Universidade Nova de Lisboa

Instituto de Higiene e Medicina Tropical

Cost-effectiveness of rotavirus and human papillomavirus vaccines in children and girls, in Mozambique.

Esperança Lourenço Alberto Mabandane Guimarães

THESIS TO OBTAIN THE PHD DEGREE IN TROPICAL DISEASES AND GLOBAL HEALTH

OCTOBER 2025

Universidade Nova de Lisboa

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Thesis to obtain the PhD degree in Tropical Diseases and Global Health

Financial Support

Bill and Melinda Gates Foundation, Through PATH subawards numbers: GAT.2111-01707508-SUB and KFW.0888-38-01709966-SUB.

SCIENTIFIC PUBLICATIONS

Published articles related to doctoral thesis:

1. **Guimarães, E.L**.; Chissaque, A.; Pecenka, C.; Debellut, F.; Schuind, A.; Vaz, B.; Banze, A.; Rangeiro, R.; Mariano, A.; Lorenzoni, C.; Carrilho, C.; Martins, M.d.R.O.; de Deus, N.; Clark, A. **Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study.** Vaccines 2023, 11, 1058. https://doi.org/10.3390/vaccines11061058.
2. **Guimarães EL**, Chissaque A, Pecenka C, Clark A, Vaz B, Banze A, Canana N, Romão C, Martins MRO, Nilsa de Deus, Frédéric Debellut, **Cost-effectiveness of rotavirus vaccination in Mozambique**, Vaccine, 2022, Aug 3; S0264-410X(22)00940-9.

Presentations in conferences related to the thesis

1. **Guimarães EL,** Chissaque A, Pecenka C, Clark A, Vaz B, Banze A, Canana N; Romão C, Martins MRO, de Deus N, Debellut F. Cost-effectiveness of Rotavirus Vaccination in Mozambique. 14th African Rotavirus Symposium. Abuja, Nigeria, Nov. 2023. Oral Presentation.
2. **Guimarães EL,** Chissaque A, Pecenka C, Clark A, Vaz B, Banze A, Canana N; Romão C, Martins MRO, de Deus N, Debellut F. *Cost-Effectiveness of alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique*. Health Economics, Health Policy, and Healthcare Management. Paris, France, Apr. 2023. Oral presentation.
3. **Guimarães EL,** Chissaque A, Pecenka C, Clark A, Vaz B, Banze A, Canana N; Romão C, Martins MRO, de Deus N, Debellut F. *Cost effectiveness of monovalent Rotavirus vaccine in Mozambique*. European Health Economics Conference. Oslo, Norway, Jul. 2022. Oral presentation.

Dedication

To my parents, Lourenço Alberto M. Guimarães (in memoriam) and Adélia João Chivambo Guimarães, who never stopped believing in me.

Acknowledgements

To the Almighty God I´m thankful for giving me the opportunity to come so far.

To my parents, Adélia and Lourenço Guimarães (in memoriam), who gave me unconditional love and support. Thank you for teaching me how to navigate the world with strength and for teaching me the paths to the person and professional I am.

To my husband Cláudio Ndimande, thank you for inspiring me to keep God first, for being the genuine partner, for easing my workload and for making part of my professional growth.

To my kids, Binilson, Ethél and Elishah, my God´s gift, you give me inspiration to be a better version of me. Thank you, babies, for being so patient and understanding mommy's growing process.

To my sisters (Kátia Dionn Guimarães and Lina Guimarães) and brother (Lourino Guimarães), it is a privilege to be your old sister, thanks for the infinite love and support.

To Nilsa de Deus, my 10 years' supervisor and mentor, you inspire me in personal and professional life. Thank you for your immensurable support, guidance and friendship.

To professors Maria do Rosário Oliveira Martins and Clint Pecenka, my co-supervisors, for your timely assistance with practical, technical and theoretical aspects, and for giving me the opportunity to develop my skills towards the present thesis and my professional growth, I am grateful.

To my friends and fellows, Assucênio Chissaque, Nozipho manjate, Adilson Bauhofer and Marta Cassocera (in memoriam) for your immensurable support and friendship.

To Frédéric Debellut and Andrew Clark, who gave me a great technical support, thank you.

To the Expanded Program of Immunization technical group and Comité de Peritos em Immunização (the Mozambique NITAG), thank you for all your efforts clarifying about immunization strategies, decision making on model parameters and help put everyone together for the workshops.

To the colleagues and staff from INS, IHMT and PATH who were part of my path towards my Ph.D., a big thanks.

Finally, to everyone who direct or indirectly supported my Ph.D. journey, thank you so much.

Resumo

Introdução: A gastroenterite associada a rotavírus (RVGE) e o câncer cervical (CC) são globalmente doenças com elevada carga de mortalidade em crianças e mulheres, respetivamente, sobretudo em países de baixa e média renda. Para prevenir estas doenças, em 2015 e 2021, Moçambique introduziu no Programa Alargado de Vacinação as vacinas contra Rotavirus, Rotarix® e contra o Papilomavírus Humano (HPV) Gardasil® tetravalente (Gardasil-4®). Porém, antes deste projeto não havia evidências de longo prazo das implicações da RVGE e do CC, nem sobre o custo-efetividade da vacinação de crianças e raparigas contra o RV e o HPV (agente causal do CC). Objetivou-se estimar o impacto e o custo-efetividade da vacinação com Rotarix® e Gardasiil-4® atualmente usados no país, e de potencias alternativas futuras, como Rotavac® e Rotasiil® contra RV, e Cervarix™ e Cecolin® contra HPV.

Métodos: Usou-se um modelo de coorte estático de análise de decisão (UNIVAC), para estimar o impacto e o custo-efetividade das vacinas Rotarix, Rotasiil e Rotavac em crianças, (2021 a 2030), e das vacinas Gardasiil-4, Cecolin e Cervarix em raparigas de 9 anos, incluindo uma campanha de vacinação multietária em raparigas dos 10-14 anos (2022 a 2031). O resultado primário foi o custo incremental por ano de vida ajustado para incapacidade (DALY) prevenido, na perspetiva governamental. Cada vacina foi comparada à ausência de vacina e entre si. Análises de sensibilidade determinística e probabilística foram realizadas para avaliar as incertezas do modelo.

Resultados: A projeção de dez anos revelou que sem a vacina contra RV, 11.000 mortes infantis ocorreriam em Moçambique. As vacinas potencialmente reduzem a carga de RVGE em 41% (Rotarix) e 48% (Rotavac e Rotasiil). Com o suporte da Gavi, o custo da vacinação foi menor com a Rotarix (US$ 31 milhões), porém, sem suporte, Rotasiil foi menos dispendiosa (US$ 75,8 milhões). Com o suporte da Gavi todas as vacinas foram custo-efetivas (limiar 0,5 vezes o Produto Interno Bruto (PIB) per capita (p.c) (US$ 224,3)). Rotarix dominou as demais (US$ 102/DALY evitado), apresentando 98% de probabilidade de ser custo-efetiva. Porém, sem o apoio da Gavi, Rotasiil foi a melhor, com 30% de probabilidade de ser custo-efetiva. Quanto ao CC, sem a vacinação contra o HPV, 282.687 mortes associadas à doença decorreriam no país. Considerando a proteção cruzada, as vacinas preveniriam entre 53% e 70% dos casos e mortes pelo CC. Sem o

subsídio da Gavi o custo do programa de vacinação é menos dispendioso com Cecolin (US$ 60 milhões). Todas as vacinas foram custo-efetivas. Com o suporte da Gavi e proteção cruzada, Cervarix foi dominante, mas, sem suporte da Gavi, Cecolin foi a melhor (US$ 26/ DALY evitado), com 100% de probabilidade de ser custo-efetiva ao limiar de 0,35xPIB p.c. (US$ 175).

Conclusão: As vacinas contra RV e HPV têm potencial para reduzir a carga de RVGE em crianças e CC em mulheres. As vacinas são custo-efetivas considerando uma variedade de assunções. Com o suporte da Gavi, Rotarix é a opção mais custo-efetiva, inversamente, sem o suporte, Rotasiil seria a melhor opção. Quanto às vacinas contra HPV, todas as vacinas foram custo-effectivass, contudo sem o suporte da Gavi Cecolin foi dominante. Para melhorar a eficiência da tomada de decisão, estas vacinas devem ser reavaliadas usando estimativas atualizadas.

Palavras-chave: Diarreia; Rotavírus A; câncer cervical; Papillomavírus; modelagem.

Abstract

Introduction: Rotavirus gastroenteritis (RVGE) and cervical cancer (CC) are life-threatening diseases in children and women worldwide, respectively, with the largest mortality burden in low- and middle-income countries. To prevent these diseases, Mozambique introduced vaccines against Rotavirus (RV), Rotarix® and Human Papillomavirus (HPV), Gardasil® tetravalent (Gardasil-4®) vaccines, into the Expanded Program on Immunization, in 2015 and 2021, respectively. However, before this project, there was no long-term evidence on the implications of RVGE and CC, neither the cost-effectiveness of vaccination of children and girls against RV and HPV (causal agent of CC). We aimed to estimate the impact and cost-effectiveness of the currently used Rotarix® and Gardasiil-4®, and other alternatives that could be used in the future, in Mozambique, such as Rotavac® and Rotasiil® for RVGE and Cervarix™ and Cecolin® for HPV.

