Health and economic effects of introducing single-dose or two-dose human papillomavirus vaccination in India

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ABSTRACT
Background Cervical cancer is a major public health problem in India, where access to prevention programmes is low. The WHO-Strategic Advisory Group of Experts recently updated their recommendation for human papillomavirus (HPV) vaccination to include a single-dose option in addition to the two-dose option, which could make HPV vaccination programmes easier to implement and more affordable.

Methods We combined projections from a type-specific HPV transmission model and a cancer progression model to assess the health and economic effects of HPV vaccination at national and state level in India. The models used national and state-specific Indian demographic, epidemiological and cost data, and single-dose vaccine efficacy and immunogenicity data from the International Agency for Research on Cancer India vaccine trial with 10-year follow-up. We compared single-dose and two-dose HPV vaccination for a range of plausible scenarios regarding single-dose vaccine protection, coverage and catch-up. We used a healthcare sector payer perspective with a time horizon of 100 years.

Results Under the base-case scenario of lifelong protection of single-dose vaccination in 10-year-old girls with 90% coverage, the discounted incremental cost-effectiveness ratio (ICER) of nationwide vaccination relative to no vaccination was US$406 (INR30 000) per DALY (disability-adjusted life-years) averted. This lays below an opportunity-cost-based threshold of 30% Indian gross domestic product per capita in each Indian state (state-specific ICER range: US$67–US$593 per DALY averted). The ICER of two-dose vaccination versus no vaccination vaccination was US$1404 (INR104 000). The ICER of two-dose vaccination versus single-dose vaccination, assuming lower initial efficacy and waning of single-dose vaccination, was at least US$2282 (INR169 000) per DALY averted.

Conclusions Nationwide introduction of single-dose HPV vaccination at age 10 in India is highly likely to be cost-effective whereas extending the number of doses from one to two would have a less favourable profile.

INTRODUCTION
Cervical cancer is a major public health problem. Globally, an estimated 604000 women were diagnosed with cervical cancer, and 342000 died from cervical cancer in 2020.1 Most of the cancer burden is located in low-income and middle-income countries (LMICs), and in particular, one-sixth of the future cervical cancer cases will be diagnosed in India.2 Human papillomavirus (HPV) vaccination has a high efficacy for preventing cervical cancer3 4 and is a key component of the WHO strategy for worldwide elimination of cervical cancer as a public health problem.5 The prospect of introducing HPV vaccination into the Indian national immunisation programme (NIP) has improved following the recent marketing authorisation

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ In 2020, the WHO launched a global call for elimination of cervical cancer as a public health problem, of which human papillomavirus (HPV) vaccination is a key pillar. However, access to HPV vaccination in India is still very low.
⇒ In April 2022, the WHO Strategic Advisory Group of Experts issued a recommendation for countries to update their dosing schedules to include a single-dose option. Single-dose HPV vaccination is likely to be more affordable and would greatly facilitate the implementation of HPV vaccination.
⇒ The key questions for India are whether, with a realistic cost-effectiveness threshold (30% gross domestic product (GDP) per capita), single-dose HPV vaccination would be a cost-effective intervention; and whether two-dose vaccination could still be affordable and worthwhile compared with a single-dose schedule, given the uncertainty in its initial efficacy and long-term protection.

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WHAT THIS STUDY ADDS

⇒ We used state-specific cancer incidence and locally collected cost data and built plausible vaccination efficacy scenarios based on the International Agency for Research on Cancer India trial to inform the cost-effectiveness estimates.

⇒ Single-dose vaccination in India would be cost-effective under a cost-effectiveness threshold of 30% of the Indian GDP per capita and the annual investment would be less than 10% of the cost of the current Indian universal childhood vaccination programme.

⇒ Even though there was substantial heterogeneity, we confirmed that single-dose vaccination would be cost-effective across all Indian states.

⇒ Catch-up single-dose vaccination to age 15 or 20 in the first year of introduction is a cost-effective strategy. However, the decision to implement catch-up will depend on the willingness of the health authorities to support a higher initial investment. We found two-dose vaccination to have a less favourable cost-effectiveness profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Single-dose vaccination achieved a better balance between health benefits and financial burden than two-dose vaccination, even after taking into account uncertainty in the level of protection provided by single-dose HPV vaccination.

⇒ Our results could be used by Indian health authorities at the national and state level to inform their decision and planning of the implementation of HPV vaccination in India and could convey several lessons for other low-income and middle-income countries.

granted to a nationally produced vaccine. However, at its current cost, implementing two-dose HPV vaccination still requires a large investment, while the health benefits could take decades to accrue.

