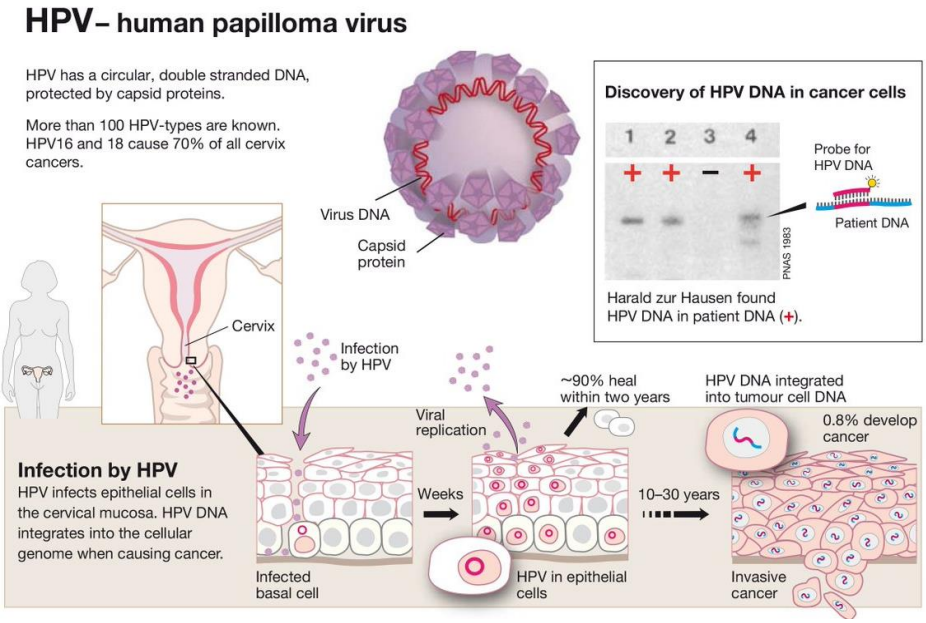

Fig 3: Pathology of HPV.

- The mechanism that leads to oropharyngeal cancer because of HPV differs from the carcinogenic processes in cervical and anal tissues. There is a greater chance for HPV infections to become abortive rather than productive within tonsillar crypt epithelium because this tissue forms the oropharynx. Such a situation heightens the probability that abnormal viral gene expression patterns could lead to cancer development.[40]

Treatment

Medical specialists have not discovered any effective treatment options for human papillomavirus infections at present. The various treatments target both cancer and warts together with the diseases resulting from HPV infections. Medical professionals treat genital warts through topical medications while also eliminating them manually or causing their destruction. The treatment options for genital warts consist of four medications which include isotretinoin and imiquimod alongside podophyllotoxin and sine catechins but imiquimod and podophyllotoxin remain the most frequently used topical drugs. Medical experts use photodynamic treatment along with electrocauterization and liquid nitrogen ablation and simple surgical excision and physical removal and destruction methods for treatment. The strategy enhanced the ability of countries to detect and stage cervical cancer through use of local resources in particular low-middle-income countries.[41]

Cross-sectional imaging and pathology were included to the staging system by the International Federation of Gynaecology and Obstetrics (FIGO) in 2018.[42] Simple hysterectomy or conization may be used to treat earlier stages, but hysterectomy, radiation, and/or chemotherapy may be necessary for later stages.[43,44] Treatments for anal cancer depend on stage, same like for cervical cancer. Small lesions that do not involve sphincters can be excised locally, and they frequently don't need additional care. Before being removed, patients with more severe disease must get treatment, usually chemotherapy and radiation.[45]

Prevention for HPV

Preventing HPV infection can be achieved through post-vaccination sex or by keeping sexual abstinence. Female subjects who engaged in more than five sexual partners throughout their lives aged between 35 and 60 had double the probability of identifying high-risk HPV in comparison to women with less partners according to research.[46] Eight studies within a meta-analysis of condom use toward HPV infections found protective effects from condom usage while four reports showed powerful protective impact in stopping HPV.[47] Research indicates that DNA of human papillomavirus (HPV) transmitted from mothers to newborns can be detectable in 5.2% of newborns. Preventing HPV infection in women constitutes the most reliable approach to blocking its transmission from mother to child. Proper hand hygiene remains essential to stop both indirect transmission between individuals and self-infection through touch.[48]

Efficacy and safety of HPV vaccines

The HPV vaccine has shown significant effectiveness in preventing infections and diseases, with a 75% reduction in genital warts appearance and 50% decrease in their development. Studies have shown that the bivalent HPV vaccine, administered between ages 12 and 13, prevents invasive cervical cancer. Additionally, the vaccine lowers anal and oropharyngeal infections, preventing future cancer. Therapeutic vaccinations, similar to current injection-based vaccines, offer hope for treating HPV infections and preventing future illnesses.**[49-53]**

Dose of vaccination

As per WHO guidelines women between 15 and 20 years old along with girls from 9 to 14 need either one or two doses of the vaccine but patients over 21 years old require two doses with at least six months between them. The available vaccine age range creates more practical options for healthcare providers in their delivery of care.[54]

Nonetheless, the vaccination works best if administered before a sexual debut.[55] The ideal age to finish the immunization series should therefore be decided by performing a risk assessment and include all patients in the decision-making process. Not every nation in the globe has access to the vaccine.[56]

Global vaccination strategies and coverage

School-aged children and adolescents face challenges in accessing HPV vaccines, necessitating specific approaches to improve vaccine accessibility and equity. School-based programs have shown potential for increasing vaccine uptake, but many LMIC countries lack supportive programs and can be expensive. Integrating HPV vaccination with other medical services could increase access and reduce costs, as suggested by SAGE's proposal of a simpler, lower-dose vaccination schedule.[57-59]

