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Cost-utility analysis of free HPV immunization for girls in Rajasthan, India

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Abstract

Objective This paper aims to analyze the cost-utility of implementing a government policy to vaccinate adolescent girls (aged 11 years) against Human Papillomavirus (HPV) for free in the state of Rajasthan in India, compared to the current scenario where the HPV vaccination is not part of the state immunization scheme.

Methods A static, decision-analytic Markov model was used to determine the costs and QALYs associated with the intervention and comparator therapies (arms), necessary to calculate the Incremental Cost-Effectiveness Ratio (ICER) from the payer perspective, in this case, the Rajasthan state-funded healthcare perspective. The model parameters were taken from existing studies and expert opinions. Uncertainties in the model were addressed by conducting a sensitivity analysis.

Results Given the costs and the QALYs gained for the model, the intervention of introducing free HPV immunization in Rajasthan is a cost-effective measure with an ICER of -\$9548.24/QALY (8,37,822 INR/QALY). Considering all the uncertainties associated with the model, the intervention is not just cost-effective, but cost-saving as well, at a willingness-to-pay threshold of one or three times the Net State Domestic Product (NSDP) per capita of the state of Rajasthan.

Conclusion Overall, the program's high cost-effectiveness indicates that HPV immunization should be explored at a national level, addressing the evidence gaps identified in this study. Because it is extremely cost-effective to introduce an HPV immunization program for girls in the state of Rajasthan, it serves as a scalable model in similar geo-demographic regions.

Clinical trial number Not applicable.

Keywords HPV vaccine, Cost-effectiveness, Young girls, India, Southeast Asia

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Introduction

Cervical cancer remains a significant cause of morbidity and mortality among women in India, ranking as the second most common cancer among women [1]. It is responsible for approximately 60,000 deaths annually, with 70% of cases attributed to persistent infection with Human Papillomavirus (HPV), particularly types 16 and 18. [1, 2] HPV-related cervical cancer is preventable through vaccination, a strategy that has been available since 2006 [3]. HPV immunization not only reduces the spread of HPV infection, but it can also potentially lead to herd immunity, as it is a sexually transmitted infection [1]. Despite the demonstrated efficacy of the HPV vaccine [4], its high cost remains a major barrier to widespread adoption, especially in low- and middle-income countries, including India [5]. So far, 172 countries have incorporated the HPV vaccine into their national immunization programs [6], and even though the financial burden prevents many low- and middle-income countries from implementing such programs without substantial subsidies from international organizations like UNICEF and Gavi, the Vaccine Alliance [5]. Furthermore, several of India's neighbouring and other South-East Asian countries have included HPV Immunization in their National Immunization Programme, which include Bhutan, Sri Lanka, Myanmar, Thailand, Cambodia, Laos, Malaysia, Indonesia, and Singapore [7]. The National Immunization Programme of these countries should serve as an example for India to include HPV immunization in its National Programme as well.

Policymakers must make an informed decision about including HPV immunization in the National or Provincial Immunization scheme and assessing cost-effectiveness is crucial for allocating limited healthcare resources [8]. In this context, assessing the cost-effectiveness of offering free HPV vaccination to adolescent girls becomes essential to determine the most efficient allocation of limited resources. In particular, Rajasthan, a large state with a female population of 33 million [9], faces the challenge of balancing competing health priorities. Rajasthan allocates 7.4% of its budget to healthcare, compared to the national average of 2.1% [10] yet faces significant resource limitations. The state has a cervical cancer incidence rate of 11.77 per 100,000 women and a mortality rate of 6.26 per 100,000 women [2], making the potential for a cost-effective HPV vaccination program even more pressing. Cervical cancer also imposes a financial and societal burden in Rajasthan, leading to productivity losses from treatment, so Rajasthan government should leverage Gavi's recent initiatives in Indian states to expand its HPV vaccination efforts [10].

This study aims to evaluate the cost-utility of offering free HPV immunization to adolescent girls in Rajasthan, with a focus on assessing the potential for a single-dose

HPV vaccination schedule. While the current vaccination regimen consists of two or three doses, recent evidence has suggested that a single-dose schedule could be just as effective with a demonstrated efficacy of 97.5% (95% CI 82–100) in preventing HPV infections [11–14].

