



Human Papillomavirus (Hpv) Vaccination of The Girl Child: An Intervention for Primary Prevention of Cervical Cancer in India

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Abstract: This review gives a comprehensive account of the currently available HPV vaccines including the Nonavalent vaccine which was not covered by some articles. The review includes the current burden of cervical cancer globally and in India. It also outlines the cervical cancer elimination initiative envisaged by the National Health Mission and the World Health Organization. This review aims to highlight the importance of cervical cancer prevention through HPV vaccination and regular screening program. The Human Papillomavirus infection is an established cause of cervical cancer in women. Cervical cancer is the second leading cause of cancer deaths among women in India. India has a young population with more than 436.7 million women aged 15 years and older at risk of developing cervical cancer. There is mounting evidence that cervical cancer is highly preventable. Primary prevention can be done effectively by vaccinating adolescent girls aged 9 to 14 years with the HPV vaccine. Three HPV vaccines, namely the Bivalent, Quadrivalent, and Nonavalent, are currently licensed for use. As part of the National Health Mission, the Government of India launched for the year 2016 for the first time, a population-based prevention, screening, and control program for cervical cancer. The World Health Organization has launched a cervical cancer elimination initiative that looks forward to a cancer-free future. The review concludes that though there are challenges at every level, the solution points in only one direction. All need to work together to ensure the HPV vaccination program is included in our National Immunization Program as the top priority.

Keywords: HPV vaccination, Nonavalent vaccine, human papillomavirus (HPV), cervix, cancer elimination and Pap smear

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I. INTRODUCTION

The epidemiological pattern of cervical cancer has changed dramatically in recent decades with the introduction of the HPV vaccine in the national schedule in some of countries along with the launch of nationwide screening programs. HPV infection, death, and DALYs due to cervical cancer have been showing a decreasing trend at the global and national levels since the 1990s. However, this decline is relatively slow, and there are significant regional differences. Hence, cervical cancer remains a major public health problem. Cervical cancer is the fourth most common cancer affecting women globally, with an estimated 6,04,000 new infections and 3,42,000 deaths in 2020. It has been estimated that 90% of cervical cancer cases and deaths in 2020 occurred in developing countries. In India, 122,844 women are diagnosed with cervical cancer, and 67,477 women die

annually. India contributes to nearly 1/3 of the global cervical cancer deaths^{2,3}. The human papillomavirus (HPV) is a small double-stranded DNA virus infects the mucosal and cutaneous epithelium. More than 100 serotypes of HPV have been identified. However, only specific serotypes of the HPV virus cause cervical cancer in women. The most crucial risk factor for developing cervical cancer is the persistent infection of HPV⁴. The vast majority of HPV infections clear spontaneously within 1 to 2 years. Only a small proportion of them persists or progress to pre-neoplastic lesion and cancer. The peak prevalence for transient HPV infection occurs in the late teens and 20s after initiation of sexual activity. The peak prevalence for precancerous conditions appears about 10 years later, and the peak prevalence for invasive cervical cancer occurs around 40 to 50 years of age. The natural history of HPV infection and its transformation to precancerous and cervical cancer is shown in figure 1.