Methods: An *Excel* proportionate outcomes static cohort decision-support model (UNIVAC) was used to estimate the lifetime benefits and costs of using Rotarix, Rotasiil and Rotavac in infants from 2021-2030, and HPV vaccines Gardasiil-4, Cecolin and Cervarix in girls aged 9 years, including a Multiple-Age Cohort catch-up campaign in 10–14-year-old girls, from 2022 to 2031. The primary outcome was the incremental cost per disability-adjusted life-year (DALY) averted from the government perspective. Each vaccine was compared to no vaccination and to each other. Uncertainty was assessed through deterministic and probabilistic sensitivity analyses.

Results: Ten-year-projections revealed that without RV vaccine 11.000 deaths would occur in Mozambique. The vaccines potentially reduce RVGE burden by 41% (Rotarix) and 48% (Rotavac and Rotasiil). With Gavi support, the vaccine program cost is lowest for Rotarix (USD31 million), however without Gavi support, Rotasiil (USD75.8 million) is less expensive. At 0.5 times Gross Domestic Product (GDP) per capita (p.c.) threshold (USD224.3), considering Gavi support, the vaccines are cost-effective, with Rotarix dominating others (USD 102/DALY averted), with 98% probability of being cost-effective. Nevertheless, without Gavi support, Rotasiil is close to the threshold, with 30% probability to be cost-effective. Regarding CC, without HPV vaccination 282,687 disease-related deaths would happen nationwide. Considering cross-protection, the three

vaccines could prevent between 53 and 70% CC cases and deaths. The program cost without the Gavi subsidy was cheapest for Cecolin (USD60 million). The HPV vaccines were cost-effective at a WTP threshold of 0.35xGDP p.c. (USD175). With Gavi support and cross protection, Cervarix dominated others (cost saving), however without support, Cecolin dominated (USD26/DALY averted), with 100% probability to be cost-effective.

Conclusion: RV and HPV vaccines have potential for reducing burden of RVGE in children and cervical cancer in women. Similarly, the studied vaccines are cost-effective considering a variety of assumptions. With the Gavi subsidy, Rotarix is the most cost-effective choice, conversely, without Gavi support Rotasiil would be the best option. Among the HPV vaccines, all the vaccines were potentially cost-effective, however without the Gavi subsidy Cecolin was dominant. To improve decision-making efficiency, the studied vaccines should be re-evaluated using updated estimates.

Key words: Diarrhoea; Rotavirus A; cervical cancer; Papillomavirus; modelling.

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CC	Cervical cancer
CIN	Cervical intraepithelial neoplasia
DALYs	Disability-Adjusted-Life-Years
EPI	Expanded Program of Immunization
FIGO	Federation of Gynaecology and Obstetrics
Gavi	Global alliance for vaccines and immunization
HPV	Human Papillomavirus
ICER	Incremental cost-effectiveness ratio
RV	Rotavirus
TNM	Tumor Node and Metastases
UNIVAC	Universal vaccine cost-effectiveness and impact modelling framework
US$	American Dollars
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

1. CHAPTER 1 – INTRODUCTION

1.1. Mozambique country profile

1.1.1. Location and Population

Mozambique is a country on the south-eastern part of the African continent (Fig 1), located between the parallels 10/27' and 26/52' of latitude South and between meridians 30/12' and 40/51' of longitude East (1). It was a Portuguese colony and became independent in 1975. One year later, the civil war began and lasted 16 years (1976 – 1992), weakening infrastructure and impoverishing human capital, with lasting effects (2).

Figure 1 - Map of Mozambique with borders and boundaries.
Source: (3)

The country comprises 11 provinces distributed in three regions (Figure 1). According to the most recent census (2017), it has 27.909.799 inhabitants (Table 1), of which a significant part (46.6%) is younger than 15 years of age, and 38% are between 15 and 40 years (Figure 2). Nampula (North) and Zambézia (Centre) provinces account for 39% of

the population. And the majority (66.6%) live in rural areas. Catholicism is the most prevalent religion in the country, being practiced by 27% of the population (4). According to the most recent Demographic and Health Survey (2022-2023), the average literacy rate is at 58%, where men are the most literate (69% vs 47%) (5).

Table 1 - Mozambique population distribution by provinces and regions.

Indicator		N	%	Region	Total by region
Provinces	Niassa	1,810,794	6.5	Northern	
	Cabo Delgado	2,320,261	8.3	Northern	9,889,975
	Nampula	5,758,920	20.6	Northern	
	Zambézia	5,164,732	18.5	Center	
	Tete	2,648,941	9.5	Center	12,018,915
	Manica	1,945,994	7.0	Center	
	Sofala	2,259,248	8.1	Center	
	Inhambane	1,488,676	5.3	Southern	
	Gaza	1,422,460	5.1	Southern	1,488,676
	Maputo Província	1,968,906	7.1	Southern	
	Maputo Cidade	1,120,867	4.0	Southern	
	Total	**27.909.799**	**NA**	**NA**	**NA**

NA - Not applicable
Source INE (4)

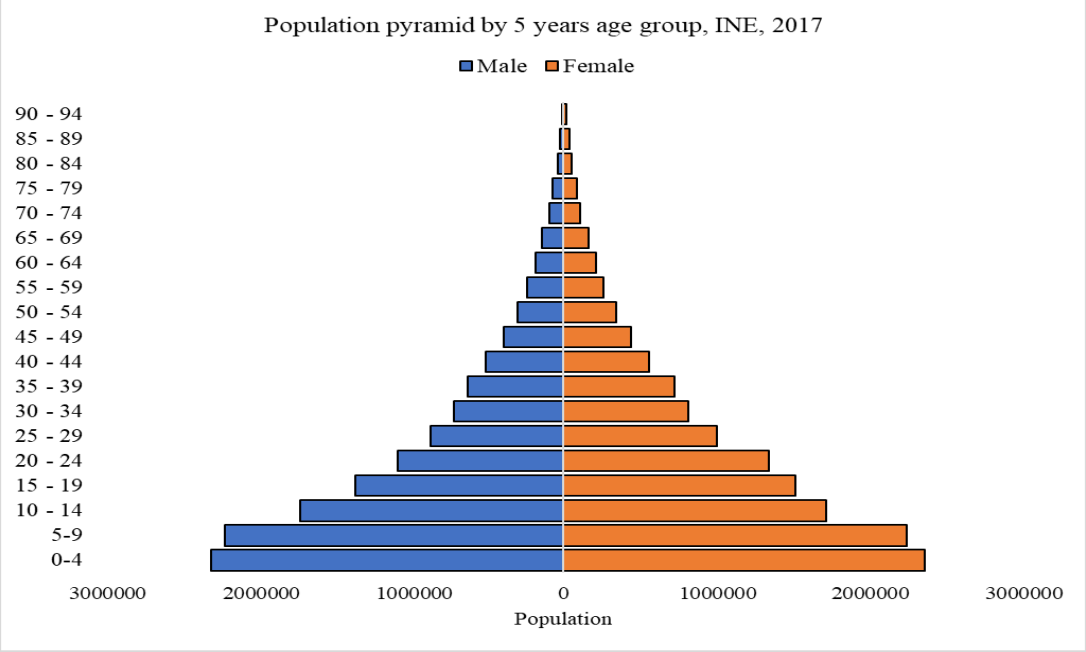

Figure 2 - Mozambique population pyramid in 2017 (showing a larger youth population).
Source: INE, 2019 (4).

1.1.2. Access to water and sanitation

Although drinking water and sanitation have improved during the years, the population still experiences poor access (5), which probably contributes to the prevalence of diarrhoeal-related infections (6). Fifty-five percent of the Mozambican population have access to improved water sources. In parallel, basic sanitation infrastructure is available for 36% of the population (5).

1.1.3. Economic profile

Mozambique´s economy is based in ascending order on services provision, agriculture, extractive industry and manufacturing. Agriculture employs 70% of the population, however services provision represents 54% of the Gross Domestic Product (GDP) (7).

GDP per capita was growing at an average rate of 7%, however, since 2015 it has been declining (8) due to financial debt, terrorism, and natural disasters (9). In 2022, the GDP per capita was at USD558, on the other hand the GNI was U$S440 (8). It is estimated that 63% of the Mozambican population falls below the international poverty line of USD 1,90 per day (10).

The latest events in Mozambique (financial debt, terrorism, and natural disasters), worsened literacy, life expectancy and health conditions, driving the country to the 11th lowest Human Development Index (0.456) in the world (10).

1.1.4. Health financing

Historically, the health sector in Mozambique is financed by the state budget and external funds (Non-Governmental Organizations, bi- and multilateral external support). The letter is the most prominent internal source , supporting 58% of the budget in 2021 (12).

In the past (1997), the proportion of the state budget allocated to health was 7.7% (11), which has been increasing slowly over the years to the extent that in 2024, this proportion corresponded to 9.7% (13).

Inequalities in the budget allocation between provinces are evident. Provinces from the South (Maputo City, Gaza, and Inhambane) retain a budget corresponding to more than the national per capita average. Maputo city is more than four times the national average and 6 to 7 times the Nampula and Zambezia provinces average (14).

This scenario limits access to care for needy people and increases the impact of out-of-pocket expenditures in the provinces that are least benefited.

