Feasibility of introducing comprehensive program of HPV vaccination and cervical cancer screening in India

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EXECUTIVE SUMMARY

India bears a quarter of cervical cancer burden of the world with 1,23,000 new cases diagnosed and 67,500 deaths reported due to the disease every year.[6] Cervical cancer is the second most common cancer in Indian women accounting for 22.86% of all cancer cases among them.[6] It ranks as the second leading cause of cancer deaths in women aged 15 to 44 years in India[7] with one woman dying of cervical cancer every 8 minutes in the country.[6] By 2025, the number of new cervical cancer cases in India is projected to increase to 226,084 provided if the incidence continues to rise in the same fashion.[8] Sexually transmitted human papillomavirus (HPV) infection is the most important risk factor for cervical cancer and 83.2% of cervical cancer in India is attributed to HPV – 16, 18.[36] HPV infection is so common that it happens to infect almost all sexually active men and women at some point in life.[3]

Cervical cancer is one of the few highly preventable cancers with a significantly high cure rate if detected early. The two recommended modes of prevention are - primary prevention through vaccination best administered at an early age of 9-13 years before sexual debut and secondary prevention through screening women preferably 30 years and above to detect the disease at precancerous stage and prevent its further progression. With HPV vaccine combating 83.2% of cervical cancer incidence, the need for cervical cancer screening remains though the required frequency decreases substantially.[58,59] WHO recommends a comprehensive approach of vaccination as well as screening for prevention and control of cervical cancer.[3] Though India has launched its very first National screening program for cervical cancer, it is still reluctant to introduce the vaccine in its National immunization program due to multiple reasons.

This paper assessed the feasibility of facilitating a comprehensive cervical cancer prevention and control program for India by including HPV vaccination in National immunization program

alongside screening, in terms of cost-effectiveness, financial sustainability and socio-cultural and ethical acceptability. The cost-effectiveness of three policy alternatives i.e. vaccination, screening and a comprehensive program was calculated. The vaccination and comprehensive program interventions were found to be more cost-effective options over screening, providing larger health benefits for the price invested. However, as the impact of screening can be observed instantly, it would take decades to realize the impact of vaccination until once the vaccinated cohort reaches certain age. As India already has National screening program in place, the cost-effectiveness of introducing a comprehensive program over a screening program was also assessed in terms of costs and health benefits. As per WHO cost-effectiveness threshold, the comprehensive program of HPV vaccination of 10-year-old cohort and screening of women above 30 years old for four times in a lifetime was found to be highly cost-effective over an exclusive screening program which recommends screening a woman 8 times in a lifetime (from age 30-65 every 5 years); averting 2.44 times more cases, 2.68 times more deaths and 2.54 times more DALYs than a screening program at an extra cost of 11.9%. The comprehensive program was also found to be financially sustainable and socio-culturally and ethically acceptable, provided if carried out aptly.

Lastly, given that India bears the highest share of global burden of cervical cancer, it is recommended that the policy makers in India should consider the complementary roles of vaccination and screening and initiate measures to implement both through a comprehensive program to reduce the burden of a preventable cancer.

BACKGROUND

Cervix is the cylinder-shaped tissue in lower part of uterus (womb) that connects the body of uterus to vagina (birth canal) in female reproductive system.[1] Cervical cancer occurs when healthy cells lining the cervix begin to grow abnormally. Sexually transmitted human papilloma virus (HPV) infection is the most important risk factor for cervical intraepithelial neoplasia and invasive cervical cancer.[2] Human papillomavirus is the most common sexually transmitted viral infection of the reproductive tract and happens to infect almost all sexually active women and men at some point in their lives[3] as the lifetime probability of ever encountering HPV is as high as 80-90%.[10] The peak time for acquiring infection for both women and men is shortly after becoming sexually active.[3] According to WHO, cervical cancer is by far the most common HPV-related disease and nearly all cases of cervical cancer can be attributed to HPV infection.[3] However, out of almost 200 strains of HPV known till date, only 13 are carcinogenic and are known as high risk type.[3] The two high risk HPV types 16 and 18 contribute to almost 70% of cervical cancers worldwide and types 31, 33, 45, 52, and 58 cause an additional 20 percent.[10] While in India, almost 83.2% of cervical cancer is attributed to carcinogenic HPV types 16, 18.[36] Other risk factors for cervical cancer are smoking, weak immune system, positive family history of the disease, oral contraceptive use, having multiple sexual partners, multiple pregnancies and early debut of sex life. Though most of the HPV infections clear up on their own but in few HPV positive women, elements like high parity, long-term oral contraceptive use, smoking, and co-infection with other sexually transmitted agents act as environmental co-factors and influence the risk of progression from cervical HPV infection to high grade squamous intraepithelial lesion (HSIL) and invasive cervical cancer.[4] Women with early cervical cancers and pre-cancers usually have no symptoms.[1] Symptoms often do not begin until the cancer becomes invasive and grows into nearby tissue.[1]