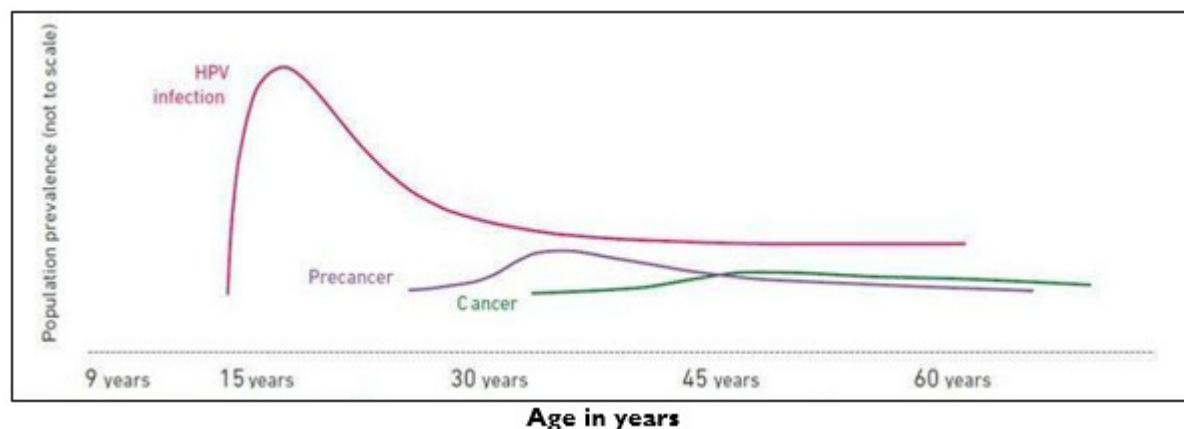


Fig1. The natural history of HPV infection⁵

The immune system spontaneously eliminates most of HPV infections, but in a small proportion of women, the infection persists and causes precancerous changes in the cells. Other contributing factors associated with cervical cancer are early age at the time of marriage, having multiple sex partners, poor genital hygiene, undernutrition, multiple pregnancies, and a lack of awareness of the condition. The three main steps, namely primary prevention, secondary prevention, and tertiary prevention, contribute toward effectively eliminating cervical cancer. Primary prevention can be effectively by vaccinating adolescent girls aged 9 to 14 with the HPV vaccine. Secondary prevention involves screening and treatment of cervical cancer, and tertiary prevention aims to provide palliative care. The HPV vaccine is of great public health importance and has dramatically reduced the risk of cervical cancer at the population level.^{6,7} Cancer developed at other sites caused by HPV infection can also be prevented by vaccination.⁷

2. BASIS OF VACCINATION

The Human Papillomavirus infection is the established cause of cervical cancer in women.¹ Serotypes 16 and 18 are responsible for causing more than 70% of cervical cancers and precancerous lesions.^{8,9}

3. TARGET POPULATION

Infection with HPV is common after sexual initiation. Hence, the HPV vaccine primarily targets young adolescents to

prevent disease before exposure¹⁰. Therefore, the vaccine is advocated for adolescent girls aged 9 to 14. The Indian Academy of Pediatrics (IAP) has included the HPV vaccine in its schedule. It has been estimated that this vaccine's effective implementation would prevent approximately 1,00,000 cervical cancer cases and 60,000 deaths.¹⁰

4. CURRENTLY AVAILABLE HPV VACCINES

Three HPV vaccines are currently licensed for use. The Bivalent vaccine contains HPV serotypes 16 and 18. The Quadrivalent vaccine contains serotypes 6, 11, 16, and 18. These two vaccines have been licensed since 2008. The Nonavalent vaccine, a second-generation vaccine with additional serotypes, was introduced and approved in 2018. The Nonavalent vaccine contains HPV serotypes 16/18/31/33/45/52/58 and genital warts related to HPV types 6 and 11. The safety and efficacy of this vaccine in preventing persistent infection and precancerous lesions have been extensively studied¹¹⁻¹³. The vaccines are manufactured by recombinant DNA technology, producing non-infectious virus-like particles (VLPs). The VLPs have the same outer L1 protein coat as the virus with no genetic material.¹⁴ All three vaccines are recombinant L1-capsid virus-like particles¹⁵ and offer adequate protection against cervical cancer and premalignant genital lesions of the cervix, vulva, and vagina. In addition, the Quadrivalent and the Nonavalent Vaccine offer protection against genital warts. The characteristics of the individual HPV vaccines are shown in table I.

Table 1. Characteristics of HPV vaccines¹⁵

ATTRIBUTES	BIVALENT	QUADRIVALENT	NONAVALENT
Vaccine type	Recombinant L1-capsid virus-like particles (VLP)	Recombinant L1-capsid virus-like particles (VLP)	Recombinant L1-capsid virus-like particles (VLP)
HPV types in vaccine	16, 18	6,11,16,18	6,11,16,18,31,33,45, 52,58
Disease protection	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina)	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina) Genital warts	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina) Genital warts
Cross-protection against HPV-types	31,33	31,45	Not necessary
Number of doses required	2	2	2
Attributes	BIVALENT	QAUDRIVALENT	NONAVALENT
Dosing interval	0 and 6 months	0 and 6 months	0 and 6 months
Method of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Presentation and Type of vaccine	1-dose vial; VVM 30 2-dose vial; VVM 30	1-dose vial; VVM 30	1-dose vial; VVM TBD
Vial Monitor (VVM)			
Shelf-life	48 months at 2-8-degree C for 1-dose vial; 36 months at 2-8-degree C for 2-dose vial Vaccine is freeze sensitive	36 months at 2-8 degree C, vaccine is freeze sensitive	36 months at 2-8 degree C, vaccine is freeze sensitive