1.1.4.1.Gavi support to immunization

Gavi, The Vaccine Alliance (Gavi) is a public-private organization aimed to improve the health of populations by strengthening health systems through the support to immunization programs, especially in low-income countries. To get Gavi support countries apply for support through proposals that includes health priorities, specially related to immunization. Gavi country funding is for a fixed period, depending on the ability of the governments to cover immunization expenses, measured through Gross National Income (GNI) per capita (15). Countries are eligible for Gavi support if the average GNI per capita over the previous three years doesn´t exceed the threshold of US$1,730 (16).

In 2022, Mozambique´s GNI was U$S440 (17), which is below the World Bank low-income threshold (U$S1,085), filling requirements for eligibility to the initial self-financing transition phase, in which the government pays US$0.20 for any vaccine financed. Upon reaching this eligibility limit, the country will enter “phase II” of preparatory transition, in which the government gradually assumes the immunization costs, adding 15% of co-financing each year. When the average of the previous three years´ GNI per capita (p.c.) and the most recent GNI p.c. are above the US$1,730 threshold, the country moves to “phase III”, the accelerated transition for eight years, where the co-financing by the government is at least 35% of vaccine costs. The subsequent phase is the Fully self-financing phase (phase IV), when the government ultimately assumes the vaccine expenses without the support of Gavi, Figure 4 (16).

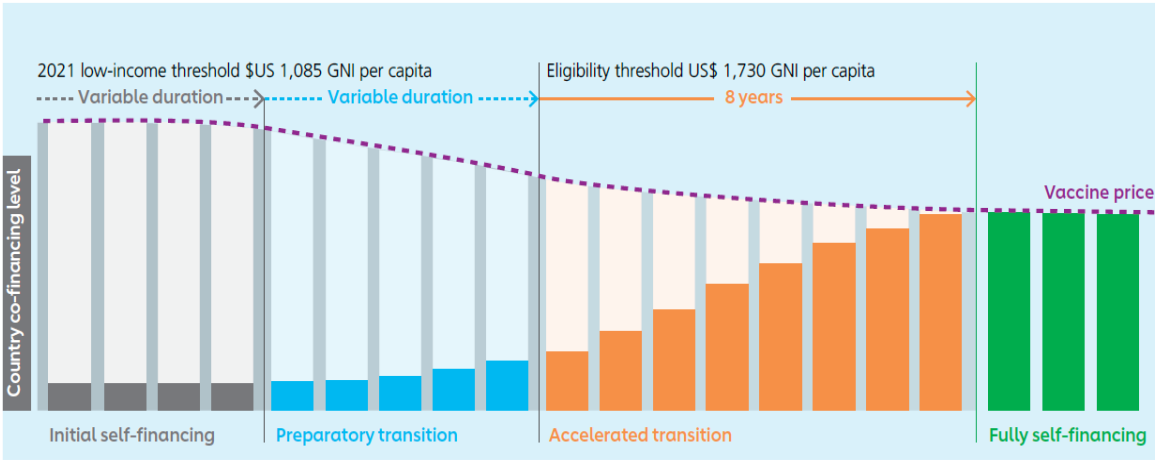

Figure 3 - Gavi eligibility thresholds and co-funding transitioning phases.
Source: (16)

1.1.5. Health and Demographic Indicators

The country´s birth and death rates are higher, corresponding to 37.9 and 11.8 per 1000 inhabitants, respectively (4), with the fertility rate at 4.9 children per woman (5). The child death rate at 60 per 1000 live births and the life expectancy is 53.7 years. The maternal death rate is estimated at 233 per 100,000 live births (4).

1.1.6. Access to Health Services

Although the Mozambican health system has considerably improved, unfortunately, there are still inequalities in access to health care. Less than 80% of the national population have access to health facility less than 10km away. The Centre provinces, Tete (59%) and Zambezia (68%) has the less access, while the South region has the highest percentage (91%), with Maputo province having almost 100 % of people with easy access to public health facilities (18).

According to DHS, half of women have limited access to health services, mainly due to long distances to reach a health facility and financial constraints for buying medicines. Centre provinces, such as Zambezia and Manica, and Niassa in the north, are the most affected by this event, and Maputo, in the South, was the least affected (5). Regarding the proportion of health facilities with readiness for children care, only 40% provide Zinc and 56% has growth chart (18).

1.1.7. Disease burden and death cause

According to national data, infectious diseases play an important role in the burden of disease in under-fives, with emphasis on malaria, and respiratory and gastroenteric infections (5,19).

Malaria was reported as the main cause of morbidity, with prevalence of 32% during 2022-2023 DHS data collection (5). The last DHS report registered chronic undernutrition affecting 37% of the children (5). This evidence is very important since undernutrition unpairs the immune system, increasing the risk for infections such as gastroenteric and respiratory pathogens, which historically pose an important burden in Mozambican children (20,21).

Regarding diarrhoea, the introduction of vaccination against Rotavirus (RV), the leading cause of severe gastroenteritis in children younger than 5 years old, has reduced the disease burden, especially in children aged 12 to 23 months. In 2011 the DHS reported a disease prevalence of 18.5% in this age group (22), while the most recent DHS data revealed a prevalence of 15% in 2022-2023 in the same age group (5).

Between 1990 – 2019, the country experienced a change in the ranking of deaths causes among under-fives. In 1990, the leading cause of mortality were enteric infections, followed by respiratory infections and Tuberculosis, and maternal and neonatal conditions. With the scenario changing, in 2019, maternal & neonatal issues, HIV/AIDS & Sexually Transmitted Infections, neglected tropical diseases, and malaria lead the ranking (23).

On the other hand, as shown in figure 3, according to verbal autopsies performed from 2018 to 2020, a variety of infections accounted for 62% of neonate deaths. Lower respiratory infections, HIV/AIDS, diarrhoea, malaria, and tuberculosis were responsible for over half (53%) of children mortality from 1 to 59 months old. Among people aged 15 onwards, HIV/AIDS was the most important cause of death (25%), followed by other infections (22%) (such as meningitis/encephalitis, dengue fever, and others), injury (13%), cancer (10%) and cardiovascular diseases 5% (19). Regarding cancer, Kaposi Sarcoma is the most common and lethal cancer in men, accounting for 25.6% (2.616/7.391) of total deaths by cancer. In contrast, cervical cancer causes the most deaths in women, being responsible for 4000 (34.4%) of the cancer deaths in females (24).

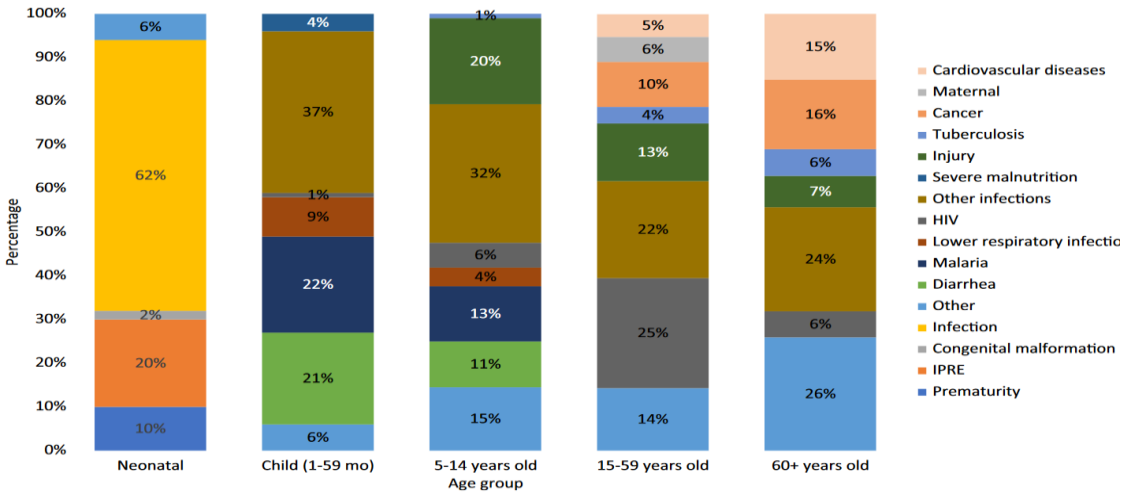

Figure 4 - Cause of death fraction (%) by age group in Mozambique (COMSA data, 2019 – 2020).
Source: (19).

The country has been negatively affected by vulnerabilities such as terrorism (in Cabo Delgado, North Region) and climate changes, which intensify drought, cyclones and cyclic floods in all country regions. These impacts affect the population in all contexts, including health, education, and economics (25).

1.2. Global burden of diarrhoea

Diarrhoea is historically an important cause of disease burden in children under five years old in the world (26–28). In 1990, the mortality rate from diarrhoea was globally 189 per 100,000 live births (26).

A case-control hospital-based multicentric study performed from 2007 to 2011 in African countries (Gambia, Kenia, Mali, and Mozambique – southern region) and Asian countries (Bangladesh, India, and Bangladesh), revealed that the annual incidence of moderate-to-severe gastroenteritis was overall 30.8 per 100,000 child-years (29).

According to a modelling study based on systematic analysis of 2000 to 2016 data from 195 countries, the mortality rate due to diarrhoea in children under five was 70.1 per 100,000. The same study appointed diarrhoea as accountable for 8.92% (95% UI 7.95–9.94) of total under-five children's deaths and 40.1 million DALYs (30).

From 1990 to 2019, the world experienced a gradual reduction of deaths associated with diarrhoea in children under five years old, from 1.65 million to 500,664 (60% reduction) (26). According to several evidence, this reduction is supported by the gradual introduction of the RV vaccine Globally, which started in 2006 and currently covers 126 (31–36).