If proven to be cost-effective, the single-dose schedule could further reduce the economic barriers to implementing an HPV vaccination program, making it more feasible in low-resource settings like Rajasthan. As Professor Walter Orenstein stated, "Vaccines don't save lives. Vaccinations save lives." [15] Thus, it is essential to not only make HPV vaccines available but also to ensure they reach the target population. Prioritizing prevention over treatment is crucial for long-term health and economic gains, particularly for women of reproductive age [16].

No prior studies have evaluated the specific cost-utility of offering free HPV vaccination in Rajasthan, and this research seeks to fill that gap. By addressing this specific economic context, the study will provide crucial information for the state's health policymakers, ensuring that any HPV vaccination program is optimized for both health outcomes and resource allocation.

This study aims to lay the groundwork for HPV vaccination policy and rollout in Rajasthan, as well as answer the question- Is it cost-effective to introduce a free HPV immunization program compared to the current scenario of no free HPV immunization in the state immunization scheme?

Methodology

A Cost-utility analysis (CUA) was chosen for this study to provide an estimate of the costs and outcomes of providing free HPV immunization compared to the current standard of its exclusion and the cost of treating cervical cancer [5, 17]. This analysis aids policymakers in determining whether the new intervention of introducing HPV immunization is worth funding by evaluating cost-effectiveness, expressed as cost per Quality-Adjusted Life Year (QALY) gained. CUAs enable comparisons across different diseases, since all results are expressed as costs per QALY gained, helping policymakers make informed trade-offs when allocating resources [17]. Despite Disability-Adjusted Life Years (DALYs) being commonly used in low- and middle-income countries (LMICs), QALYs were chosen for this analysis as India under the HTAIn agency (Health Technology Assessment in India), has developed its own value set of QoL using the EQ5D5L tool but there is no data regarding utility values for being in different health states for individuals who develop cervical cancer yet [18]. Hence, the quality-of-life utility values for different stages were taken from the study by Endarti et al., done for the Indonesian population [19].

Study design

Incremental cost-effectiveness ratio (ICER)

CUAs provide the additional cost of per unit of additional health unit gained from the intervention (free HPV vaccination here) as compared to the comparator

$$\text{ICER} = \frac{(\text{Total costs of intervention}) - (\text{Total costs of the comparator})}{(\text{QALYs gained from intervention}) - (\text{QALYs gained from comparator})}$$

The ICER value thus obtained is provided significance by its position on the cost-effectiveness plane (Fig. 1) or the CE plane, where the horizontal axis measures the differences in QALYs gained and the vertical axis measures the differences in costs [5]. ICER is represented as a point on the plane, and this representation of the results of an economic evaluation on a plane helps decision-makers interpret the results more graphically and with greater insight [5].

Sample population

The sample population for this economic evaluation was girls aged 11 years old in the state of Rajasthan, assuming 11-year-old girls have never had sexual intercourse. Globally, countries that include HPV vaccination in their national immunization program start immunization for girls between 9 to 14 years of age [3, 20].

Intervention

The intervention of interest in this study is providing a single-dose schedule of HPV vaccination for free to girls in Rajasthan under the state immunization program.

(no free vaccination here) of the analysis. It informs the incremental cost of additional effectiveness for the given condition and is reported as the incremental cost-effectiveness ratio or ICER [17]. ICER is calculated:

Comparator

The comparator of interest for this study is the current standard of care in Rajasthan, which includes no immunization for HPV but screening and treatment of cervical cancer.

Perspective

The perspective for this study is the Rajasthan state-funded health care. The perspective on outcomes is direct health costs and consequences of cervical cancer.

Time horizon

A lifetime horizon was considered as that would allow all the relevant differences in future costs and Quality-Adjusted Life Years (QALYs) gained to be captured.