5. DOSAGE & SCHEDULE FOR HPV VACCINE

The HPV vaccine is available as a sterile suspension for use either as a single-dose vial or as a pre-filled syringe. This should be shaken well before use. The vaccine is stored between +2 to +8°C. The vaccine dose is 0.5 ml and is administered in the deltoid region (preferred site in adolescent girls) or anterolateral thigh. Indian Academy of Pediatrics Committee on Immunisation (IAPCOI) recommended the following vaccination schedule in 2020-21: For adolescents between 9 to 14 years old, two doses are recommended at six months' intervals. Three doses are recommended for adolescents from 15 years onwards; those who are immunocompromised, three doses are recommended. For HPV2, (Bivalent vaccine) 0-1-6-month schedule is followed, and for HPV4, (Quadrivalent vaccine) 0-2-6-month schedule is followed^{16,17}. Catch-up Vaccines can be provided for 26 years old. The Food and drug administration (FDA) has approved the vaccine up to 45 years of age. This must be discussed with the patients on a one-to-one basis as the HPV vaccine in this age group provides less benefit since most of the women have already been exposed to the virus.¹⁸ At present, there is no recommendation for a booster dose. If the vaccine schedule is interrupted, the vaccine series need not be restarted. If the vaccine schedule is interrupted after the first dose, the second dose should be administered as soon as possible and the third dose within an interval of at least 12 weeks. If a third dose is delayed, it should be given as soon as possible.¹⁹

6. EFFICACY & DURATION OF PROTECTION OF HPV VACCINE

The HPV vaccine is highly immunogenic. Studies have shown that the vaccine provides 99 to 100% seroconversion against all the targeted HPV types. The efficacy and effectiveness of the HPV vaccine are very high among young women. However, the vaccine efficacy is slightly lower among older adult women²⁰. The HPV vaccine was introduced in 2006 in the USA, and follow-up studies done over the last 10 years found no evidence of decreasing protection over time.

7. ADVERSE EVENTS FOLLOWING IMMUNIZATION

The vaccine's safety and efficacy have been studied extensively, and the adverse events following immunization are not severe. The most common adverse reactions following vaccination are pain in 83%, swelling and redness in 25%, and fever in 4% of the adolescents who received the vaccine. It is recommended that the vaccine be administered in the sitting or lying down posture, and the patient should be observed for at least 15 minutes' post-vaccination for syncope. The contraindication for this vaccine includes severe allergic reaction to the previous dose, pregnancy, and acute severe febrile illness. The vaccine is not recommended for use during pregnancy, though there are no reports regarding its association with adverse pregnancy outcomes. The vaccine can safely be given during lactation.¹⁴

8. TYPES OF HPV VACCINES

8.1 Prophylactic Vaccines

The currently available HPV vaccines protect more than 70% of cervical cancers. The vaccine is effective in preventing new and persistent HPV infections and also in preventing the development of precancerous lesions.

8.2 Therapeutic Vaccines

The currently available HPV vaccines are ineffective in eliminating pre-existing HPV infection/disease. Therefore, it is desirable to develop such a vaccine to benefit about 5 million women globally who are already infected with HPV and at risk for developing invasive cervical cancer.

8.3 Chimeric Vaccines

Chimeric vaccines generate both humoral and cell-mediated immunity, prevent new HPV infections, and eliminate existing HPV infections. Clinical trials with chimeric VLP vaccines in healthy volunteers are being conducted. Such vaccines would

benefit women who do not undergo routine cervical cancer screening but already have HPV infection.²¹

8.4 HPV Vaccination and Issues in Developing Countries

Several limitations and issues must be addressed, particularly in developing countries. First, the vaccine cost is a significant concern for implementing the HPV vaccine in mass vaccination programs. This becomes more relevant as cervical cancer affects women from lower socioeconomic backgrounds. The other issue is each region's social and cultural practices that must be addressed. Increasing general awareness about HPV infection and not stigmatizing HPV infection is vital before introducing mass vaccination of adolescent girls in India.²¹

9. PROS AND CONS OF HPV VACCINATION

9.1 The Arguments for the HPV Vaccine

Human Papillomavirus is the most common sexually transmitted infection in the world. It has been proven by several studies that the HPV vaccine offers about 70% protection against cancer caused by HPV in young women. The fact that this vaccine is life-saving and can prevent deaths due to cancer needs to be explained to the parents by the pediatricians and other healthcare providers.

