

Supplementary Materials

Clinical Drug Investigation

Economic evaluation of rotavirus vaccination in children aged under five years in South Africa

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Table S1. Details of the vaccines used in the analysis

	Form	Number of doses per FIC	Doses per vial	Vials/tubes per pack	Storage volume per dose (cm ³)	Cost per dose (PAHO)	Vaccine type	Indication	Administration	WHO pre-qualification (year)
HRV	Liquid	2	1	Box of 10 tubes	43.3 [1]	\$6.50 [2]	Live attenuated monovalent G1P[8] vaccine	Prevention of rotavirus gastroenteritis	2-dose schedule, approved for use in infants in the first 6 months of life. Should not be administered to children over 24 weeks of age [3]	2009
HBRV	Liquid	3	1	Box of 10 tubes	75.26 [4]	\$5.20 [5]	Live human-bovine reassortant pentavalent vaccine	prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9	3-dose schedule approved for use in infants 6 weeks to 32 weeks of age [6]	2008
BRV-PV 1-dose vial	Lyophilized powder	3	1	Carton of 50 vials (50 doses); diluent: carton of 50 vials	35.14 [7]	\$3.00 [2]	Live, attenuated human-bovine rotavirus reassortant G1, G2, G3, G4, and G9 vaccine	Prevention of gastroenteritis due to rotavirus infection	3-dose schedule beginning at 6 weeks of age [8]	2018
BRV-PV 2-dose vial	Lyophilized powder	3	2	Carton of 50 vials	21.08 [7]	\$0.95 [2]	Live, attenuated human-bovine rotavirus reassortant G1, G2, G3, G4, and G9 vaccine	Prevention of gastroenteritis due to rotavirus infection	3-dose schedule beginning at 6 weeks of age [8]	2018

Information on secondary packaging was obtained from the WHO [4, 7]. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; FIC: fully immunized child; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine; PAHO: Pan American Health Organization; WHO: World Health Organization.

Table S2. Summary of cost inputs included in the cost analysis and cost-effectiveness analysis

Analysis	Cost analysis		Cost-effectiveness analysis	
	Country payer	Societal	Country payer	Societal
Vaccination costs (waste-adjusted vaccine acquisition, vaccine administration, waste disposal)	✓	✓	✓	✓
Supply chain costs (international transportation/handling and local storage/transportation)	✓	✓	✓	✓
Caregiver costs (transportation to receive vaccine)	X	✓	X	✓
RVGE management costs (home care treatment, medical visits, hospitalization)	X	X	✓	✓
Direct non-medical costs (transportation to manage RVGE)	X	X	X	✓
Productivity losses of caregivers to manage RVGE	X	X	X	✓

RVGE: rotavirus gastroenteritis.

Table S3. Inputs used for calculating vaccine wastage rate for South Africa using the WHO vaccine waste calculation tool

Inputs	Value
Number of supply chain levels	4
Frequency of daily vaccination sessions	0%
Frequency of weekly vaccination sessions	100%
Number of days of weekly sessions	5
Frequency of monthly vaccination sessions	0%
Vaccine type	Liquid (HRV and HBRV) or lyophilized (BRV-PV)
Number of doses	2 or 3
Coverage	70% (for 2 dose vaccine) and 65% (for 3 dose vaccine) [9, 10]

BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine WHO: World Health Organization.

Table S4. Vaccine administration costs

Inputs	Value
Dose preparation based on vaccine presentation and volume per dose*	HRV 3 minutes, HBRV 3.5 minutes, BRV-PV 5 minutes
Dose administration	Assumed to take 1 minute for all vaccines
Vaccination record completion	Assumed to take 1 minute for all vaccines

The costs associated with the administration of each vaccine were calculated using the healthcare worker hourly fee, which utilized data from the World Bank (net: \$4,862; hourly fee: \$2.53; access date 29 May 2022) and assumed a total of 1,920 working hours per year [11]. *HRV: liquid, 1.5mL; HBRV: liquid 2.5mL; BRV-PV: lyophilized powder 2.5mL. Total time to administer one dose was varied by $\pm 50\%$ for sensitivity analysis. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine.

Table S5. Inputs used to calculate supply chain and waste disposal costs

Inputs	Value	Source/Reference
Cost of incineration of health care waste per kg	R3.69	[7]
Refrigerated storage volume/dose (cm ³)	43.3	[12]
Vaccine pallet net weight	151.87 kg	HRV logistics data
Number of units per pallet	1,560	
International transportation cost as a percentage of vaccine purchase price	1.67%	
International handling cost as a percentage of the vaccine purchase price	1.06%	
Cost of local storage per unit*	R36.48	
Cost of local transportation per unit*	R24.32	
Number of vaccine shipments in one year**	9	
Average transport distance between the central location and the relevant health facility	50 km	Assumption

kg: kilogram; km: kilometer; R: South African rand.

*The combined costs of warehousing and distribution of rotavirus vaccines were estimated to be R60.80 per unit (10-doses box), assuming 60-40 split of this cost between storage and transportation.

**The number of shipments per year was informed by the local logistics information based on 2021 HRV shipment data for South Africa.

Table S6. Probability of RVGE health states

Health states	Events per 100,000*			Probability (calculated)		
	Base	Low	High	Base	Low	High
RVGE home care**	10,000	7,000	14,000	0.1	0.07	0.14
RVGE medical visit***	2,234	968	5,081	0.02234	0.00968	0.05081
RVGE hospitalization	320	73	918	0.0032	0.00073	0.00918
RVGE-related deaths	32.22	20.8	49.92	0.0003222	0.000208	0.0004992

*Data reported by Debellut et al [13]. **Combined non-severe and severe RVGE cases. ***Combined non-severe and severe RVGE clinic visits. RVGE: rotavirus gastroenteritis.

