Original Article

Cost-Effectiveness of Human Papillomavirus Vaccination for Adolescent Girls in Punjab State: Implications for India's Universal Immunization Program

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BACKGROUND: Introduction of human papillomavirus (HPV) vaccination for adolescent girls is being considered in the Punjab state of India. However, evidence regarding cost-effectiveness is sought by policy makers when making this decision. The current study was undertaken to evaluate the incremental cost per quality-adjusted life-years (QALYs) gained with introduction of the HPV vaccine compared with a no-vaccination scenario. **METHODS:** A static progression model, using a combination of decision tree and Markov models, was populated using epidemiological, cost, coverage, and effectiveness data to determine the cost-effectiveness of HPV vaccination. Using a societal perspective, lifetime costs and consequences (in terms of QALYs) among a cohort of 11-year-old adolescent girls in Punjab state were modeled in 2 alternate scenarios with and without vaccination. All costs and consequences were discounted at a rate of 3%. **RESULTS:** Although immunizing 1 year's cohort of 11-year-old girls in Punjab state costs Indian National Rupees (INR) 135 million (US dollars [USD] 2.08 million and International dollars [Int$] 6.25 million) on an absolute basis, its net cost after accounting for treatment savings is INR 38 million (USD 0.58 million and Int$ 1.76 million). Incremental cost per QALY gained for HPV vaccination was found to be INR 73 (USD 1.12 and Int$ 3.38). Given all the data uncertainties, there is a 90% probability for the vaccination strategy to be cost-effective in Punjab state at a willingness-to-pay threshold of INR 10,000, which is less than one-tenth of the per capita gross domestic product. **CONCLUSIONS:** HPV vaccination appears to be a very cost-effective strategy for Punjab state, and is likely to be cost-effective for other Indian states. ***Cancer* 2017;123:3253-60.** © *2017 American Cancer Society.*

KEYWORDS: cancer, cervical cancer, cost-effectiveness analysis, health technology assessment, human papillomavirus (HPV) vaccine, universal health care, universal immunization program.

INTRODUCTION

Cervical cancer is the second leading cause of cancer among women in India. With an age-standardized incidence rate of 22 per 100,000 women, a total of 122,844 cases of cervical cancer occur every year in India.[1] To compound the prognosis further, the majority (88%-92%) of these cervical cancer cases are detected late during the course of disease, when the chances of radical therapy with a curative intent decline further.[2-4] The introduction of cytology-based screening programs has led to a reduction in the incidence of invasive cancer in several developed countries,[5,6] although it has been reported to be difficult to implement in India.[7]

Although screening is for early detection, the most promising intervention for the prevention of cervical cancer is vaccination against human papillomavirus (HPV). It is estimated that HPV types 16 and 18 (HPV-16 and HPV-18) together contribute to approximately 70% of all invasive cervical cancer cases worldwide.[8,9] Two vaccines against HPV currently are available in India, which cover 4 and 2 strains of HPV, respectively. Gardasil (Merck Frosst Ltd, Montreal, Quebec, Canada) is a quadrivalent recombinant vaccine that covers HPV-6, HPV-11, HPV-16, and HPV-18.[8] Cervarix (GlaxoSmithKline, Toronto, Ontario, Canada) is a bivalent vaccine that covers HPV-16 and HPV-18.[10] Clinical trials have shown a high degree of efficacy in preventing incident cervical intraepithelial neoplasia (CIN) for both vaccines.

Despite significant health system investment for curative care, and somewhat for screening, to our knowledge little is being done to initiate preventive measures. In addition to information regarding effectiveness and the feasibility of

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Additional supporting information may be found in the online version of this article

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implementation, evidence concerning the cost-effectiveness of a new vaccine is an important consideration when making a policy decision for its introduction. However, the generalizability of cost-effectiveness estimates from other countries is not very straightforward, and therefore local evidence always is preferred. In the context of the HPV vaccine, several studies have evaluated its cost-effectiveness in a variety of countries.[11,12] Diaz et al reported that the HPV vaccine is cost-effective in India. However, several methodological issues in the previous study limit its applicability to the current policy debate. First, it evaluated the cost-effectiveness of a 3-dose schedule instead of the 2-dose schedule that currently is being considered in India.[13] Second, the cost of vaccination appears to be an underestimation in the current context. Third, the cost of treating cervical cancer is based on expert opinions rather than empiric assessment. Better estimates regarding the cost of care now are available. Hence, a fresh assessment of the cost-effectiveness of the HPV vaccine in India is considered to be imperative from a policy perspective. The National Immunization Technical Advisory Group in India also has recommended such an assessment.