9.2 The Arguments against the HPV Vaccine

Two main concerns need to be addressed, one is the cost, and the second is the parent's anxiety regarding promoting promiscuity among adolescents. All the National Immunization Schedule vaccines are free to all children and adolescents. The high price of the current HPV vaccines makes the affordability and accessibility of these vaccines difficult for mass vaccination programs in developing countries like India. Over the decades, there have been arguments that the HPV vaccine will promote promiscuity

among adolescents. These concerns should be allayed, and it has to be explained by the health care providers that this vaccine prevents cancer just like the hepatitis B vaccine and should be considered a health promotion priority.²²

10. THE CURRENT STATUS OF HPV VACCINE IN INDIA

The HPV vaccine can be a game-changer in controlling cervical cancer in India, a country with a high disease burden. The World Health Organization position paper recommends HPV vaccines to be included in national immunization programs worldwide.²³ The Indian Academy of Pediatrics Committee on immunization (IAPCOI) has included the HPV vaccine for adolescent girls who can afford this vaccine¹⁰. An international NGO, PATH - (Program for Appropriate Technology in Health), collaborated with state governments and the Indian Council of Medical Research (ICMR) to conduct a post-licensure study of the HPV vaccine to prevent cervical cancer. This program was initiated in the two states of Andhra Pradesh and Gujarat in 1996. The study aimed to guide the development of a vaccine delivery strategy, establish a community communication strategy, and develop advocacy strategies for the policymakers. In 2016, the Gavi board approved HPV vaccine program to scale up and cover girls in the age group of 9 to 14 years. Eighteen high-burden countries have successfully introduced HPV vaccine in the national immunization programme through Gavi support. The HPV vaccination is still not included in India's national vaccination program but would definitely be considered in the next planning period in consultation with the National Technical Advisory Group on Immunization (NTAGI) as part of the GAVI (Global Alliance for Vaccine and Immunization) initiative.

11. EPIDEMIOLOGY & BURDEN OF CERVICAL CANCER GLOBALLY²⁴

The age-adjusted Incidence and Mortality Rates of Cervical Cancer globally are shown in Figures 2 &3.

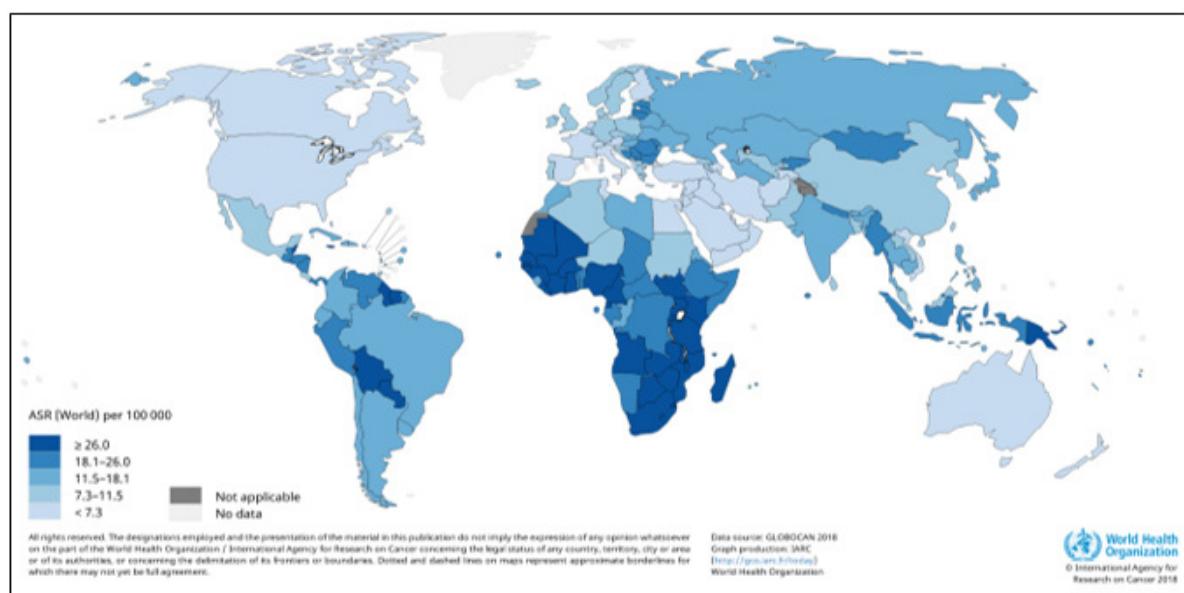


Fig 2: Worldwide Age-Adjusted Incidence Rates of Cervical Cancer (GLOBOCAN 2018)²⁴