Table S7. Parameters included in the probabilistic analysis, base values, ranges, and distributions

Variable	Base case value	Reference	Distribution type	Range of uncertainty
Vaccination costs				
Vaccine purchase price per dose	See table 1	[2, 5]	Lognormal	±20%
Percent of wastage (HRV, HBRV and BRV-PV 1-dose)	4%	[14]	Beta	±50%
Percent of wastage (BRV-PV 2-doses)	38%	[14]	Beta	±50%
Healthcare worker fee for vaccine administration/hour	\$2.53	[11]	Gamma	±50%
Waste disposal cost per m ³	\$163.5	Calculated	Gamma	±50%
Supply chain costs				
Cost of refrigerated storage of vaccines per m ³ per day	\$13.35	Calculated	Gamma	±50%
Cost of refrigerated transportation of vaccines per m ³ per km	\$6.03	Calculated	Gamma	±50%
Caregiver costs				
Cost of transportation per administered dose	\$0.59	Assumption	Gamma	±50%
Income per hour	\$2.53	[11]	Lognormal	±50%
Costs of RVGE management				
Cost of RVGE medical visit	\$18	[13]	Lognormal	±50%
Cost of RVGE hospitalization	\$394	[13]	Lognormal	±50%
Transportation cost for RVGE medical visit	\$1.77	Assumption	Lognormal	±50%

Variable	Base case value	Reference	Distribution type	Range of uncertainty
Transportation cost for RVGE hospitalization	\$5.31	Assumption	Lognormal	±50%
Probability of RVGE home care per person in the total population, per year of age*				
0–1 years	0.03870	[13, 15]	Beta	0.02706, 0.05418
1–2 years	0.02720	[13, 15]	Beta	0.01902, 0.03808
2–3 years	0.01650	[13, 15]	Beta	0.01154, 0.02310
3–4 years	0.00980	[13, 15]	Beta	0.00685, 0.01372
4–5 years	0.00650	[13, 15]	Beta	0.00454, 0.00910
Probability of RVGE medical visit per person in the total population, per year of age*				
0–1 years	0.00865	[13, 15]	Beta	0.00375, 0.01966
1–2 years	0.00608	[13, 15]	Beta	0.00263, 0.01382
2–3 years	0.00369	[13, 15]	Beta	0.00160, 0.00838
3–4 years	0.00219	[13, 15]	Beta	0.00095, 0.00498
4–5 years	0.00145	[13, 15]	Beta	0.00063, 0.00330
Probability of RVGE hospitalization per person in the total population, per year of age*				
0–1 years	0.00124	[13, 15]	Beta	0.00028, 0.00355
1–2 years	0.00087	[13, 15]	Beta	0.00020, 0.00250
2–3 years	0.00053	[13, 15]	Beta	0.00012, 0.00151
3–4 years	0.00031	[13, 15]	Beta	0.00007, 0.00090
4–5 years	0.00021	[13, 15]	Beta	0.00005, 0.00060
Probability of RVGE death per person in the total population, per year of age*				
0–1 years	0.00012	[13, 15]	Beta	0.00008, 0.00019
1–2 years	0.00009	[13, 15]	Beta	0.00006, 0.00014

Variable	Base case value	Reference	Distribution type	Range of uncertainty
2–3 years	0.00005	[13, 15]	Beta	0.00003, 0.00008
3–4 years	0.00003	[13, 15]	Beta	0.00002, 0.00005
4–5 years	0.00002	[13, 15]	Beta	0.00001, 0.00003
Health state utility values[§]				
Baseline (all age groups)	0.94	[16]	Beta	0.752–1.00
RVGE home care (0–1 and 1–2 years age groups)	0.891	[17]	Beta	95% CI (0.839–0.943)
RVGE home care (2–3 to 4–5 years age groups)	0.844	[17]	Beta	95% CI (0.777–0.911)
RVGE medical visits (0–1 and 1–2 years age groups)	0.781	[17, 18]	Beta	95% CI (0.678–0.884)
RVGE medical visits (2–3 to 4–5 years age groups)	0.688	[17, 18]	Beta	95% CI (0.553–0.823)
RVGE hospitalization (0–1 and 1–2 years age groups)	0.425	[17, 18]	Beta	95% CI (0.330–0.520)
RVGE hospitalization (2–3 to 4–5 years age groups)	0.200	[17, 18]	Beta	95% CI (0.049–0.351)
Vaccine efficacy for all vaccines in full schedule[†]	57.5%	[19]	Beta	±50%

*Probabilities were derived by multiplying the probability of each health state (presented in Table S6) [13], by the country specific age-group distribution obtained from the National Institute for Communicable Disease [15]. §The baseline utility values used in this analysis were EuroQol (EQ)-5D index population norms for the UK adult population aged 18–24 [16]. Range of sensitivity analysis of the baseline utility value was assumed to be ±20% of the UK EQ-5D index population with a maximum of 1 [16]. 95% CIs were calculated from the reported standard deviation values [17, 18]. †Vaccine efficacy was assumed to be the same for all RVGE health states and all age groups from 0–5 years. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; CI: confidence interval; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine; RVGE; rotavirus gastroenteritis; UK: United Kingdom.

Table S8. Vaccine efficacy decrements used in the analysis

	HRV			HBRV		
Relative vaccine efficacy [20]	Home treated cases	Cases treated in primary care	Hospitalizations	Home treated cases	Cases treated in primary care	Hospitalizations
Partial protection between first and second dose	78.4%	80.9%	90%	60.7%	78%	82%
Partial protection between second and third dose	N/A	N/A	N/A	62.2%	79.9%	84%
Vaccine efficacy with complete schedule	87.1%	89.9%	100%	72%	92.5%	97.3%
Calculated vaccine efficacy decrements used in the analysis						
	For HRV			For 3-dose vaccines		
Relative vaccine efficacy reduction between first and second dose	10%	10%	10%	2.4%	2.4%	2.4%
Relative VE reduction between second and third dose	N/A	N/A	N/A	13.6%	13.6%	13.6%

N/A: not applicable.

