Supplementary Online Content

Clinical Drug Investigation

Cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV vaccination in South Africa.
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This supplementary material has been provided by the authors to give readers additional information about their work.

	Bivalent (Cervarix®)	**Quadrivalent (Gardasil®)**	**Nonavalent (Gardasil9®)**	**% per Dose**
Cost per dose	54.30	67.87	1,523.79	
Waste	2.71	3.39	76.19	5%
Transportation and handling	5.43	6.79	152.38	10%
Distribution	8.14	10.18	228.57	15%
Promotion and communication	1.36	1.70	38.09	2.5%
Planning, monitoring, management	5.43	6.79	152.38	10%
Total cost (two doses)	**139.82**	**174.78**	**3,923.75**	

Table e1 Vaccination cost estimation for two doses of the bivalent, quadrivalent, and nonavalent HPV vaccine

Vaccination costs were estimated from the perspective of the South African Department of Health based on guidelines issued by the World Health Organization (WHO) and previous studies [1–3]. Costs are displayed in 2019 R. HPV: human papillomavirus; R: South African Rand.

	Bivalent (Cervarix®)	**Quadrivalent (Gardasil®)**	**Nonavalent (Gardasil9®)**	**% per Dose**
Cost per dose	54.30	67.87	1,523.79	

	Bivalent (Cervarix®)	**Quadrivalent (Gardasil®)**	**Nonavalent (Gardasil9®)**	**% per Dose**
Cost per dose	54.30	67.87	1523.79	
Waste	2.71	3.39	76.19	5%
Transportation and handling	5.43	6.79	152.38	10%
Distribution	8.14	10.18	228.57	15%
Total cost (booster shot)	**70.59**	**88.24**	**1,980.92**	

Table e2 Booster shot cost estimation for bivalent, quadrivalent, and nonavalent HPV vaccination

Vaccination costs were estimated from the perspective of the South African Department of Health based on guidelines issued by the World Health Organization (WHO) and previous studies [1–3]. Costs are displayed in 2019 R. HPV: human papillomavirus; R: South African Rand.

	Prevalence	Efficacy			References
		Bivalent	**Quadrivalent**	**Nonavalent**	
HIGH-RISK INFECTION					
HPV types 16 and 18	40.60%	98.00%	98.00%	98.00%	[4, 5, 5–8]
Other high-risk types	59.40%	30.20%	25.00%	97.00%	[4, 9–11]
Overall		**57.73%**	**54.64%**	**97.41%**	
LOW-RISK INFECTION					
HPV types 6 and 11	76.20%	0.00%	98.00%	98.00%	[4, 5, 5–8]
Other low-risk types	23.80%	0.00%	0.00%	0.00%	[4, 12]
Overall		**0.00%**	**74.68%**	**74.68%**	

Table e3 Bivalent, quadrivalent, and nonavalent HPV vaccine efficacy for high-risk and low-risk infections

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 respective HPV types' prevalence in South Africa. Consequently, overall efficacy against high-risk infections were estimated at 57.73% for bivalent, 54.64% for quadrivalent, and 97.41% for nonavalent vaccination. Efficacy against low-risk infections were calculated 0% for bivalent and 74.68% for quadrivalent and nonavalent vaccination. HPV: human papillomavirus.

Willingness-To-Pay Threshold	Value	References
Practical evidence (HIV case)	4,880	[13]
Based on GDP	45,812	[14]
Economic model (opportunity cost)	20,196	[15]
Average	**23,630**	

Table e4 Willingness-to-pay threshold estimation in South Africa

Costs are displayed in 2019 R. GDP: gross domestic product; HIV: human immunodeficiency virus; R: South African Rand.

