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Potential health impact and cost-effectiveness of human papillomavirus vaccination in Tunisia: A comparative modeling study

Oumaima Laraj [a,c], Beya Benzina [a], Ahlem Gzara [a], Amira Kebir [a,b], Kaja Abbas [d,e,f,g,h], Slimane BenMiled [a,*]

[a] Public Health Modeling Team, IPT-BIMS, Pasteur Institute of Tunis, University of Tunis el Manar, Place Pasteur, Tunis, 1000, Tunisia
[b] IPEIT, University of Tunis, Montfleury, Tunis, 1000, Tunisia
[c] Math. Dep., Univ. Mohammed V, Rabat, Morocco
[d] London School of Hygiene and Tropical Medicine, London, UK
[e] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[f] Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[g] Public Health Foundation of India, New Delhi, India
[h] National Institute of Infectious Diseases, Japan Institute for Health Security, Tokyo, Japan

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ABSTRACT

Background: Cervical cancer is one of the most prevalent cancers affecting women especially in low- and middle income countries and is caused by persistent infection with human papillomavirus (HPV). HPV vaccination can significantly reduce the cervical cancer burden. However, HPV vaccination is not yet included in the Tunisian immunization program. To inform decision-making on HPV vaccine introduction in Tunisia, we conducted a comparative modeling study to project the health impact and cost-effectiveness of four HPV vaccines (Cecolin, Cervarix, Gardasil, 4, and Gardasil-9) targeted to 12-year-old girls in 2025.

Methods: We used two static cohort models (UNIVAC and Papillomavirus Rapid Interface for Modeling and Economics (PRIME)) to estimate the health and economic impact of HPV vaccination from the health system and societal perspectives. Our data inputs to the model include demography and cervical cancer burden as well as unit costs for treatment, vaccines, and vaccine delivery. We estimated health impact in terms of cases, deaths, and disability-adjusted life years (DALYs) averted by HPV vaccination, and economic impact in terms of vaccination costs, treatment costs saved, net cost, and incremental cost-effectiveness ratios (ICERs).

Results: We estimated that Cecolin is the most cost-effective HPV vaccine in Tunisia, particularly when cross-protection is considered. Despite Cervarix offering greater health benefits of 70% versus 62% reductions in cervical cancer cases and deaths at 87% coverage, Cecolin has lower net costs and is more favorable across different willingness-to-pay (WTP) thresholds. At a WTP of USD 1169 per DALY averted (30% of Tunisia's GDP per capita), Cecolin and Cervarix demonstrate similar probabilities of being cost-effective.

Conclusion: Based on the vaccine impact estimates generated by the UNIVAC and PRIME models, we inferred that the four HPV vaccines (Cecolin, Cervarix Gardasil,4, and Gardasil-9) were cost-effective in the Tunisian context. This evidence is useful to inform HPV vaccine introduction in Tunisia.

1. Introduction

In November 2020, the World Health Organization (WHO) launched a global initiative to accelerate the elimination of cervical cancer as a public health problem. This initiative focuses on three key strategies: vaccination, screening, and treatment [1]. Cervical cancer is primarily caused by human papillomavirus (HPV) infection, which accounts for over 90% of cases [2]. HPV is a DNA virus with several genotypes, some of which are categorized as high-risk due to their cancer-causing potential. Specifically, HPV genotypes 16 and 18 are responsible for about 70% of global cervical cancer cases, while other high-risk genotypes include HPV 31, 33, 45, 52, and 58 [3].

Effective prevention strategies include vaccination against the most common HPV genotypes and regular screening through cervical cytology and HPV testing. The WHO's goal is to achieve 90% HPV vaccination coverage for girls by age 15, screen 70% of women, and ensure that 90% of those diagnosed receive treatment (90-70-90). Thus, HPV vaccination is a crucial component of cervical cancer prevention efforts.

* Corresponding author.
E-mail address: slimane.benmiled@fst.utm.tn (S. BenMiled).

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In Tunisia, HPV genotypes 16 and 18 are the most prevalent, with HPV 16 (61%) and HPV 18 (8.5%) being the most frequently detected in cervical cancer cases. Additionally, HPV 45, 35, and 56 were also identified in cervical cancer cases, though they were found at significantly lower rates [4].

In January 2024, Tunisia's Ministry of Health announced plans to incorporate the quadrivalent HPV vaccine into the national school vaccination program starting in 2025 for girls in the 6th year of primary school (*i.e.* aged 12 years old) [5]. With a vaccination program (DTaP/IPV vaccine) of an approximately 97% vaccination coverage in schools and a 92% enrollment rate, Tunisia is well-positioned for widespread HPV vaccination.

Mathematical models are useful for studying the spread and control of HPV, as they simulate its progression in populations using demographic, epidemiological, and clinical data [6,7]. The vaccine impact models estimate the health benefits of cases, deaths, and disability-adjusted life years (DALYs) averted by vaccination, and the economic impact in terms of incremental cost per DALY averted. For our analysis in Tunisia, we used and compared the outputs of the PRIME model (Papillomavirus Rapid Interface for Modeling and Economics) [8] and the UNIVAC model [9].

Given budget constraints, it is important for decision-makers to conduct an epidemiological and economic analysis to determine the optimal vaccination strategies for Tunisia, including the choice of vaccine. The national technical vaccination committee initially decided to follow the WHO's strategy of using a single dose of the quadrivalent vaccine [10]. The negotiated price of this vaccine is USD 17, including all related charges. However, bivalent vaccines (Cervarix and Cecolin) might offer a better cost-effectiveness ratio at a lower prices of USD 12 and USD 5, respectively,

The primary objective of our study is to evaluate the health and economic impacts of HPV vaccination for 12-year-old girls in Tunisia, considering various vaccine options, their costs and cost-effectiveness. Specifically, we assess the health benefits of different HPV vaccines (Cecolin, Cervarix, Gardasil-4, and Gardasil-9) by estimating the reduction in cervical cancer cases, deaths, and DALYs over the lifetime of a birth cohort vaccinated in 2025, both with and without cross-protection. We assess the economic outcomes of each vaccine option, including discounted implementation and treatment costs, and evaluate the cost-effectiveness from both governmental and societal perspectives. We present a comparative analysis of vaccine impact projections using the PRIME and UNIVAC models, and evaluate the projected cost-effectiveness of incorporating the HPV vaccine into Tunisia's national immunization program.

2. Methods

2.1. Modeling approach

We used the PRIME and UNIVAC models to project the health and economic impact of HPV vaccination at the national level in Tunisia. Both the PRIME and UNIVAC models are static multi-cohort, proportional impact models used to estimate the impact of HPV vaccination on cervical cancer cases, deaths, and DALYs. The UNIVAC model uses United Nations (2019 revision) population estimates and evaluates catch-up campaigns, stratified cervical cancer cases by stage, and hospitalizations, while the PRIME model focuses on the cost-effectiveness of vaccinating females before sexual debut, utilizing country-specific data and customizable inputs. Both models do not account for indirect effects, thereby making their estimates conservative. Appendix Table 1 outlines the similarities and differences between these models.