Although the burden of the disease has globally declined over time, it continues being an important public health problem in children under five years old, mostly in lower- and middle-income countries (LMICs), especially from sub-Saharan Africa and South Asia (26,37,38).

It is estimated that in 2019 the disease was the fourth cause of mortality in under five children (26). From the five million children´s deaths globally, 500,664 (10%) were caused by diarrhoea in this age group. The Sub-Saharan African countries, which includes Mozambique, represented 72% of the global estimated diarrhoea-related deaths. Equally, accounted for 70% of the global 45,544,641 DALYs due to the disease (26).

Verbal autopsy interviews performed from 1997 to 2006 in Mozambique revealed that diarrhoeal disease was the fourth cause of death in children under five years of age, accounting for 7.2% of the deaths in this age group (39).

Data from 2007 to 2011´s case-control hospital-based study in Manhiça district (southern Mozambique) showed a moderate-to-severe diarrhoea mortality rate of 10.2 deaths per 1000 persons -week at risk (40).

From 2010 to 2016, there was an annual average of 7.086 deaths in the country, which corresponded to 8,0% of annual deaths by all causes in children under five years old (41).

Data from urban and rural hospitals in Maputo City and Province, respectively, showed that from 2015 to 2019, children between 12 and 23 years of age were the most affected by diarrhoea, accounting for 28% of the cases (42).

The 2015 Mozambique national community survey showed that 11% of under-five children had a diarrhoea episode in the last two weeks before the survey (43), which improved in 2022´s survey (9%) (5).

In 2019, Mozambique was one of the most affected by diarrhoeas among the sub-Saharan countries, having experienced the 14th highest mortality rate, with 83 per 100,000 live births (4,231 deaths) and an estimated 385,959 DALYs (26). Although diarrhoeal deaths declined, the disease still poses an important cause of death, representing 6% of all cause's deaths in under-fives in the country (26).

In this country, diarrhoea is the 6th leading infectious cause of mortality in children under five years old (44). Further, it responds for 5 to 10% of the deaths among children under five years old (38).

Globally, among the infectious causes of diarrhoea in children under-five years old, RV is the most important cause of severe diarrhoea, followed by *Shigella*, norovirus, enterotoxigenic *Escherichia coli* and *Cryptosporidium* (45).

1.2.1. Epidemiology of Rotavirus

1.2.1.1.History

Before 1973, the aetiologic agent of around 80% of children with gastroenteritis was unknown due to a lack of laboratory techniques for agent identification (46).

The name of RV is the combination of the Latin rota (translated to wheel in English) *plus* virus, a denomination given due to the virus´s wheel-like presentation (47).
RV was for the 1st time reported in 1963 by Australian investigators after its identification through electron microscopy of newborn mice´s (48,49), and newborn calves´ (50) faecal samples. Later in 1973, the human RV was identified in samples from children with diarrhoea (51). In the following years, several studies associated RV with hospitalization and death in children under five years old from low-income countries in Africa, Asia, and America (52–55).

1.2.1.2.Global burden of Rotavirus

RV is an ubiquitous agent, which for long years leads the importance of infectious causes of severe diarrhoea globally in children under five years of age, mostly in those between six months and two years (20,56,57). The transmission of RV occurs via the faecal-oral route, through consumption of contaminated water and/or food, direct person-to-person contact and with contaminated objects/surfaces (58,59).

In 1990, around 659,053 under-five child deaths (314,974–1,125,598) occurred due to RV Gastroenteritis (RVGE) (60). In 2000, around half a million deaths due to RV-related diarrhoea were estimated (61). In 2013, these estimates decreased to 215,000, with the majority (56.3%) in Sub-Saharan African countries (61). In 2016, the incidence of RV-related diarrhoea was 0.42 cases per child-year, globally (30). In the same year, 1,537,000 hospitalizations and 128,500 deaths were estimated, of which 80% (104,733) occurred in Sub-Saharan countries, especially Nigeria, Tchad, Niger, and Central African Republic, mortality as shown in figure 5 (62).

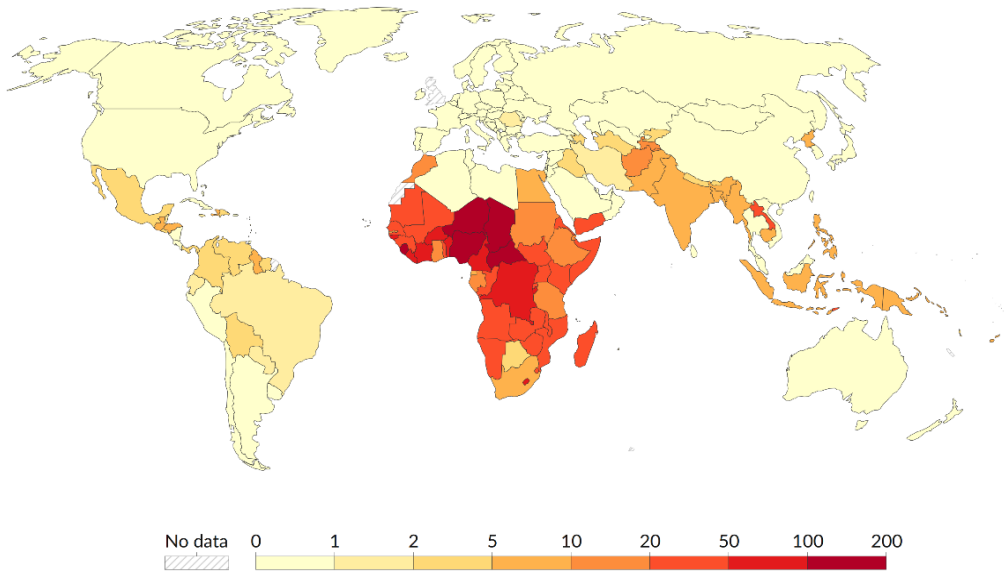

Figure 5 - Global Burden of RVA in under five-year-old children, showing the number of deaths per 100,000 live births, highlighting the highest incidence of sub-Saharan countries in 2016.

Source: Our Word in Data (62)

In 2021 RV related diarrhoea remains an important cause of death in Southern Sub-Saharan Africa (where Mozambique is included), accounting for 107,605 (75,450 - 151,281) deaths and mortality rate of 9.50 (7 - 13) per 100,000 live births (26,60).

1.2.1.3.Rotavirus burden in Mozambique

A case-control hospital-based Global Enteric Multicentre Study (GEMS), performed in some African and Asian countries from 2007 to 2011, including Mozambique, showed

that RV was the most attributable cause of moderate-to-severe diarrhoea in children under five years old (27.8; 21.0 – 34.6), especially in infants (0-12 months) (29), and reported that 97% of the diarrhoea hospitalizations were attributable to RV (63).

In Mozambique, according to the same study, 7.1% of children under five were dying from moderate-to-severe diarrhoea (29).

In Manhiça District (south Mozambique), a hospital-based study using data collected between 2001 and 2012 informed 42% of RV frequency in infants (< 1 year old) (64).

A hospital-based cross-sectional study performed from April 2012 to September 2013 (in Chokwé - southern rural district) reported the frequency of RV infection at 24%, of which 97% were RV (65). Another similar study conducted between February 2012 and September 2013 in Manhiça district and Maputo city showed an average frequency of 42.8% (de Deus et al. 2018). Similarly, in 2015, in Nampula province (Northern Mozambique), the frequency of RV infection was 34.9% (67).

Most RV infections occur in infants, especially those between 6 and 11 months of age, ranging from 38% to 60% of all the included cases (20,65,68,69).

Data from 2021 reveals that in Mozambique, 1,564 children die due to RV-related diarrhoea, which corresponds to a mortality rate of 30.19 per 100.000 children (26).

As a strategy to reduce the burden of RV associated diarrhoea in children under five years old, in September 2015 the Mozambique Expanded Program of Immunization introduced RV vaccine. Since then, the frequency of RV infection in children has reduced, and consequently impacted on decrease of diarrhoea-related-hospital admissions (67,68).
According to the National Diarrhoea Surveillance data (2016 – 2017), the overall frequency of RV infection reduced to 12.2 in 2016 and 13.5 in 2017 (68). In Nampula, data from this surveillance revealed that the overall frequency of RV reduced from 34.9 in 2015 to 21.8% from 2016 to 2019 (67). A cross-sectional study performed in a rural area from Maputo-Mozambique showed a reduction of laboratory-confirmed RV cases in infants from 27.9% to 9.6% in pre- and post-vaccine periods, respectively (70).

In this context it is important to generate evidence of the long-term impact of immunization with currently used RV vaccine and with the potential alternative vaccines that provide better heath results and long-term sustainability.

1.2.1.4.Risk factors

A wider range of risk factors are reported as associated with RVGE. Unsafe sanitation and unimproved drinking water (71,72) are attributable for 80.4% of diarrhoea–related-deaths (73).

Other important risks for the infection have been reported, such as the age range of 0 to 11 months , the presence of a person with RVGE (57,71,75), weaning or mixed feeding before 6 months of age (67,74,76), contact with different animal species associated lower hygiene (67,77), low weight at birth, more than one hour initiation of breast feeding, youngest mothers, poorest families, less maternal education (78).