Transition probabilities	Value	95% Confidence Interval		Bivalent vs. Quadrivalent		Bivalent vs. Nonavalent		Quadrivalent vs. Nonavalent	
				Lower CI	Higher CI	Lower CI	Higher CI	Lower CI	Higher CI
from Healthy to HR Infection	0.1320	0.1173	0.1485	-120,944	-112,072	15,204	10,834	1,995	-1,379
from Healthy to LR Infection	0.0650	0.0548	0.0761	-116,694	-116,102	12,591	13,468	163	445
from HR Infection to CIN I (9-34 years)	0.0878	0.0591	0.1164	-121,962	-112,161	16,806	9,854	3,479	-2,356
from HR Infection to CIN I (35-70 years)	0.0824	0.0298	0.1351	-124,852	-111,565	30,624	2,136	16,625	-9,605
from HR Infection to CIN II/III (9-34 years)	0.0070	0.0020	0.0120	-126,095	-108,816	17,780	9,039	4,088	-2,843
from HR Infection to CIN II/III (35-70 years)	0.0287	0.0080	0.0494	-120,699	-113,712	43,044	-5,307	28,884	-16,706
from LR Infection to Genital Warts	0.0297	0.0001	0.0592	-98,089	-141,630	13,725	12,402	301	295
from LR Infection to Healthy	0.4100	0.3100	0.5100	-115,908	-116,741	13,705	12,546	521	148
from CIN I to CIN II/III (9-34 years)	0.0567	0.0159	0.0975	-125,631	-109,819	18,106	9,146	4,406	-2,809
from CIN I to CIN II/III (35-70 years)	0.2321	0.0726	0.3916	-117,621	-115,295	36,647	1,390	22,846	-10,575
from CIN I to Healthy	0.4982	0.2079	0.7884	-107,278	-107,278	-24,151	-24,151	-33,462	-33,462
from CIN II/III to Cervical Cancer	0.0480	0.0370	0.0750	-324,614	-324,614	-33,314	-33,314	-55,648	-55,648
from CIN II/III to Healthy	0.0370	0.0170	0.0570	-119,707	-119,707	-9,396	-9,396	-20,991	-20,991
from Cervical Cancer to Healthy	0.1560	0.1250	0.1870	-72,593	-72,593	10,203	10,203	1,036	1,036
from Cervical Cancer to Dead	0.1060	0.0850	0.1270	-226,220	-226,220	18,306	18,306	-333	-333
from Genital Warts to Healthy	0.7140	0.5881	0.8124	-116,397	-116,397	13,013	13,013	297	297

Utilities	Value	95% Confidence Interval		Bivalent vs. Quadrivalent		Bivalent vs. Nonavalent		Quadrivalent vs. Nonavalent	
				Lower CI	Higher CI	Lower CI	Higher CI	Lower CI	Higher CI
QALYs associated with state HR Infection	1.00	0.80	1.00	-33,869	-116,397	4,910	13,013	109	297
QALYs associated with state LR Infection	1.00	0.80	1.00	10,131	-116,397	5,802	13,013	333	297
QALYs associated with state CIN I	0.91	0.86	0.96	-108,847	-125,071	12,426	13,659	283	313
QALYs associated with state CIN II/III	0.87	0.83	0.91	-102,657	-134,383	11,951	14,283	272	328
QALYs associated with state Cervical Cancer	0.56	0.48	0.65	-112,107	-121,633	12,691	13,396	290	307
QALYs associated with state Genital Warts	0.82	0.80	0.84	-122,700	-111,749	12,947	13,067	297	297

Direct Medical Costs	Value	95% Confidence Interval		Bivalent vs. Quadrivalent		Bivalent vs. Nonavalent		Quadrivalent vs. Nonavalent	
(ZAR)				Lower CI	Higher CI	Lower CI	Higher CI	Lower CI	Higher CI
Costs associated with state CIN I	1,385.66	1,108.53	1,662.79	-115,149	-117,644	13,846	12,180	1,171	-577
Costs associated with state CIN II/III	2,767.34	2,213.87	3,320.81	-116,003	-116,791	13,277	12,750	574	21
Costs associated with state Cervical Cancer	118,506.78	94,805.43	142,208.14	-93,951	-138,842	27,831	-1,805	15,865	-15,270
Costs associated with state Genital Warts	1,095.42	547.71	1,643.13	-122,337	-110,456	13,595	12,432	238	357

Drug and Equipment Costs	Value	95% Confidence Interval		Bivalent vs. Quadrivalent		Bivalent vs. Nonavalent		Quadrivalent vs. Nonavalent	
(ZAR)				Lower CI	Higher CI	Lower CI	Higher CI	Lower CI	Higher CI
Bivalent vaccine cost	139.82	133.58	146.07	-116,776	-116,017	13,055	12,972	297	297
Quadrivalent vaccine cost	174.78	166.97	182.58	-115,922	-116,871	13,013	13,013	344	251
Nonavalent vaccine cost	3,923.75	3,748.51	4,098.98	-116,397	-116,397	11,852	14,174	-750	1,344
Bivalent booster shot cost	70.59	67.33	73.85	-117,470	-115,323	13,130	12,896	297	297
Quadrivalent booster shot cost	88.24	84.16	92.31	-115,054	-117,739	13,013	13,013	429	165
Nonavalent booster shot cost	1,980.92	1,889.49	2,072.35	-116,397	-116,397	9,730	16,297	-2,664	3,258
PAP smear cost	623.61	498.88	748.33	-116,417	-116,377	13,000	13,027	283	312