We evaluate the impact of HPV vaccination across of the lifetime of 12-year-old girls vaccinated in 2025 (that is analyzing a cohort of girls born in 2013) who are followed up to the age of 100 years. Input data on birth and vaccination cohort sizes were obtained from the Tunisian National Institute of Statistics [11]. We estimated the number of cases, deaths, and disability-adjusted life years (DALYs) with and without vaccination. Burden estimates were aggregated over the lifetimes of the cohort of vaccinated girls. The direct impact of vaccination is calculated for each year of age by multiplying vaccine coverage by vaccine efficacy, adjusted for the HPV type distribution and the assumed efficacy of each vaccine product against each HPV type. The model also estimates the costs of the HPV vaccination program and healthcare costs, with and without vaccination.

Model inputs related to vaccine aspects (*e.g* efficacy, program costs, and delivery expenses), as well as cervical cancer considerations, including disease burden and treatment costs, were sourced from a combination of published local and global Refs. [4,12,13] and insights provided by the ministerial commission for HPV and the cancer registry officials at the MoH [14].

To eliminate the effect of the time value of money, all future costs and health benefits were discounted at a rate of 3% over a lifetime time horizon, in line with WHO guidelines on health economics for immunization programs. However, as per WHO recommendations, an additional discounting scenario of 0% for health benefits and 3% for costs could also be considered [15]. All costs represent USD 2024. We calculated the probability of vaccine being cost-effective over a range of alternative possible WTP thresholds up to 0.3 times the national GDP per capita (USD 3747 in the year 2024) [11] as Tunisia does not have a strict willingness-to-pay (WTP) threshold for determining the cost-effectiveness of an intervention.

We conducted our analysis from societal and governmental perspectives. We compared the costs and health effects of the HPV vaccination strategies in comparison to no vaccination. The results of the economic evaluation were expressed by incremental cost-effectiveness ratios (ICER), and ICER indicators that were constructed based on the disability-adjusted life years (DALYs), were reported for the two modeling approaches. The evaluation assumed that the target population had not been infected with HPV prior to vaccination. The primary outcome measure is the cost (USD) per DALY averted, accounting for all costs and benefits aggregated over the cohort of vaccinated girls (2025).

2.2. Disease burden

We used age-specific rates of cervical cancer cases and deaths estimated for Tunisia from the global database of GLOBOCAN 2022 [12] and assumed these rates related to local, regional and distant stages [16] would remain constant over time in the absence of vaccination. For the proportion of cervical cancer that is attributed to the HPV genotype targeted by the vaccines (*e.g.,* HPV 16/18 and HPV 16/18, 31, 33, 45, 52, and 58), we used estimates provided by [4]. Inputs for disease burden are summarized in Appendix Table 2.

The disability weights and durations for the different phases of cervical cancer are used to estimate the years of life lost due to disability. These weights are evaluated for the various phases of cervical cancer: the diagnosis and primary treatment phase, the non-terminal sequelae phase, and the terminal phase, based on the Global Burden of Disease (GBD) studies [17]. In the UNIVAC model, we assumed that cases were distributed into local, regional, and distant cancer categories, using the International Federation of Gynecology and Obstetrics (FIGO) staging system and information from published studies in Tunisia [16]. Age-specific disease incidence, mortality and cancer distribution are reported in Fig. 1. Average five-year survival rates were based on a recent report of cervical cancer survival in Tunisia from National Cancer Institute in 2023 [14].

2.3. Healthcare costs

While the cancer care system in Tunisia is generally effective, early screening is still not widely implemented. For the purposes of our analysis, we assumed that all women reflected in the GLOBOCAN

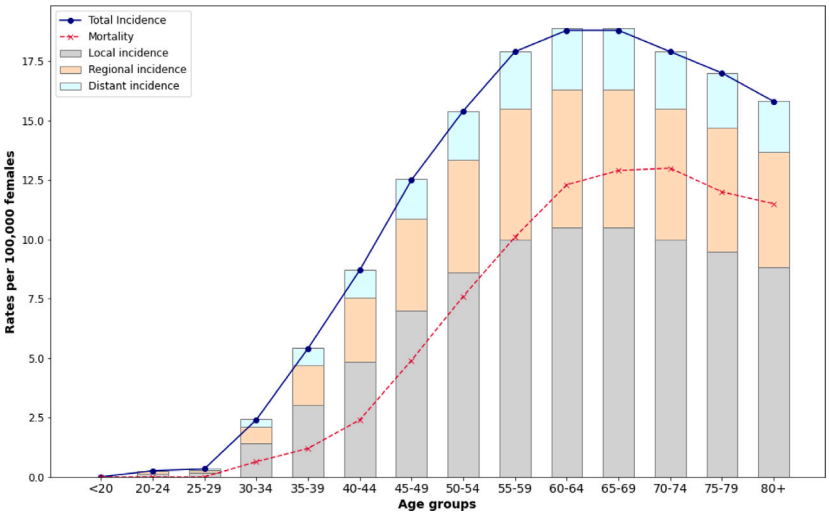


Fig. 1. Age-specific cervical cancer burden by stage in Tunisia (2022).

incidence rates [12] would be diagnosed and treated, allowing us to apply the average cost of cervical cancer treatment to this population.

Direct treatment-related costs were derived from an existing cost study in the Salah Azaiez Institute that estimated the stage-specific treatment costs for cervical cancer in Tunisia. Each stage of cancer classification required different medical interventions including clinical, biological, radiological, and pharmaceutic resources. The economic direct cost of treating the various stages of cervical cancer in Tunisia in 2023 ranged between USD 532 and USD 2603, depending on the stage of the disease [14]. This includes costs related to diagnosis and staging, surgery (simple/radical hysterectomy), chemotherapy, radiotherapy, and palliative care. In PRIME, the cancer treatment cost per episode over lifetime was calculated as the average cost of treatment for the different procedures related to three stages. Inputs for healthcare costs are summarized in Appendix Table 3. In contrast, direct medical costs of cervical cancer treatment by stage is considered in the UNIVAC model. The FIGO (International Federation of Gynecology and Obstetrics) staging system, ranging from early localized stages (IA and IB) to more advanced stages (II, III, IVA) and distant metastases (IVB), is used to classify the extent of cervical cancer. Costs associated with these stages vary significantly, reflecting the complexity and intensity of required interventions. For FIGO Stage IA, involving very early and localized cancer, the cost is approximately USD 550, covering the initial gynecological examination, inpatient stay, and necessary pre-operative tests. In contrast, stages IB1 and IB2, which involve more extensive but still localized cancer, have a mean cost of USD 585, including laparoscopy, curettage, radical hysterectomy or trachelectomy, and possible hospital stays. More advanced stages, such as IB3, II, IIIA, IIIB, and IVA, which require complex treatments like PET scans, radiotherapy, chemotherapy, and brachytherapy, incur significantly higher costs, averaging USD 2603. Stage IIIC, characterized by lymph node involvement, also requires intensive treatment with a mean cost of USD 1800. For Stage IVB, involving distant metastasis, the cost averages USD 750, covering palliative chemotherapy and related hospital care. Thus, we estimated the overall costs of cervical cancer treatment at USD 2603 for local stages, USD 1800 for regional stages, and USD 750 for distant stages, with an assumed average cancer treatment cost of USD 2445.14 in the PRIME model.