While considering the introduction of the HPV vaccine, the state government of Punjab established an expert group to undertake an economic evaluation of the introduction of the HPV vaccination for the prevention of cervical cancer in the state. As part of this technical consultation, the current study was undertaken to assess the incremental cost per quality-adjusted life-year (QALY) gained for the introduction of the HPV vaccination in Punjab state. A rigorous sensitivity analysis was undertaken to assess the generalizability of the findings from India.

MATERIALS AND METHODS

Model Overview

A static progression model comprised of a combination of decision tree and Markov modeling was used to estimate the cost-effectiveness of the introduction of the HPV vaccine for preadolescent girls in Punjab state compared with a counterfactual of current practice (ie, no vaccination). Based on current practice, the comparator does not include an organized screening program, but consists of treating only those cases of pathologically confirmed cervical cancer. A lifetime study horizon was used to model the costs and consequences in a 1-year cohort of 11-year-old preadolescent girls for the 2 alternating scenarios. Consequences were valued in terms of QALYs. Future costs and consequences were discounted at a rate of 3%.[14,15] We present the findings of the current study in terms of incremental cost per QALY gained with the introduction of the HPV vaccine from a societal perspective.

Cost

In the intervention scenario, we estimated the cost of vaccination for a 1-year's cohort of preadolescent girls, along with the lifetime costs associated with the treatment of cervical cancer cases among the cohort. For the cost of vaccination, the state government of Punjab was planning to procure the vaccine through the United Nations International Children's Emergency Fund (UNICEF) at the Global Alliance for Vaccine Initiative (GAVI) price. Hence, we used the US dollar (USD) 4.5 per dose price (Indian National Rupees [INR] 293) of GAVI.[16] For social and other contextual reasons, unlike the global experience of success with school-based vaccination programs, the state government decided to integrate delivery of the HPV vaccination with routine immunization at health facilities. In accordance with this strategy, we derived the cost of the delivery of the immunization program using data from previously published studies regarding the cost of health care services at subcenter, primary health center, and community health centers undertaken in 3 north Indian states, including Punjab.[17,18] These studies had reported the unit cost of 1 dose of immunization in routine immunization programs. Using the primary data from these studies, we computed the cost of delivering immunization by deducting the cost of the vaccine alone from the overall cost of vaccination. This represents the opportunity cost of human resource time for immunization; capital items such as building, space, and equipment (such as a hub cutter); consumables such as syringes, needles, cotton, etc; and the cost of vaccine storage and vaccine transport. Although we considered the additional requirements for vaccine storage, in consultation with the state government officials it was agreed that no extra storage space and equipment would be required. Overall, we estimated this cost of service delivery for immunization as INR 332 (USD 5.1 and International dollars [Int$] 15.4) per dose.

It was observed that staff training would need to be performed. In consultation with state immunization officers regarding the average cost of training at the block, district, and state level, we computed the overall cost for undertaking training in 143 blocks, 22 districts, and at the state level. Similarly, we estimated the cost of undertaking additional media sensitization and behavior change communication activities at the state, district, and block level.

Second, we considered the cost of treating cervical cancer. To assess the same, estimates from another study that used bottom-up costing methods to estimate the economic health system cost of providing radiotherapy in a tertiary care hospital in Chandigarh (Punjab state) were used (unpublished data). In addition to the health system cost, out-of-pocket expenditures for the treatment of cancer (including surgery, chemotherapy, and radiotherapy) were estimated in this study based on a sample of 340 patients.

