



# Cost-Effectiveness of Bivalent, Quadrivalent, and Nonavalent HPV Vaccination in South Africa

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## Abstract

**Background and Objectives** In South Africa, the prevalence of human papillomavirus (HPV) and associated diseases, such as cervical cancer and genital warts, is among the highest in the world. This study evaluates the cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV vaccination for 9- to 14-year-old girls from the South African healthcare system perspective.

**Methods** A Markov model portraying the natural HPV disease progression from high-risk infection to cervical intraepithelial neoplasia (CIN) I, CIN II/III, or cervical cancer and from low-risk infection to genital warts was built. Transition probability, utility, and efficacy data were sourced from peer-reviewed literature. Vaccination costs were calculated based on the World Health Organization (WHO) guidelines. The model was populated with a cohort of 520,000 9-year-old girls to calculate incremental cost-effectiveness ratios (ICER) in South African Rand (R) per quality-adjusted life-years (QALYs) gained for each vaccination strategy.

**Results** All HPV vaccination strategies dominate the no vaccine strategy. Compared with the bivalent vaccine, the nonavalent strategy increases QALYs by 0.14 and costs by R1793 (ICER: R13,013 per QALY) per person, while the quadrivalent vaccination provides -0.02 incremental QALYs and R1748 costs (ICER: -R116,397 per QALY). Consequently, at the South African willingness-to-pay threshold of R23,630 per QALY, nonavalent vaccination is the preferred strategy, with a

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Julia Caroline Michaeli and Thomas Michaeli contributed equally to this work.

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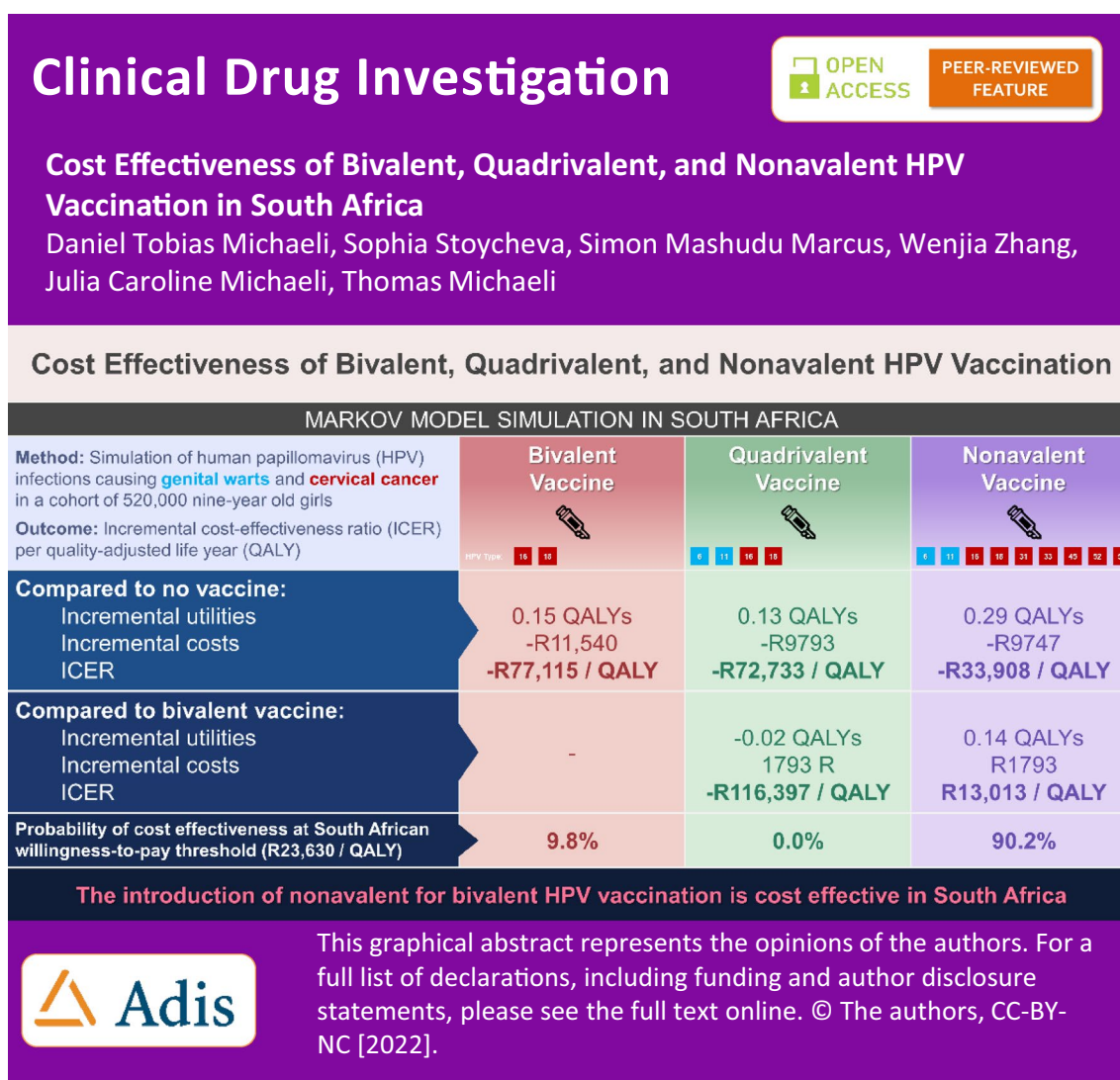
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probability of 90.2%. Scenario analysis demonstrated that results are influenced by vaccine coverage, efficacy, and duration of efficacy.