Treatment costs from a societal perspective were evaluated for the cost-effectiveness analysis. These costs included both direct medical costs and indirect costs (opportunity costs of women's time for procedures). Indirect treatment costs, limited to productivity loss due to ill health, include convalescence if they had hospital stays or recovery time, time waiting for test results and time costs associated with travel to/from hospital visits. Productivity loss related to absenteeism was derived using the human capital approach; the total number of workdays lost multiplied by the average daily wage of a cervical cancer patient. Due to data limitations, the number of days lost due to productivity was derived from a previous micro-costing study conducted in Vietnam [18]. For productivity loss due to illness, we applied the Tunisia 2023 median wage, reported as 30 Tunisian dinars corresponding to USD 9.68 per day. Thus, average cancer treatment cost from a societal perspective is the sum of average cancer treatment cost from a healthcare perspective and productivity loss (estimated to be USD 1452 for 150 days of absence due to ill health).

2.4. Vaccination scenarios and related parameters

Plausible strategies for introducing the HPV vaccine in Tunisia were developed with input from key stakeholders, including the Tunisian Ministry of Health. The modeling assumed that vaccination would start in 2025, using a school-based delivery strategy with an expected coverage of 87%. We considered four highly effective and safe HPV vaccines currently available worldwide: **Cervarix bivalent** (GlaxoSmithKline Biologicals, Belgium), **Cecolin bivalent** (Xiamen Innovax Biotech Co, China), **Gardasil quadrivalent** (Merck & Co., USA), and **Gardasil-9 nonavalent** (Merck & Co., USA). The bivalent vaccines target HPV types 16 and 18, the quadrivalent targets types 16, 18, (plus types 6, and 11 which cause genital warts), and the nonavalent vaccine covers additional high-risk strains (e.g., HPV 31, 33, 45, 52, 58) not included in the bivalent or quadrivalent vaccines.

Our analysis compared these vaccines against no vaccination (with no changes to existing cervical cancer screening and treatment strategies) and against each other. For our central estimates, we assumed a single-dose administration for each vaccine to a cohort of 12-year-old girls. Tunisia's recommended school-based model is based on a 87% coverage rate. We evaluated the impact of HPV vaccination for a single cohort of 12-year-old girls in 2025, assigning protection rates of 90%–98% against genotypes directly targeted by the vaccines. Specifically, we assumed 97% protection for HPV-16 and 18 with Cecolin [19], 98% efficacy against HPV-16/18/6/11 with Gardasil-4 [20], and 96.7% protection against HPV-16/18/31/33/45/52/58 with Gardasil-9 [21], all for a single-dose vaccination schedule. Efficacy estimates for Cervarix were taken from [22]. We evaluated three strategies: single-dose nonavalent vaccine at the best negotiated price, single-dose quadrivalent vaccine at the manufacturer's listed price, and single-dose bivalent vaccines at different listed prices for Cecolin and Cervarix. The baseline scenario was no vaccination, representing the current state in Tunisia.

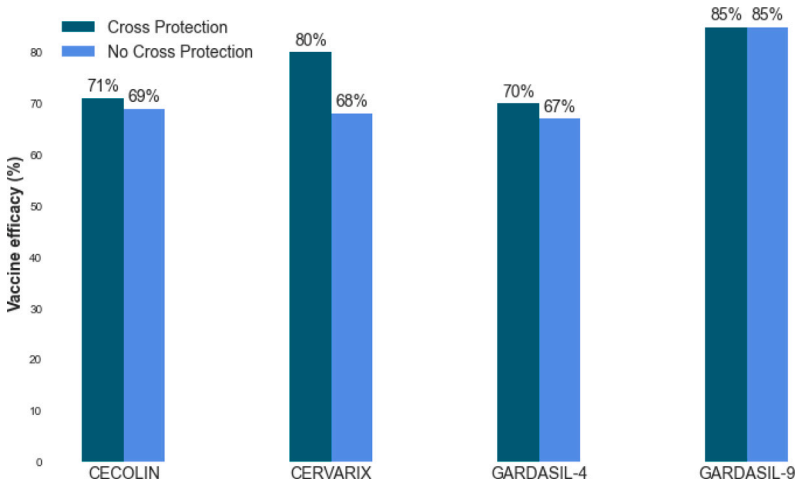


Fig. 2. Weighted vaccine efficacy of one dose against cervical cancer cases and deaths in Tunisia with and without cross-protection.

Vaccine impact calculations. The HPV type distribution in Tunisia was taken from estimates identified among invasive cervical cancer cases, reported by the HPV Information Center [4]. The top three prevalent HPV types were 16 (61%), 18 (8.5%) and 45 (5%).

Studies have shown that one dose of HPV vaccination could provide similar benefits to two doses [23] and that vaccines offer some level of cross-protection against genotypes not covered by the vaccine [19,20]. In our analyses, we also accounted for this cross-protection against non-vaccine types. We relied on evidence from a systematic review to estimate the degree of cross-protection offered by HPV vaccines against various genotypes [24]. In cases where multiple commercial brands of the same type of vaccine (bivalent, quadrivalent, or nonavalent) were mentioned, we averaged the degree of protection across these brands.

There is uncertainty about the scale of cross-protection to non-vaccine types that might be associated with each of the four vaccine products, so weighted efficacy values were derived by multiplying the efficacy assumed for each HPV type by the proportion of cervical cancers caused by each type in Tunisia. Based on these interpretations, we adjusted the cross-protection matrix of vaccines to reflect these observations. This updated matrix was used to estimate the effectiveness of vaccines against the HPV genotypes. The overall weighted efficacies of the four products (Cecolin, Cervarix, Gardasil, Gardasil-9) were estimated to be 69% [19], 68% [22], 67% [20], and 85%, respectively, without cross-protection. For Cervarix, we assumed there could be cross-protective efficacy against types 31, 33, 45, 51, 52, and 56 based on a study by Wheeler et al. [25]. The influential cross-protection assumptions for Gardasil-4 were taken from a study by Brown et al. [24] and was used with cross-protective efficacy against type 31. Additionally, the analysis of cross-protection was performed only for bivalent and quadrivalent vaccines, as we did not find documentation on the evaluation of the nonavalent vaccine, introduced in 2014. Fig. 2 provides a detailed presentation of the cross-protection matrix of vaccines. Due to the similarity in efficacy with and without cross-protection for Cecolin, Gardasil-4 and Gardasil-9, we restricted our primary analysis to five scenarios. The first four scenarios assumed no cross protection for each product. We then ran two additional scenarios for Cecolin and Cervarix with cross-protection.