When this happens, the most common symptoms may include abnormal vaginal bleeding, pelvic pain, unusual vaginal discharge and pain or bleeding during or after sex.[1] Though HPV is a sexually transmitted infection, penetrative sex is not essentially required for transmission.[3] HPV can spread through a meagre genital skin contact that may not be covered by a condom. So even when used correctly, condoms do not provide 100% protection against HPV infection.[17] Moreover, as the infection largely remains asymptomatic except for genital warts[2]; there are high chances of transmission across couples having unprotected sex with an intent to conceive and plan a parenthood. There is compelling evidence that if detected early, cervical cancer is the most preventable forms of cancer and has a very high cure rate.[17] Centers for disease control and prevention (CDC) claims that as many as 93% of cervical cancers could be prevented by screening and HPV vaccination.[18]

BURDEN OF DISEASE

Cervical cancer is the fourth most common cancer among women worldwide with an estimated 5,28,000 new cases and 2,67,000 cervical cancer deaths annually.[5] India bears a quarter of cervical cancer burden of the world with 1,23,000 new cases diagnosed and 67,500 deaths reported due to the disease every year.[6] Cervical cancer is the second most common cancer in Indian women accounting for 22.86% of all cancer cases among them.[6] It ranks as the second leading cause of cancer deaths in women aged 15 to 44 years in India[7] with one woman dying of cervical cancer every 8 minutes in the country.[6] By 2025, the number of new cervical cancer cases in India is projected to increase to 226,084 provided if the incidence continues to rise in the same fashion.[8] Cervical cancer qualified as the top third cause of DALYs in women globally, costing 6.9 million DALYs in 2013[9] with around 85% occurring in less developed regions of the world.[5] In India, cervical cancer poses a major public health menace causing higher mortality in Indian

women than women of any other country[11] due to late diagnosis which is evident from the fact that 85% of the cases present in advanced and late stages.[4] As routine screening of asymptomatic women practically remains absent, survival rate among cancer patients also remains poor with less than 50% women diagnosed with cervical cancer been able to survive for more than 5 years.[4]

RECOMMENDED MODES OF CERVICAL CANCER PREVENTION AND CONTROL

Primary Prevention - Prophylactic HPV vaccination has provided a powerful tool for primary prevention of cervical cancer and other HPV-related diseases.[10] "Three HPV vaccines now available are:

- Quadrivalent HPV vaccine (Gardasil) targets HPV types 6, 11, 16, and 18.
- 9-valent HPV vaccine (Gardasil 9) targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
- Bivalent HPV vaccine (Cervarix) targets HPV types 16 and 18."[12]

Since 2006, the quadrivalent and bivalent vaccines have been licensed globally and are also available in India.[11] The recommended age for initiation of vaccination is 9–14 years and the catch-up vaccination is permitted up to the age of 26 years.[11] Although the vaccine is approved for women up to the age of 26, it is generally considered to be best administered at the age of 9-13 years, before girls become sexually active and potentially exposed to HPV.[13] Large trials have been conducted showing the safety, immunogenicity and high efficacy of these vaccines in the prevention of pre-invasive lesions and infection, especially when administered at young ages; prior to HPV exposure.[10] These vaccines give 100% protection against infection from HPV types 16 and 18, which are responsible for around 70% of all cervical cancers.[13] Quadrivalent and 9-valent vaccine provides added protection against HPV strains 6 and 11 which are the most common cause of anogenital warts. However, the 9-valent HPV vaccine offers extended protection against HPV than the quadrivalent HPV vaccine as it combats 5 additional strains of HPV type 31, 33, 45, 52,

and 58 which happen to cause 20% of all cervical cancers.[10] HPV vaccines are typically administered along a 3-dose schedule, with the second dose occurring 1−2 months after the first, and the third occurring six months later.[22] Since evidence suggests that these vaccines produce a more robust immune response in younger children who have not yet contracted the virus, in 2014 the WHO amended its guidance to recommend a 2-dose regimen for children aged 9−14, with an interval of at least six months between doses.[22] This recommendation is expected to improve vaccine coverage and reduce implementation barriers in LMICs by reducing the total cost of vaccination and the number of clinic visits required to complete the series.[22] But, the WHO continues to recommend the 3-dose schedule for children and adults aged 15 or older and immunocompromised (e.g., HIV-positive) children.[22]

For HPV vaccines, "the vaccination schedule depends on the age of the vaccine recipient:

- Females <15 years at the time of first dose: a 2-dose schedule (0, 6 months) is recommended.
- Females ≥15 years at the time of first dose: a 3-dose schedule (0, 1-2, 6 months) is recommended."[14]

As HPV vaccination does not provide protection against all carcinogenic HPV strains, screening continues to be essential to detect precancerous changes in cervical cells before they develop into cancer.[16]