**Conclusions** The introduction of nonavalent for bivalent HPV vaccination is a cost-effective intervention in South Africa. HPV vaccination should be part of a multifaceted public health strategy entailing screening, condoms, and education of all stakeholders to reduce the significant burden of sexual transmitted diseases in South Africa. Sex-neutral and catch-up vaccinations are subjects for further research.

### Graphical Abstract



## Key Points

Human papillomavirus (HPV) infections and associated diseases, such as genital warts and cervical cancer, cause a significant burden to patients and the healthcare system in South Africa.

Based on a Markov model, we found that nonavalent HPV vaccination is cost effective compared with bivalent HPV vaccination (incremental cost-effectiveness ratio [ICER]: South African Rand (R) 13,013 per quality-adjusted life-year [QALY]) for 9- to 14-year-old girls at the South African willingness-to-pay threshold of R23,630 per QALY.

Targeted policies aimed at improving vaccination coverage rates are substantial to further reduce ICERs for HPV vaccines in South Africa.

## 1 Introduction

Human papillomavirus (HPV) infections cause a significant burden of disease in South Africa. With prevalence rates of 67% among certain populations of young women [1], diseases caused by HPV are among the highest in the world—cervical cancer is the most frequent cancer type among women aged 14–44 years (incidence rate per year: 0.04%) [2]. Even though three screenings with Papanicolaou (Pap) smears are recommended for women older than 30 years, in 10-year intervals, their coverage rate remains below 20% [3]. Consequently, in 2014 a national school vaccination program was introduced to vaccinate girls who are over the age of 9 years, in fourth grade, with the bivalent HPV vaccine (Cervarix<sup>®</sup>) [4]. The bivalent vaccine is primarily effective against the high-risk cervical cancer causing HPV types 16 and 18, and the aim of the program is to prophylactically reduce the incidence and prevalence of HPV and associated cancerous diseases [5]. The quadrivalent vaccine (Gardasil<sup>®</sup>) is additionally effective against HPV types 6 and 11, which cause genital warts, and both vaccines have some degree of cross-protective efficacy against other high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59) [6–8]. The nonavalent vaccine (Gardasil 9<sup>®</sup>) not only offers protection against HPV types 6, 11, 16, and 18 but also provides more substantial protection against HPV types 31, 33, 45, 52, and 58 than the cross-protection offered by the bivalent and quadrivalent vaccines [9].

The majority of Western countries have already included multivalent HPV vaccines in their vaccination schedule, as studies established their superior efficacy and cost-effectiveness in their respective nations [10–14]. The World Health

Organization (WHO) recommends a two-dose vaccination regimen (bivalent, quadrivalent, or nonavalent) with doses administered 6 months apart [15]. While studies have demonstrated the cost-effectiveness of the bivalent vaccine compared with cervical cancer screening alone [16], to date no cost-effectiveness analysis of the quadrivalent and nonavalent vaccines in South Africa exists. This study will aim to fill this gap by conducting a cost-effectiveness analysis comparing the bivalent, quadrivalent, and nonavalent vaccines for 9- to 14-year-old girls from the perspective of the South African healthcare system.

## 2 Data and Methods

A Markov model was built in Microsoft Excel (2016; Microsoft Corporation, Redmond, WA, USA) to assess the cost-effectiveness of non-vaccinated compared with bivalent, quadrivalent, and nonavalent vaccination schemes for 9-year-old girls in South Africa (Fig. 1) [17, 18]. The model displays the different health states in the progression of HPV-related disease. A healthy individual may be infected with either high-risk HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) or low-risk HPV (primarily types 6 and 11). Patients with high-risk infections may then develop cervical cancer, whereas patients with low-risk infections may develop genital warts. Cervical cancer health states model the pathologic disease progression: ‘cervical intraepithelial neoplasia (CIN) I’, ‘CIN II/III’, and ‘cervical cancer’. Other cancer types (head and neck, vaginal, and vulvar cancer) were not included due to their relatively low prevalence and incidence rates in South Africa [19]. Patients may be cleared from the infection at any disease stage. Due to the low progression rate of cervical cancer and genital warts at the same time, this simultaneous progression characteristic was neglected in the model but is included in an alternative model structure (electronic supplementary material [ESM] Fig. e1). All states of health may ultimately lead to death.