Markov decision analytical model

A static progression model was used to estimate the cost-effectiveness of introducing free HPV immunization for 11-year-old girls in Rajasthan, compared to no immunization. The decision tree assessed the costs and QALYs of both arms, while the cohort simulation using the Markov

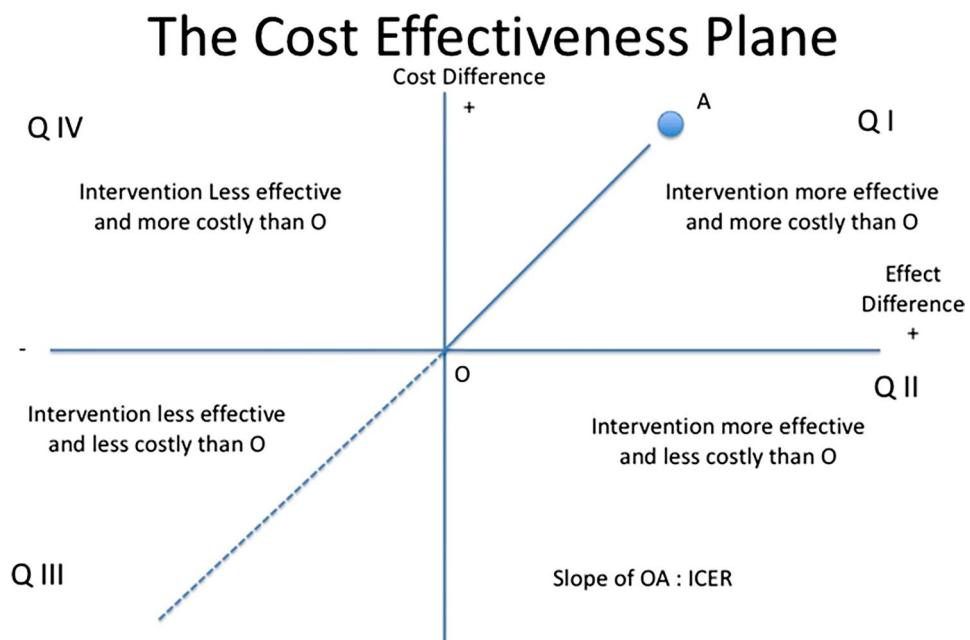


Fig. 1 Cost-effectiveness plane (Reprinted from Black (1990), Prevention Effectiveness. Haddix a)

model was chosen for the decision analytical tree [21]. Given the chronic nature and high treatment costs of cervical cancer, this model was ideal, as it captured lifetime benefits and costs. The time-dependent Markov cycles represented changes in costs and utilities for each year of an individual's life and age-related changes in their predicted life expectancy [22]. The model is based on the natural course of the infection and the subsequent disease, but it has not been validated.

Markov health states

This study utilized the following health states to denote the progression of cervical cancer: 1.) Healthy or disease-free state; 2.) Cervical Intraepithelial Neoplasia 1 or CIN 1; 3.) Cervical Intraepithelial Neoplasia 2 & 3 or CIN 2 & 3; 4.) Invasive cervical cancer Stage 1; 5.) Invasive cervical cancer Stage 2; 6.) Invasive cervical cancer Stage 3; 7.) Invasive cervical cancer Stage 4; 8.) Death. (Fig. 2)

The Markov model had a cycle length of one year. Since the study focuses on the single-dose schedule of administering HPV vaccination, the intervention is given only

once at the start. Successive cycles were exhausted till 99% of the patients in the cohort had entered the death health state. Future costs and QALYs were discounted at a rate of 3% [5]. The Markov model, all calculations, and the sensitivity analyses were constructed in specially designed Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA).

Assumptions

- An efficacy of 96% for the single-dose regimen is assumed [14].
- The disease state of only HPV infection was excluded from the study. This was assumed since most HPV infections are asymptomatic and spontaneously recover without any treatment [3].
- Due to the limited scope of this study, screening for HPV infections and cervical cancer has not been addressed. Screening has not been included in the costs for treatment or calculated as a part of the intervention.