Vaccine program costs. Tunisia is not eligible for vaccine financial support from Gavi. We accounted the full cost of the vaccine program to be borne by the government. Input data for vaccine program costs are summarized in Appendix Table 4, and include the costs of the vaccines, syringes, and safety boxes together with the costs of international delivery and other supplies associated with the delivery strategy (e.g., additional staff time, training, cold-chain capacity etc.). As Tunisia is not eligible for receiving support through the GAVI mechanism, the prices of self-procurement of Cecolin, Cervarix, and Gardasil-4 were evaluated at USD 3.65, USD 10.25 and USD 14.14, respectively [13]. Gardasil-9 is not yet supported from GAVI, thus, we assumed a price of USD 25.00 per dose based on the lowest negotiated price for a non-Gavi country according to the MI4A/V3P vaccine purchase data [26]. Self-financing countries initially receive either a lump sum from Gavi vaccine introduction grants (VIGs) to subsidize the costs of HPV vaccination delivery, or support for the vaccine prices to facilitate the initial introduction of vaccination. Tunisia will receive support from Gavi, which will cover 50% of the cost of the vaccine to be procured in the first year. Additionally, funding for medical staff training and other incremental costs associated with the delivery strategy will be provided. International handling fees and costs for other supplies (syringes and safety boxes) were based on data reported from UNICEF Supply Division [27], while the delivery fee was sourced from Vodicka et al. [28]. These fees are obtained as a percentage of the dose price. We assumed a 3% international handling fee including transport and logistics, a 5% vaccine wastage rate for vaccines available in a one-dose vial presentation (Cecolin, Gardasil-4 and Gardasil-9) and a two-dose vial for Cervarix. We assumed further a 10% international delivery fee to cover the cost of insurance, customs duties and taxes. Prices for syringes were evaluated at USD 0.07 per dose and USD 1.30 per box (with 100 syringes per safety box), respectively. The incremental health system cost per dose was estimated based on the HPV introduction plan budget made by the Tunisian government. In PRIME model, a total vaccine delivery cost per dose was calculated based on all these incremental costs.

2.5. Sensitive and uncertainty analysis

Sensitivity analysis was performed to evaluate the robustness of the model results. We conducted for each vaccine, a probabilistic sensitivity analysis to assess the impact of combined parameter uncertainty on the cost-effectiveness ratios. We ran separate PSAs for each vaccine product without cross-protection and two additional scenarios for Cecolin and Cervarix with cross-protection (1000 runs per scenario). All parameters were varied simultaneously with random draws from their plausible ranges. Prices were assumed to be fixed within the PSA and 95% uncertainty intervals was assumed to represent the 2.5th and 97.5th percentiles of probabilistic simulations. For each probabilistic simulation, parameters were drawn from a distribution with a mean equal to the point estimate and range equal to the low and high values

Table 1
Lifetime health effects of each vaccine option (Bivalents: Cecolin, and Cervarix, quadrivalent: Gardasil-4 and nonavalent: Gardasil-9) compared to no vaccine and to each other in the UNIVAC model for Tunisian girls aged 12 years old vaccinated in 2025 without cross protection.

No cross protection	No vaccine	Cecolin	Cervarix	Gardasil-4	Gardasil-9
Health outcomes					
Cervical cancer cases (local)	440	176	180	183	115
Cervical cancer cases (regional)	243	97	99	101	63
Cervical cancer cases (distant)	106	42	43	44	28
Cervical cancer cases with treatment	788	315	322	329	205
Cervical cancer deaths	462	185	189	193	120
DALYs (discounted)	2495	997	1019	1041	650
Differences (comparator = no vaccine)					
Cervical cancer cases (local)	–	264	260	256	325
Cervical cancer cases (regional)	–	146	144	142	180
Cervical cancer cases (distant)	–	63	62	62	78
Cervical cancer cases with treatment	–	473	466	459	583
Cervical cancer deaths	–	277	273	269	342
DALYs (discounted)	–	1498	1476	1454	1845
Reduction in disease burden (%)	0%	60%	59.2%	58.3%	74%

Table 2
Lifetime health effects of each vaccine option (Bivalents: Cecolin and Cervarix, quadrivalent: Gardasil-4 and nonavalent: Gardasil-9) compared to no vaccination in the UNIVAC model for Tunisian girls aged 12 years old vaccinated in 2025 with cross protection.

Cross protection	No vaccine	Cecolin	Cervarix	Gardasil-4	Gardasil-9
Health outcomes					
Cervical cancer cases (local)	440	168	134	172	115
Cervical cancer cases (regional)	243	93	74	95	63
Cervical cancer cases (distant)	106	40	32	41	28
Cervical cancer cases with treatment	788	301	240	308	205
Cervical cancer deaths	462	177	140	181	120
DALYs (discounted)	2495	954	758	976	650
Differences (comparator = no vaccine)					
Cervical cancer cases (local)	–	272	306	268	325
Cervical cancer cases (regional)	–	150	169	148	180
Cervical cancer cases (distant)	–	65	74	64	78
Cervical cancer cases with treatment	–	487	549	480	583
Cervical cancer deaths	–	285	322	281	342
DALYs (discounted)	–	1541	1737	1519	1845
Reduction in disease burden (%)	0%	61.8%	69.7%	60.9%	74%

of the uncertainty range. In the absence of information about the shape of each distribution, the low, mid and high values for each input parameter were assumed to represent the mode and range within a series of PERT-Beta distributions. PSA results were represented as clouds on a cost-effectiveness plane and used to estimate the probability that each vaccine would be cost-effective at different WTP thresholds (cost-effectiveness acceptability curves).

3. Results

3.1. Health benefits

Vaccinating 12-year-old girls in 2025 involves vaccinating a single birth cohort of girls (born in 2013). Without HPV vaccination in Tunisia, based on the UNIVAC model, we estimated 788 cases, 462 deaths and 2495 DALYs (discounted) attributed to cervical cancer over the lifetime of this birth cohort.

Without cross-protection, Cecolin, Cervarix, and Gardasil-4 would each have a similar projected health impact (around 60% reduction in cervical cancer cases and deaths) during the lifetime of the vaccinated cohort. The impact of Gardasil-9 is estimated to be around 74% (Table 1).

In scenarios with cross-protection, Cecolin and Gardasil-4 would be expected to avert 62% and 61% of cervical cancer cases and deaths, respectively. In contrast, the health impact of Cervarix increased to around 70% and had substantially more health benefits than the other two products. Equivalent estimates for Gardasil-9 were 74% (Table 2).

Over the same period, based on the PRIME model, we estimated 608 cases, 338 deaths and 1621 DALYs (discounted) attributed to cervical cancer. The UNIVAC model projects a higher number of cervical cancer cases and deaths averted than the PRIME model by 23% and 27%, respectively (Fig. 3) assuming no cross protection. Specifically, the range of the potential health impact of HPV vaccination, in terms of the number of cervical cancer cases averted among girls vaccinated in 2025, is as follows: 364 to 473 for Cecolin, 359 to 466 for Cervarix, 354 to 459 for Gardasil-4, and 449 to 583 for Gardasil-9. Similarly, as both the years lived with disability for the estimated cervical cancer cases and the years of life lost for the estimated cervical cancer deaths contribute to the estimates of DALYs averted by the HPV vaccine, the UNIVAC model estimated 26% more DALYs averted than the PRIME model. However, the differences between the models in terms of the projected health outcomes of vaccination impact assuming no cross protection are slighty different by less than 1% (Fig. 4(a)).