In April 2022, the WHO Strategic Advisory Group of Experts recommended countries to update their dosing schedules to include a single-dose option. This recommendation was based on data from the IARC (International Agency for Research on Cancer) India vaccine trial, the randomised controlled trial in Kenya, and other evidence demonstrating high efficacy of single-dose protection against persistent HPV 16/18 infection, comparable to two doses. Single-dose vaccination could make HPV vaccination more affordable. However, there is uncertainty regarding the protection afforded by single-dose vaccination beyond 10 years, since antibody levels induced by single-dose vaccination appear to be lower than by multiple-dose vaccination.

In this study, we derived a comprehensive projection of the health and economic effects of vaccinating girls against HPV in India. As decisions on introducing HPV vaccination and on the required dose schedule must be made well ahead of obtaining information on long-term single-dose protection, this modelling analysis aimed to help inform Indian policymakers in their decision-making on cervical cancer prevention by assessing the cost-effectiveness of single-dose and two-dose HPV vaccination, under a more stringent cost-effectiveness threshold suggested for LMICs (30% gross domestic product (GDP) per capita) in recent health economics literature. For this, we used a 10-year follow-up data from the IARC India vaccine trial to derive single-dose vaccine efficacy and duration of protection scenarios, and demographic, epidemiological and cost data on a state-specific level, to obtain nationwide and state-specific projections for India.

METHODS

Patient involvement

No patients were involved in the design and conduct of this research.

Modelling approach

We combined an HPV transmission model and a cervical cancer progression model to estimate the health and economic effects of HPV vaccination. The first model, EpiMetHeos, is an agent-based model which extends an open source framework (EpiModel) for the simulation of dynamic contact networks, and describes transmission of 13 type-specific HPV infection types in India. This model is extensively described in Man et al. Using HPV incidence estimated from EpiMetHeos, a microsimulation model (described in online supplemental appendix 1) was used to simulate each individual’s disease progression, from multiple HPV infections to cervical intraepithelial neoplasia (CIN), cervical cancer and death.

We assumed that while HPV infection incidence can be country-specific or state-specific, the natural history of HPV infection to cervical cancer does not vary across countries. This is a biologically plausible assumption for women who are not immunocompromised and is commonly adopted in multicountry modelling studies. Natural history parameters were estimated in previous publications based on longitudinal follow-up in the POBASCAM study and by statistically linking the age distributions of CIN2+ and cervical cancer, based on data from the Dutch National Pathology Databank and the Dutch Cancer Registry. Further details are provided in online supplemental table A.1 and figure A.1.

Model adaptation to India

We calibrated the model to Indian national and subnational data to derive nationwide-specific and state-specific impact projections of HPV vaccination. Since not all Indian states had high-quality data on cervical cancer incidence, we derived state-level projections in three steps: (1) we identified clusters of states with high or low cancer incidence; (2) we calibrated EpiMetHeos to type-specific HPV prevalence and sexual behaviour data from a representative high (Tamil Nadu) and low (West Bengal) cancer incidence state (online supplemental figure A.2); (3) we used the resulting projections to extrapolate cancer incidence to other states within the same cluster. Details about the calibration and clustering are provided elsewhere.

Furthermore, we adjusted the cancer detection rates to match the observed cervical cancer stage distribution.
in India (online supplemental table A.2), and we used key Indian demographic and epidemiological data, including background mortality rate, age distribution and hysterectomy rate (online supplemental table A.3).23

Finally, we extracted a 5-year Indian cancer survival based on a literature review (online supplemental table A.4). Throughout this study, we assumed that no screening took place in India, which is justified by the current very low uptake of opportunistic screening.24

Cost data collection

We collected Indian data on cervical cancer treatment costs from four hospitals and from the literature (online supplemental tables A.5–A.8).25 Cost of the HPV vaccine was set at the GAVI (Global Alliance for Vaccines and Immunisation) price (US$4.5 per dose). Costs of vaccination programme implementation and delivery were collected for the state of Sikkim, where a pilot HPV programme was implemented. In order to extrapolate these costs to the rest of India, we used state-level delivery cost estimates of the childhood vaccination programme, and assumed that the relative differences in delivery costs between states were the same for these programmes (online supplemental tables A.9–A.12).26
Vaccination scenarios