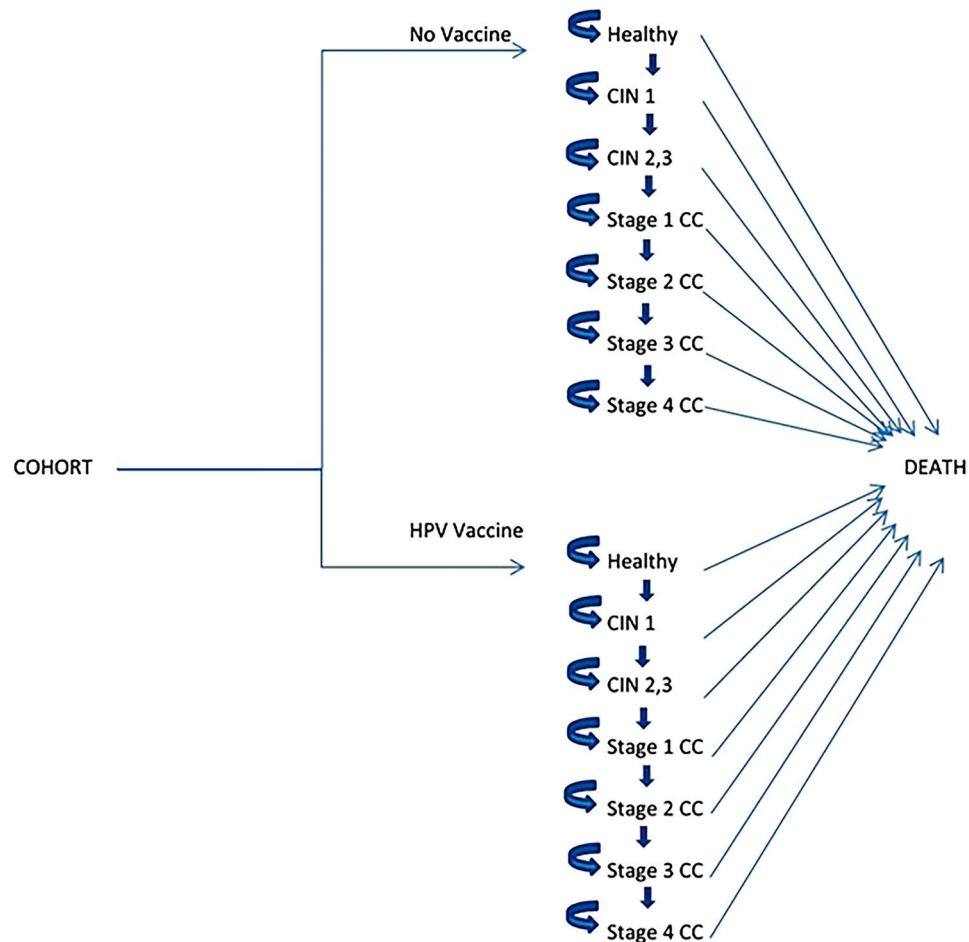


Fig. 2 Schematic representation of the Markov model

- For the simplicity of the model design and since it is a preliminary-level study, it is assumed that there is no reversal of disease states. Once an individual enters a disease state, they can either stay in the same state in the succeeding cycles or progress to the next disease state.
- It is assumed that every individual progresses through every disease state sequentially or enters a death state in that particular cycle. This is due to the natural course of cervical cancer, where an individual progresses through each stage even if it is undiagnosed [3].
- There is no cost of chemotherapy for CIN 1 and CIN 2 & 3 disease states, as clinically there is no chemotherapy prescribed for these stages [3].
- There are no costs associated with a transition from Stage 4 cervical cancer to death due to cervical cancer because it is assumed that there is no cost of dying.
- There is an assumption that there is no cost incurred in the healthy state.

Model parameters

The model parameters used for the base case scenarios have been listed in Table 1, provided in the Appendix.

Transition probabilities

Transition probabilities were taken from a cross-sectional study by Endarti et al. and another cost-utility study by Prinjha et al. [19, 23]. Since the survival rates for cervical cancer are reported on a 5-year basis but the Markov model for this study was annual, there was an assumption of uniform progression between different stages during the 5-year interval. The age-related probability of dying from all other causes was taken from the Census of India Sample Registration System (SRS) life tables for the female population of Rajasthan [24].

Costs

The cost of immunization in this study was set at a subsidized rate of US\$4.5 (395 INR) per dose, based on the Gavi procurement price through UNICEF [5]. Additional costs, such as delivery, were estimated at 260 INR (US\$ 2.96) from previous studies [23]. Immunization delivery is proposed to be integrated with routine services at state health facilities, rather than through school-based programs.