Secondary Prevention – "Secondary prevention aims at detecting the disease in its early pre-cancerous stages through screening and subsequently prevent its further progression.[11] Screening tests are done in apparently healthy women to diagnose abnormal changes in the cervix which could be pre-cancerous and develop into cervical cancer in future."[11] Regular screening for

cervical cancer is important, since during the early stages, women may experience no symptoms and by the time they develop, cancer might have begun to spread.[19] Available screening tests for cervical cancer include Pap smear test, Visual Inspection with Acetic acid (VIA), Visual Inspection with Lugol's Iodine (VILI) and HPV DNA test.[11]

WHO recommends a comprehensive approach for prevention and control of cervical cancer through HPV vaccination and regular cancer screening.[3] By putting such an endeavor in place, not only can women be traced at early stages of cervical cancer, they can also be prevented from falling victim to the disease; consequently, decreasing its incidence and mortality rates.

SITUATION OF CERVICAL CANCER PREVENTION AND CONTROL IN INDIA

The Government of India has launched country's first National Cancer screening program in March 2017 under an integrated National Program for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS).[20] The program provides a population based cervical cancer screening in all 36 States/UTs through Visual Inspection with Acetic Acid (VIA) technique[19] which is the most convenient and cost-effective screening method for resource constrained settings as the procedure requires very little equipment, needs no laboratories or transfer of specimens unlike pap smear and provides immediate test results.[11] "As per the National Guidelines for Cervical Cancer Screening, all women above 30 years of age are to be screened by VIA, at least once in 5 years at the level of PHC to start with. Once an abnormality is detected, the individual should be referred to the PHC/CHC/District Hospital (DH)/ General Hospital (GH) for further evaluation and management of pre-cancerous conditions."[19]

There are two HPV vaccines commercially available in India which are approved by the Drug Controller General of India (DCGI), US Food and Drug Administration, European Medicines

Agency and prequalified by the World Health Organization.[2] Though, both quadrivalent and bivalent HPV vaccines are licensed to be administered to females (in some countries they are licensed to be administered in both males and females); only few can have access to the vaccine since it is expensive (Gardasil - INR 3000 per dose & Cervarix – INR 2000 per dose) and is primarily available with the private sector.[4]

Since 2009,"WHO has recommended the inclusion of HPV vaccination into national immunization programs in countries where cervical cancer is a public health priority."[21] Despite bearing 25% of global burden of cervical cancer, India lags behind in this venture; while on the other hand, not only lower middle-income countries (LMICs) but also lower income countries (LICs) similar to Indian context have not only nationally introduced the vaccine, but have also attained commendably high vaccination coverage amongst target populations.[22] More than 80 countries have introduced HPV vaccination in their National immunization programs, of which 33 are low- and middle-income countries (LMICs); and 25 LMICs have introduced pilot programs before a phased national expansion.[15] There are enormous amount of studies suggesting that in countries where cervical cancer screening and testing programs are already in place, integrating HPV vaccination would increase cost-effectiveness by reducing implementation costs and increasing uptake, while also leading to a more robust comprehensive programs for cervical cancer prevention.[22]

In addition to the hefty logistics and fiscal implications of facilitating a comprehensive program, the following inadequacies of current screening program should also be considered:

- VIA method of screening has comparatively low sensitivity and low specificity, resulting in high false positive and false negative results leading to unnecessary investigations on false positives (non-cases) and a failure to detect adequate true positives (cases).

- The screening coverage is far lower than vaccination coverage in the country amounting to 22.3% and 62% respectively.[39]

STUDY OBJECTIVE – To assess the feasibility of facilitating a comprehensive cervical cancer prevention and control program for India by including HPV vaccination in National immunization program alongside screening, in terms of cost-effectiveness, financial sustainability and socio-cultural and ethical acceptability.

POTENTIAL BARRIERS TO COMPREHENSIVE PROGRAM

1. Financial constraints – In the presence of other competing health priorities, the high direct cost of HPV vaccine as compared to other vaccines, prohibits its inclusion into the National Immunization Program.[27] Also, the high cost of vaccine raises concerns about affordability and accessibility of these vaccines for a mass vaccination program in developing countries like India.[2]

   Moreover, the low public-sector spending in health (4.7% of GDP in 2014)[28], makes it difficult for the government to independently take on the task of introducing the vaccine in the National Immunization Program, without external support.[27] Thus, although the vaccine is available for personal use in India, it has not been implemented at the population level.[27]

2. Lack of awareness in community about causal relationship between HPV infection and cervical cancer – This is majorly due to HPV not been prioritized in the health system as other diseases like tuberculosis, AIDS, etc. There is lack of advocacy about HPV as a major cause of cervical cancer; hence left to be perceived as a less harmful STD rather than a highly carcinogenic agent. This makes HPV vaccination an unfelt community need with no or minimal demand.