Table S9. Base-case RVGE events and QALY loss with HRV compared with HBRV, BRV-PV 1-dose vial, and BRV-PV 2-dose vial

	HRV	HBRV, BRV-PV 1-dose vial and 2-dose vial	Difference between HRV and HBRV, BRV-PV 1-dose vial and 2-dose vial
RVGE events in the year of vaccinating the birth cohort (2022)			
RVGE home care	58,182	59,290	-1,107
RVGE medical visits	12,998	13,245	-247
RVGE hospitalization	1,862	1,897	-35
RVGE-related deaths	187	191	-4
QALY loss accumulated over the model duration			
Undiscounted	11,519	11,738	-219
Discounted	3,831	3,904	-73

HRV is a 2-dose vaccine, HBRV, BRV-PV 1-dose vial and 2-dose vial are 3-dose vaccines. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; FIC: fully immunized child; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine; QALY: quality-adjusted life year; RVGE: rotavirus gastroenteritis.

Table S10. Base-case cost-effectiveness analysis results comparing costs of HRV with HBRV, BRV-PV 1-dose vial and BRV-PV 2-dose vial

	Total costs				Incremental costs		
	HRV	HBRV	BRV-PV 1-dose vial	BRV-PV 2-dose vial	HRV vs HBRV	HRV vs BRV-PV 1-dose vial	HRV vs BRV-PV 2-dose vial
Costs from the country payer perspective							
Vaccination	\$14,282,111	\$17,353,616	\$10,502,015	\$5,618,556	-\$3,071,505	\$3,780,096	\$8,663,556
Supply chain	\$830,032	\$1,632,501	\$812,102	\$639,648	-\$802,469	\$17,929	\$190,384
Direct medical treatment costs	\$967,580	\$985,997	\$985,997	\$985,997	-\$18,417	-\$18,417	-\$18,417
Total costs from country payer perspective	\$16,079,723	\$19,972,114	\$12,300,114	\$7,244,200	-\$3,892,391	\$3,779,609	\$8,835,523
Costs from the societal perspective							
Direct non-medical costs	\$32,893	\$33,519	\$33,519	\$33,519	-\$626	-\$626	-\$626
Productivity loss	\$6,289,592	\$6,409,307	\$6,409,307	\$6,409,307	-\$119,716	-\$119,716	-\$119,716
Caregiver attendance	\$14,992,484	\$22,488,726	\$22,488,726	\$22,488,726	-\$7,496,242	-\$7,496,242	-\$7,496,242
Total costs from societal perspective	\$37,394,691	\$48,903,66	\$41,231,666	\$36,175,753	-\$11,508,975	-\$3,836,975	\$1,218,939

BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; FIC: fully immunized child; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine.

Scenario analysis methods

Caregiver attendance costs for a vaccine administration trip were assumed to reflect the number of vaccines required in the complete vaccination dosing schedule. However, transportation costs and hours of productivity loss for a vaccination administration trip may be the same regardless of the number of vaccines administered. The scenario analysis tested the assumption that caregiver attendance costs would not be affected by the number of vaccines in the complete dosing schedule.

Scenario analysis results

Table S11. Costs associated with each vaccine in the scenario analysis

	HRV	HBRV	BRV-PV 1-dose vial	BRV-PV 2-dose vial	HRV vs HBRV	HRV vs BRV-PV 1-dose vial	HRV vs BRV-PV 2-dose vial
Direct medical costs	\$967,580	\$985,997	\$985,997	\$985,997	-\$18,417	-\$18,417	-\$18,417
RVGE home care	\$58	\$59	\$59	\$59			
RVGE medical visits	\$233,962	\$238,415	\$238,415	\$238,415			
RVGE hospitalization	\$733,560	\$747,522	\$747,522	\$747,522			
Direct non-medical costs	\$32,893	\$33,519	\$33,519	\$33,519	-\$626	-\$626	-\$626
Transport costs	\$32,893	\$33,519	\$33,519	\$33,519			
Other costs	\$0	\$0	\$0	\$0			
Productivity losses	\$6,289,592	\$6,409,307	\$6,409,307	\$6,409,307	-\$119,716	-\$119,716	-\$119,716
Vaccination	\$14,282,111	\$17,353,616	\$10,502,015	\$5,618,556	-\$3,071,505	\$3,780,096	\$8,663,556
Supply chain	\$830,032	\$1,632,501	\$812,102	\$639,648	-\$802,469	\$17,929	\$190,384

	HRV	HBRV	BRV-PV 1-dose vial	BRV-PV 2-dose vial	HRV vs HBRV	HRV vs BRV-PV 1-dose vial	HRV vs BRV-PV 2-dose vial
Caregiver attendance	\$44,977,453	\$67,466,179	\$67,466,179	\$67,466,179	-\$22,488,726	-\$22,488,726	-\$22,488,726
Total costs from country payer perspective							
	\$16,079,723	\$19,972,114	\$12,300,114	\$7,244,200	-\$3,892,391	\$3,779,609	\$8,835,523
Total costs from societal perspective							
	\$67,379,660	\$93,881,119	\$86,209,119	\$81,153,205	-\$26,501,459	-\$18,829,459	-\$13,773,545

BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine; RVGE; rotavirus gastroenteritis.