For cervical cancer treatment, only state-funded costs were considered. Under the Chiranjeevi health scheme used in Rajasthan state-funded health insurance, treatment rates include: cervical conisation – US\$52.42 (4600 INR), biopsy- US\$21.65 (1900 INR), trachelectomy- US\$72.93 (6400 INR), and radical hysterectomy US\$100.28 (8800 INR). Radiation therapy costs

US\$968.70(85000 INR), and high-dose brachytherapy US\$153.85 (13500 INR) [25].

There is notable heterogeneity in cervical cancer treatment costs, which results in parameter uncertainty in cost estimates and should be addressed in a sensitivity analysis, though this was beyond the scope of the study. Future analyses should address this variability.

Utility values

Utility values for the study were based on local demographic and epidemiological data to estimate cervical cancer cases due to HPV types 16 and 18, under both HPV immunization and no immunization scenarios [24]. Each individual was assigned a utility value for each health state per year.

Since India lacks specific utility data for cervical cancer patients, the study used quality of life (QoL) utility values from an Indonesian study by Endarti et al. [19].

Addressing uncertainty in the model

To address uncertainty in the model, a one-way deterministic sensitivity analysis (DSA) was performed by varying one parameter at a time and observing its impact on the ICER. Key parameters analyzed included HPV vaccine efficacy using confidence intervals from a Thai study [26] and vaccine cost that varied from half to four times the base cost. Other variables tested were Stage 4 cervical cancer utility values and discount rates for costs and outcomes.

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine (LSHTM MSc Ethics Ref: 29,401).

Results

Cost-effectiveness

The model analysis estimates that introducing free HPV immunization for 11-year-old girls in Rajasthan using a single-dose schedule is both clinically effective and cost-efficient. The intervention costs 6,641 INR (US\$75.68) per QALY gained and demonstrates a negative ICER of -837,822, indicating that it is cost-saving as it is less expensive and more effective than no immunization. [8] This is primarily due to the subsidized vaccine cost compared to the expenses associated with treating cervical cancer. With a vaccine efficacy of 97.5%, the intervention significantly reduces cervical cancer cases, leading to substantial savings in treatment costs as well as a severe reduction in morbidity and mortality due to the disease.

Rajasthan, or even India, does not have an explicit or implicit cost-effectiveness threshold (CET) to compare a given ICER against [27]. In the absence of which, based on the criteria suggested by the World Health Organization – Choosing Interventions that are Cost Effective (WHO-CHOICE), interventions that have an ICER of

less than 3 times the national annual GDP per capita are considered cost-effective, and those less than or equal to the national annual GDP per capita are highly cost-effective [28]. Using that criterion, Rajasthan's Net State Domestic Product (NSDP) per capita is 156,148 INR (US\$1780) [29], while India's GDP per capita is 191,958 INR (US\$2187.64) [30], confirming that the intervention is not only highly cost-effective but cost-saving as well, at both levels.

Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis was conducted, illustrated in a Tornado diagram (Fig. 3). Among the four parameters analyzed, the ICER was most affected by a higher discount rate for costs and QALYs, showing a 22.5% increase when discounted at 6%. Increasing vaccine effectiveness had a minor effect on the ICER, while a decrease in effectiveness resulted in a 6.59% change. Interestingly, variations in the cost of immunization had minimal impact on the ICER—halving or quadrupling the cost changed the ICER by less than 1%. This indicates that the cost-effectiveness of the intervention is primarily driven by the significant savings from reduced cervical cancer cases and associated treatment costs, rather than the immunization costs themselves.

Budget impact analysis

The cost to immunize a cohort of 11-year-old girls in Rajasthan is 1.28 crores INR (US\$1,45,875), representing just 0.64% of the state health budget of 20,111 crores INR (US\$2.3 Billion) [31]. We adopted a simplistic multiplication technique. When considering the net savings from reduced cervical cancer cases, the financial impact of

HPV immunization is even less than 0.64%. This demonstrates that introducing HPV vaccination is both fiscally prudent and financially feasible for Rajasthan's healthcare system.

Discussion

This cost-utility analysis shows that introducing HPV immunization for 11-year-old girls in Rajasthan is not only highly cost-effective but extremely cost-saving as well, due to its negative ICER. The findings align with similar studies globally, which also indicate the cost-effectiveness of HPV immunization, even with varying input parameters [19, 23, 26].