1.2.2. Treatment

There isn´t a specific drug for RV infection. Normally the treatment is based on the observed symptoms (79,80). Mild and moderate diarrhoeas is commonly successfully handled through oral rehydration combined with an improved diet. However, severe cases may need hospitalization for intravenous rehydration therapy (27,81). The treatment protocol may also include supplements of minerals and vitamins, which include Zinc and vitamin A, to reduce diarrhoea episodes and improve the immune system (82,83). The duration of the hospitalization varies according to the age strata, the severity and the related aetiologic agent and can vary between 3 to 7 days. When compared with the other agents, infection by RV commonly increases the hospitalization duration by 1 or 2 days (57).

1.2.3. Prevention

Prevention of RV infection is based on exclusive breastfeeding during the first six months of life, food hygiene, consumption of improved water, personal hygiene through correct hand hygiene with soap or another substitute, health education to promote good attitudes and the administration of the human RV vaccine (46,84,85).

1.2.3.1.Human Rotavirus vaccines

Research on RV vaccines started immediately when it was realized that RV infection was an important burden in children.Soon there was an understanding of the efficacy of the vaccination on the infection incidence and severity of RV related diarrhoea specially in the 1st year of children age (86–90).

The first investigated vaccines were RIT 4237, based on Single bovine strain RIT and RRV-TV based on Simian/human reassortant G1 – 4 (91–94). RIT was not approved because has inconsistent efficacy (93). However, RRV-TV was licenced and introduced to the United States Health system but was retrieved due to a high risk of intussusception (95).

In 2006, only two RV live attenuated vaccines pre-licenced by the World Health Organization (WHO) were available for global use, the Pentavalent RotaTeq® (Merck & Co, EUA) and monovalent Rotarix® (GlaxoSmithKline, Belgium). In 2018, two additional products, the bivalent Rotavac™ (Bharat Biotech, India) and monovalent RotaSiil™ (Serum Institute of India), were prequalified (96). The last three vaccines are eligible for Gavi co-funding, depending on the country eligibility. Rotarix® is Belgian, composed by a single live attenuated human RV strain (G1P[8]), and administered in two doses, between 6 and 8 weeks of life (97). Rotavac and Rotasiil are Indian products that contain a single live attenuated human RV strain (G9P[11]), they are given in three doses with 04 weeks apart, not exceeding the 08 months of life of the child (97,98).
New generation vaccines are being investigated and expected to be prequalified in the next years, such as the parenteral neonatal vaccine (RV3-BB), Trivalent P2-VP8 (injectable killed or subunit vaccine - iNGRV) and LLR reassortants (97,99–101).

In 2006, eight countries, seven from the Americas and one European, had adhered to the RV vaccine. In 2009, when WHO´s Strategic Advisory Group of Experts recommended the introduction of the vaccine in all countries, especially in the LMICs where the RVGE-associated fatality rates are high, there were 22 countries using the RV vaccine in their immunization program. From then to 2023, the number of countries using the vaccine increased to 126 (Figure 6), of which 48 were from sub-Saharan Africa, which includes Mozambique, where the vaccine was introduced on 4th September 2015 (102).

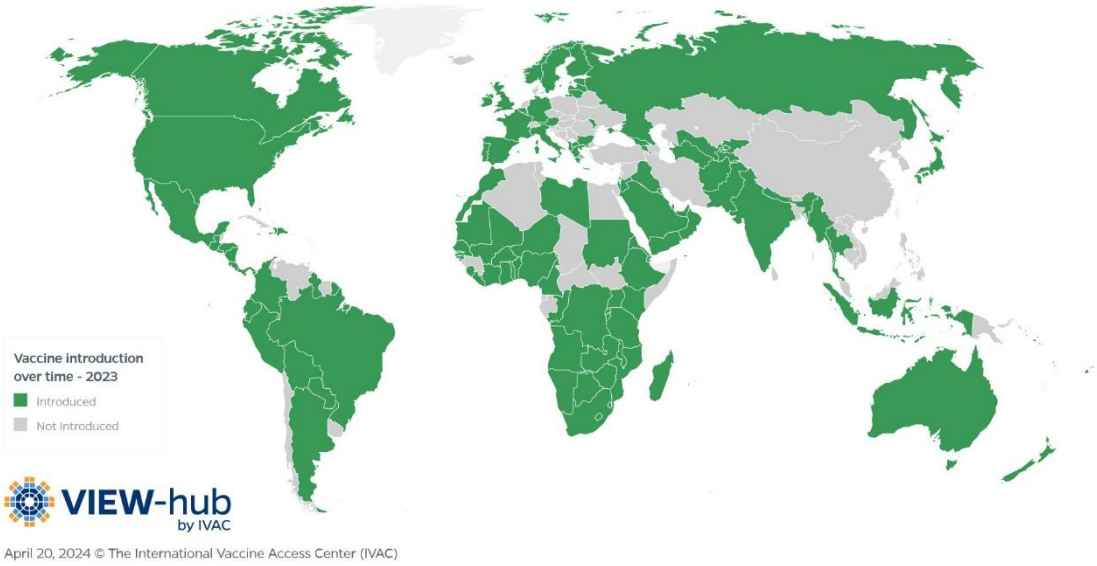

Figure 6 - Rotavirus vaccine Global distribution, 2023.

Source: IVAC (102)

As a result of the increasing availability of alternative vaccine brands, countries have been performing regular vaccine choice reviews. This culminates with alternative product introduction or switch in several countries, including African countries, which have switched from Rotarix vaccine to other brands due to a variety of reasons. Among the African countries, eight countries have switched vaccines, namely: i) Burkina Faso and Mali have switched from Rotateq to Rotasiil, ii) Cote d'Ivoire, Gambia, and Rwanda replaced the same vaccine by Rotarix, iii) Ghana and Tanzania have switched from Rotarix to Rotavac. The main reasons for switching were challenges related to vaccine supply (including vaccine shortage) and the increase of costs due to graduation from Gavi support (103–105).

1.2.3.2.Rotavirus vaccine efficacy

The use of the human RV vaccine protects vaccinated children and their contacts (85). Evidence shows that RV vaccine provides lower efficacy in LMICs (106). A systematic review reported RV vaccine efficacy against severe RV episodes by a group of countries according to mortality rate and development level. This study reported 91% of effectiveness in High Income Countries (HICs) from the Americas and Europe, 88% in low-mortality rate countries from North Africa and Asia, 50% in sub-Saharan Africa

(known as high mortality rate region due to RV infection) and 42.7% in high mortality countries in Asia (107). Similarly, another study showed an efficacy of 90.6% in HICs, 50.0% in South Asia, and 46.0% sub–Saharan Africa (35).

It is thought that the low efficacy in these countries is due to greater and early exposure to the risk of infection, non-compliance with the vaccine schedule, and coverage (85) of co-infection with other enteric agents nutritional deficiency, which possibly decreases the immune response to the vaccine (34,108,111,112), immunodeficiency, interference caused by other vaccines, or by maternal antibodies (34,113) and the genetic diversity of the virus among the target population (114,115).

New generation vaccines candidates currently being studied (iNGRV and RV3-BB) were reported to be cheaper and confer increased efficacy in low-income countries, being promising on improving health effects at lower costs in several LMI settings, compared with the currently used products (100,116,117).

A modelling analysis conducted with 2010´s birth cohorts from 116 countries on different continents showed that monovalent and pentavalent vaccines had the potential to prevent 45% and 41% of deaths, respectively. Further, found that vaccination prevented a total of 3.3 million hospitalizations and more than 290,000 deaths (118).

In 2016 the vaccine was estimated to have averted around 28,000 deaths (84% of them in sub-Saharan Africa) which could almost be triplicate if the 100% vaccine coverage had been achieved that year (119).

Authors modelled data from 73 countries benefiting from Gavi support and reported the potential of RV vaccines to prevent around 600,000 deaths between 2018 and 2027 (120).

The monovalent vaccine (Rotarix®/GSK, Belgium) was included in the Mozambican Health System since September 2015 (68).

The first vaccine impact study was on the hospital-based diarrhoea surveillance and showed that the introduction of the RV vaccine has contributed to a reduction of around 67% of the infection cases in the first two years of vaccine use (2016 and 2017) (68). In 2016, another cross-sectional study based on the Global Burden of Disease data to estimate diarrhoeal disease burden and the respective etiologic agents estimated that the vaccine contributed to prevent 545 deaths due to RV-diarrhoea in the country (119). A

subsequent study analyzed data from 2017 to 2019 and reported 52% vaccine effectiveness against hospitalization in children between 6 and 11 months (121).

1.2.4. Economic burden of Rotavirus diarrhoea

In addition to being a public health problem due to its morbidity and mortality, RVGE in young children poses an economic burden for the families and for the governments. The financial implications of RVGA treatment include direct medical and non-medical costs, healthcare indirect costs and lost wages from caregivers (122–124) and represent a catastrophic expenditure for low-income families (125,126). These costs have a higher impact in LIC and MIC (122) because of the high disease burden, the weaker health system, and limited funds availability (127,128).

In Kenya, in 2007 a study showed a health system expenditure of USD10.8 million threating RV diarrhoea (129).

Study performed in low-income African countries, showed that the daily cost of hospitalization of a patient with RV associated diarrhoea was estimated at US$43.84 and outpatient treatment was estimated at US4.10 (130).

In Nigeria, the direct costs associated with the treatment of RV diarrhoea was US$9.08 per patient treated (123).

Analysis performed in 7 low-income countries, including 4 Sub-Saharan (Mozambique, Gambia, Mali and Kenya), demonstrated that the average out of pocket costs incurred by the families of with RV-related-diarrhoea was 12.83 US$ (131).