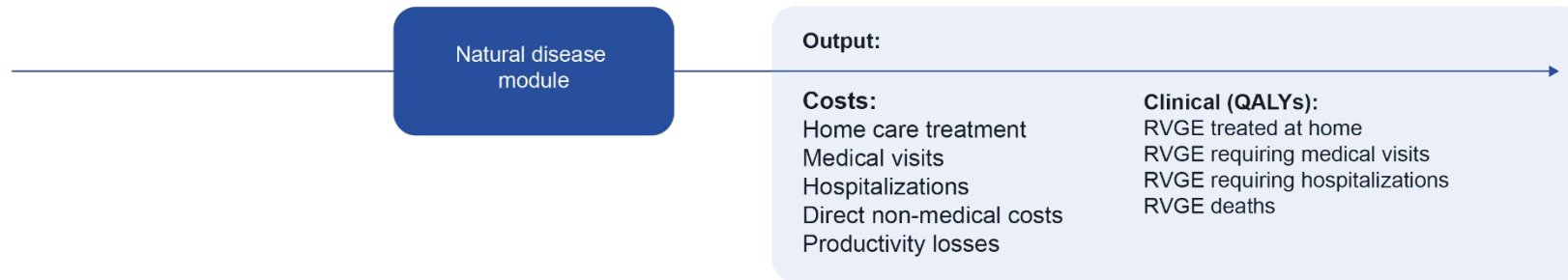
Table S12. Scenario analysis Incremental Cost-Effectiveness Ratios (ICERs) reported in the cost-effectiveness analysis from the country payer and societal perspectives

Reference	Comparator	Δcosts (reference-comparator)	ΔQALYs undiscounted	ΔQALYs discounted	ICER undiscounted	ICER discounted
Country payer perspective						
HRV	HBRV	−\$3,892,391	219	73	HRV was dominant	HRV was dominant
	BRV-PV 1-dose vial	\$3,779,609	219	73	\$17,239	\$51,834
	BRV-PV 2-dose vial	\$8,835,523	219	73	\$40,299	\$121,171
Societal perspective						
HRV	HBRV	−\$26,501,459	219	73	HRV was dominant	HRV was dominant
	BRV-PV 1-dose vial	−\$18,829,459	219	73	HRV was dominant	HRV was dominant
	BRV-PV 2-dose vial	−\$13,773,545	219	73	HRV was dominant	HRV was dominant

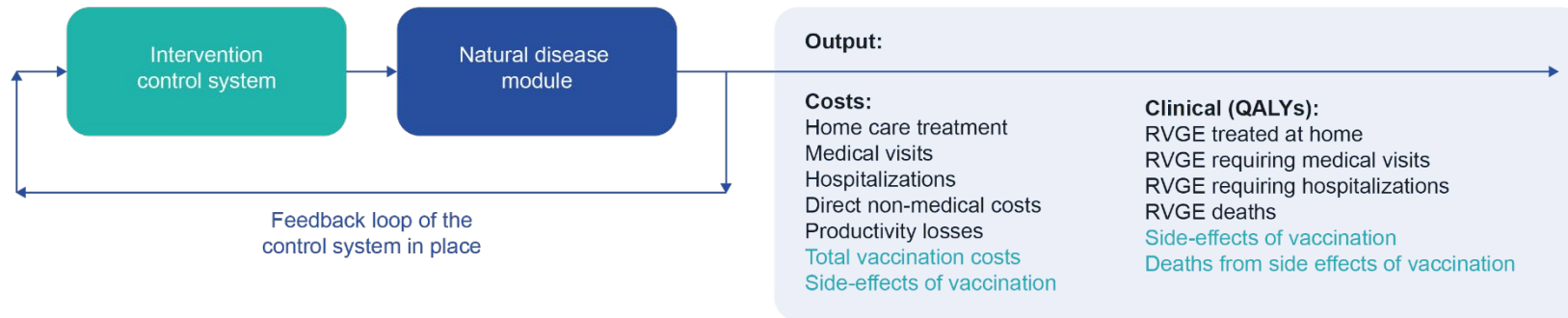
BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HRV: human rotavirus, live, attenuated, oral vaccine; QALY: quality-adjusted life year. Dominance represents the vaccine that is the most cost saving, i.e., with greater QALY gains at a lower cost.

Figure S1. Description of the cost-effectiveness model structure

Step A: Natural disease module

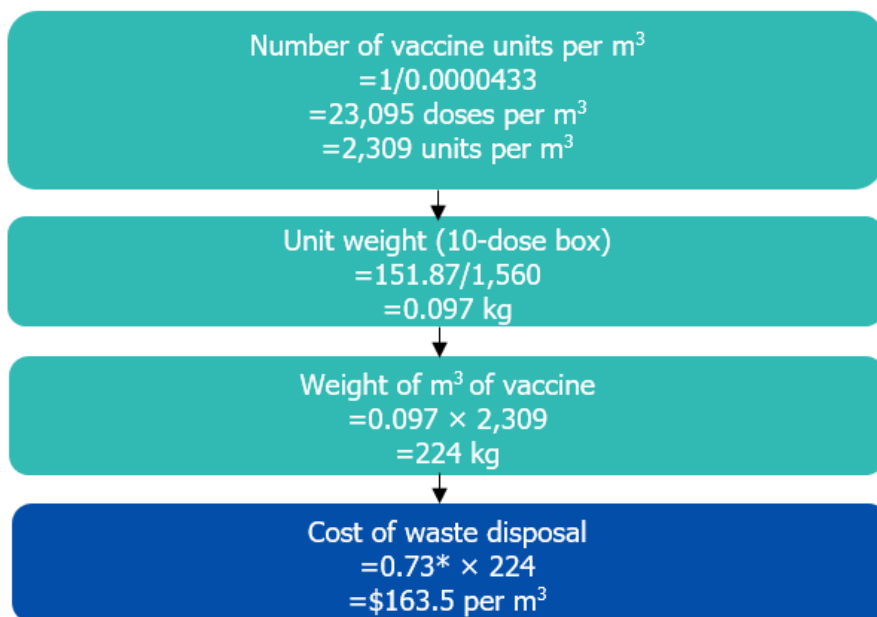


Step B: Natural disease module + intervention control system



This model in this study was developed based on the model structure published by Bakir et al., (2013) [21]. The model construct was a static, deterministic, population model of the at-risk group of children aged below 5 years old. DALY: disability-adjusted life year; QALY: quality-adjusted life year; RVGE: rotavirus gastroenteritis.