For the cost of surgical treatment for cervical cancer, which was not estimated as part of this primary evaluation, rates of reimbursement under India's Central Government Health Scheme, a social health insurance scheme, were used.[19] The percentage of patients with cancer who received treatment at public or private facilities was estimated using the data from the 71st round of the National Sample Survey.[20]

Although we used the estimates from the bottom-up costing to parameterize the cost of treatment in the public sector in the model, we estimated the cost of treating cervical cancer in the private sector by reviewing the package rates for cancer treatment in a sample of private hospitals that were empaneled under Punjab's cashless insurance scheme for cancer. Finally, there was significant heterogeneity of treatment of cancer in terms of treatment using surgery, chemotherapy, and radiotherapy. We used patterns of stage-wise cervical cancer treatment delivered to patients at the Post Graduate Institute of Medical Education and Research in Chandigarh, which to our knowledge also is the largest hospital registry for cancer in this region.[21]

In the control scenario, which implies no HPV vaccination, only the cost of treatment for cervical cancer was considered. All the costs were reported in INR and the values were converted to USD as well as Int$ using USD and purchasing power parity conversion rates for the year 2015, respectively. Furthermore, these were inflated for 1 year to report all costs for 2016.[22]

Valuation of Consequences

We used local demographic and epidemiological data to populate the decision model to estimate the number of cervical cancer cases due to HPV-16 and HPV-18 that will develop in the 2 alternate scenarios with and without HPV vaccination. In the base case, we assumed that 2 doses of the bivalent vaccine would be administered to the cohort of preadolescent (aged 11 years) girls. To estimate the number of cases in the control scenario, we assumed a lifetime risk of developing HPV infection to be 80%,[23] and the probability of HPV-16 and HPV-18 among these infections to be 32%.[24] Furthermore, we assumed that the majority of these infections would resolve, whereas approximately 31% would progress to CIN.[25] Again, most of the early CIN lesions (CIN types 1 and 2) will regress and only approximately 30% will progress to CIN type 3 (carcinoma in situ),[26] approximately 31.3% of which would develop into invasive cervical cancer.[27] For the vaccination scenario, we assumed a modest overall immunization coverage rate of approximately 70% for the HPV vaccine among the cohort, considering that the full immunization coverage rate for childhood vaccines in Punjab is approximately 89%.[28] Furthermore, we assumed a vaccine efficacy rate of 93% in the base case (see Supporting Information Table 1).[29]

To model the life course of those patients who progress to cervical cancer, we developed a Markov model using the natural history of the disease. We used Indian studies that reported the stage-wise progression-free survival and probability of dying of cervical cancer to compute transition probabilities of moving from one state to another.[30-33] Because the survival rates were reported on a 5-year basis whereas our Markov cycle length was annual, we assumed a uniform progression between different stages during the intervening period of 5 years (see Supporting Information Table 2). The age-wise probability of dying of any other cause was obtained from the Census of India Sample Registration System life tables for the female population.[34] To the best of our knowledge, there are no Indian data regarding utility values in different health states for those individuals who develop cervical cancer. Therefore, we used the stage-wise use quality-of-life values reported in Endarti et al using the EuroQol 5 dimensions, 3-level questionnaire (EQ-5D-3L) method (see Supporting Information Table 1).[35]

Sensitivity Analysis

We undertook a sensitivity analysis to test the robustness of our analysis to various structural, model, and parameter uncertainties. First, we identified 3 model assumptions that are critical to the overall conclusions regarding whether HPV vaccination is cost-effective. These included the lifetime risk of developing cervical cancer and the price and efficacy of the vaccine. The age-standardized incidence of cervical cancer varies from 4.9 to 30.2 per lakh population among different states of India.[36] Although our model estimated a lifetime risk of developing cervical cancer of 0.54%, it is reported to be as high as 2.4% in India.[1] We varied the annual lifetime risk widely and reported the variation in the incremental cost-

effectiveness ratio (ICER). Similarly, we varied the price of the vaccine from INR 410 to INR 760 and the efficacy from 40% to 100%.

The effect of joint parameter uncertainty was analyzed by applying a probabilistic sensitivity analysis.[14] The probability of HPV vaccination remaining cost-effective at a willingness–to-pay threshold equal to the per capita gross domestic product was estimated using a societal perspective. For undertaking probabilistic sensitivity analysis, we used log-normal distribution for cost parameters and beta distribution for parameters related to overall and progression-free survival. For the rest of the parameters, we used uniform distribution to simulate random values. Upper and lower limits were computed assuming a variation of 20% on either side of the base estimate for disease progression and other clinical parameters, and 50% variation for the risk of mortality, treatment patterns, and cost parameters. The Monte Carlo method was used for simulating the results >999 times. The median was computed along with 2.5 and 97.5 percentiles to estimate the 95% confidence interval.