Other Parameters	Value	95% Confidence Interval		Bivalent vs. Quadrivalent		Bivalent vs. Nonavalent		Quadrivalent vs. Nonavalent	
				Lower CI	Higher CI	Lower CI	Higher CI	Lower CI	Higher CI
Discount rate of utilities	0.03	0.01	0.05	-44,655	-294,011	5,551	28,229	125	654
Discount rate of costs	0.03	0.01	0.05	-290,000	-50,349	-5,112	20,907	-33,105	13,906
Long-run inflation rate (South Africa)	0.05	0.04	0.05	-93,894	-144,648	15,672	9,773	4,906	-5,400
Hazard ratio for CIN I,II, and III mortality	1.2	1.1	1.3	-122,881	-110,525	12,734	13,271	-404	947
Vaccine coverage	0.90	0.85	0.95	-115,053	-117,844	16,528	9,521	3,027	-2,420
Age of sexual debut	18.5	17.1	20.3	-114,272	-120,470	11,877	15,475	-452	1,960
Duration of vaccine efficacy	20	10	30	-121,430	-114,730	72,386	-6,641	53,342	-17,262

Table e5 Univariate sensitivity analysis

Costs are displayed in 2019 R. CI: confidence interval; CIN: cervical interstitial neoplasia; HR: high-risk; ICER: incremental cost-effectiveness ratio; LR: low-risk; PAP: Papanicolaou; QALY: quality-adjusted life year; R: South African Rand.

	Value	Alpha	Beta	Distribution
TRANSITION PROBABILITIES				
from Healthy to HR Infection	0.1320	62.00	407.57	Dirichlet
from Healthy to LR Infection	0.0650	34.74	499.73	Dirichlet
from HR Infection to CIN I (9-34 years)	0.0878	8.47	88.05	Dirichlet
from HR Infection to CIN I (35-70 years)	0.0824	2.17	24.11	Dirichlet
from HR Infection to CIN II/III (9-34 years)	0.0070	1.94	276.32	Dirichlet
from HR Infection to CIN II/III (35-70 years)	0.0287	1.84	62.20	Dirichlet
from HR Infection to Healthy	0.3900	8.89	13.90	Dirichlet
from LR Infection to Genital Warts	0.0297	0.95	31.00	Dirichlet
from LR Infection to Healthy	0.4100	9.51	13.68	Dirichlet
from CIN I to CIN II/III (9-34 years)	0.0567	1.77	29.40	Dirichlet
from CIN I to CIN II/III (35-70 years)	0.2321	1.39	4.61	Dirichlet
from CIN I to Healthy	0.4982	0.98	0.99	Dirichlet
from CIN II/III to Cervical Cancer	0.0480	6.03	119.55	Dirichlet
from CIN II/III to Healthy	0.0370	3.26	84.82	Dirichlet
from Cervical Cancer to Healthy	0.1560	21.22	114.79	Dirichlet
from Cervical Cancer to Dead	0.1060	22.67	191.21	Dirichlet
from Genital Warts to Healthy	0.7140	10.89	4.36	Dirichlet
UTILITIES (in QALY)				
associated with state HR Infection	1.00	384.16	0.0026	Beta
associated with state LR Infection	1.00	384.16	0.0026	Beta
associated with state CIN I Cancer	0.91	1536.64	0.0006	Beta
associated with state CIN II/III Cancer	0.87	1536.64	0.0006	Beta
associated with state Cervical Cancer	0.56	166.74	0.0034	Beta
associated with state Genital Warts	0.82	7207.83	0.0001	Beta
DIRECT MEDICAL COSTS (in R)				
associated with state CIN I Cancer	1,385.66	96.04	14.43	Gamma
associated with state CIN II/III Cancer	2,767.34	96.04	28.81	Gamma
associated with state Cervical Cancer	118,506.78	96.04	1,233.93	Gamma
associated with state Genital Warts	1,095.42	15.37	71.29	Gamma
VACCINE AND EQUIPMENT COST (in R)				
Bivalent vaccine (Cervarix®)	139.82	1,926.06	0.07	Gamma
Quadrivalent vaccine (Gardasil®)	174.78	1,926.06	0.09	Gamma
Nonavalent vaccine (Gardasil9®)	3,923.75	1,926.06	2.04	Gamma
Bivalent booster shot (Cervarix®)	70.59	1,803.42	0.04	Gamma
Quadrivalent booster shot (Gardasil®)	88.24	1,803.42	0.05	Gamma
Nonavalent booster shot (Gardasil9®)	1,980.92	1,803.42	1.10	Gamma
PAP smear	623.61	96.04	6.49	Gamma

Table e6 Input variables' alpha and beta parameters

Costs are displayed in 2019 R. CIN: cervical interstitial neoplasia; HR: high-risk; LR: low-risk; PAP: Papanicolaou; QALY: quality-adjusted life year; R: South African Rand.