3. Socio-cultural barriers - The HPV vaccine might pose certain sociocultural obstacles due to the facts that the vaccine is against a sexually transmitted infection (STI) and is advocated only for women, at least to begin with, and the target age group is adolescent girls.[38]

   A vaccine targeting an STI has the potential to be stigmatized. The parents might not give consent being concerned that if they give consent for administering HPV vaccine to their daughters, it might get conveyed as a 'no objection to sex' message to them.[38]

4. Lack of trust on HPV vaccine - In 2007, during a pilot HPV vaccine program funded by the Bill and Melinda Gates Foundation and run by PATH and the Indian Council of Medical Research (ICMR), 23,000 girls aged 10 to 14 were vaccinated in the Indian states of Andhra Pradesh and Gujarat.[29]

   The trial created an uproar in May, 2011 when it was revealed in a report by the ICMR that 7 girls had died after receiving the vaccine.[29] Because of public safety concerns, the study was deferred and an enquiry Committee was established by the Govt. of India to enquire into "Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine" by PATH in India.[29]

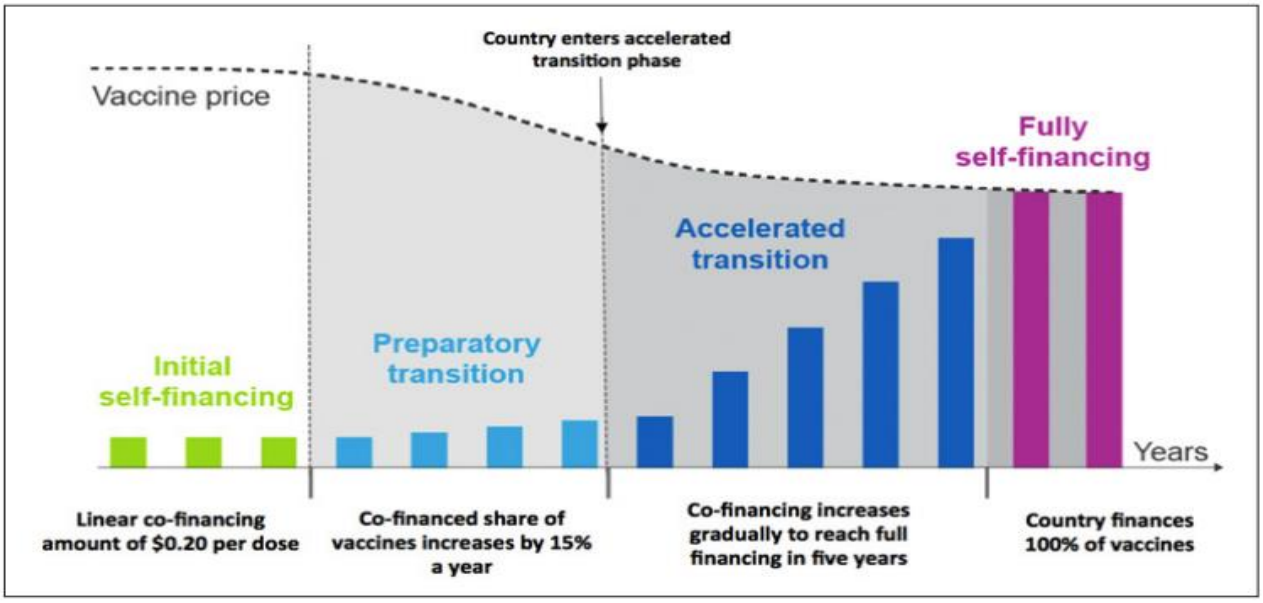
   Even though later these deaths were found to be unrelated to the HPV vaccine, this entire incidence stirred distrust towards the vaccine amongst people and the government in India which lead to a low community interest and a low political will to introduce the vaccine at a national level.

COST-EFFECTIVENESS OF COMPREHENSIVE PROGRAM

Vaccine financing is crucial to make HPV vaccines available through national immunization programs. Key issues for government consideration are the price of introducing a new vaccine, HPV disease burden, availability of cervical cancer screening, implementation capacity, and

competing health priorities also requiring vaccine introduction (such as pneumococcal and diarrheal diseases).[22] GAVI, the Vaccine Alliance, is a major donor enabling low-income countries to procure essential vaccines, and in 2011 it began offering support for HPV vaccination.[22] In general, countries with a gross national income (GNI) per capita at or below US$1,580 on average for the past three years are eligible for Gavi support.[24] Countries must also participate in a two-year HPV demonstration program and successfully deliver the HPV vaccine to at least 50% of a cohort of girls in a representative district.[22] For applications of HPV-specific vaccine support, countries must additionally demonstrate national diphtheria-pertussis-tetanus dose 3 (DTP3) vaccine coverage greater than or equal to 70%.[25] Once Gavi eligible countries surpass the economic threshold, they are known as "graduating" countries and enter a five-year accelerated transition phase toward fully self-financing their own immunization programs.[22] After five years, these countries "graduate" and are no longer eligible to receive financial support from GAVI (Fig. 1).