### 2.1 Transition Probabilities

Transition probabilities used to populate the model can be found in Table 1. Rates, hazard ratios, odd ratios, and probabilities with a different time horizon than 1 year were converted to 1-year probabilities, similar to previous peer-reviewed methodologies and cost-effectiveness studies [20, 21]. This widely used calculation considers the rate of patients progressing between disease states and the observation’s follow-up period [21]. To adjust for age-related changes in infection rates, sexual behavior, and disease progression, probabilities are split into two age groups: 9–34 years and 35–70 years). Mortality data were obtained from the South African Department of Statistics [22].

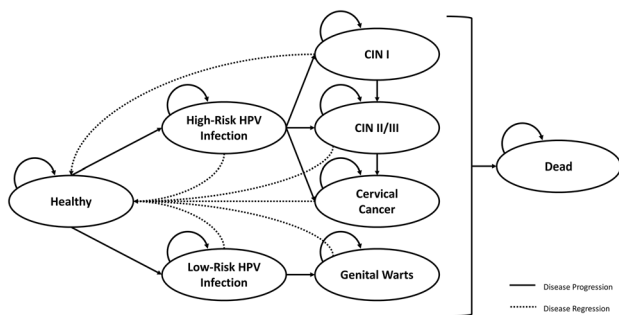
## 2.2 Vaccination Strategy

The current bivalent HPV vaccination program in South Africa consists of a two-dose schedule consistent with WHO recommendations [15]. However, due to all vaccines' novelty, the ultimate protective duration is not yet known, with recent literature suggesting a duration of at least 10 years [23]. As immunity is likely to wane, affecting the impact of the vaccines on transition probabilities, we used a three-dose schedule that included a booster shot after 20 years, after which lifelong immunity is assumed.

## 2.3 Costs

Vaccine and booster shot costs are estimated based on WHO guidelines and previous studies (ESM Tables e1 and e2) [24–26]. Based on the market costs per dose of South African Rand (R) 54 (bivalent), R68 (quadrivalent), and R1524 (nonavalent), the total cost is calculated using previous data for transportation (10%), waste (5%), distribution (15%), communication (2.5%), and administration expenses (10%) [25]. Training costs for medical staff are not included as personnel were previously trained to administer vaccine shots for the rollout of the bivalent HPV vaccination scheme in 2014. The total cost for the public health system amounts to R140 (bivalent), R175 (quadrivalent), and R3924 (nonavalent) per vaccinated girl. Costs for the booster shots were calculated to be similar to the total vaccination costs and hence include costs for waste, transportation, and distribution.

Direct medical costs are computed for each disease state. Costs for cervical cancer states originate from previous



**Fig. 1** Markov model structure of cervical cancer and genital warts disease progression. The graph illustrates the Markov model that remodels cervical cancer and genital warts disease progression to evaluate the cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV vaccination. Within the model, each individual transits between health states. A healthy individual may be infected with high-risk HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and thereafter develop CIN I, CIN II/III, and cervical cancer. Similarly, individuals can also be infected with low-risk HPV (types 6 and 11) and thereafter develop genital warts. Across all disease states, individuals may experience disease regression to the healthy state or eventually die. *CIN* cervical interstitial neoplasia, *HPV* human papillomavirus

literature on bivalent HPV vaccine economic evaluations (Table 1) [27]. These disease states include expenses for Pap smear screening (R624), treatment (conization: R1386; cryotherapy: R1386; hysterectomy: R15,218; chemoradiation: R120,174; radiotherapy: R117,150), and follow-up. Spending associated with genital warts is based on provider perspective mixed bottom-up and top-down data from Swaziland [28]. Data from Swaziland is justifiably the closest possible approximation due to its similarity to South Africa in terms of social, economic, healthcare, and geographical vectors.

The model also included costs for three cervical cancer screenings for women aged 30, 40, and 50 years, with a coverage rate of 20%. Previous literature estimates that the overall health system cost (including laboratory, consumable, and personal expenses) for one cervical cytology screening summed up to R624 in 2019 [30]. All costs are inflation and purchase price parity adjusted to 2019 R.