In the base-case scenario, we set vaccination age at 10 years and coverage at 90% as per WHO recommendations. We evaluated both a single-dose and a two-dose schedule. For the two-dose schedule, we assumed no drop-out between the first and second dose. We derived four assumptions of vaccine efficacy, based on the lower bound of the vaccine efficacy estimate of the IARC India vaccine trial,9 and duration of single-dose protection, informed by trial immunogenicity data, based on the time until antibody levels of HPV 16/18 have decreased below different detection thresholds. We refer to Man et al.9 for details on the construction of these assumptions. In assumption A (used in the base-case scenario), vaccine efficacies under single-dose schedule were assumed to be 95% for HPV 16/18, 9% for HPV 31/33/45 and 0% for the remaining oncogenic HPV types, with lifetime duration of vaccine protection. This contrasts with assumptions B, C and D who have a decreasing vaccine efficacy. Assumption B has the same initial efficacy as assumption A while assumptions C and D had a lower initial efficacy equal to 90% and 85% for HPV16 and 85% and 55% for HPV18. Twenty years after the start of vaccination, assumptions B, C and D corresponded to a remaining vaccine efficacy of approximately 80%, 75% and 65% of the initial efficacy for HPV 16/18, respectively. (online supplemental table A.13).

In combination with vaccine efficacy and waning assumptions A–D, we evaluated multiple levels of vaccination coverage (60%–100%). Finally, we also considered scenarios with catch-up (CU) vaccination to age 15 or 20 when vaccination was introduced. Catch-up was defined as a one-time vaccination campaign in the first year of vaccination. An overview of vaccination scenarios is shown in online supplemental table A.14.

Model outcomes

We provide model-based projections of cervical cancer incidence reductions (online supplemental table A.15) and disability-adjusted life-years (DALYs) averted compared with no vaccination, as well as the costs of vaccination and savings from cancer treatment costs. We used these outcomes to compute the incremental costs and health effects relative to no vaccination and return on investment (ROI) of single-dose vaccination. ROI was calculated as the ratio between saved cancer treatment costs and vaccination costs and converted to a percentage. We also reported the total cost in the first year of the introduction of vaccination. We estimated the incremental cost-effectiveness ratio (ICER) of single dose versus no vaccination, and of two dose versus single dose and no vaccination, using a healthcare sector perspective.27 This perspective includes direct medical costs and out-of-pocket costs for the patient. ICER was estimated for the whole country and for each Indian state separately.

Model outcomes are presented by year since the start of vaccination. Time horizon of the analysis is 100 years starting at the year in which vaccination was introduced. This time horizon was chosen to account for the very long-term consequences of introducing HPV vaccination. Costs are shown in US$ (₹INR in the online supplemental file) and as a sensitivity analysis in $IUSD (international US dollars), for international comparisons. We use 2020 prices and 2020 INR/USD and purchasing power parity conversion rates. We used a discount rate of 3% for DALYs and costs as recommended by WHO and also show undiscounted results. Disability weights and durations associated with each cervical cancer health state were based on the Global Burden of Disease 2017 version (online supplemental table A.16). We considered two cost-effectiveness thresholds for the ICER: (a) 100% of Indian GDP per capita, as per WHO recommendation (US$1995, ₹INR148 000) and (b) 30% of Indian GDP per capita (US$598, ₹INR44 000), based on previous estimates of actual cost-effectiveness thresholds for LMICs.12–14

This study adheres to HPV-FRAME, a quality framework for mathematical modelling evaluations of HPV-related cancer control.28 The checklist is reported in online supplemental tables A.17–A.20.

Univariate sensitivity analyses and probabilistic analysis

We varied several economic parameters used for the base-case vaccination scenario. We considered an increase from 3% to 6% in discount rate, a change in cancer treatment costs of ±50%, a change of ±50% in the costs of implementation and delivery of vaccination, and 2% yearly reduction in vaccine price, in the first 20 years after the introduction of vaccination, informed by longitudinal GAVI data on pneumococcal vaccine prices (online supplemental file).

In the probabilistic analysis, we included uncertainty distributions for the type-specific duration from CIN2/3 to cancer, 5-year stage-specific cancer survival probabilities, costs of cancer treatment, vaccination implementation and delivery costs. We also included variation in type-specific HPV incidence, based on the 100 best-fitting parameter sets of the transmission model. We ran 100 Monte Carlo simulations of the no vaccination and base-case scenarios, with sampled parameter values based on the distributions shown in online supplemental table A.21. Results are shown in a scatterplot and as a cost-acceptability curve. For the base-case scenario, we also report an uncertainty interval (UI) based on the 10th and 90th percentiles of the model outcomes.