Figure 1. Transition process for Gavi-eligible countries from initial self-financing to fully self-financing[26]



Of the countries in Southeast Asia without national HPV programs, ten are eligible for Gavi support and India is one of them.[26] The cost of HPV vaccine varies considerably worldwide, ranging from the lowest GAVI procured price of $13.50 for the three HPV vaccine doses ($4.5 per dose) to more than $300 at non-Gavi market prices.[2]

Be it a developed or a developing country, cost-effectiveness of any health intervention is one of the most significant factors in determining whether an intervention is to be implemented or not. Several cost-effectiveness studies have been published to determine the most cost-effective way to prevent and control cervical cancer in LMICs.[23] In this paper, the cost-effectiveness of introducing a comprehensive program of vaccination and screening, was calculated and assessed in terms of costs and health impact achieved.

Policy alternatives assessed

Three different policy scenarios were assessed in terms of cost-effectiveness to analyze the best alternative possible to control and prevent cervical cancer in India. The first scenario was introducing the HPV vaccination in National immunization program for 10-year-old girls as a target population. The second alternative was what India has currently; the screening program for women aged 30 years and above till 65 years of age with VIA as a method of screening through 'screen and treat' approach of precancerous lesions. The third alternative was a WHO recommended comprehensive program of vaccination of a cohort between 9-13-year-old girls and screening for women above 30 years old. For screening frequency in third scenario, four times in a lifetime screening for women above 30 years of age was considered, as screening a women 1-3 times in a lifetime under a comprehensive program has shown to be quite cost-effective in LMICs.[40]

Approach

To assess the cost-effectiveness of facilitating a comprehensive cervical cancer prevention and control program for India by including HPV vaccination in National immunization program alongside screening, two widely used models were employed. First model used was the PRIME "Papillomavirus Rapid Interface for Modelling and Economics" model, created by scientists at the London School of Hygiene and Tropical Medicine in London and Université Laval in Quebec in conjunction with the World Health Organization, Geneva.[36] This helped in calculating cost-effectiveness of HPV vaccination program against no other intervention available. The second model used was the CERVIVAC model, the excel based model developed by the PAHO's ProVac Initiative to enable health decision makers to conduct cost-effectiveness analysis of cervical cancer prevention.[37] This model was used as a guide to calculate cost-effectiveness of second policy alternative i.e. screening program intervention. And eventually, using both these models as a guide, the cost-effectiveness of WHO recommended comprehensive program was calculated.

Data

All the estimates used in this study have been considered with an intent to help make this analysis favorable from the perspective of health decision makers in India. For example, if the vaccine delivery cost was estimated at a range of $3-7, the maximum value of $7 was considered to find if the intervention turns out to be cost-effective even if the extreme estimates were used. Similarly, to calculate the years lost due to disability (YLD) saved, the average duration of the case until remission or death (years) has been taken as a minimum value of 5 years; to seek minimal average benefit that could be earned by an intervention. Furthermore, every cost-effectiveness study for HPV vaccination reviewed for this paper had considered the overall cervical cancer mortality to calculate the deaths prevented by vaccinating a cohort. While in this paper an estimated percentage

of cervical cancer mortality due to HPV 16, 18 was considered to calculate the deaths averted through vaccination which gives a more precise estimate of health benefits earned.

Table 1. Sources of data used in cost-effectiveness analysis

Parameter	Source
Female cohort size by single age for India	UN population division data (2015)[41]
Vaccine operational cost $7	preliminary data based on WHO-PATH analysis for GAVI- eligible countries[42]
Cervical cancer incidence and mortality data on India	Excel based PRIME tool which contains country specific data on cervical cancer and reliability of this data was checked from PRIME modelling study[36] which identifies GLOBOCON 2012 as the source of this data.
Percentage of cervical cancer incidence due to HPV 16, 18 in India	PRIME modelling study[36] and country specific report by HPV information centre[7]
Percentage of cervical cancer mortality due to HPV 16, 18	Estimated using different literatures[51]
Cost of cervical cancer treatment in India	Excel based PRIME tool[52] provided cervical cancer treatment cost (2013) which was converted into present (2017) value using online price inflators.
Screening cost (VIA, colposcopy/biopsy, cryotherapy)	Study on Comprehensive Global Cervical Cancer Prevention by Harvard School of Public Health using CERVIVAC model.[37]
Life expectancy at various ages	Sample Registration System (SRS) based Life table (2011-2015) census of India.[53]
Disability weights	"Global Burden of Disease Study 2015 (GBD 2015) by Institute for Health Metrics and Evaluation (**IHME**)"[54]
Sensitivity and specificity of VIA	"The Alliance for Cervical Cancer Prevention (ACCP), International Agency for Research on Cancer (IARC)"[43]