## 2.4 Utilities

Outcomes are measured by quality-adjusted life-years (QALYs) associated with each health state (Table 1). These QALYs represent patient-reported outcome data gathered with standardized and nationally adjusted EQ-5D survey scales. Utility decrements for infection, cervical cancer, and genital warts states were extracted from global studies and peer-reviewed literature. Ultimately, the absorbent state death is valued with a QALY worth 0.

## 2.5 Other Model Parameters and Vaccine Efficacy

The model has a cycle length of 1 year because the examined cancer types progress slowly and disease treatment schedules fall within a similar timeframe (Table 1) [31]. The simulation runs for 61 years, as it models the vaccination effect of the female cohort born in 2010 (cohort size: 520,000), with a life expectancy of 70 years. HPV infection will start with the median age of sexual debut (18.5 years) for South African girls [32]. Costs and benefits are calculated from the perspective of the South African public healthcare system. A discount rate of 3% is applied to all costs and utilities according to the WHO vaccination guidelines (which also falls within the South African Ministry of Health suggestion of 0–10%) [33]. Vaccination coverage is expected to remain at the current level of 90% [1].

HPV vaccination reduces the probability of progression to HPV infection states by  $(1 - \text{efficacy})$ . HPV type specific efficacy rates were sourced from global phase III clinical trials that were also the basis for each vaccine's marketing authorization [34–37]. The overall vaccine efficacy against high-risk/low-risk HPV is calculated by weighting the efficacy against HPV 16, 18/HPV 6, 11 and the cross-protection efficacy against other high-risk/low-risk HPV types with the prevalence of the respective HPV types in South Africa

**Table 1** Markov model input parameters: transition probabilities, utilities, and costs

Parameter	Value	95% CI		Distribution	References
<i>Transition probabilities</i>					
From healthy to HR infection	0.1320	0.1173	0.1485	Dirichlet	[36]
From healthy to LR infection	0.0650	0.0548	0.0761	Dirichlet	[36]
From healthy, infection, or genital warts to dead (9–34 years)	0.0024				[22]
From healthy, infection, or genital warts to dead (35–70 years)	0.0105				[22]
From HR infection to CIN I (9–34 years)	0.0878	0.0591	0.1164	Dirichlet	[48–50]
From HR infection to CIN I (35–70 years)	0.0824	0.1351	0.0298	Dirichlet	[48–50]
From HR infection to CIN II/III (9–34 years)	0.0070	0.0020	0.0120	Dirichlet	[48–50]
From HR infection to CIN II/III (35–70 years)	0.0287	0.0080	0.0494	Dirichlet	[48–50]
From HR infection to cervical cancer	0.0000				[48–50]
From HR infection to healthy	0.3900	0.2900	0.4900	Dirichlet	[48–50]
From LR infection to genital warts	0.0297	0.0001	0.0592	Dirichlet	[48, 49, 51]
From LR infection to healthy	0.4100	0.3100	0.5100	Dirichlet	[48–50]
From CIN I to CIN II/III (9–34 years)	0.0567	0.0159	0.0975	Dirichlet	[48–50]
From CIN I to CIN II/III (35–70 years)	0.2321	0.0726	0.3916	Dirichlet	[48–50]
From CIN I to healthy	0.4982	0.2079	0.7884	Dirichlet	[48–50]
From CIN II/III to cervical cancer	0.0480	0.0370	0.0750	Dirichlet	[27]
From CIN II/III to healthy	0.0370	0.0170	0.0570	Dirichlet	[48–50]
From cervical cancer to healthy	0.1560	0.1250	0.1870	Dirichlet	[48–50]
From cervical cancer to dead	0.1060	0.0850	0.1270	Dirichlet	[48–50]
From genital warts to healthy	0.7140	0.5881	0.8124	Dirichlet	[53]
<i>Utilities (in QALY)</i>					
Associated with state healthy	1.00				
Associated with state HR infection	1.00	0.80	1.00	Beta	[27, 50]
Associated with state LR infection	1.00	0.80	1.00	Beta	[27, 50]
Associated with state CIN I cancer	0.91	0.86	0.96	Beta	[30, 54]
Associated with state CIN II/III cancer	0.87	0.83	0.91	Beta	[30, 54]
Associated with state cervical cancer	0.56	0.48	0.65	Beta	[30, 54]
Associated with state genital warts	0.82	0.80	0.84	Beta	[40]
Associated with state dead	0.00				
<i>Direct medical costs (in R)</i>					
Associated with state healthy	0.00				
Associated with state HR infection	0.00				
Associated with state LR infection	0.00				
Associated with state CIN I cancer	1385.66	1108.53	1662.79	Gamma	[27]
Associated with state CIN II/III cancer	2767.34	2213.87	3320.81	Gamma	[27]
Associated with state cervical cancer	118,506.78	94,805.43	142,208.14	Gamma	[27]
Associated with state genital warts	1095.42	547.71	1643.13	Gamma	[28]
Associated with state dead	0.00				
<i>Vaccine and equipment costs (in R)</i>					
Bivalent vaccine (Cervarix®)	139.82	133.58	146.07	Gamma	[24–26]
Quadrivalent vaccine (Gardasil®)	174.78	166.97	182.58	Gamma	[24–26]
Nonavalent vaccine (Gardasil9®)	3923.75	3748.51	4098.98	Gamma	[24–26]
Bivalent booster shot (Cervarix®)	70.59	67.33	73.85	Gamma	[24–26]
Quadrivalent booster shot (Gardasil®)	88.24	84.16	92.31	Gamma	[24–26]
Nonavalent booster shot (Gardasil9®)	1980.92	1889.49	2072.35	Gamma	[24–26]
PAP smear	623.61	342.98	966.59	Gamma	[30]