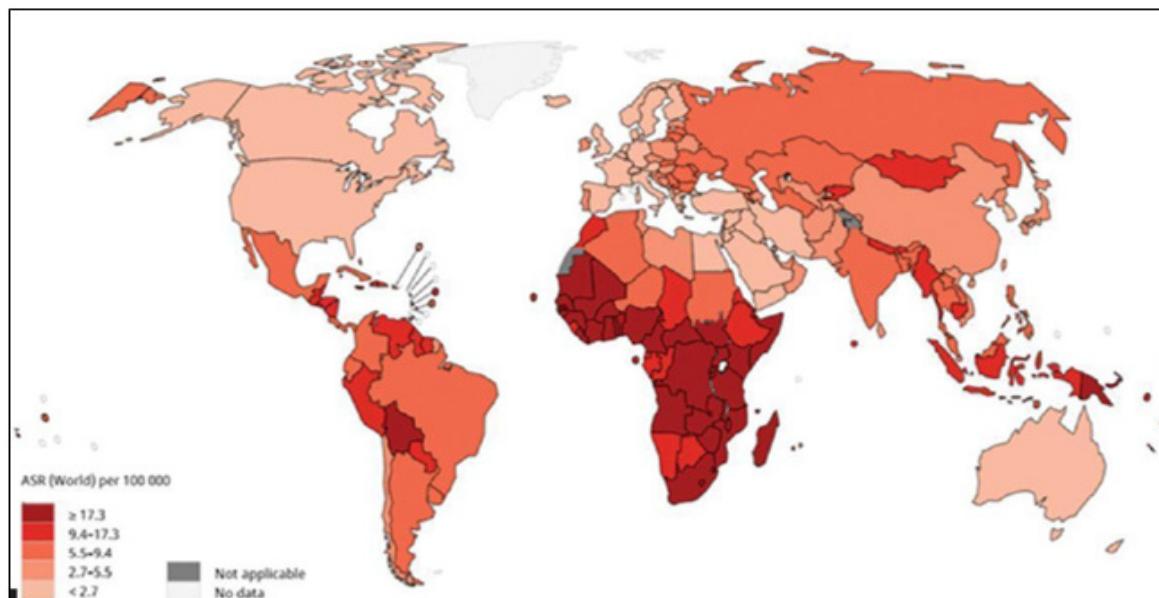


Fig 3. Worldwide Age-Adjusted Mortality Rates of Cervical Cancer (GLOBOCAN 2018)²⁴

12. EPIDEMIOLOGY & BURDEN OF CERVICAL CANCER IN INDIA

As per the estimates for the year 2012, in India 1,22,844 women are diagnosed with cervical cancer, and 67,477 die from the disease every year²⁵. India has a young population with more than 436.70 million women aged 15 years and older at risk of developing cervical cancer²⁶. As per the Hospital-based cancer registries, cervical cancer was the leading cancer in Chennai and Bangalore. The National Cancer Registry Program reported that cervical cancer accounted for 30.7% of all cancers in women in Chennai²⁷.

The World Health Organization recommends that the epidemiology and the burden of the disease in a country should be known before introducing the vaccine and that there should be a strong surveillance and monitoring system capable of assessing the impact of vaccine intervention after introducing the vaccine. In India, the National Cancer Registry program includes data from the cities, hospitals, and Medical colleges. Still, they need to extend their coverage to every region of India for the information to be comprehensive. As per the Global Cancer Observatory²⁸, the cervical cancer burden in India is shown in table 2.