The WHO's Global Initiative to Prevent Cervical Cancer

The World Health Organization aims to eradicate cervical cancer by 2030, but some nations have experienced unpredictable drops in HPV vaccine coverage, while others, like the US, have seen increasing coverage over time.[60,61]

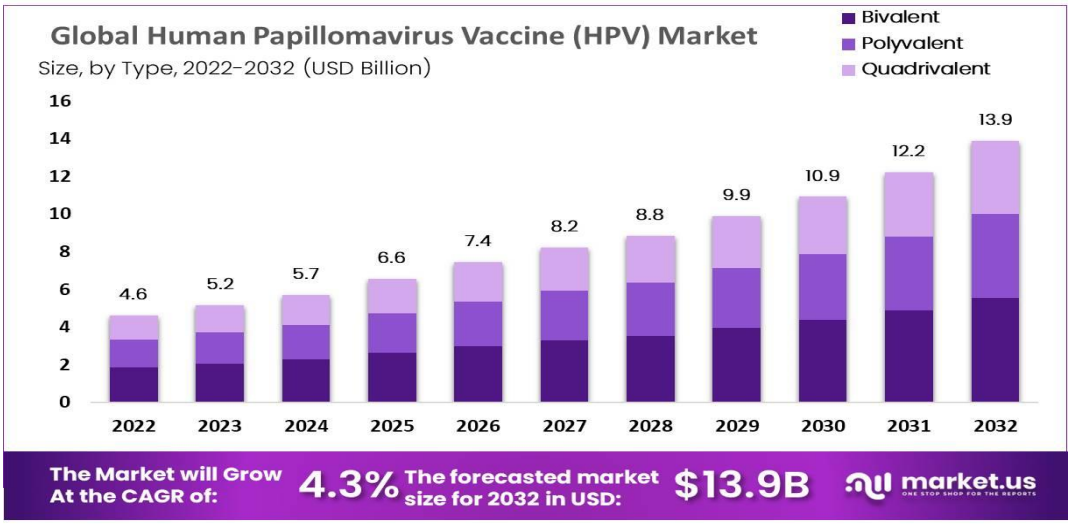

Fig 3: Global Status of HPV.

India

The Indian government has been working on pilot projects since 2018 to introduce the HPV vaccine in limited ways, particularly in a few states like Telangana and Haryana. These small-scale pilot studies were conducted to determine the best way to distribute vaccinations throughout the nation.[62,63]

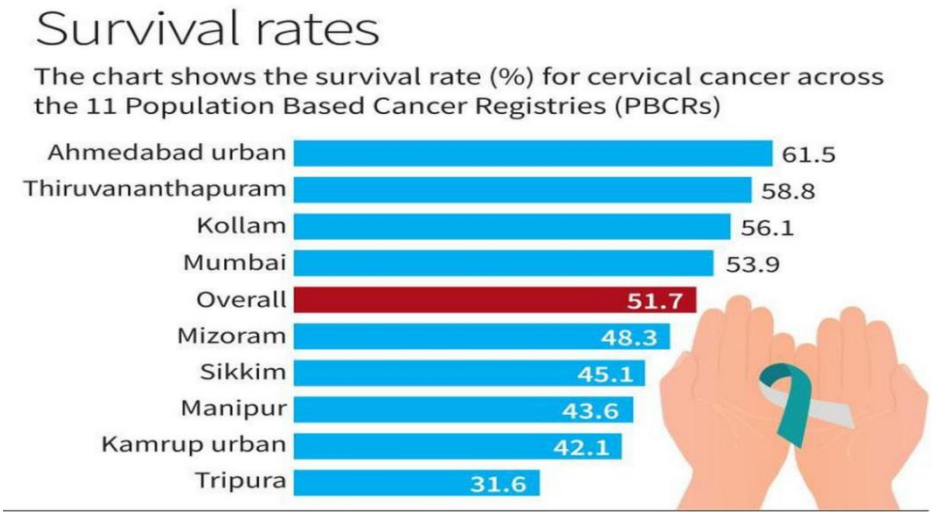

Fig. 4: Vaccination Status in India.

The National Immunization Program: The Government's Strategic Approach and International Assistance:

National Immunization Program (NIP)

At this time, India's NIP does not cover the HPV vaccination. However, the government is considering include cervical cancer in the program due to the growing awareness of the importance of cancer prevention, especially as it is one of the leading causes of cancer-related deaths among Indian women.[64]

Impact on the economic and public health

By combining single-dose vaccination campaigns with sufficient distribution of HPV vaccine supplies, public health has a unique chance to significantly increase the prevention of HPV-driven malignancies. Because a single-dose regimen requires fewer resources than the more complex two-dose strategy, HPV vaccines become more accessible and economical to adopt. The opportunity to reach more community populations in need of HPV protection is created by single-dose HPV vaccination. According to research, young adult women should have the HPV vaccine since it will hasten the control of cervical cancer. Public health officials must determine which health goals would benefit most from the money that is freed up as a result of a reduced timetable for HPV-related cancer prevention and the methodical expansion of HPV vaccinations among girls.[65]

CONCLUSION

Researchers found that Indian women show both adequate knowledge and positive opinions about cervical cancer yet lack proper behaviour change related to their screening activities. The health system of India requires prompt enhancement to ensure successful cervical cancer screening implementation for both organizations and community awareness initiatives. These efforts would rescue numerous young women together with their families from a tragic end.

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