We assumed that Cecolin would have approximately the same cross-protection as Gardasil-4, and no cross-protection was assumed for Gardasil-9. In scenarios with cross-protection, Cecolin could prevent around 62% of cervical cancer cases and deaths, while Cervarix could avert around 70% using both PRIME and UNIVAC models (Fig. 4(b)).

The main difference in the projected health outcomes of vaccination impact (estimates for cases, deaths, and DALYs averted) between the two models may be due to variations in population demography and age-specific life expectancy. As cervical cancer deaths are directly estimated from cervical cancer cases, the mortality estimation approach: stage-specific (UNIVAC) versus age-specific (PRIME) is likewise the main driver of the differences in the vaccination impact. However, the reduction in disease burden by vaccination compared to the baseline scenario of no vaccination, using the two different models with and without cross protection, differs only slightly (Fig. 4).

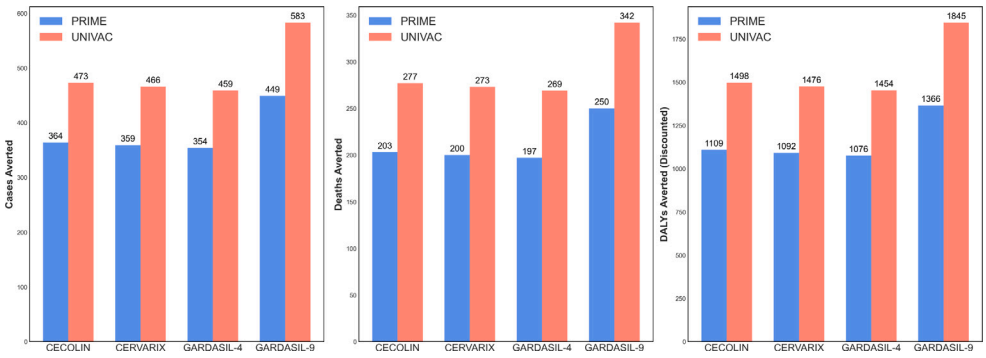
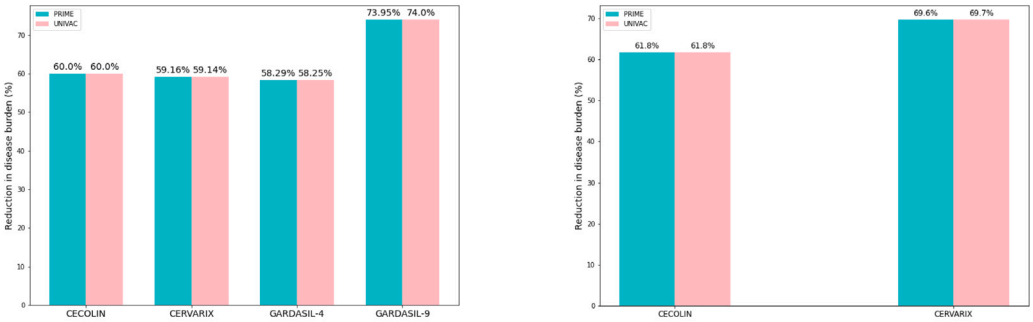


Fig. 3. Cervical cancer cases, deaths and DALYs averted by the four products (Cecolin, Cervarix, Gardasil-4 AND Gardasil-9) among girls vaccinated in 2025 over lifetime using PRIME and UNIVAC models without cross protection.



(a) No cross protection (b) Cross protection

Fig. 4. Vaccination impact in terms of reduction in disease burden among girls vaccinated in 2025 over lifetime for the four products (Cecolin, Cervarix, Gardasil-4 and Gardasil-9) using PRIME and UNIVAC models.

3.2. Economic outcomes

A single year of routine one-dose HPV vaccination requires substantial upfront investments in vaccine procurement and delivery. However, these costs are offset in the long term by the reduction in future cancer cases. The discounted costs of implementing each vaccine, according to the PRIME and UNIVAC models, are estimated as follows: USD 416,797 versus USD 416,801 for Cecolin, USD 1,157,421 versus USD 1,154,245 for Cervarix, USD 1,593,941 versus USD 1,588,890 for Gardasil-4, and USD 2,812,605 versus USD 2,802,320 for Gardasil-9 (Fig. 5).

From a governmental perspective, and assuming no cross-protection, we estimated the three vaccines (Cecolin, Cervarix, and Gardasil-4) to avert USD 235,000 in healthcare costs. In contrast, Gardasil-9 is projected to avert around USD 293,000 in healthcare costs in both the PRIME and UNIVAC models. Compared to no HPV vaccination, the averted healthcare costs for the three vaccines represent 60%, 59%, and 58% of the base case treatment costs, respectively. Gardasil-9 vaccination program, due to its higher effectiveness in preventing cancer cases, results in even lower overall disease-specific costs, with averted healthcare costs representing 74%. From a societal perspective, the healthcare costs averted by Cecolin, Cervarix, and Gardasil-4 are also around 60% of the base case costs, while for Gardasil-9, this figure is 74% (Fig. 5). When considering cross-protection, Cecolin is projected to avert 62% of healthcare costs compared to no HPV vaccination, both from governmental and societal perspectives. For Cervarix, the estimated healthcare costs averted rise to 70% (see Table 3).

When comparing economic outcomes between the PRIME and UNIVAC models, the results are closely aligned. Both models estimate similar costs for each vaccine, with only marginal differences in projected outcomes. For instance, the costs associated with implementing Cecolin, Cervarix, Gardasil-4, and Gardasil-9 differ by less than 1% between the two models. Additionally, both models project similar levels of healthcare costs averted across the different vaccines, reinforcing the robustness of the findings across varying modeling approaches (Fig. 5 and Table 3).

3.3. Cost-effectiveness analysis

National pre-adolescent HPV vaccination in Tunisia was projected to be cost-effective compared to no vaccination in all scenarios evaluated as the cost-effectiveness ratios were less than GDP per capita.

In PRIME, without cross protection, one-dose bivalent vaccination (Cecolin) has the lowest estimated net cost and most favorable cost-effectiveness ratio (0.04 (PRIME) times the national GDP per capita, evaluated at USD 3747 in Tunisia). Cecolin vaccination was projected to avert 1109 DALYs compared to no vaccination over the birth cohort. Vaccination under this scenario was expected to incur USD 179,198 more in discounted costs from the government perspective and USD 38,104 more from the societal perspective compared to no vaccination. Further, the incremental cost per DALY averted was USD 845 (government perspective) and 718 (societal perspective) for Cervarix vaccine. If cross-protection was not considered, Cervarix would be dominated by Cecolin because Cervarix would generate less impact at a higher net cost. Gardasil-4 is dominated by Cecolin and Cervarix because it averts fewer DALYs and costs more than both of these options. The cost per DALY averted was estimated to be USD 1266 from the government perspective and USD 1139 per DALY averted