Costs are displayed in 2019 R

Vaccine cost calculations are enclosed in electronic supplementary Tables e1 and e2

CI confidence interval, CIN cervical interstitial neoplasia, HR high-risk, LR low-risk, PAP Papanicolaou, QALY quality-adjusted life-year, R South African Rand



(ESM Table e3) [23, 38]. Consequently, overall efficacy against high-risk infections were estimated at 57.73% for bivalent vaccination, 54.64% for quadrivalent vaccination, and 97.41% for nonavalent vaccination. Efficacy against low-risk infections was calculated at 0% for bivalent vaccination and 74.68% for both quadrivalent and nonavalent vaccination. After the model structure was built, it was subsequently populated with the described data and prevalence rates were cross-checked and adjusted to match actual observed South African epidemiology.

## 2.6 Outcomes

Main outcomes of interests were the incremental cost-effectiveness ratios (ICERs) per QALY.

## 2.7 Sensitivity and Willingness-to-Pay Analyses

Univariate sensitivity and scenario analyses were conducted by assessing the impact of 95% confidence intervals displayed in Table 1 of the point estimate input parameters on calculated ICER. A probabilistic sensitivity analysis (PSA) with 1000 iterations evaluated the simultaneous variation of uncertain input variables. Results of the PSA are presented as means with 95% confidence intervals. A willingness-to-pay (WTP) analysis was conducted to evaluate which vaccination strategy is preferred at an estimated threshold of R23,630 per QALY (ESM Table e4).

## 2.8 Model Structure Sensitivity Analysis

A second model structure helps to account for the uncertainty associated with the first model that is predominantly used in the literature for cervical cancer and genital warts (Fig. 1). The second alternative model (ESM Fig. 1) is based on previous HPV cost-effectiveness models from Singapore and The Netherlands [38, 39]. It accounts for the possibility of simultaneous infections with high- and low-risk HPV types by running two distinct Markov models; however, it structurally underestimates mortality from CIN I–III and cervical cancer and thereby overestimates QALY gained due to the two separate Markov model runs.

## 3 Results

Base-case results of the cost-effectiveness analysis are presented in Table 2. All HPV vaccination strategies dominate the no vaccine strategy as they provide higher incremental QALYs and save costs. Compared with no vaccine, the bivalent provides 0.15 incremental QALYs at savings of R11,540 (ICER: –R77,115 per QALY), the quadrivalent offers 0.13

incremental QALYs whilst saving R9793 (ICER: –R72,733 per QALY), and the nonavalent strategy yields 0.29 incremental QALYs at savings of R9747 (ICER: –R33,908 per QALY) per person.

The bivalent strategy dominates the quadrivalent strategy given that the later yields 0.02 lower QALYs and R1748 higher costs (ICER: – R116,397 per QALY) per person. Compared with the bivalent vaccine, the nonavalent strategy increases QALYs by 0.14 and costs by R1793 (ICER: R13,013 per QALY) per person. Consequently, the nonavalent's base-case ICER is below the estimated South African WTP threshold of R23,630 per QALY relative to the bivalent vaccination.

## 3.1 Univariate Sensitivity and Scenario Analysis

Results of the univariate sensitivity and scenario analysis can be found in ESM Table e5 and ESM Fig. e2. ICER mainly varied by transition probabilities from infection to CIN I and CIN II/III, from CIN I to CIN II/III, and from CIN II/III to cervical cancer, as well as costs associated with cervical cancer and discount rates for costs and utilities. A longer vaccine efficacy duration reduced the estimated ICER, and vice versa. The comparative ICER between the bivalent and nonavalent strategies varied by  $\pm 27\%$ , with  $\pm 5\%$  fluctuations in vaccine coverage rates.