Assumptions

The analysis was conducted from a payer perspective. For all three policy alternatives, 80% coverage of target population was considered over a five year roll out period from 2018-2023 and program costs and health benefits were calculated against no other intervention in place and discounted at a rate of 3% annually. The costs, cervical cancer incidence and mortality rates were considered as per 2017 estimates and were assumed to remain constant till 2023. In all three scenarios, the program was assumed to intervene in a particular age cohort and cost-effectiveness of all three interventions was calculated for executing the program as per the guidelines in one particular cohort. For example, for the 2 dose HPV vaccination program, 10-year-old cohort was taken as the target population, with an intent to intervene before sexual debut and avoid the sex stigma associated with the vaccine (HPV being an STD) which could potentially stir up while vaccinating a teen aged candidate. Another reason for considering this age group is that HPV vaccination could be integrated with existing expanded program on immunization under which the booster dose of Diphtheria-Tetanus is administered at around 10 years of age.[38] This would not only help vaccinate an otherwise hard to reach adolescent population but also promote sharing of resources and knowledge across programs, optimize costs and logistics, and serve to integrate a variety of services in a more efficient, effective and sustainable way.[42] While for screening, 30-year-old cohort was followed over 5 years interval till 65 years of age to calculate the cost-effectiveness of screening program in a single cohort over lifetime. In the comprehensive program scenario including vaccination and screening, 10-year-old cohort was taken as the target population for vaccination which was followed for screening at the age of 30, 40, 50 and 60 years to fulfill the criteria of screening a woman four times in a lifetime. Taking PRIME modelling study as a reference, the prevalence of HPV 16, 18 in women with cervical cancer in India i.e. 83.2% was considered as the percentage of cervical cancer incidence attributed to HPV 16, 18[36] and the

percentage of cervical cancer mortality attributed to HPV 16 and 18 has been estimated as 70%. After aggressive literature review, the efficacy of HPV vaccination against HPV 16,18 was taken as 100%[40] and for screening, the sensitivity and specificity of VIA method of screening was taken as 81% and 83% respectively.[43]

In screening scenarios, it was assumed that all cases were diagnosed at precancerous stages and treated through screen and treat approach (inclusive of screening the target population through VIA, colposcopy/biopsy as a confirmatory diagnostic test for positively screened patients and cryotherapy as a treatment for precancerous lesions); saving the cancer treatment cost of advanced stages. But even when diagnosed at precancerous stages, the survival rate of cervical cancer is almost 90-95%; [55,56] hence, it was assumed that out of the cases detected through screening 90% were saved and 10% lead to advanced stages and consequently death. The cancer treatment cost was considered to be exclusive of VIA, colposcopy/biopsy and cryotherapy treatment costs. The average duration of cervical cancer in a patient in India was assumed as 5 years and for standard life expectancy at age of death (used to calculate years of life lost; YLL), the average life expectancy was considered using Sample Registration System (SRS) based life tables by census India. To calculate the years lost due to disability (YLD) for vaccination program, two extreme case scenarios were considered, assuming 70% cases were screened at advanced stages and 30% were screened at initial stages,[44,45] and hence disability weights were used accordingly for both using GLOBOCON disability weights 2015.

In comprehensive program scenario, the 80% cohort taken up for screening at age 30, 40, 50 and 60 was assumed to be the same cohort which has been vaccinated at the age of 10. Hence, the incidence of cervical cancer prevented by screening was considered as the incidence caused by reasons other than HPV- 16, 18 as the incidence due to HPV- 16, 18 was assumed to be taken care

by HPV vaccination. This analysis did not consider the herd immunity and protection by HPV vaccination for genital warts or other HPV related cancers, consequently underestimating the overall cost-effectiveness of the vaccination program.

Results

Table 2. Results of cost-effective analysis *(U) Undiscounted cost, (D) Discounted cost

PARAMETERS	VACCINATION PROGRAM	SCREENING PROGRAM	COMPREHENSIVE PROGRAM
COSTS			
• Program cost	$154,188,800 (U) $98967923 (D)	$132,525,969 (U) $85,063,377 (D)	$ 225,567,482 (U) $ 144,783,183 (D)
• Cancer treatment cost saved	$91,348,599 (U) $58,633,190 (D)	$ 33,303,756 (U) $ 21,376,414 (D)	$ 114,565,742 (U) $ 73,535,390 (D)
• Net Program cost	$62,840,201(U) $40,334,733 (D)	$ 99,222,213 (U) $ 63,686,963 (D)	$ 111,001,740 (U) $ 71,247,793 (D)
• Proportion of treatment cost saved through an intervention in the target population	67%	28%	83%
HEALTH OUTCOMES			
• Cases prevented	175,670 (U) 112,756 (D)	64,046 (U) 41,108 (D)	220,319 (U) 141,414 (D)
• Deaths prevented	80,828 (U) 51,880 (D)	32,192 (U) 20,663 (D)	118,326 (U) 75,949 (D)
• DALYS averted	3,361,027 (U) 2,157,316 (D)	1,415,544 (U) 908,584 (D)	5,011,505 (U) 3,216,694 (D)
• % cases prevented	67%	28%	83%
• % deaths prevented	56%	26%	82%
• % DALYs prevented	57%	28%	85%
COST-EFFECTIVENESS			
• ICER per case prevented	$358 (D, U)	$1549 (D, U)	$504 (D, U)
• ICER per death prevented	$777 (D, U)	$3082 (D, U)	$938 (D, U)
• ICER per DALY averted	$19 (D, U)	$70 (D, U)	$22 (D, U)