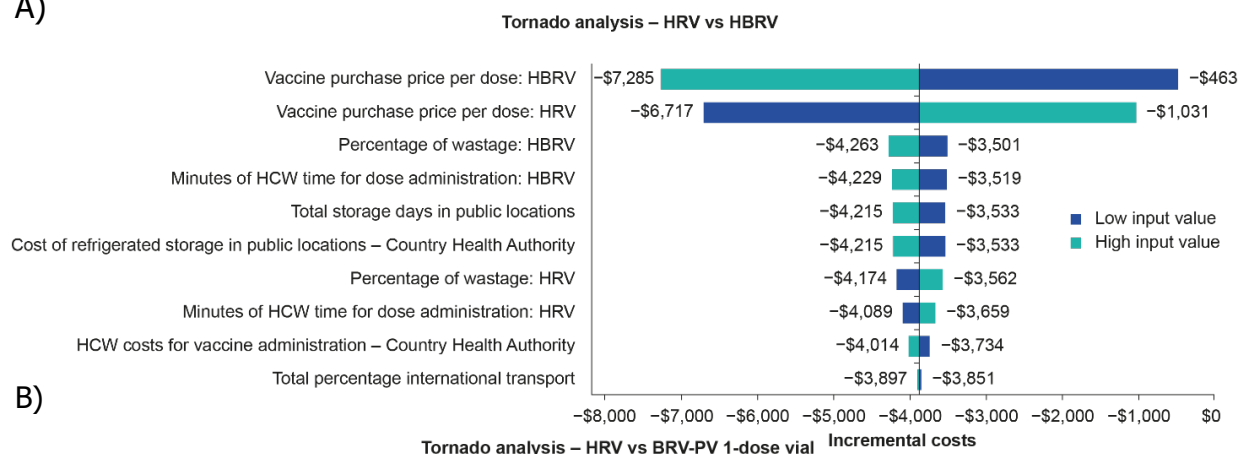
Figure S2. Calculation of the cost of vaccine waste disposal



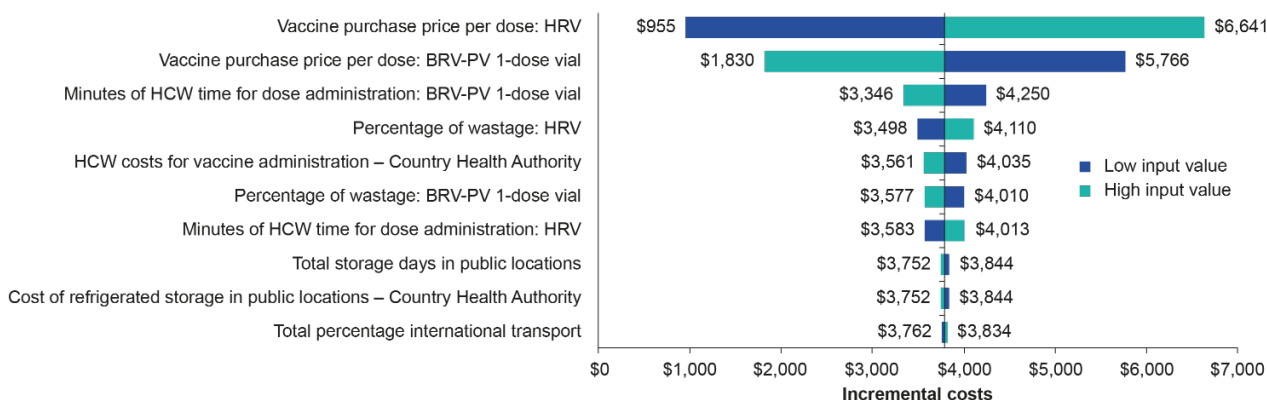
*The cost of incineration of health care risk waste in South Africa was reported to be R4.58 per kg (250 kg per hour plant capacity) reducing to R3.69 per kg (1,000 kg per hour plant capacity) in 2007 costs [22]. The more conservative estimate (R3.69 per kg) was used. The cost of incineration of healthcare waste was converted to 2022 USD using OECD conversion rates [23] and CPI inflation calculator to be \$0.73 per kg [24]. These costs were calculated for HRV and assumed to be the same for HBRV and BRV-PV. kg: kilogram; m: meter; OECD: Organisation for Economic Co-operation and Development; R: South African rand; USD: United States Dollar.

Figure S3. Cost analysis deterministic sensitivity analysis (country payer perspective)