A modelling study which included 137 countries, estimated the cost of treating an outpatient case of diarrhoea at USD52.16 and the inpatient at USD216.36, being the lost wages a significant part of these costs (132).

In Malawi, a study demonstrated that the median total cost of treating diarrhoea, from the families' perspective, was US$293.74, and the direct costs (medical expenses) were US$251.74, which exceeded the monthly income of 25% of the studied families (122).

1.3. The Double burden of infectious and non-communicable diseases in Mozambique

Although infectious disease poses an important burden in Mozambique, there is an increase in non-communicable diseases (NCDs), such as cardiovascular diseases, diabetes, cancers, and others (133). From 1990 to 2015, the country registered a slow reduction in infectious diseases and increasing of NCDs in the general population (134). Further, from 2000 to 2021, cancers shifted from the 9th to 7th raking of deaths in Mozambique (135). In 2021, infectious diseases caused death to around 149,409 people, while NCDs killed 113,304 (135). This double burden of disease shows the need for a health system that improves attention to NCDs. However, in the WHO African region there is a huge inequity in healthcare services provision for NCDs, which are mostly available in the major urban centres, leaving the countryside with exacerbated health and economic burden of disease (136). On the other hand, access to information regarding the availability of preventive methods such as screening and vaccination, especially for cervical cancer may not reach girls and women in remote areas, leading to lower coverage (137,138).

Evidence-based approaches contribute to improvements in clinical practice and health service management, ensuring the choice of the effective and appropriate interventions (139). Thus, generating evidence on interventions against both infectious diseases and NCDs would allow advocate for attention on this double burden at national level, which in turn would lead to improve the Mozambican health system targeting both problems.

1.4. Epidemiology of cervical cancer

1.4.1. History

Cervical Cancer was discovered in 450 Before Christ (BC) by Hippocrates, who called it cancer of the uterus. In 1793 Mathew Bailie realized that the disease was characterized by a chronic ulceration until the complete destruction of the uterus. In 1842, Rigoni-Stern, an Italian physician, provided evidence that it was potentially related to sexual practice, reporting that it was mostly prevalent in married and widowed women, while less frequent in Jewish and unmarried women and absent in Italian nuns (140). In 1861, it was realized that diagnosed people were part of the group with frequent sex, and in 1872, the socio-economic status was identified as one of the potential risk factors for the disease in South Carolina, USA (141) as cited by (140).

Several investigators, started to investigate an effective treatment for cervical cancer, without success. Hippocrates tried local fumigation using herbs; in 600 AD, Aetius experimented baths, cataplasm, and irrigation with herbs, and in 1837, Duparcque advised bloodletting and cervix purging using leeches. In 1813, the 1st effective treatment was performed by JM Langenbeck through an abdominal hysterectomy, a method improved by other investigators in subsequent years. In 1898, Marie Curie discovered radiotherapy and improved the prognosis of the disease (140).

In 1916, Georgios Nicholas Papanicolaou (a Greek scientist) made an important discovery in the diagnostic method with the investigation of single cell types. In 1928 he reported differences between normal and malignant cells, when these cells were swabbed from cervix and observed under the microscope (140,142). However, only in 1941 there was evidence on the relevance of vaginal smear for cervical cancer diagnosis, the reason why the test was named as Papanicolau test (140).

1.4.2. Global burden of cervical cancer

In 2022 cervical cancer was the second most diagnosed cancer among women after breast cancer, with an estimated age-standardized incidence rate (ASIR) of 14.1, reflected in 660,000 new cases in the year (143). Still, in 2022, 1,948,521 women lived with the disease, most of them in Asia (60.9%) and Africa (14.7%) (144). Further, the disease was globally the fourth leading cause of cancer mortality in women, accounting for 350,000

deaths (8.1% of total deaths by cancer), and 7.1 age-standardized mortality rate (ASMR) (143).

The disease is the principal cause of female deaths in 37 countries, including the most of sub-Saharan countries (Figure 7) (144). Sub-Saharan Africa presents the highest ASMR in the globe (22,6), which represents 76,140 annual deaths, 22% of the global estimative (145). Further, as consequence of the burden, it is estimated that in 2020 there were 1.4 million orphans' children (under 18 years old) due to cervical cancer, globally, of which 210,000 (20% of the total orphan number) occurred in the mentioned year (146).

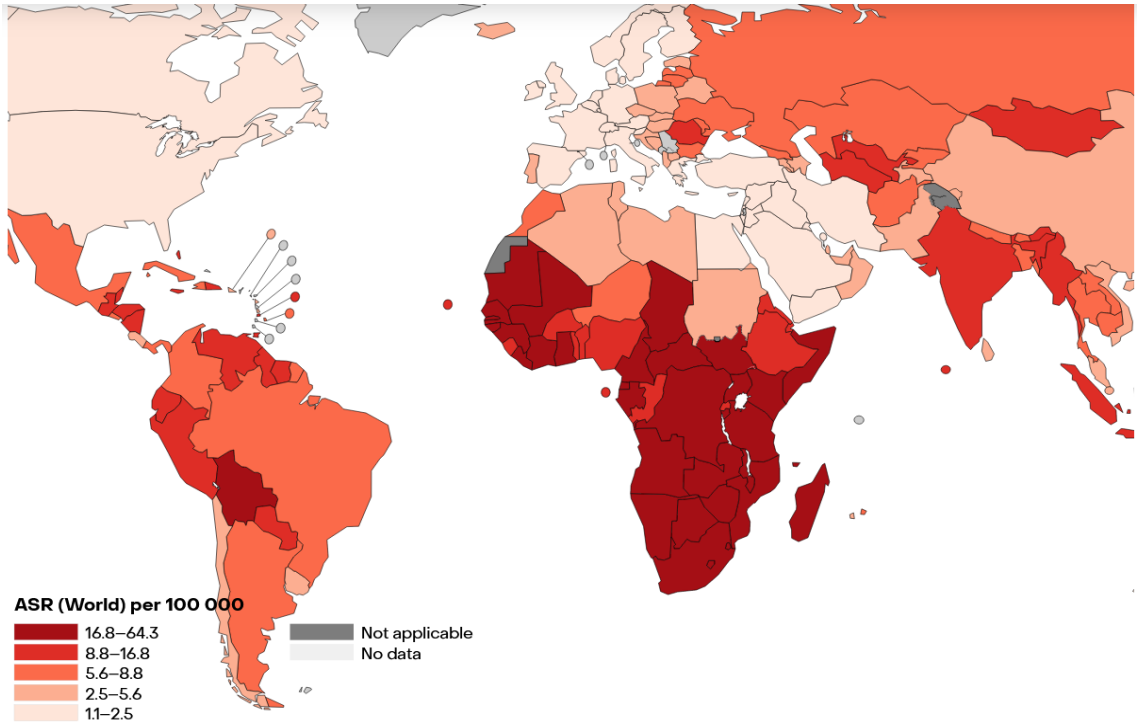

Figure 7 - Cervical cancer distribution in the world, showing the highest ASMR in sub-Saharan Africa.

Source: (145).

1.4.3. Burden of cervical cancer in Mozambique

According to recent reports from the Information Centre on HPV and Cancer, and Global Cancer Statistics, Mozambique is one of the most affected countries by CC in the world. The disease is the most prevalent cancer among women (followed by breast cancer), with 5,325 new cases (50.2 ASIR) and standing for 33% of all cancer types. Similarly, it is the

leading cancer mortality cause, accounting for 4000 deaths (38.7 ASMR), 34.4% of the total cancer deaths in this group (143,147).

In Maputo city (South Mozambique), the disease was the most prevalent cancer in women. From 1991 to 2008, the ASIR increased from 34,3 (1991 to 1996), to 43,3 (1997 to 2002) and 62,0 (2003 to 2008) per 100.000 (148). From 2015 to 2017, CC remained the main cancer in the province of Maputo, with 494 cases (29,9% of all types of cancer) and an ASIR of 38,6 per 100,000. In Beira city (Sofala Province), from 2014 to 2017, there were 319 cases (37,3%) and 46,8 ASIR (149).

It is estimated that in 2020, the prevalence of under 18-years-old orphans in the country was 119,065, of which 15,655 were new orphans. Tthe proportion of cervical cancer orphans globally (20%) corresponds to the prevalence of 24,000 and an incidence of 3,000 orphans in 2020 (146). Orphanhood has long term impact, especially in Mozambique as a low-resource country. Orphans are subject to psychological problems, less access to education, and other health and social vulnerabilities that can impact adulthood and the next generations (150–152).

1.4.4. Aetiology

Cervical cancer is caused by Human Papillomavirus (HPV) persistent infection, transmitted primarily through the sexual contact. The screening for pre-cancerous lesions and immunization against HPV, are the best alternatives to prevent the disease (153,154). However, vertical transmission during pregnancy can also occur (155,156).

1.4.5. Epidemiology of Human Papillomavirus

1.4.5.1.Characterization of HPV

HPV belongs to the *Papillomaviridae* family, genus *Alphapapillomavirus*, which includes several species (157) and more than 200 genotypes, with at least 40 of them responsible for a variety of health conditions in men and women (158). It is transmitted through sexual contact and can cause pre-malignant lesions and cancers that affect the head, oropharynx, cervix, vulva, vagina and anus (153).