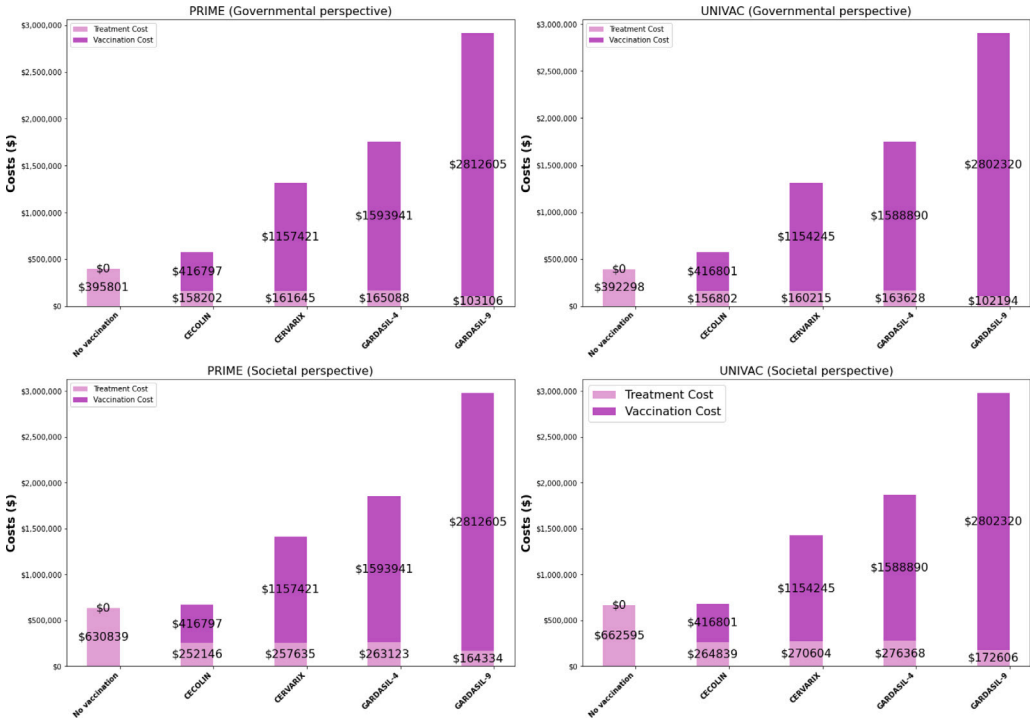


Fig. 5. Total discounted economic costs associated with one-dose human papillomavirus (HPV) vaccination at 87% coverage, over the lifetime of girls vaccinated at age 12 years alive in 2025. Vaccine program costs are estimated for each scenario of vaccination (Cecolin, Cervarix, Gardasil-4 and Gardasil-9). Healthcare treatment costs reflect disease costs associated with each strategy from a government and societal perspective (no cross protection).

Table 3
Discounted costs of HPV vaccination compared to no vaccination for Cecolin and Cervarix from government and societal perspectives. Lifetime economic outcomes using PRIME and UNIVAC models with cross protection.

Economic outcomes	PRIME			UNIVAC		
	No Vaccination	Vaccination	Difference	No Vaccination	Vaccination	Difference
Cecolin						
Vaccine program costs	0	416797	416797	0	416801	416801
Government healthcare costs	395800	151315	−244486	392298	149976	−242323
Societal healthcare costs	630839	241170	−389670	662595	253310	−409285
Cervarix						
Vaccine program costs	0	1157421	1157421	0	993271	993271
Government healthcare costs	395800	120323	−275477	392298	119259	−273040
Societal healthcare costs	630839	191775	−439064	662595	201429	−461166

from the societal perspective for this scenario. Gardasil-9 could achieve more benefit than Cecolin but would be substantially more expensive with incremental cost-effectiveness of USD 1845 from the government perspective (49% the national GDP per capita) and USD 1718 from the societal perspective (0.46 times the national GDP per capita) (Table 4). With cross protection, Cecolin had less favorable net cost than Cervarix (USD 172,311 versus USD 881,944) but Cervarix achieved substantially more health impact (70% versus 62%). In addition, Cecolin would have favorable incremental cost-effectiveness (USD 151 per DALY averted, or 0.04 times the national GDP per capita) when compared directly to Cervarix.

In scenrios without cross protection, UNIVAC estimates that the incremental cost per DALY averted was USD 121 for Cecolin, USD 625 for Cervarix, USD 935 for Gardasil-4 and USD 1362 for Gardasil-9 from a government perspective. From a societal perspective, the incremental cost per DALY averted was USD 13 for Cecolin, USD 516 for Cervarix, USD 827 for Gardasil-4 and USD 1253 for Gardasil-9. Overall, when compared to no vaccination, all four vaccines were cost-effective strategies for the prevention of cervical cancer. The incremental cost per DALY averted for all four vaccines was below USD 3747 (Tunisia's GDP per capita). Cecolin has the lowest net cost and most attractive cost-effectiveness (USD 121 per DALY averted from a government perspective and cost-saving from a societal perspective). Cervarix and Gardasil-4 would be dominated by Cecolin because these options would generate less impact at a higher net cost. The incremental cost-effectiveness of the remaining alternative (Gardasil-9) would exceed 0.3 times the national GDP per capita from either a government or societal perspective (Table 4). If cross protection was assumed, the estimated incremental cost per DALY averted by Cecolin was lower than Cervarix.

We estimate that all HPV vaccination in Tunisia will prevent a substantial number of cervical cancer cases and deaths. Dominated options are more expensive and generate fewer benefits than at least one alternative option. The efficiency frontier links the interventions that are not dominated and provides guidance. Any strategy that is placed on the frontier is reasonably efficient. Without cross-protection, Cecolin is likely to be the preferred product, generating lower net costs and

Table 4
Cost per DALY averted for each scenario (Cecolin, Cervarix, Gardasil-4 and Gardasil-9) compared to no vaccination (with and without cross protection).

Cost-effectiveness	PRIME		UNIVAC	
	Government Perspective	Societal Perspective	Government Perspective	Societal Perspective
Cecolin				
Discounted net costs (USD)	179198	38104	181304	19045
Discounted DALYs averted	1109	1109	1498	1498
ICER (Cost per DALY averted)	162	34	121	13
Cervarix				
Discounted net costs (USD)	923266	784217	922161	762254
Discounted DALYs averted	1092	1092	1476	1476
ICER (Cost per DALY averted)	845	718	625	516
Gardasil-4				
Discounted net costs (USD)	1363229	1226225	1360219	1202663
Discounted DALYs averted	1076	1076	1454	1454
ICER (Cost per DALY averted)	1266	1139	935	827
Gardasil-9				
Discounted net costs (USD)	2519911	2346100	2512216	2312331
Discounted DALYs averted	1366	1366	1845	1845
ICER (Cost per DALY averted)	1845	1718	1362	1253
Cecolin (*cross protection*)				
Discounted net costs (USD)	172311	27127	174478	7516
Discounted DALYs averted	1141	1141	1541	1541
ICER (Cost per DALY averted)	151	24	113	5
Cervarix (*cross protection*)				
Discounted net costs (USD)	881944	718357	881205	693079
Discounted DALYs averted	1285	1285	1737	1737
ICER (Cost per DALY averted)	686	559	507	399