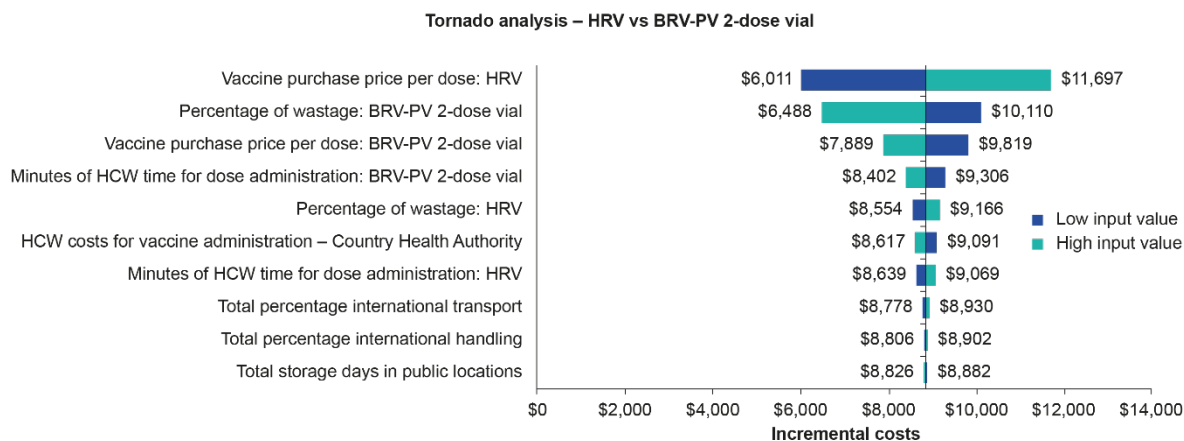
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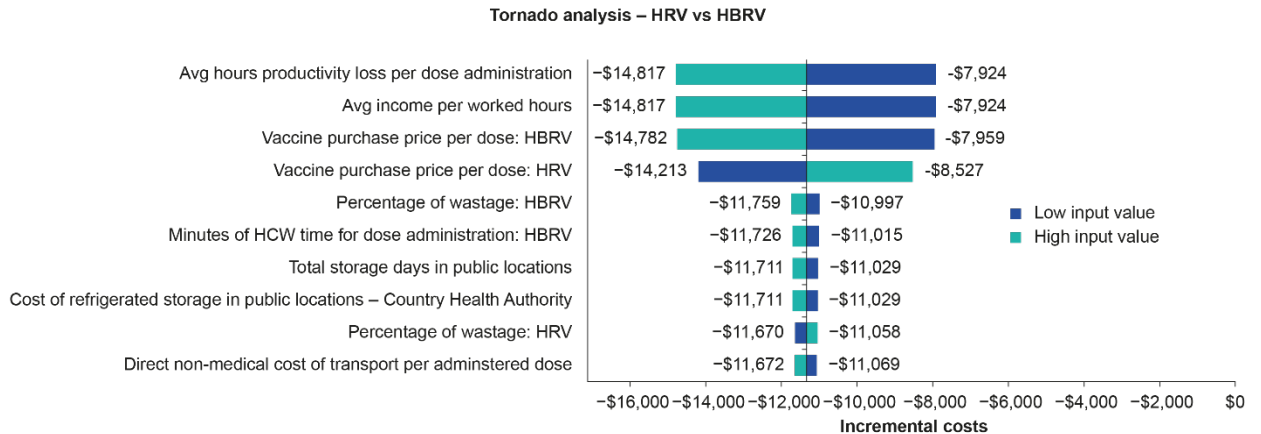
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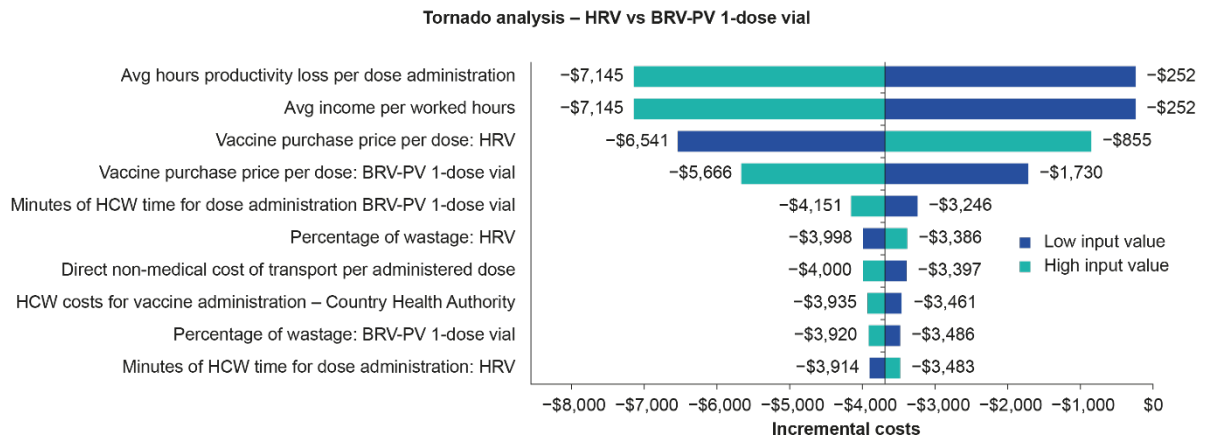
A) Tornado plot depicting HRV vs HBRV; B) Tornado plot depicting HRV vs BRV-PV 1-dose vial; C) Tornado plot depicting HRV vs BRV-PV 2-dose vial. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HCW: healthcare worker; HRV: human rotavirus, live, attenuated, oral vaccine.

Figure S4. Cost analysis deterministic sensitivity analysis (societal perspective)