RESULTS

Costs

The overall cost of immunizing a 1-year cohort of 11-year-old girls in Punjab state amounted to INR 135 million (USD 2.08 million and Int$ 6.25 million). The lifetime cost of treating cervical cancer cases in this cohort was INR 52 million (USD 0.8 million and Int$ 2.4 million) and INR 149 million (USD 2.29 million and Int$ 6.89 million) in the alternate scenarios with and without HPV vaccination, respectively. Lower treatment costs in the vaccination scenario were the result of a reduced number of cases attributable to HPV-16 and HPV-18. Hence, the net cost of immunizing a 1-year's cohort of 11-year-old girls in Punjab state was INR 38 million (Table 1).

Consequences

Based on our model estimates, 1140 cases of cervical cancer due to HPV-16 and HPV-18 occur in Punjab among a given year's cohort during their lifetime in the current scenario with no vaccination. This suggests a lifetime risk of developing cancer of 0.54%. However, this would reduce the number to 400 cases, suggesting a reduction of 740 cases. This indirectly points to the fact that 1 case of cervical cancer would be prevented for every 283 girls vaccinated. Ultimately, it would lead to a reduction of 733 deaths due to cervical cancer (396 vs 1129 deaths among vaccinated and unvaccinated girls, respectively). Together, this reduction in mortality and morbidity in a cohort of adolescent girls translates to an increase of 18,477 life-years and 20,999 QALYs as a result of HPV vaccination (Table 2).

TABLE 1. Costs of HPV Vaccination and Cervical Cancer Treatment in Different Arms of the Cost-Effectiveness Model

	Base Case			LL	UL
Parameters	INR	USD	Int$	INR	INR
Costs: no HPV scenario (in millions)					
Treatment costs	149	2.29	6.90	85	238
Total costs	149	2.29	6.90	85	85
Costs: HPV scenario (in millions)					
Vaccination costs	135	2.08	6.25	84	195
Treatment costs	52	0.80	2.42	26	147
Total costs	187	2.88	8.68	151	292
Incremental costs in HPV scenario (in millions)					
Vaccination costs	135	2.08	6.25	84	195
Treatment costs	−97	−1.49	−4.48	−59	−91
Total costs	38	0.59	1.77	66	207

Abbreviations: HPV, human papillomavirus; INR, Indian National Rupees; INT, international dollars; LL, lower limit; UL, upper limit; USD, US dollars.

Cost-Effectiveness of the HPV Vaccination

Vaccinating girls in Punjab against HPV-16 and HPV-18 would incur an incremental cost of INR 1827 (USD 28.1 and Int$ 84.6) per QALY gained. Discounting at a rate of 3%, the incremental cost per QALY gained for HPV vaccination is INR 73 (USD 1.1 and Int$ 3.38). Similarly, the incremental cost per cervical case prevented and death averted was found to be INR 51,808 (USD 797 and Int$ 2398) and INR 52,330 (USD 805 and Int$ 2422), respectively (Table 2).

Budget Impact

The increase in outlay for immunization amounts to INR 135 million (USD 2.08 million and Int$ 6.25 million) (Table 1). This amounts to 0.1% of the state health budget. However, accounting for the net cost savings in treatment, the net incremental cost of immunization will amount to INR 38 million, which amounts to 0.028% of the state health budget.

Sensitivity Analysis

We varied the lifetime annual risk of developing cancer and vaccine cost as well as efficacy to determine the plausible ranges over which the HPV vaccine continues to remain a cost-effective option. We found that the strategy continues to remain very cost-effective even if the current GAVI value of INR 585 for 2 doses per girl vaccinated is increased to INR 1600 (2 doses per girl vaccinated) (see