It was found that the comprehensive program would prevent more cases, deaths and DALYs, saving larger proportion of cancer treatment costs than vaccination or screening program interventions. However, in terms of cost-effectiveness, both vaccination and comprehensive program turned out to be the suitable options over screening program. But, an important fact to be considered here is that while the health impact of screening can be observed immediately, the benefits of vaccination will be hard to realize for decades to come. The vaccination program, would avert few deaths until the vaccinated cohorts would reach older ages i.e. another 30-35 years. Therefore, even by 2050, the cumulative number of deaths averted from screening would be higher than deaths averted from HPV vaccination. However, the cumulative deaths averted over the populations' entire lifetime will be greater for vaccination than a screening intervention, indicating that a large share of the deaths prevented by vaccination would have occurred after 2050. Therefore, a comprehensive program with both vaccination and screening is required for the foreseeable future. By preventing 83% of cases, 82% of deaths and 85% of DALYs, the comprehensive program would significantly reduce cervical cancer mortality and morbidity than any other intervention at a cost slightly higher than screening but moderately higher than vaccination program intervention; making it more cost-effective than other two in terms of health benefits achieved.

As India already has National screening program in place, the cost-effectiveness of introducing a comprehensive program over a screening program was assessed in terms of costs and health benefits.

Table 3. Cost-effectiveness of introducing comprehensive program over screening program in India

PARAMETERS	SCREENING PROGRAM	COMPREHENSIVE PROGRAM	% DIFFERENCE
Net Program cost	$ 99,222,213 (U)	$ 111,001,740 (U)	$11,779,527 11.9% more than screening
Cases prevented	64,046 (U)	220,319 (U)	156,273 2.44 times more than screening
Deaths prevented	32,192 (U)	118,326 (U)	86,134 2.68 times more than screening
DALYs prevented	1,415,544 (U)	5,011,505 (U)	3,595,961 2.54 times more than screening

ICER for introducing comprehensive program of cervical cancer prevention and control in India over a screening program:

$$\frac{\textbf{Cost (comprehensive) – cost (screening)}}{\textbf{Health outcome (comprehensive) – health outcome (screening)}}$$

Table 4. ICER of introducing comprehensive program over screening program

PARAMETER	Undiscounted
• **ICER per case prevented**	$75
• **ICER per death prevented**	$137
• **ICER per DALY averted**	$3

"According to WHO, an intervention that costs less than three times the national annual GDP per capita, per disability-adjusted life-year (DALY) avoided, is considered cost–effective, whereas one that costs less than once the national annual GDP per capita is considered highly cost–effective."[46] Taking this approach into account, the comprehensive program turned out be highly cost-effective over screening; providing larger health benefits by spending minimal extra cost. The comprehensive program was estimated to avert 2.44 times more cases, 2.68 times more deaths and 2.54 times more DALYs than a screening program at an extra cost of 11.9%. Also, as screening once to thrice in a lifetime is also considered highly cost-effective for a comprehensive program in LMICs, India can facilitate a comprehensive program with lesser frequent screenings over a lifetime, at a price equal to or less than the current screening program and gain comparatively extensive health benefits.

In November 2016, Punjab launched HPV vaccination program in its two districts, Bathinda and Mansa with technical support from WHO Country Office for India and became the first state in the country to include HPV vaccination in its immunization program. The cost- effectiveness study for the same concluded HPV vaccination to be a very cost-effective strategy for Punjab state, and likely to be cost-effective for other Indian state.[30]

FINANCIAL SUSTAINABILITY OF COMPREHENSIVE PROGRAM

Currently, India manufactures 60% of all Gavi-procured vaccines and is working to build a more sustainable global and domestic vaccine manufacturing base within the country.[47] India has recently launched a National Biotechnology Development Strategy for 2015−2020, which includes an agenda for in-country manufacturing of HPV vaccines which if attained could highly reduce vaccine price.[22]

Moreover, both GlaxoSmithKline and Merck have pledged to offer lowered prices to developing countries for their HPV vaccines and are likely to use multi-level pricing to ensure availability of the vaccines in the resource-poor countries.[48] Also, they have made commitments to continue providing GAVI graduating countries with same price as they are currently paying for set periods of time after they have transitioned out of GAVI's financial support.[49] This could further buy India sometime to manufacture its own vaccines.