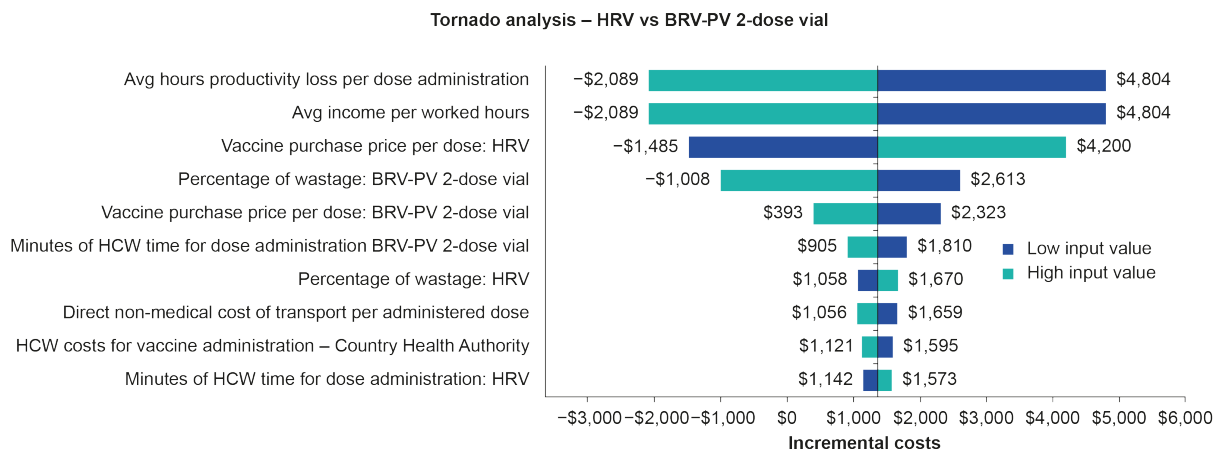
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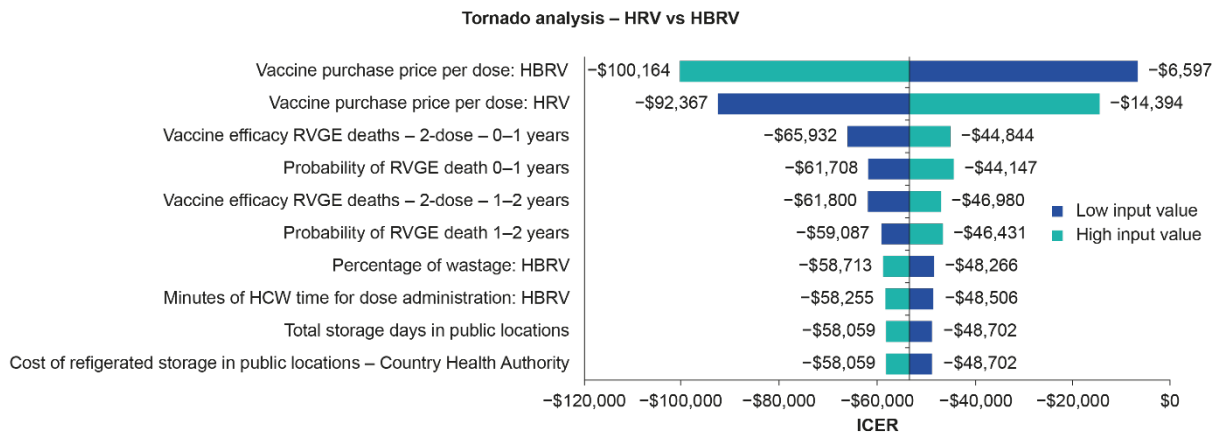
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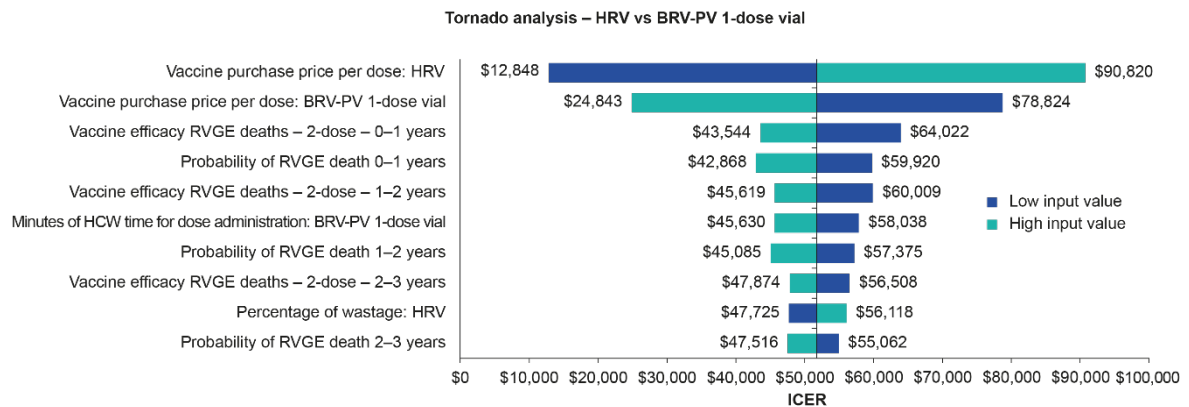
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Figure S5. Cost-effectiveness analysis deterministic sensitivity analysis (country payer perspective)