RESULTS

Base-case scenario

The base-case scenario consisted of single-dose HPV vaccination of girls aged 10 with 90% coverage and lifetime protection (assumption A). Thirty years after the start of vaccination, annual cancer incidence was projected to decrease by 10% (UI: 4%, 14%). After 50, 75 and 100 years since start of vaccination, annual cancer incidence...
was projected to decrease by 45% (UI: 39%, 55%), 68% (UI: 63%, 76%) and 72% (UI: 65%, 79%), respectively (Figure 1, online supplemental figures B.1–B.6 and table B.1).

The total cost of introducing single-dose HPV vaccination was estimated at about US$106 million (UI: US$100 million, US$112 million) in the first year. With no discounting, the intervention would save US$388 000 per 100 000 women (UI: US$34 000, US$1607 000). The ROI was 32% (UI: 3%, 133%), meaning that US$1 spent on single-dose HPV vaccination results in a return of US$1.32 (online supplemental figures B.7 and B.8 (INR)). However, when discounting costs and DALYs averted at 3% per year, the costs of vaccination outweighed the costs saved from cancer treatment, resulting in an incremental cost of US$167 000 per 100000 women and a negative ROI of −42% (UI: −57%, 10%) (Figure 2). The ICER in the base-case scenario relative to no vaccination was US$406 per DALY averted (UI: cost saving to US$771), which is below the threshold of 30% of the Indian GDP per capita (Figure 2).

State-level ICERs are shown in Figure 3 and online supplemental table B.2. These ranged from US$67 to US$593 per DALY averted and, therefore, all states had an ICER below the 30% of GDP per capita threshold.

Figure 2 Incremental costs and health effects of single-dose and two-dose vaccination versus no vaccination. Costs are given in US$ at 2020 prices. Costs and disability-adjusted life-years (DALYs) averted are discounted at 3%. ICER denotes incremental cost-effectiveness ratio per DALY averted relative to no vaccination. Darker colours denote lower values. ICER, incremental cost-effectiveness ratio.
For states classified as high cancer incidence, the ICERs ranged between US$67 and US$336, while for states classified as low cancer incidence, the ICERs ranged between US$220 and US$593 per DALY averted.

**Scenarios of single-dose vaccine protection and vaccination coverage**

For the worst-case assumption D with 90% coverage, annual cancer incidence decreased by 51% after 100 years since start of vaccination, compared with 72% in the base case. ICERs under 90% coverage (relative to no vaccination) of assumptions B, C and D were equal to US$471, US$575 and US$733 per DALY averted, respectively, compared with US$406 per DALY averted in the base case. For 60% coverage, the ICER was US$307 for assumption A and US$707 for assumption D (figure 2). All scenarios had an ICER below the WHO threshold and all scenarios except D had an ICER below 30% of the Indian GDP per capita (figure 2, online supplemental figure B.9 for INR results).

**Two-dose vaccination**

We assumed that the health effects of two-dose vaccination were the same as for single-dose vaccination in the base case (assumption A). The total costs of two-dose vaccination in the first year were US$200 million. Relative to no vaccination, the incremental costs were US$578 000 per 100 000 women, compared with US$167 000 for single-dose vaccination, and the resulting ICER was US$14043 per DALY averted (figure 2 and online supplemental figure B.8). This is about 70% of the Indian GDP per capita. The ICER of two-dose vaccination compared with single-dose vaccination for scenarios under assumptions B, C and D was between US$2282 and US$19 502 per DALY averted (figure 4, online supplemental table B.1 and figure B.10 for INR results), above the WHO threshold (US$1995).

**Catch-up vaccination**

With catch-up to ages 15 and 20, we predicted a faster decline in annual cervical cancer incidence, for instance, of 16% and 21% after 30 years, instead of 10% without catch-up. Over time, however, annual cervical cancer incidence will become similar to the scenarios without catch-up. The total cost in the first year for catch-up to age 15 was US$475 million. With catch-up to ages 15 and 20, the ICER ranged between US$373 and US$410 per DALY averted (figure 4, online supplemental table B.3 and figure B.11 for INR results).

**Sensitivity analyses**

Valuing costs in $IUSD instead of US$ resulted in ICERs more favourable towards vaccination (online supplemental figure B.13–B.17). In the cost sensitivity analyses, we found that a 6% discount rate would substantially increase the ICER from US$406 in the base-case scenario to US$2513 per DALY averted (figure 5). Decreasing the treatment costs by 50%, or increasing implementation or delivery costs by 50%, resulted in an increase in the ICER to US$684 or 596 per DALY averted, respectively. When we assumed that vaccine price would drop at a rate of 2% per year, the ICER would decrease to US$127 per DALY averted.