TABLE 2. Outcomes and Cost-Effectiveness of HPV Vaccination

Outcome Parameters	Base Case	LL	UL
Health outcomes: no HPV scenario			
Total life-years (undiscounted)	9,421,535	9,406,569	9,433,404
Total life-years (discounted)	1,881,785	1,879,984	1,883,217
Total QALYs (undiscounted)	9,417,651	9,400,481	9,430,984
Total QALYs (discounted)	1,881,125	1,878,948	1,882,802
Cervical cancer deaths	1129	652	1729
Cervical cancer cases	1140	647	1784
Health outcomes: HPV scenario			
Total life-years (undiscounted)	9,440,012	9,423,197	9,445,114
Total life-years (discounted)	3,401,369	1,140,304	3,260,492
Total QALYs (undiscounted)	9,438,650	9,419,328	9,444,433
Total QALYs (discounted)	3,400,922	1,139,990	3,259,828
Cervical cancer deaths	396	188	1063
Cervical cancer cases	400	187	1089
Incremental benefits with HPV vaccination			
Total life-years (undiscounted)	18,477	16,628	11,710
Total life-years (discounted)	1,519,585	−739,679	1,377,274
Total QALYs (undiscounted)	20,999	18,846	13,449
Total QALYs (discounted)	1,519,797	−738,958	1,377,027
Cervical cancer deaths	−733	−464	−666
Cervical cancer cases	−740	−460	−695
Incremental cost-effectiveness ratio: societal perspective			
Cost (INR) per life-year gained (undiscounted)	2075	−198	16,730
Cost (INR) per life-year gained (discounted)	73	−2272	1883
Cost (INR) per QALY gained (undiscounted)	1826	−180	14,748
Cost (INR) per QALY gained (discounted)	73	−2282	1875
Cost (INR) per cervical cancer death averted (undiscounted)	52,330	−5078	426,488
Cost (INR) per cervical cancer case prevented (undiscounted)	51,808	−5087	425,529

Abbreviations: HPV, human papillomavirus; LL, lower limit; QALY, quality-adjusted life-year; UL, upper limit; INR, indian national rupee.

Supporting Information Fig. S1). Similarly, even if the vaccine effectiveness drops up to 45% due to programmatic failures, the vaccine remains very cost-effective (see Supporting Information Fig. S2). Although our model predicted a lifetime risk of developing cervical cancer of 0.54%, the vaccine continues to be cost-effective even if it is introduced in a setting with 43% less incidence (ie, a lifetime risk of 0.31%). If the vaccine is introduced in a high-burden state, the strategy to immunize becomes dominant (less cost and more QALYs) if the annual lifetime risk is 4.42% (see Supporting Information Fig. S3).

In our probabilistic sensitivity analysis, we found that, from a societal perspective, HPV vaccination has a 90% probability of being cost-effective at a willingness-to-pay threshold of INR 10,000 (Fig. 1), which is less than one-tenth of India's per capita gross domestic product and one-twelfth of Punjab state's per capita gross domestic product. This suggests that the results are quite robust to parameter uncertainties.

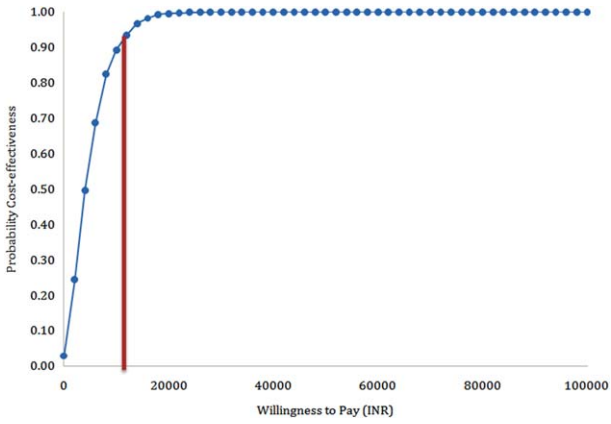

Figure 1. Cost-effectiveness acceptability curve at different points of willingness to pay. INR indicates Indian National Rupees.