There are two classifications of the virus according to its virulence. High-risk or oncogenic HPV, with the potential to cause cervical cancer or other anogenital cancers,

such as genotypes 16, 18, 31, 33 35, 45, 51, 52, among which genotypes 16 (HPV-16) and 18 (HPV-18) are related to 70% of CC in the world (159–161). On the other hand, the low-risk or non-oncogenic cause benign or low-grade abnormalities of cervical cells, such as genotypes 6, 11, 42, 43, and others (158,160,162,163).

1.4.5.2. Global distribution of HPV infection

Globally, the prevalence of HPV in women with normal cytology is 3.9%. This prevalence increases in women with high-grade lesions and with cervical cancer, 51.9% and 69.4%, respectively. The highest prevalence of the HPV in CC cases is in Oceania (76.6%), followed by Europe (74%), and Asia and the Americas sharing the same (68%) (161).

Men can also be infected by HPV. A systematic review and metanalysis performed in 5 continents targeting sexually active men reported a prevalence of 21% high-risk HPV, on which HPV-16, one of the most oncogenic types, was the most common (5%), suggesting that they play an essential role in the epidemiology of CC, as asymptomatic reservoir (164).

1.4.5.3.Distribution of HPV infection in Mozambique

The prevalence of HPV infection in the country occurs mostly in women, being those with lower educational level (165) and those aged 14 to 40 years the most affected by the HPV (166).

Recent studies on HPV are concentrated in a reference public hospital for cancer treatment in Maputo City and show the prevalence of several HPV types in healthy and non-healthy groups (149,165,167–169).

In 2010, Lio and others carried out a study which registered the presence of HPV in 89.4% and 66% of HIV-infected and HIV-uninfected women, respectively. In this study, the prevalence of oncogenic HPV genotypes was higher in HIV-positive than in HIV-negative women. The most observed HPV oncogenic genotypes in HIV-positive women were 58 (12,1%), 16 (10,7%), and 6 (7,6%) (170).

An analysis of cervical cone biopsies from five women with Cervical Intraepithelial Neoplasia (CIN) showed 100% frequency of oncogenic HPV genotypes, being the most frequent genotypes 6, 33, 35 and 58 (169).

Another study performed from 2009 to 2011 reported the prevalence of HPV in 63,6% and 10,2% of HIV-positive women and men aged 18 to 24, respectively. Further, noted the high risk for infection among women with early sexual debut and historic of sexually transmitted diseases (165).

Among women with CC the most prevalent HPV genotype in the country is 16 (34,6%) followed by 18 (16.4%), 45 (9.6%), 35 (7.9%), 51 (2,4%), 52 (2,1%) and others (147).

1.4.5.4.Risk factors

Factors associated with a high risk of HPV infection and progression to cancer are immunosuppressive conditions (HIV infection, medication, or others), co-infection with sexually transmitted agents, such as Chlamydia trachomatis, a high number of births, a high number of sexual partners, smoking, and long term use of oral contraceptives (164,171–174).

1.4.6. Cervical cancer treatment

There is no effective antiviral drug for treating HPV infection. However, the precancerous cervix lesions can be treated by surgery or ablation (freezing or heating) (174).

The treatment of CC depends on the stage of the disease and may involve more than one procedure, including surgery, radiotherapy, chemotherapy, cryotherapy, and immunotherapy (175–178). In the early stages of the disease, surgery, or radiotherapy, combined with chemotherapy, are most used. For advanced stages, radiotherapy combined with chemotherapy has been the main approach (175–177).

1.4.7. Cervical cancer prevention

1.4.7.1.Cervical cancer screening Globally and in Mozambique

To eradicate CC as a public health problem, WHO proposed a global strategy based on: i) a vision of a world where cervical cancer is eliminated, ii) a CC incidence rate of less than 4 per 100,000 women-years, iii) the 90-70-90 targets met by 2030, comprised by 90% of girls fully vaccinated with HPV vaccine by 15 years old, 70% of women screened by 35 years of age and again by 45 years of age and 90% of women diagnosed with precancer or cancer receiving a treatment (179). Further, among other initiatives, in 2009 the *Programa Nacional de Prevenção e Controlo do Cancro do Colo Uterino e da Mama*

(the national program for cervical and breast cancer control and prevention) was created (176), followed by the *Plano Nacional de Controlo do Cancro* 2019-2029 (the national plan for cancer control) (180), both aiming to implement actions for reducing cancer disease burden, including cervical cancer.

Screening for precancerous lesions and vaccination against HPV before sexual debut are the best preventive measures for CC (153,154). Screening can be carried out through visual inspection with acetic acid (VIA) (181), Pap smear for early identification of abnormal squamous cells on the cervix, allowing the treatment before the cancer is developed, and DNA test to detect HPV. If the test is HPV positive, more specific tests are performed to check if abnormal cells or cancer is present and therefore perform the immediate treatment (174).

The screening methods available for Mozambique are VIA (182), and Papanicolaou (138,183). In the country, the screening coverage it still very low and consequently a great portion of CC (more than 60%) is diagnosed in advanced stages (178,184). Thus, efforts are being made to increase it and reduce the mortality rate associated to this cancer (147). In 2014/2015, the self-reported coverage (using cytology and visual inspection) among women aged 30-55 years was estimated to be only 3.5% (138). Later, a review manuscript revealed that Mozambique has the third-worst screening coverage in the world, having reached 3% of women aged 35–49 in the last five years (182). And, the most recent DHS reported an improvement, from the 12,172 interviewed women, 7% had done the screening (5).

1.4.7.2.Human Papillomavirus Vaccines

In the 1990´s, after the discovery of the aetiology of CC, a series of investigations towards the development of HPV vaccine was performed by Lowy and Schiller. In 2006, successful results of experiments with Gardasil® tetravalent (Gardasil-4) were obtained by the U.S. Food and Drug Administration (185).

Table 2 presents the characteristics of the available HPV vaccines. There are currently four prequalified vaccines by WHO for use globally. Gardasil®-4, presently the most used (introduced in 46% of the countries using HPV vaccine), was the first to be approved in

May 2009, followed by Cervarix™ three months leter. In 2018 Gardasil® nonavalent (Gardasil-9) and finally Cecolin® (Xiamen Innovax Biotech Co. Ltd.), in 2021, were prequalified (186).

All the available vaccines are intramuscular suspension containing virus like particles (VLPs) from the L1 structural protein (186). They are specific for the most oncogenic HPV genotypes 16 and 18, however, the tetravalent also comprises genotypes 6 and 11 and the nonavalent, contains genotypes 31, 33, 45, 52 and 58 (187).

The main target group for vaccination is girls from 9 to 14 years of age (assuming anticipation of sexual debut). However, if feasible and affordable, older women, young - adult men, or men who have sex with men are recommended to be vaccinated, considering that all vaccines except Cecolin are approved for use in men (188).

Table 2 - World Health Organization Human Papillomavirus prequalified vaccines profile.

Commercial Name	**Cervarix™**	**Gardasil-4®**	**Gardasil-9®**	**Cecolin®**
Year of prequalification	2009	2009	2018	2021
Manufacturer	GlaxoSmithKline Biologicals (GSK) Belgium	Merck Sharp & Dohme limited liability company. USA	Merck Sharp & Dohme limited liability company. USA	Xiamen Innovax Biotech Co. Limited China
HPV types included	16/18	16/18 and for anogenital warts 6/11	16/18/31/33/45/52/58 and for anogenital warts 6/11	16/18
Adjuvant	ASO4 (aluminum hydroxide, 3-O-deacylated 4'-monophosphoryl lipid A)	AAHS (amorphous aluminum hydroxy phosphate sulfate)	AAHS (amorphous aluminum hydroxy phosphate sulfate)	Al (aluminum adjuvant)
Route of Administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Age indication	≥ 9 years	≥ 9 years	≥ 9 years	≥ 9 years

Source: (187)

By 2022, the HPV vaccine was introduced in the national immunization program of 144 countries, among which 26 are African, and 54 countries also targeted both girls and boys (189) – Figure 8

The first WHO recommendation for vaccine schedule in the main target age group was to administrate three doses; then, this was updated to two vaccine doses, six months apart, based on evidence that the vaccine immunogenicity against HPV types in women was similar. However, based on new evidence about the relevant efficacy from several countries, including those from sub-Saharan Africa (190–192), in 2022, a single-dose HPV vaccination schedule was advocated for this group (193).

Currently 36 are countries following this recommendation, 12 of them from Sub-Saharan Africa – Figure 8 (189).

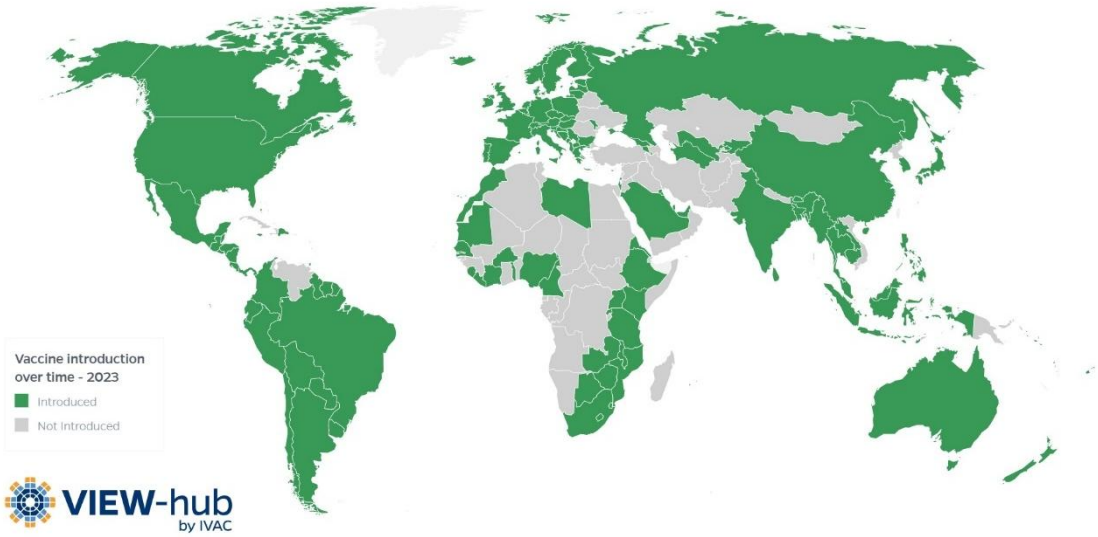

Figure 8 - Global status of HPV vaccine introduction in 2023, showing 144 countries using the vaccine.