	Bivalent vs quadrivalent			Bivalent vs nonavalent			Quadrivalent vs nonavalent		
	ICER	95% CI		ICER	95% CI		ICER	95% CI	
Base case	-117,160	-145,967	-92,564	12,031	-2,764	26,563	-547	-15,540	14,165
Transition probabilities modeled with beta distribution	-94,076	-250,780	46,261	32,779	-36,248	135,120	19,858	-44,312	119,810
Costs modelled with log-normal distribution	-117,848	-144,769	-94,178	13,389	-1,062	27,941	598	-13,319	15,223

Table e7 ICER results under different parameter distributions

Costs are displayed in 2019 R. CI: confidence interval; ICER: incremental cost-effectiveness ratio; R: South African Rand.

	Bivalent vs quadrivalent			Bivalent vs nonavalent			Quadrivalent vs nonavalent		
	ICER	95% CI		ICER	95% CI		ICER	95% CI	
Base case	-117,160	-145,967	-92,564	12,031	-2,764	26,563	-547	-15,540	14,165
Transition probabilities modeled with beta distribution	-94,076	-250,780	46,261	32,779	-36,248	135,120	19,858	-44,312	119,810
Costs modelled with log-normal distribution	-117,848	-144,769	-94,178	13,389	-1,062	27,941	598	-13,319	15,223

Vaccination Strategy	Total QALYs	Total Costs (R)	Compared to No Vaccine			Compared to Bivalent Vaccine		
			Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
No Vaccine	25.32	62,703						
Bivalent	25.40	37,250	0.08	-25,453	-307,663			
Quadrivalent	25.40	38,840	0.08	-23,863	-289,906	0.00	1,590	-3,801,152
Nonavalent	25.48	23,852	0.16	-38,851	-239,974	0.08	-13,398	-169,239

Table e8 Cost-effectiveness results for the alternative Markov model structure

The Table shows the results for the alternative Markov model structure presented Supplement, Figure e1. Similar to the base case model, the alternative model also considers vaccination boosters. Input parameters can be found in Table 1. Costs are displayed in 2019 R. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; R: South African Rand.
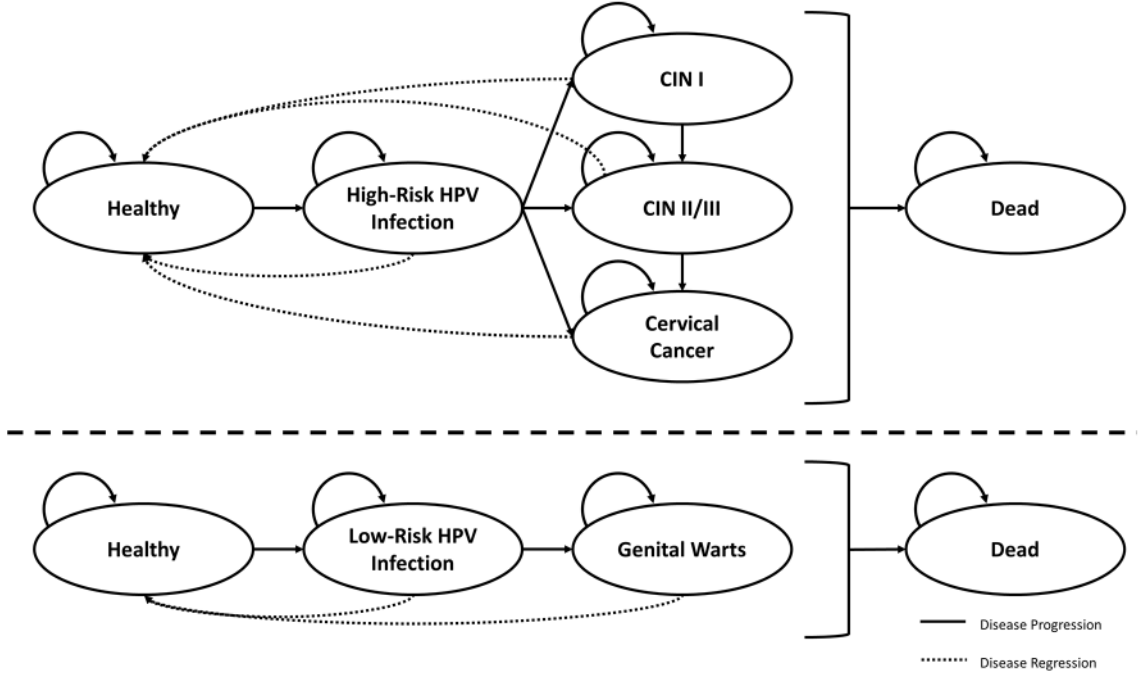
Figure e1 Alternative Markov model structure