## 3.2 Probabilistic Sensitivity Analysis

Figure 2 illustrates the results of the PSA with 1000 iterations under the input parameters' defined distribution (ESM Table e6) per vaccination strategy. The simulation demonstrates that all vaccines provide higher incremental QALYs (bivalent: 0.15 [0.13 to 0.17]; quadrivalent: 0.13 [0.12 to 0.16]; nonavalent 0.29 [0.25 to 0.33]) at cost savings (bivalent: R11,666 [9586 to 13,883]; quadrivalent: R9001 [8169 to 11,817]; nonavalent: R10,012 [6134 to 14,191]) compared with the no vaccination strategy. Similar to base-case results, the PSA confirms that quadrivalent vaccination is dominated by bivalent vaccination. Relative to bivalent vaccination, the nonavalent strategy offered 0.14 QALYs [0.12 to 0.16] and higher expenditures of R1654 [–408 to 3593] at an ICER of R12,031 per QALY [– 2764 to 26,563]. ESM Table e7 shows that results further vary by the input parameters' defined distribution.

## 3.3 Willingness-to-Pay Analysis

Results of the WTP analysis are presented in Fig. 3. In this graph, the cost-effectiveness acceptability curve maps the

**Table 2** Base-case cost-effectiveness results of the bivalent, quadrivalent, and nonavalent HPV vaccination strategy: QALY, costs, and ICER

Vaccination strategy	Total QALYs	Total costs (R)	Compared with no vaccine			Compared with bivalent vaccine		
			Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
No vaccine	25.16	30,805						
Bivalent	25.31	19,265	0.15	−11,540	−77,115			
Quadrivalent	25.29	20,013	0.13	−9793	−72,733	−0.02	1748	−116,397
Nonavalent	25.45	21,058	0.29	−9747	−33,908	0.14	1793	13,013

Costs are displayed in 2019 R

HPV human papillomavirus, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-year, R South African Rand

probability that a certain vaccination strategy is preferred over others in South Africa across varying WTP ratios. Above a WTP threshold of R11,750 per QALY, nonavalent vaccination is the preferred strategy, while below this threshold bivalent vaccination is preferred. At the South African WTP threshold of R23,630 per QALY, nonavalent vaccination is the preferred strategy, with a probability of 90.2%.

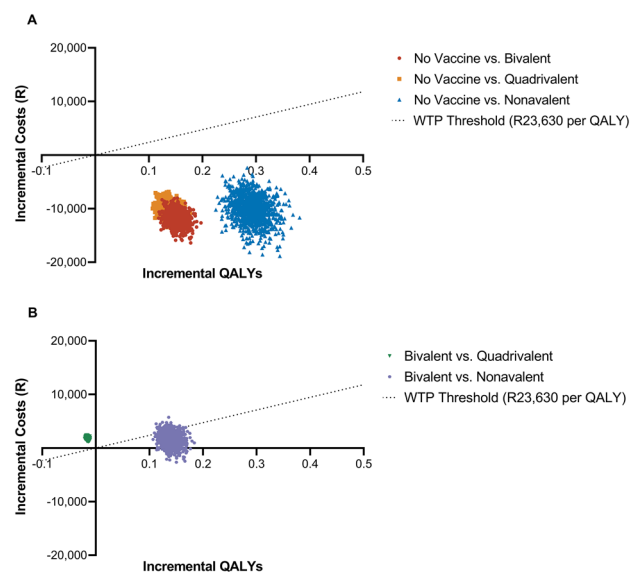
### 3.4 Model Structure Sensitivity Analysis

Results for the alternative model structure are displayed in ESM Table e8. Similar to the first model, all HPV vaccines dominate the no vaccination strategy. Quadrivalent vaccination is again dominated by the bivalent strategy; however, in the alternative model, nonavalent dominates bivalent, with incremental QALYs of 0.08 and savings of R13,398 (ICER: − R169,239 per QALY) and, consequently, quadrivalent vaccination also.

## 4 Discussion

This study presents the first cost-effectiveness analysis comparing bivalent, quadrivalent, and nonavalent vaccination programs in South Africa. In our model, bivalent, quadrivalent, and nonavalent vaccines provide higher QALYs and lower costs than no vaccine for 9- to 14-year-old girls. Compared with a bivalent vaccination strategy, the nonavalent vaccine provided an ICER of R13,013 per QALY. This calculated ICER is therefore always within the estimated South African WTP threshold of R23,630 per QALY. To introduce the nonavalent vaccination program for 520,000 girls aged 9–14 years, the South African Department of Health has to lay out an initial investment of R1.8 billion.