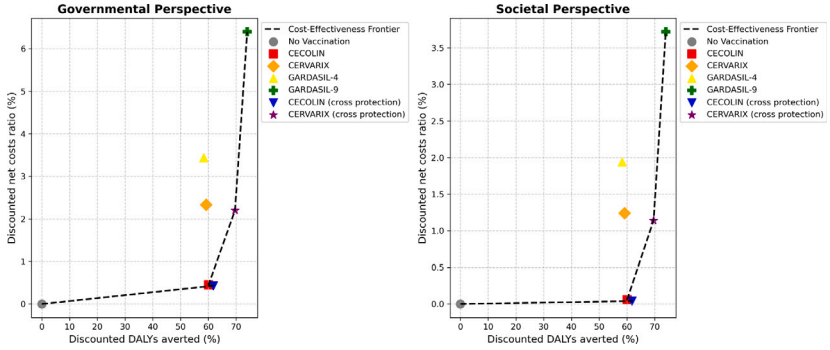


Fig. 6. Cost-effectiveness frontier between total discounted costs per scenario and discounted DALYs. Discounted costs (vaccination and treatment) and DALYs are drawn for all the strategies assessed in the base case scenario. Strategies include vaccination with Cecolin, Cervarix, Gardasil-4 and Gardasil-9. Bivalent vaccines differ by assuming cross protection or not.

similar benefits to both Gardasil-4 and Cervarix. With cross-protection, Cecolin also had the most favorable cost-effectiveness, even if Cervarix generated substantially more health benefits than Cecolin (70% versus 62% vaccine impact). With an incremental cost-effectiveness of USD 113 per DALY averted compared to USD 507 per DALY averted for Cervarix, Cecolin stands out as the more viable option. Our findings also suggest that Gardasil-9 is unlikely to be a viable option unless the assumed price per dose is substantially reduced (see Table 4 and Fig. 6).

3.4. Sensitivity analysis

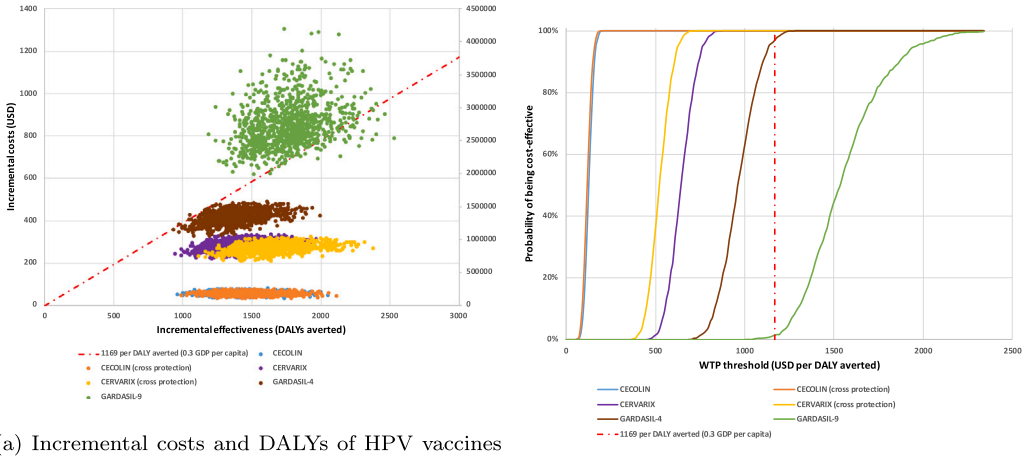
One-way deterministic sensitivity analysis was performed to evaluate the robustness of the results for the most cost-effective options (Cecolin and Cervarix with cross-protection) compared to no vaccination. Age of vaccination, cancer incidence rate, the proportion of cases that end in cervical cancer death, treatment cost from government perspective, and discount rate were varied to determine the effect of uncertainty on the results of incremental cost per DALY averted (Table 5) from the government perspective.

The sensitivity results show that the annual discount rate for future benefits and costs, and disease burden rates tended to have the most influence on model outcomes. Other variables, such as the target age group and healthcare treatment costs, were less influential on cost-effectiveness results; across reasonable ranges of values for these parameters (results are provided in Appendix Figure 1). Across scenarios and perspectives, when varying individual parameters for uncertainty impact, the cost per DALY averted for vaccination among girls ranged from cost-saving to USD 13,114. This represents up to three times the Tunisia's GDP per capita of USD 3895.4 (USD 2023). Adjusting the discount rate by +7% caused the biggest change in the ICER value and may change the conclusions. Under this scenario, the cost per DALY averted was equivalent to 1.32 times (USD 5154) and 3.37 times (USD 13,114) of the GDP per capita for Cecolin and Cervarix with cross protection. The model results were robust, and the discount rate was the main factor affecting the baseline analysis.

Tunisia, like many countries, does not have established cost-effectiveness thresholds for health interventions, including vaccination. However, results from the probabilistic sensitivity analyses determined

Table 5
Input parameters for univariate sensitivity analysis.

Parameter	Base case	Lower limit	Upper limit	Source
Discount rate	3%	0%	10%	[15]
Disease event rates	Appendix table 2	−50% of base case assumption	+50% of base case assumption	[29]
Target age group	12	9	14	[30]
Healthcare costs (government perspective)	2445.14	1833.85	3056.43	±25% of base-case assumption



(a) Incremental costs and DALYs of HPV vaccines compared to no vaccination.

(b) Cost-effectiveness acceptability curves.

Fig. 7. Probabilistic clouds showing the incremental costs (USD) and effectiveness (DALYs averted) of each HPV vaccine product (Cecolin, Cervarix, Gardasil-4 and Gardasil-9) without cross protection and with cross protection for the favorable cost-effective vaccines (Cecolin and Cervarix), compared to no vaccine. The cost-effectiveness acceptability curves (right) demonstrate the likelihood of vaccines being cost-effectiven across varying willingness to pay thresholds (government perspective).

100% credible ranges around the ratios for each of the five cost-effective vaccination scenarios (Cecolin, Cervarix, with and without cross protection and Gardasil4) at a willingness-to-pay threshold (WTP) of USD 1169 per DALY averted (which corresponds to 30% GDP per capita) from the government and the societal perspectives (Figs. 7(b) and 8(b)).

Without cross protection, Cecolin and Cervarix had a similar probability of being cost-effective compared to no vaccination and probabilistic uncertainty clouds associated overlap from both a government and societal perspective (Figs. 7 and 8). Cecolin had the most favorable cost-effectiveness, but Gardasil-9 provided greater health benefits given the available alternatives and could also be considered if affordable (less than 5% probability that would be cost- effective at a threshold set at around USD 1169 the national GDP per capita). It should be noted that vaccine prices were fixed for the probabilistic sensitivity analysis and varied for Gardasil-9 only, therefore, the relative position of the probabilistic clouds will be sensitive to changes in other vaccine prices.