Table 2. Cervical cancer burden in India 2020²⁸

Population	
Women at risk (= >15 years)	483.5 million
The burden of cervical cancer	
Annual cervical cancer cases	123, 907
Crude incidence rates*	18.7
Age standardized rates*	18
Annual cervical cancer deaths	77348
Cervical cancer screening practices	
Cervical cancer screening coverage**	3.1%

*Rates per 100,000 women per year

**All women 25-64 screened every 3 years

Cervical cancer is the leading cause of death among all cancers of all ages.²⁹

Table 3. HPV Prevalence in cervical cancer cases in India³⁰

Authors	Study type	Study area	HPV types	Case-specific HPV prevalence
Das et al ³¹ (2013)	Hospital based study	East	HPV 6/11	6%
			HPV 16	88%
			HPV18	15%
			HPV31	4%
			HPV45	3%
			HPV58	1%
			HPV59	4%
Srivastava et al ³² (2012)	Population-based study	North	HPV	9.9%
			HPV 16&18	78.3%
			South	HPV 16 &18
			East	HPV 16 &18
Basu et al ³³ (2009)	Multicentric study	Central	HPV 16 &18	76.1%
			South	HPV
Franceschi et al ³⁴ (2005)	Community based study	South	HPV	16.9%

Since the vaccine does not prevent all HPV serotypes that can cause cervical cancer, women vaccinated are still advised to undergo screening as per recommendation.

13. SCREENING FOR CERVICAL CANCER

Three screening tests are currently available for cervical cancer screening.
Visual inspection with acetic acid (VIA)
Pap smear
HPV test looks for the virus (Human Papillomavirus)

Cervical cancer screening should start at 21 years of age. The Pap smear test is to be done every three years between the ages of 21 to 29 years. The PAP screen test and HPV test (co-testing) are recommended for women aged 30 to 65 or a Pap smear every three years³⁵. Pap smear can detect cancer early but has some limitations. The interpretation can be faulty if the smear is taken from an area of inflammation commonly encountered, particularly among women from lower socioeconomic backgrounds. The sensitivity of the Pap smear cytology for CIN is 51%, and the specificity is 98%. The new test for detecting cancer cervix is the HPV DNA used across several India centres. The sensitivity of the test varies from 45.7% to 80.9%. This molecular test is expensive and requires a good laboratory infrastructure. Hence, it is beyond the reach of women of a lower socioeconomic group who need this most³⁰. The recommended age group for cancer screening is as follows: If the screening program is effectively implemented, it is possible to diagnose the precancerous condition 10 years ahead of cancer, which is eminently treatable.³⁶

14. CANCER CERVIX SCREENING IN INDIA

As part of the National Health Mission in 2016, the Government of India launched for the first time population-based prevention, screening, and control program for cervical cancer. Visual Examination of the cervix's acetic acid (VIA) has been included in screening for cervical cancer. All women above 30 years of age are recommended to undergo screening. Effective implementation of this population-based program is the need of the hour and it will go a long way in improving the health outcome of our women.³⁷

15. CERVICAL CANCER ELIMINATION INITIATIVE -WHO

The World Health Organization (WHO) has launched a cervical cancer elimination program looking forward to a cancer-free future. This is the first-ever global commitment toward the elimination of cancer.³⁸ In November 2020,

WHO announced an ambitious plan to eliminate cervical cancer on a global level. The WHO global strategy to accelerate the elimination of cervical cancer involves three key steps: vaccination, screening, and treatment. The targets set by WHO are as follows:^{39,40} Vaccination: 90% of the girls to be given HPV vaccines before 15 years of age Screening: 70% of women should be screened by age 35 and again by age 45. Treatment: 90% of women with precancerous lesions are to be treated, and 90% of women with invasive cancer to be managed. The above milestones are to be achieved by 2030 so that all countries will be on the path toward cervical cancer elimination. Successful implementation of the above targets is estimated to reduce more than 40% of new cases and 5 million related deaths by 2050.

16. CONCLUSION

There is mounting evidence that cervical cancer is highly preventable. Though there are challenges at every level, the solution points in only one direction: we will all have to work together to get the HPV vaccine included in the National Immunization Program as a top priority. Increasing the awareness regarding cervical cancer prevention by vaccination among the public and policymakers alike, reducing the cost and increasing the supply of the vaccine, and taking the support of international funding agencies, would help to include the HPV vaccine as part of the national immunisation program. This will bring India closer to ensuring that cervical cancer is eliminated.

17. AUTHORS CONTRIBUTION STATEMENT

Dr Shanthi Ramesh conceptualized and gathered the data regarding this work. Dr R Somasekar and Dr S Sundari gave the necessary inputs and helped design the manuscript. Finally, all the authors reviewed the final manuscript.

18. CONFLICT OF INTEREST

Conflict of interest declared none.

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