While most studies assumed 100% efficacy against HPV-16 and HPV-18, this analysis used a modest efficacy rate of 96% due to a single-dose regimen and the intervention was still found to be cost-saving, underlining the fact that the intervention is clinically superior and economically sound even at a lower efficacy rate.

The highly negative ICER clearly indicates that running a free HPV immunization programme by the state health department in Rajasthan is a superior value proposition for the limited state health budget with competing health priorities. A further emphasis on the fact that this intervention addresses an often-neglected section of the population, i.e. young females [32], particularly in Rajasthan, at such a minimal cost that the intervention of free HPV immunization presents itself as a low-hanging fruit that should be captured at the earliest [33]. The highly subsidized vaccine costs from UNICEF and Gavi, combined with a significant reduction in cervical cancer cases and related treatment savings, contribute to the favorable ICER in this analysis. Lastly, the excellent return on

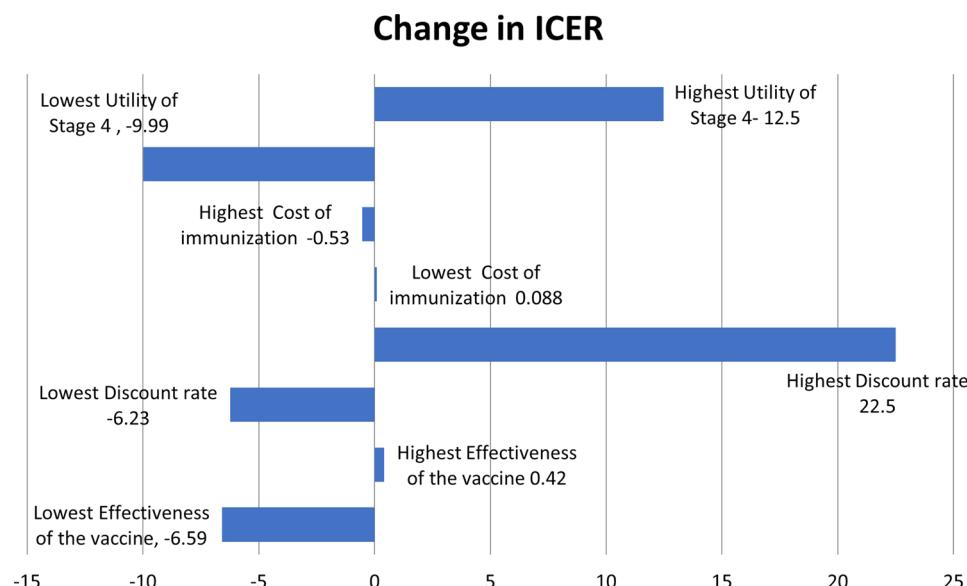


Fig. 3 Deterministic sensitivity analysis tornado diagram

investment for this intervention can be highlighted by the fact that HPV immunization can help eradicate cervical cancer in the population.

Strengths

This study has several strengths despite its limited scope. Notably, it utilizes population-specific data on disease epidemiology, immunization costs, and cervical cancer treatment within Rajasthan [2, 9, 17, 22, 26, 28, 29]. It is among the first studies to encourage the state health ministry to consider HPV immunization. A robust decision analytic model and sensitivity analyses were employed to address uncertainties. The study focuses specifically on assessing the cost-effectiveness of a single-dose HPV vaccination for 11-year-old girls, so using a static progression model is appropriate for this context. It also advocates for integrating HPV immunization into the routine vaccination schedule rather than a school-based approach.

Limitations

Several limitations of the study must be noted. Firstly, the analysis did not include screening costs or outcomes, which are crucial for HPV risk reduction [16]. Future studies should incorporate screening into the cost-utility analysis. Additionally, the high reversal rates of CIN 1, 2, and 3 cases were not considered to simplify the analysis.

An ideal model would utilize a dynamic approach to capture the impact of immunization for boys and herd immunity [34], which were excluded since they were beyond the scope of this study, primarily due to a lack of reliable data. Future research should explore comprehensive strategies that include both genders and screening.

Additionally, HPV immunization also reduces and prevents vulvar and vaginal disease, due to HPV infection, which was not included in the study [3]. Future studies should also consider the reduction of HPV infection due to HPV immunization in the presence of concomitant viral infection states like HIV and HCV.