The different efficacies of the three vaccines against HPV types result in different degrees of protection against HPV-associated disease, as demonstrated in our model. While all vaccines offer a similar protection against the high-risk HPV types 16 and 18 [9], their efficacy against other HPV types differ. Quadrivalent and nonavalent vaccination protect



**Fig. 2** Probabilistic sensitivity analysis for HPV vaccination strategies displayed on a cost-effectiveness plane compared with **a** no vaccination and **b** bivalent vaccination. The graph maps incremental QALYs across incremental costs for 1000 iterations of the conducted probabilistic sensitivity analysis. Graph A compares no vaccination with a bivalent, quadrivalent, or nonavalent vaccination strategy, while graph B compares a bivalent strategy with a quadrivalent and nonavalent vaccination strategy. Costs are displayed in 2019 R. HPV human papillomavirus, QALYs quality-adjusted life-years, R South African Rand, WTP willingness to pay

against genital warts caused by low-risk HPV types 6 and 11, unlike the bivalent vaccine. While genital warts are not as life threatening as cervical cancer, infected patients suffer a significant health burden, as exhibited by the utility decrement of −0.09 QALYs [40]. Additionally, the benefits of genital warts protection are seen more quickly after vaccination, with the benefits of cervical cancer protection taking longer to occur. While the nonavalent vaccine offers the greatest protection against high-risk HPV types 31, 33, 45, 52, and 58, the bivalent vaccine provides greater cross-protection against these types than the quadrivalent vaccine.

Combined with lower costs for the bivalent vaccines, this explains why the bivalent scenario dominates the quadrivalent but not the nonavalent scenario.

Consistent with our results, studies in high-income countries, such as Canada and Austria, have found nonavalent vaccination to be the most cost-effective strategy to prevent cervical cancer [10]. Similarly, in Germany, replacement of the quadrivalent vaccine with the new nonavalent vaccine is highly cost effective (ICER: €329 per QALY) [11]. In the US, cost-effectiveness analysis of the nonavalent vaccine suggested that universal vaccination is likely cost saving compared with the quadrivalent vaccine [12]. However, in the underlying model, the price per HPV vaccination between the nonavalent (US\$158) and quadrivalent (US\$145) vaccines are very close. Similarly, an Australian model concluded that the nonavalent vaccine is cost effective compared with the quadrivalent vaccine if the incremental price is below AU\$24 [13]. Correspondingly, in low- and middle-income countries, cost-effectiveness can be reached, with incremental costs below US\$9.80 for the nonavalent vaccine relative to the quadrivalent vaccine [14].

However, the nonavalent vaccine was not found to be ubiquitously cost effective, as a study analyzing 16- to 26-year-old girls in China concluded that the nonavalent strategy was not cost effective relative to bivalent or quadrivalent strategies [41]. Their different outcome from our analysis is likely explained by differences in HPV prevalence rates (China 19% vs. South Africa 44–85%), and nonavalent vaccine prices (South Africa R1024 vs. China R9700) [41, 42]. In summary, the cost-effectiveness of the nonavalent HPV vaccination is subject to local HPV

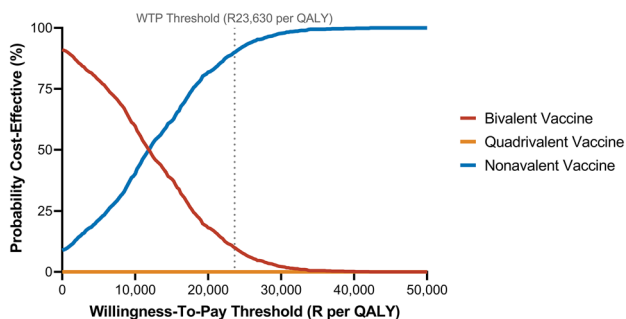
prevalence rates, vaccine prices, and the target population's age and sex.

Recently, certain Western countries have issued guidelines to expand HPV vaccination to boys, to increase herd immunity effects, and protect against several other non-cervical HPV diseases. Herd immunity is likely to result in additional utilities not displayed in our model, as well as a reduction in infection and HPV-related cancer rates for men [43]. Future research should consider sex-neutral vaccination in South Africa as boys are not only transmitters of HPV but also suffer significant health burdens from HPV-related disease.