DISCUSSION

Overview

The results of the current analysis demonstrate that HPV vaccination in Punjab results in a net incremental cost of INR 38 million (USD 0.58 million and Int$ 1.76 million) (Table 2). Considering the reduction in the number of cervical cancer cases, HPV vaccination in Punjab results in an incremental cost of INR 73 (USD 1.1 and Int$ 3.38) per QALY gained (Table 2), suggesting a high cost-effectiveness. Vaccination continues to remain very cost-effective in Punjab, even if the burden of disease decreases by approximately one-half (see Supporting Information

Fig. S3) or the vaccine price increases by 2.7 times (see Supporting Information Fig. S1) or real-world vaccine effectiveness reduces by approximately one-half (see Supporting Information Fig. S2). Given all the uncertainties in the data, there is a 90% probability of the vaccination strategy being cost-effective in Punjab at a willingness-to-pay threshold of INR 10,000. The incremental cost of vaccination represents 0.1% of the state health budget.

Findings in Context of Existing Evidence

There have been several other country analyses for the cost-effectiveness of the HPV vaccine. Two systematic reviews also have been published to date, one of which included 57 studies from 64 countries[11] whereas another examined 25 studies.[12] Despite the heterogeneity, the majority of studies in both reviews concluded that vaccination is likely to be cost-effective. This is even more pronounced for settings without organized cervical cancer screening programs. The ICER for HPV vaccination in these studies ranged from Int$ 100 to Int$ 455,100, with a mean of Int$28,399.[11] Our estimate of ICER lies within this range, but was more cost-effective than the average value.

Nearly one-half of the studies in the review had assumed 100% efficacy against HPV-16 and HPV-18, whereas other studies assumed lower figures ranging from 90% to 98%.[12] Two studies also assumed cross-protection against non-vaccine-type infections as a result of immunization. We used a modest effectiveness rate of 93% in our base analysis, and varied it significantly in the sensitivity analysis to as low as 40%. Moreover, we did not assume any cross-protection.

Our unit cost of vaccinating the girls in the current study was USD 14.1 (Int$ 42.5), of which the cost of vaccine delivery was 36.3%. These costs vary widely in different studies: for example, USD 9.86 (Int$ 17) in Peru, USD 12 to 22 (Int$ 20-36) in China, Int$ 26 in Malaysia, Int$ 65 in Thailand, and USD 90 (Int$ 127) in South Africa.[12] In view of this, our estimate of cost is comparable to that of other studies. Among the studies that have included the delivery costs, they report it to be approximately 40% of the total cost of vaccinating girls, which also is very similar to the findings of the current study (36.3%).[12]

In an Excel-based model analysis of 128 countries, Goldie and Sweet estimated that in India with 100% vaccination coverage, the lifetime risk of cervical cancer will be reduced by 73.9% and by 51.7% with 70% vaccination coverage.[37] The results of the current study also are similar to the previous study, reporting a 64% reduction in the lifetime risk of cervical cancer. Another study evaluating the impact of the HPV vaccine has reported that in GAVI-eligible countries (which includes India), 70% vaccination coverage in preadolescent girls will avoid 13 cervical cancer deaths per every 1000 girls vaccinated.[38] This appears to be a rather overoptimistic finding. We found that for every 1000 girls who are immunized, 3 to 4 cases of cervical cancer will be prevented.

Strengths

The major strength of the current study was the use of locally established data regarding disease epidemiology, cost of vaccination, cost of treating cervical cancer, and other reasonable assumptions regarding health system considerations to answer the important policy question of introducing the HPV vaccination. Use of reliable data, accompanied by a robust sensitivity analysis, also leads to less uncertainty in the estimates. The type of models examining policy questions for cervical cancer prevention strategies can be classified broadly as static and dynamic.[39] The static models could be proportionate or static progression models. The choice of which model to use to address a policy question depends on several factors. For example, if the element of herd immunity for boys needs to be incorporated, the relative value of a bivalent or quadrivalent vaccine needs to be assessed, the value of immunizing at different ages needs to be assessed, if there are significant changes in trends in cervical cancer incidence reported in the literature, or the effect of human immunodeficiency virus (HIV) along with HPV needs to be modeled, then dynamic transmission models are considered to yield a better estimate. Some of the more recent studies have used these models.[40-42] However, if the research question involves the assessment of the cost-effectiveness of bivalent HPV vaccination among girls alone (and not including boys), then static progression models that follow the costs and outcomes in a population cohort are considered to yield valid results.[39] The majority of HPV cost-effectiveness analyses for girls that are undertaken globally have used this type of modeling approach and are recommended to answer the policy question.[12] Therefore, we used the static progression model type in the current analysis.