Taking uncertainty in model parameters and cost variables into account via probabilistic analysis, we estimated that single-dose HPV vaccination had approximately 77% probability of being cost-effective at a threshold of 30% of the Indian GDP per capita. Only 1% of the sampled ICERs were above the WHO threshold. By contrast, in 13% of the draws, single-dose vaccination was cost saving (figure 6, online supplemental figure B.12 for INR results).

**DISCUSSION**

HPV vaccination is a key component of the WHO strategy towards elimination of cervical cancer as a public health problem globally. In Man et al,16 we showed that an NIP relying on single-dose vaccination for 10-year-old girls would be sufficient to meet the WHO-defined elimination target across India. Here, we show that such a programme would have an ICER of US$406 (INR30 000) per DALY averted, far below the WHO-recommended threshold for cost-effective interventions of 100% GDP per capita (US$1995, INR148 000) and a high probability of achieving an ICER below the more realistic willingness-to-pay threshold of 30% GDP per capita, suggested in previous studies.12–14 This corresponds to a total first-year
investments equivalent to 9% of the annual budget of the Indian universal childhood immunisation programme, which currently includes 12 vaccine preventable pathogens.26 We also show that catch-up single-dose vaccination up to ages 15 or 20 is a cost-effective strategy. For a one-off catch-up campaign to age 15, this cost would...
be comparable to 40% of the annual cost of the Indian universal childhood vaccination programme.

Furthermore, while we found substantial state-level heterogeneity in the ICERs, depending on the projected level of cervical cancer incidence and delivery costs, the 30% threshold was met in every state without exception. On the other hand, we found two-dose HPV vaccination to have a much less favourable cost-effectiveness profile, with an ICER against no vaccination of about 70% of Indian GDP per capita at the current GAVI supported price, and, even for the worst case scenario of single dose protection, an ICER against single-dose vaccination of US$2282 (INR169 000) per DALY averted, which is well above the WHO threshold (US$1995).

The health and economic effects of introducing HPV vaccination in India have been investigated before. Two previous studies have assessed the cost-effectiveness of two-dose vaccination in India, and one study assessed the cost-effectiveness of single-dose vaccination. All studies valued costs in IUSD and found that HPV vaccination would be cost-effective at a threshold of 100% GDP per capita. While there is no official cost-effectiveness threshold for India, and current willingness-to-pay estimates are uncertain, there is an agreement that a threshold well below 100% of national GDP better reflects opportunity costs for LMICs than the WHO recommendation. Compared with previous studies, our projections are therefore more conservative.
Another strength of our approach, relative to previous studies, is our reliance on context-specific data. Assumptions concerning efficacy and long-term protection given by single-dose HPV vaccination were based on efficacy and immunogenicity data from the IARC India vaccine trial.9 We used state-specific data on cervical cancer incidence and sexual behaviour to project the state-specific impact of HPV vaccination. Treatment costs were collected from Indian hospitals and from the literature. Implementation and delivery costs of HPV vaccination were collected from Sikkim state government. Extrapolation to obtain national cost data was informed by a recent district level cost analysis of routine childhood immunisation in India.26 This also enabled us to quantify the budgetary requirement for HPV vaccine introduction in India in terms of the Indian universal childhood immunisation programme. Estimates of first year investment and return on investment are often lacking in cost-effectiveness studies of HPV vaccine introduction in LMICs, and have not been previously available for India.

Our study also has limitations. Some of these relate to uncertainty around sexual behaviour and cancer incidence trends in India and are discussed in Man et al.16 There are also limitations concerning the economic input. While our treatment costs are based on Indian data, it was difficult to obtain a representative sample of costs for the whole country. Our implementation and delivery costs were extrapolated from Sikkim government data, however this state has a relatively small population. Furthermore, we used a payer perspective and therefore
we did not take into account costs related to productivity losses.

Implementing cervical cancer screening along with nationwide introduction of HPV vaccination could further speed up reduction in cervical cancer incidence. However, currently in India, there are multiple cultural, financial and logistical barriers restricting access to screening, with only 2% of women screened in the age group 35–50 years.24 If single-dose HPV vaccination is implemented, a screening programme could still be worthwhile to align with the WHO strategic targets for cervical cancer elimination in the near future.

In this mathematical modelling study, we have shown that single-dose HPV vaccine introduction in India is likely to be cost-effective under a stringent willingness-to-pay threshold of 30% of the GDP per capita. Two-dose vaccination would have a less favourable cost-effectiveness profile. These results could be used by Indian government health officials in their decision-making on the introduction of HPV vaccination and could convey several lessons for implementation in other LMICs.

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