Our results illustrate that the ICER is dependent on vaccination coverage. Additional resources may be deployed to increase coverage beyond school girls, and more effective campaigns may help to increase awareness of HPV infection and associated diseases. In addition, a complex combination of factors contribute to HPV vaccine hesitancy in South Africa, predominantly driven by parental concern and also current vaccination regimens do not include private sector schools [44]. Evidence suggests that integrated approaches, including communication and social mobilization, are likely to improve uptake, with one intervention showing a 40% increase in uptake when caregivers were provided with information [43]. As such, South Africa's HPV vaccination program could be improved by dialog-based interventions, including social media and mass media, targeting stakeholders in the private and public domains (parents, educators, media, policy makers, and children) to increase vaccination coverage and its cost-effectiveness.

The conducted univariate, probabilistic, and parameter distribution sensitivity analyses (ESM Table e7) demonstrate that ICERs are influenced by input parameters, their associated uncertainty, and their defined distribution. Consequently, decision makers would benefit from the knowledge associated with the actual value of input parameters. Future studies should therefore conduct expected value for perfect information (EVPI) analysis and eventually an expected value for partial parameter information (EVPPI) to inform government decision-making in resource allocation.

An additional consideration in the South African context is HIV. HIV infection and treatment were shown to affect HPV infection and cancer progression [45], and, with prevalence rates of around 20% [46], it is an important factor in any HPV vaccination program. Currently, there is no evidence on how HIV may affect the efficacy of each of the HPV vaccines, and further research on this may affect the outcome of a cost-effectiveness analysis of the different vaccines.



**Fig. 3** Cost-effectiveness acceptability curve for bivalent, quadrivalent, and nonavalent HPV vaccination. In this graph, the cost-effectiveness acceptability curve maps the probability a certain vaccination strategy is preferred over others in South Africa across varying WTP ratios. The red line represents the bivalent vaccination strategy, the orange line represents the quadrivalent vaccination strategy, and the blue line represents the nonavalent vaccination strategy. At the South African WTP threshold of R23,630 per QALY, nonavalent vaccination is the preferred strategy, with a probability of 90.2%. HPV human papillomavirus, QALYs quality-adjusted life-years, WTP willingness to pay, R South African Rand



## 4.1 Limitations

Our study has several limitations. First, the model only considers the effects of HPV vaccination on genital warts and cervical cancer, excluding other HPV-associated cancers such as head and neck, vaginal, anal, and vulvar cancer. As nonavalent HPV vaccination also directly protects against these cancer types, the overall cost-effectiveness of the nonavalent strategy may likely be lower than the estimated ICER of R13,013 per QALY.

Second, the model assumes instant screening and treatment of all patients. In practice, there are significant screening coverage gaps and time lags between screening and treatment. Not all patients in ill-health states can or want to be treated, and coverage rates, treatment costs, and time to treatment are likely to be different for the privately insured population.

Third, this paper only examines the age-specific group of 9- to 14-year-old girls in South Africa. Analyzing the cost-effectiveness of extending HPV vaccination to women aged 20–35 years or 9- to 14-year-old boys could result in valuable findings and is an important gap for future research.

Fourth, an underlying limitation of Markov models is their memoryless function—models cannot distinguish patients in a disease state. Therefore, our model does not distinguish patients after remitting from HPV infections. While this methodology has also been employed in previous cost-effectiveness studies [27], systematic reviews show that patients remain at an elevated risk for cervical cancer after treatment and remittance in earlier HPV infection stages [47]. Moreover, the alternative model structure demonstrates that ICERs are influenced by the Markov model's underlying assumption about HPV disease progression.

Fifth, the results of this study are specific to South Africa and its cost, utility, and HPV transmission characteristics. For other countries, specific cost-effectiveness studies with respective changes in vaccine pricing, medical costs, utilities, and incidence probabilities must be undertaken. Additionally, random distributions were associated with monetary cost values instead of physical cost drivers as costs were sourced from previous cost-effectiveness studies.

## 5 Conclusion

The introduction of nonavalent for bivalent HPV vaccination is a cost-effective intervention in South Africa. HPV vaccination should be part of a multifaceted public health strategy entailing screening, condoms, and education of all stakeholders to reduce the significant burden of sexual

transmitted diseases in South Africa. Sex-neutral and catch-up vaccinations are subjects for further research.

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## Declarations

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**Ethics approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Availability of data and material** All data are included in the manuscript.

**Code Availability** Not applicable.

**Author Contributions** DM: Conceptualization, methodology, investigation, formal analysis, writing – original draft, review and editing, visualization. SS: Conceptualization, methodology, investigation, writing – review and editing. SM: Conceptualization, methodology, investigation, writing – review and editing. WZ: Conceptualization, methodology, investigation, writing – review and editing. JM: Investigation, formal analysis, writing – review and editing, supervision, project management, resources. TM: Investigation, formal analysis, writing – original draft, writing – review and editing, supervision, project management, resources. All authors attest they meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

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