The graph illustrates the alternative Markov model that remodels cervical cancer and genital warts disease progression to evaluate the cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV vaccination. This Markov model entails two different models to account for simultaneous low- and high-risk HPV infections. CIN: cervical interstitial neoplasia; HPV: human papillomavirus.
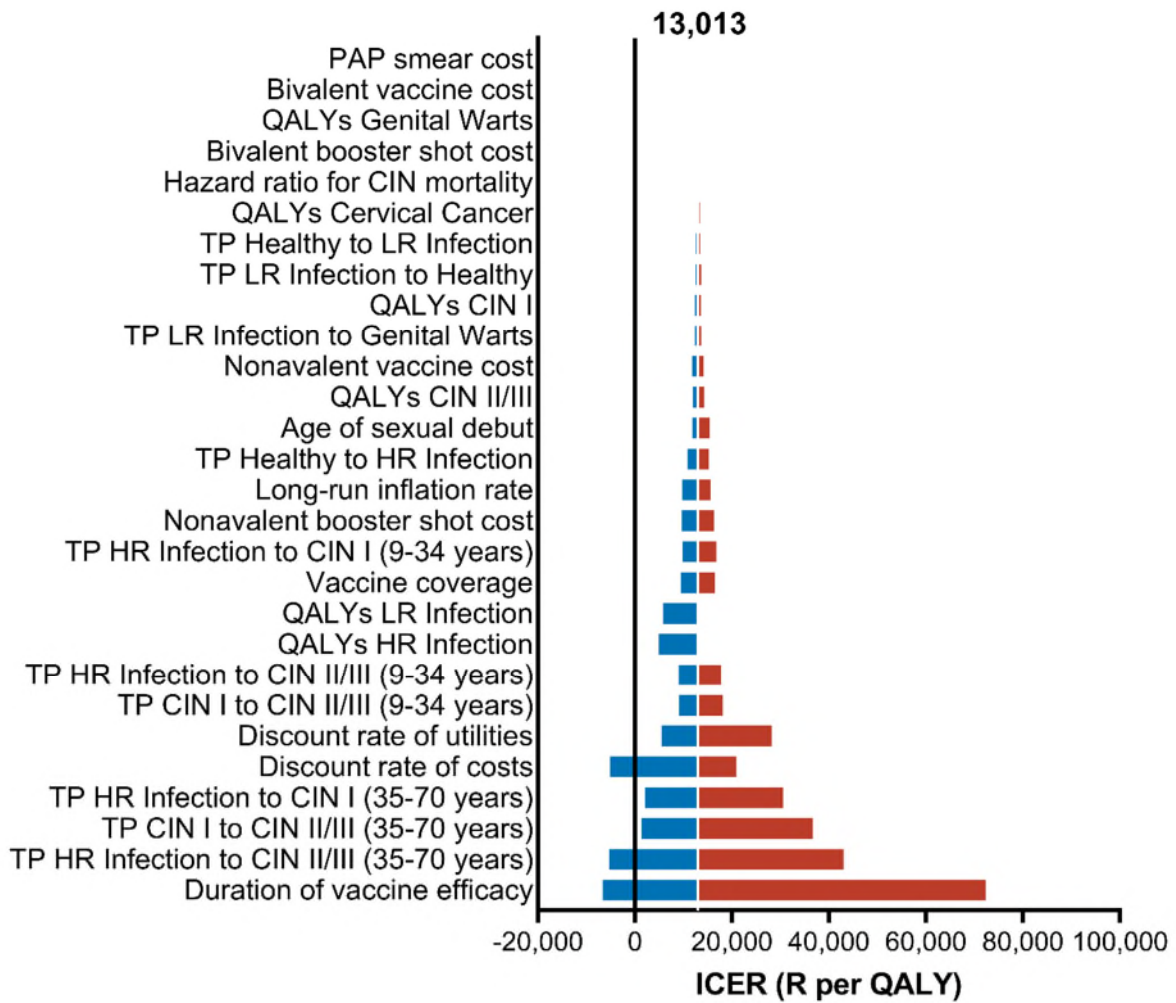
Figure e2 Tornado plot for nonavalent compared to bivalent vaccination

The graph illustrates results of the univariate sensitivity analysis in a tornado plot. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; R: South African Rand.

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