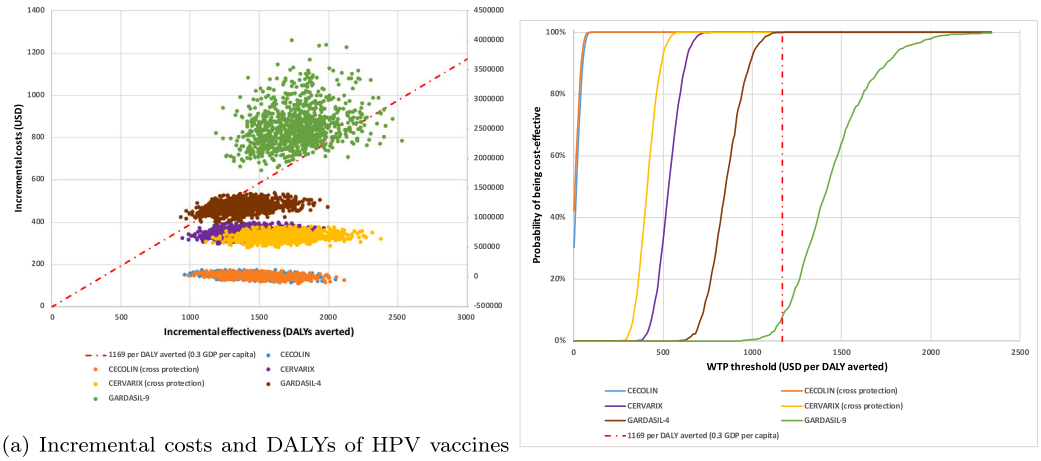
However, with cross-protection, comparing the products with the most favorable cost-effectiveness (Cecolin and Cervarix with cross-protection) had a similar 100% probability of being cost-effective at a WTP threshold set at USD 600 (15% of Tunisia's national GDP per capita) and USD 700 (18% of GDP) when compared to no vaccination from a government and societal perspective, respectively (Figs. 7(b) and 8(b)). However, Cecolin is a far more attractive option with the most favorable cost-effectiveness as it would have a 100% probability of being cost-effective at a WTP threshold set at USD 200 (5% of Tunisia's national GDP per capita) when compared to no vaccination.

4. Discussion and conclusion

We assessed the health impact and cost-effectiveness of implementing HPV vaccination for 12-year-old girls in Tunisia in 2025. We inferred that HPV vaccination could reduce cervical cancer incidence and related deaths by 58%–74%, depending on assumptions about cross-protection. The optimal vaccine choice is influenced by these assumptions, and the cost effectiveness of the vaccines should be continually re-evaluated as more data on efficacy and costs become available.

The introduction of HPV vaccination among 12-year-old girls in Tunisia is projected to be cost-effective in Tunisia across all scenarios considered, with the most cost-effective vaccine being either cost-saving or cost-effective at a willingness-to-pay (WTP) threshold of 30% of GDP per capita. However, our results are particularly sensitive to factors such as the choice of vaccine, cross-protection assumptions, vaccine price, and the discount rate, given that the benefits of HPV vaccination occur many years in the future. For instance, assigning a higher discount rate is, therefore, unfavorable to HPV vaccination.

Our estimates of the cost-effectiveness of HPV vaccination are similar to other estimates for Tunisia presented as part of health and economic evaluation analyses. A study by Kim et al. [29] on the model-based impact and cost-effectiveness of cervical cancer prevention in the extended Middle East and North Africa (EMENA) estimated a cost per DALY averted of USD 100-1400 in Tunisia (USD 2012). A second study by Jit et al. evaluating vaccine cost-effectiveness in 179 countries projected a cost per DALY averted with HPV vaccination of 597 for vaccinating 12 year old girls (USD 2014) [8]. A third study by Messoudi et al. [31] on cost-effectiveness of HPV vaccine introduction in Morocco for girls aged 14 years old concluded that vaccination alone was the most cost-effective strategy with an ICER of USD 207 per years of life saved. Furthermore, other studies have demonstrated the substantial public health benefits of vaccinating young girls, showing that such programs can prevent numerous cases of cervical cancer and save lives [28,32–35] (Kenya, Ghana, Mozambique, Burkina Fao and Ethiopia). These findings are in line with the cost-effectiveness ratios estimated in our study for each scenario: USD 151 (PRIME) and USD 24 (UNIVAC) per DALY averted from the government perspective and USD 113 (PRIME) and USD 5 (UNIVAC) per DALY averted from the societal perspective for Cecolin assuming cross protection.



(a) Incremental costs and DALYs of HPV vaccines compared to no vaccination.

(b) Cost-effectiveness acceptability curves.

Fig. 8. Probabilistic clouds showing the incremental costs (USD) and effectiveness (DALYs averted) of each HPV vaccine product (Cecolin, Cervarix, Gardasil-4 and Gardasil-9) without cross protection and with cross protection for the favorable cost-effective vaccines (Cecolin and Cervarix), compared to no vaccine. The cost-effectiveness acceptability curves (right) demonstrate the likelihood of vaccines being cost-effective across varying willingness to pay thresholds (societal perspective).

Note that [36] also evaluated the cost-effectiveness of HPV vaccination in a separate study. Using a Markov model complemented by the Online Cost-Effectiveness ANalysis (OCEAN), and assuming high efficacy of a two-dose schedule against HPV types 16 and 18, they similarly concluded that the most effective strategy combines HPV vaccination with cytological screening. These independent findings reinforce the relevance of integrated prevention approaches.

Our study had some limitations. First, UNIVAC and PRIME are static cohort models and therefore, not capture any additional indirect (herd immunity) benefits associated with vaccination. However, these effects would only have made our results more favorable to vaccination. Second, we excluded costs borne by households, such as out-of-pocket medical expenses and lost earnings. However, these costs are likely to be relatively small, and a preliminary analysis with these costs included, did not alter the cost-effectiveness results. Additionally, the models do not account for the costs or disease burden associated with the prevention, detection, or treatment of pre-cancerous lesions, which are significant contributors to the overall burden of cervical cancer. However, Tunisia lacks a national cervical cancer screening program, and current screening rates are low.

Without a substantial and immediate expansion of vaccination, screening, and treatment efforts, cervical cancer-related deaths in low and middle-income countries (LMICs) could increase by up to 50% by 2040 [19]. In Tunisia, introducing a national HPV vaccination program for 12-year-old girls would be a highly cost-effective measure to significantly reduce the burden of cervical cancer. However, the health and economic benefits of vaccination must be weighed alongside considerations of budget impact, affordability, feasibility, equity, vaccine confidence and hesitancy, and other contextual factors to ensure the successful and sustainable integration of the HPV vaccine into the national immunization programme of Tunisia.

CRediT authorship contribution statement

Oumaima Laraj: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Beya Benzina:** Writing – original draft, Validation, Resources. **Ahlem Gzara:** Resources, Methodology. **Amira Kebir:** Writing – review & editing, Resources. **Kaja Abbas:** Writing – review & editing, Methodology. **Slimane BenMiled:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Slimane Ben Miled reports financial support was provided by Bill & Melinda Gates Foundation. Amira Kebir, Oumaima Laraj reports financial support was provided by Bill & Melinda Gates Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100712.

Data availability

Data will be made available on request.

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