Moreover, costs related to raising awareness about HPV and vaccination were omitted for simplicity, but should be included, as they significantly affect vaccine uptake [20]. The study also lacked India-specific QoL utility values, which future analyses should address. Lastly, a probabilistic sensitivity analysis could enhance robustness, but time and expertise constraints limited this study.

Economic Implications

Policymakers should use the ICER as a benchmark to compare other healthcare initiatives and understand the opportunity costs involved. HPV immunization should be based on reliable evidence to ensure equity and efficiency.

Countries like the UK and Australia exemplify the health benefits and productivity gains of HPV vaccination, suggesting that Rajasthan should consider this as the first step towards a broader immunization strategy, potentially including boys and catch-up programs [35].

Education and awareness about HPV and its vaccine are essential, especially given the high prevalence of cervical cancer in India [20]. Emphasizing the vaccine's unique ability to prevent cancer can enhance community receptivity and states' health budgets' competing priorities. The potential introduction of CERVAVAC, a more affordable, locally manufactured vaccine, should also be considered as its efficacy is further evaluated [6].

Conclusion

This cost-utility analysis demonstrates that implementing HPV immunization for adolescent girls in Rajasthan, India is both highly cost-effective and financially feasible, especially if vaccine prices are well-negotiated. While introducing a new vaccine carries opportunity costs, the savings from reduced cervical cancer cases, morbidity, and mortality outweigh the initial investment, making it a viable policy option. Overall, the program's high cost-effectiveness and cost-saving indicate that HPV immunization should be explored at a national level, addressing the evidence gaps identified in this study.

Appendix

Table 1 Model parameters

Parameters	Values for model
Probability of CIN 1 from healthy	0.072
Probability of CIN 1 to CIN 2&3	0.069
Probability of CIN 2&3 to Stage 1	0.05
Probability of Stage 1 to Stage 2	0.438
Probability of Stage 2 to Stage 3	0.536
Probability of Stage 3 to Stage 4	0.684
Efficacy of HPV vaccine	96%
Probability of CIN 1 from healthy (after vaccination)	0.012
Utility of Healthy	1
Utility of CIN 1	1
Utility of CIN 2&3	1
Utility of Stage 1	0.74
Utility of Stage 2	0.76
Utility of Stage 3	0.72
Utility of Stage 4	0.63
Cost of surgery CIN 1	2000
Cost of surgery CIN 2&3	2000
Cost of surgery Stage 1	20,000
Cost of surgery Stage 2	20,000
Cost of surgery Stage 3	20,000
Cost of surgery Stage 4	20,000
Cost of Radiotherapy Stage 1	99,000
Cost of Radiotherapy Stage 2	99,000
Cost of Radiotherapy Stage 3	99,000
Cost of Radiotherapy Stage 4	99,000
Cost of Radiotherapy CIN 1	30,000
Cost of radiotherapy CIN 2&3	30,000
Cost of Chemotherapy Stage 1	1000
Cost of Chemotherapy Stage 2	1000
Cost of Chemotherapy Stage 3	1000
Cost of Chemotherapy Stage 4	1000
Cost of single dose vaccine	370
Cost of Delivery	260
Total cost per girl	630
Discount rate for costs	0.03
Discount rate for utilities	0.03
Natural death risk for age (30–34 years)	0.00688
Natural death risk for age (35–39 years)	0.00727
Natural death risk for age (40–44 years)	0.00985
Natural death risk for age (45–49 years)	0.01588
Natural death risk for age (50–54 years)	0.03047
Natural death risk for age (55–59 years)	0.05282
Natural death risk for age (60–64 years)	0.07384
Natural death risk for age (65–69 years)	0.09946
Natural death risk for age (70–74 years)	0.14065
Natural death risk for age (75–79 years)	0.22356
Natural death risk for age (80–84 years)	0.36736

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Author contributions

Conceived and designed the experiments, wrote the paper, Performed the experiments, analyzed and interpreted the data, contributed reagents, materials, analysis tools or data.

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Data availability

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Declarations

Ethics and consent to participate declarations

Non applicable.

Consent for publication

None required.

Competing interests

The authors declare no competing interests.

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