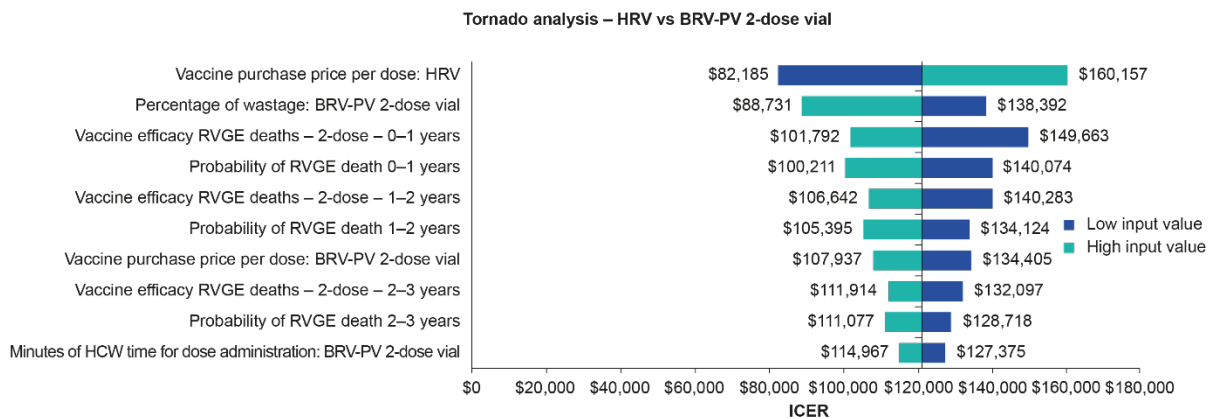
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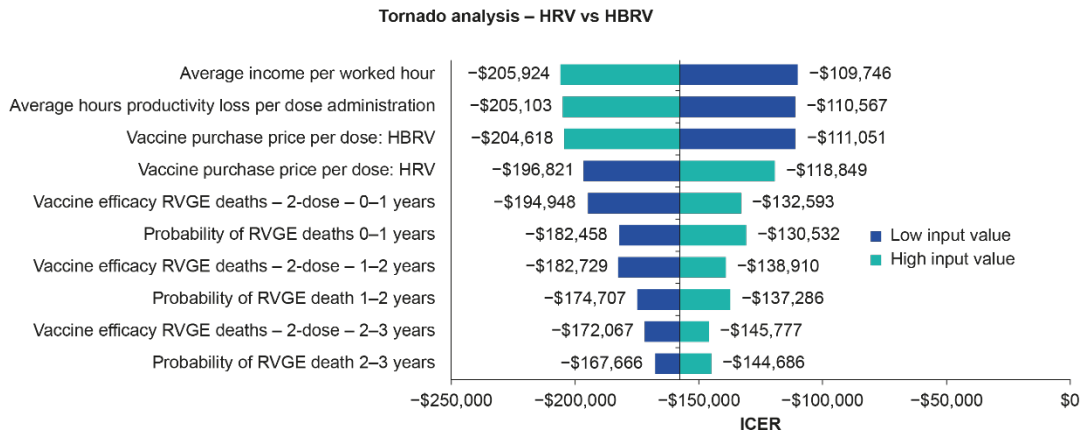
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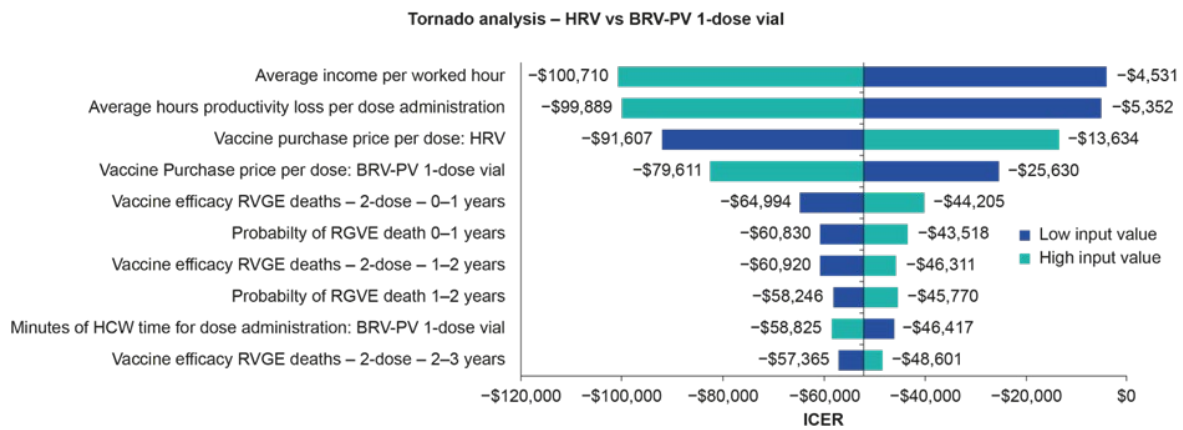
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Figure S6. Cost-effectiveness analysis deterministic sensitivity analysis (societal perspective)

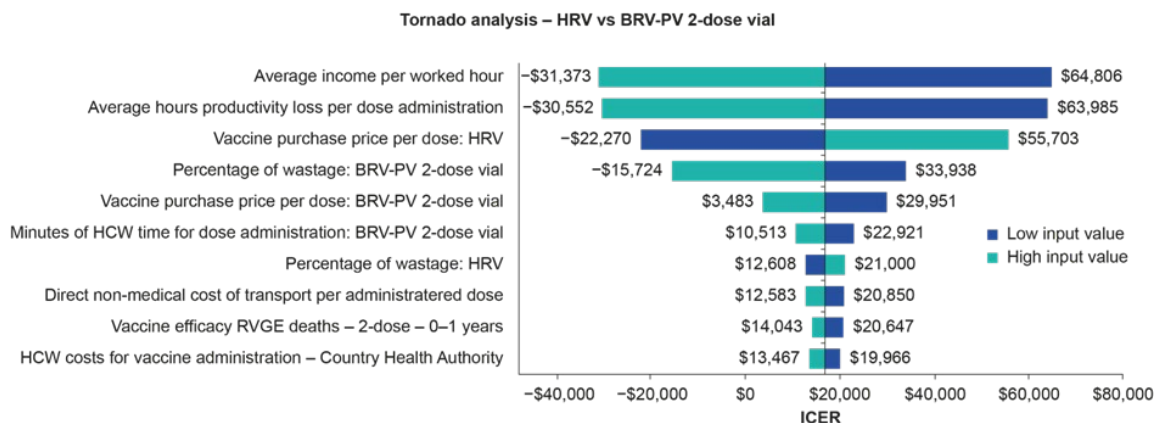
A)



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A) Tornado plot depicting HRV vs HBRV; B) Tornado plot depicting HRV vs BRV-PV 1-dose vial; C) Tornado plot depicting HRV vs BRV-PV 2-dose vial. BRV-PV: rotavirus vaccine, live attenuated oral, freeze-dried; HBRV: rotavirus vaccine, live, oral, pentavalent; HCW: healthcare worker; HRV: human rotavirus, live, attenuated, oral vaccine; ICER: incremental cost-effectiveness ratio; RVGE: rotavirus gastroenteritis.

Supplementary References

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