India could also leverage a variety of funding strategies as Bhutan to finance its nationwide HPV vaccination program. Through a partnership between the manufacturer of Gardasil (Merck), and the Australian Cervical Cancer Foundation, Bhutan became the first developing country to implement and launch a national program to vaccinate girls against HPV in 2009.[22] However, eventually in the long run, prices are going to drop with an escalating demand and introduction of more suppliers in the market.

OVERCOMING OTHER POTENTIAL BARRIERS TO COMPREHENSIVE PROGRAM

'Lack of trust' in vaccine due to a report by ICMR regarding female deaths post HPV vaccination during the pilot program, is one of the most important factor to be addressed to generate community interest and political will for such an endeavor. The final Report of the Committee appointed by the Govt. of India, to enquire into "Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine" by PATH in India clearly demonstrated that these deaths were unrelated to the vaccine.[50] However, there's a need to publicize and communicate these findings and existing evidence on safety and efficacy of the vaccine on a larger scale to generate awareness among populations and undo the adverse effects created by the death reports.

The health system needs to prioritize and advocate about HPV infection and spread efficient information about its causal relationship with cervical cancer so much so that people could relate HPV infection to cervical cancer as instantly as they can relate smoking to lung cancer. It is only then that people could acknowledge the fact that HPV infection is so common that it can spread from a single sexual partner even with condom use, the first-time person gets sexually active.[31] This level of community sensitization is required to make people realize that HPV is an unavoidable infection which might turn carcinogenic and lead to cancer. Moreover, there's a debate about popularizing HPV vaccine as an anti-cancer vaccine rather than an anti-STD vaccine to combat sex stigma associated with the vaccine; but much can't be said about how ethically sound this solution can be. Many studies have been done in India to assess the knowledge and level of awareness about cervical cancer, HPV infection and vaccine in India and all project a significant gap not only in general population but also medical professionals.[33,34] There are also studies which demonstrate that acceptability for the HPV vaccine can be considerably increased by health education programs in India.[32,35]

CONCLUSION

Prevention is any day better than cure and one of the most applauding triumphs of public health has been the ability to prevent communicable diseases with a corresponding impact on population health through immunization. Cervical cancer is one of the few preventable cancers as it is almost always caused by sexually transmitted HPV infection which can now be prevented through vaccination. While HPV vaccine has been considered as an "extraordinary invention" and a "wonder jab" in the west, India is still reluctant to introduce it at a national scale. With cervical cancer being asymptomatic till advanced stages, lack of awareness about HPV and cervical cancer and poor health seeking behavior amongst population, majority of women (almost two-third) are

diagnosed at later stages when cure rates are generally below 10%. In such a scenario, vaccination at an early age could prove to be an effective tool in combating cervical cancer incidence in India, given that 83.2% of cervical cancer in India is being caused by HPV-16, 18[36] and vaccine has been proven to have high efficacy against these two strains. However, in India, where almost 22% of population is living on less than $1.90 a day[57] and out of pocket health expenditures are so high that it can push a family into poverty, the high cost of vaccine would keep it from reaching majority of the population, benefiting only few who can afford. Hence, it calls for the public health sector to realize these gaps and facilitate a provision for vaccination to reach population at large.

Cervical cancer has a cure rate of almost 90%[55,56] if detected early and the long latent period of the disease provides enough time frame to catch it at precancerous stages. Hence, cervical cancer screening on a regular basis is the best prevention option for women population who have already had a sexual debut and are not eligible for vaccination. Also, as vaccination combats only 83.2% of risk associated with the disease, the need for screening remains though the required frequency decreases substantially.[58,59] However, screening would intervene late and only help reduce the mortality rates but, vaccination would help reduce both incidence as well as mortality due to cervical cancer. Also, while the health benefits gained through screening would be observed instantly, it would take decades to realize the health benefits achieved through vaccination program. But once the vaccinated cohorts would reach the age where difference in cervical cancer incidence before and after the intervention could be acknowledged, the vaccination program is assumed to avert more deaths and cases than screening.

WHO recommends a comprehensive program with both vaccination and screening to enable an effective intervention for prevention and control of cervical cancer especially in countries with high burden of the disease.[3] The cost-effectiveness analysis in this paper shows comprehensive

program to be a highly cost-effective option for India as compared to exclusive vaccination and screening interventions. However, there is a profound need to create awareness and sensitize the population about the disease so that the unfelt need can be converted into a felt need. Given that India bears the highest share of global burden of cervical cancer, the policy makers in India need to acknowledge the complementary roles of vaccination and screening interventions and initiate measures to implement both through a comprehensive program to reduce the burden of a preventable cancer.

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