The strategies for HPV vaccination usually are different from those for infant vaccines. However, in Punjab state, a strategy similar to routine immunization services was proposed. Therefore, we derived the delivery cost of immunization from existing ingredient-based studies published from similar settings in North India.[17,18] If alternate strategies such as school-based immunization are

considered to be more appropriate in other states within India, then determining the cost of such a strategy would be required in the future.

The model in the current study found that a total of 1140 cases of cervical cancer due to HPV-16 and HPV-18 would result from a 1-year cohort of girls in Punjab, suggesting a lifetime risk of cervical cancer of 0.54%. Assuming that the lifetime cases of a single year's cohort would be similar to the annual number of incident cases in the population that faces a similar risk at different age groups, it can be concluded that a total of 1140 cases of cervical cancer due to HPV-16 and HPV-18 would occur annually in Punjab. A total of 1568 cases of cervical cancer have been reported in Punjab state based on the data from a cancer registry.[36] The estimate of the current study was 72.7% of the reported cases from the Punjab cancer registry. Considering that HPV-16 and HPV-18 account for approximately 70% of the cervical cancer cases, the results of our model in terms of valuation of outcomes are validated.

Limitations

In addition to a reduction in cervical cancer, HPV vaccines also have gained recognition for having a high efficacy in preventing vulvar and vaginal disease related to HPV-6, HPV-11, HPV-16, and HPV-18.[11] However, we have not modeled other health benefits. Second, several studies that have been undertaken in African nations and elsewhere have considered joint HIV and HPV coinfection risks and modeled them together.[43] However, because HIV is not a generalized epidemic in Punjab state or overall in India, we did not include it in our analysis.[44] Third, we did not consider screening for women after age 30 years in combination with vaccination for preadolescent girls. Fourth, we did not include the case for the vaccination of males and the herd immunity effect. Noninclusion of screening and a male vaccination scenario was considered partly in view of the policy question at hand, but also because of a lack of reliable local data regarding the cost of organized screening programs as well as epidemiological data concerning HPV infection among males. More recent analysis of the cost-effectiveness of a universal vaccination program versus a girls-only vaccination program in Italy also reported a wide variation of the base estimate, given the significant uncertainties in parameter values.[42] Moreover, our model was not suitable for including the dynamic effects of herd immunity as well as vaccination for males. Future studies should consider a more comprehensive analysis involving various combinations of strategies for the prevention and control of cervical cancer, including screening and universal HPV vaccination including boys, as well as incorporating the herd immunity effect. Evidence from other countries has suggested that male vaccination has an incremental cost that is considered to be cost-effective in those settings.[42] Because to the best of our knowledge no Indian data exists regarding quality of life in patients with cervical cancer, further research needs to be undertaken to bridge the evidence gap.

Conclusions and Policy Implications

The results of the current study demonstrate that implementing HPV vaccination for adolescent girls in the Punjab state of India is very cost-effective. Moreover, it appears to be fiscally sustainable. The findings of the current sensitivity analysis suggest that the vaccination is likely to be a cost-effective strategy in other states of India as well. Future research should consider including other prevention strategies for cervical cancer such as screening in combination with vaccination, generating more robust Indian evidence regarding epidemiology of HPV infections, and cervical cancer risk and progression, as well as the quality of life among those with cervical cancer.

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AUTHOR CONTRIBUTIONS

Conception: **Shankar Prinja** and **Rajesh Kumar**. Study design: **Shankar Prinja** and **Pankaj Bahuguna**. Review of the literature: **Dharmjeet Singh Faujdar, Radhika Srinivasan, Sushmita Ghoshal, Vanita Suri**, and **Mini P. Singh**. Model development: **Shankar Prinja, Pankaj Bahuguna**, and **Gaurav Jyani**. Data analysis: **Shankar Prinja, Pankaj Bahuguna**, and **Gaurav Jyani**. Estimates validation: **Shankar Prinja, Radhika Srinivasan, Sushmita Ghoshal, Vanita Suri, Mini P. Singh**, and **Rajesh Kumar**. Writing-original draft: **Shankar Prinja** and **Dharmjeet Singh Faujdar**. All authors reviewed and approved the study draft.

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