Source: IVAC, 2023 (194)

In Mozambique, the HPV vaccine Gardasil-4, was introduced in the Expanded Program of Immunization (EPI) in November 2021, targeting girls of 9 years of age. The administration schedule follows the first recommendation from WHO, two doses, six months apart (195).

1.4.7.3.HPV vaccines efficacy

The HPV vaccines aim to prevent precancerous lesions and cancers affecting the cervix, vulva, vagina and anus, further to avert anogenital warts, in the case of Gardasil-4

(186,196–198). The vaccination in young girls, prior to exposition to the HPV virus (before sexual debut) improves the vaccine efficacy (186,199).

In general, the efficacy of all the vaccines is similar, varying from 62.1 to 63 (200–202). However, the adjuvant system (AS04) provides to Cervarix a grade of cross-protection against some HPV16 and 18 phylogenetically related genotypes, such as HPV31, 33, 35, 52, 58 and HPV39, 45, 59, 68, species groups respectively . This system improves considerably the vaccine efficacy to 82.7% (199).

1.4.8. Economic burden of cervical cancer

The morbidity and mortality of CC has an important socioeconomic impact for the household and the government, reflected in declining of household life quality, especially in LMICs, reduced hours of work and economic expenditures for the treatment and management of the disease (206–208).

A study conducted in Ontario, Canada, from the provider's perspective, found that the cost of healthcare per CC patient ranged from US$34,648 in those who survived the 1st year to US$69,142 in those who died within the 1st year of treatment (209).

In South Africa, a patient-perspective study estimated the average annual cost of CC in outpatients and inpatients at US$407.2 and US$404.4, respectively (210).

A study designed to identify the costs of a set of non-communicable diseases in Kenyan hospitals from the patient's perspective found that the cost for treating CC ranged from US$85.50 to US$1,575.93 in public hospitals and from US$257.25 to US$7,866.39 in private hospitals (211). In the same country, others estimated, from the modified social perspective, that the cost of CC treatment ranged from US$1,345 to US$6,514, with regional invasive cancer being the most expensive (212).

In China, a societal perspective study found that the cost of CC from diagnosis to one year after hospital discharge ranged from US$8,066 to US$22,888, with advanced stage of cancer associated with higher costs (177).

In the Kingdom of Eswatini (Swaziland), in an analysis from a societal perspective, the total annual cost of CC was estimated at US$19 million, of which direct costs accounted

for the largest share (72%) and the majority of costs were attributable to the advanced stage (FIGO IV), 45% (8.7 million) (213).

A study performed with Ugandan Women reported out of pocket costs related to the disease treatment and management ranging between 130 and 530 Canadian Dollars (206).

1.5. Justification

Although after the introduction of the RV vaccine, RV incidence has considerably reduced, RVGE still poses an important role in child morbidity and mortality in Mozambique (20,30,60), being related to more than a thousand child deaths in the country (30). Further, the vaccine shortage observed in the last months (214) may jeopardize the success achieved in combating RVGE. Therefore, it is important to consider the available alternatives for the potential switching of the Rotarix vaccine in Mozambique.

In the other hand, although infectious diseases are the most important cause of deaths in the country, cancerous diseases have been moving towards the most important deaths causes, having shifted from 9th to the 7th position from 2000 to 2021 (135). Among cancers, CC is the most important in Mozambican women, affecting more than five thousand and killing other four thousand per year (143,161). To combat the disease, in 2021, the tetravalent vaccine, Gardasil-4, was introduced in the country (195).

International health agencies such as WHO, and donors supporting immunization in low resource settings (e.g. Gavi) recommend using economic and health evaluation projections of the potential effect of vaccines before its introduction, or after, for surveillance purposes, as an integral part of decision making (215).

In 2019, when the present Ph.D. project was started, the available evidence on RV vaccine was limited to the health impact of Rotarix generated from hospital-based surveillance data from five provinces from South, Center and Noth Mozambique (68,121). And the results of HPV studies were focused on the cost of HPV vaccine delivery, performed in Manhiça, Mocímboa da Praia, and Manica districts (Alonso et al. 2019; Soi et al. 2019). However, there was no long-term evidence about the health and economic implications of RVGE and cervical cancer, neither the cost-effectiveness of vaccinating children and girls against RV and HPV respectively, in Mozambique.

In this context, this project provides, for the first time, modelled long-term projections about the health and economic impact of the currently used RV and HPV vaccines and other globally available alternative products in the country. This evidence will inform decision-making on keeping the current immunization strategies or changes as new lower price points are identified, considering the effects on population health, the budget impact, and long-term sustainability. This information will also subsidise national and

international bodies willing to support the government on health system improvements in the country. Finally, this project results will subsidize implementation of other studies in the health area.

1.6. Objectives

1.6.1. General objective

The general goal of this thesis was to assess the potential impact and cost-effectiveness of vaccination against RV in children under five years of age and against HPV in preadolescent girls in Mozambique.

1.6.2. Specific objectives

The general goal of this thesis is divided in two Chapters, corresponding to the published manuscripts, which specific goals are described below.

Study 1: Impact and Cost-effectiveness of Rotavirus Vaccines in Mozambique.
This study presents results from two analyses considering different periods of time. From 2016 to 2020, the potential impact and cost-effectiveness of oral monovalent Rotarix, compared to no intervention, is presented. Further, from 2021 to 2023, there are presented results of the impact and cost-effectiveness of vaccination with Rotarix (monovalent), Rotavac (monovalent), and pentavalent Rotasiil (Pentavalent) compared to no vaccines. And finally, the cost-effectiveness of the Rotarix vaccine compared to the Rotavac and Rotasiil vaccines.

Study 2: Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study.
To achieve the objective of this study, was estimated the potential health and economic impact of Cervarix (bivalent), Cecolin (bivalent) and Gardasil (tetravalent) vaccines against HPV, compared to no vaccines and then the cost-effectiveness of HPV vaccination, using the three vaccines, in preventing CC compared with no vaccine.

1.7. Introduction references

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2. CHAPTER 2: RESULTS

2.1.Study 1. Cost-effectiveness of rotavirus vaccination in Mozambique

Reference: Guimarães EL, Chissaque A, Pecenka C, Clark A, Vaz B, Banze A, Canana N, Romão C, Martins MRO, Nilsa de Deus, Frédéric Debellut, Cost-effectiveness of rotavirus vaccination in Mozambique, Vaccine, 2022, Aug 3; S0264-410X(22) 00940-9.

Vaccine 40 (2022) 5338–5346

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of rotavirus vaccination in Mozambique

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ARTICLE INFO

Article history:
Received 3 February 2022
Received in revised form 23 July 2022
Accepted 27 July 2022
Available online 3 August 2022

Keywords:
Diarrhea
Rotavirus
Vaccination
Modelling
UNIVAC
Cost-effectiveness
Mozambique

ABSTRACT

Introduction: Rotavirus is one of the most common cause of severe gastroenteritis in children, with the largest mortality burden in low- and middle-income countries. To prevent rotavirus gastroenteritis, Mozambique introduced ROTARIX® vaccine in 2015, however, its cost-effectiveness has never been established in the country. In 2018, additional vaccines became available globally. This study estimates the cost-effectiveness of the recently introduced ROTARIX in Mozambique and compares the cost-effectiveness of ROTARIX®, ROTAVAC®, and ROTASIIL® to inform future use.

Methods: We used a decision-support model to calculate the potential cost-effectiveness of vaccination with ROTARIX compared to no vaccination over a five-year period (2016–2020) and to compare the cost-effectiveness of ROTARIX, ROTAVAC, and ROTASIIL to no vaccination and to each other over a ten-year period (2021–2030). The primary outcome was the incremental cost per disability-adjusted life-year (DALY) averted from a government perspective. We assessed uncertainty through sensitivity analyses.

Results: From 2016 to 2020, we estimate the vaccine program with ROTARIX cost US$12.3 million, prevented 4,628 deaths, and averted US$3.1 million in healthcare costs. The cost per DALY averted was US $70. From 2021 to 2030, we estimate all three vaccines could prevent 9,000 deaths and avert US$7.8 million in healthcare costs. With Global Alliance for Vaccines and Immunization (Gavi) support, ROTARIX would have the lowest vaccine program cost (US$31 million) and 98 % probability of being cost-effective at a willingness-to-pay threshold of 0.5x GDP per capita. Without Gavi support, ROTASIIL would have the lowest vaccine program cost (US$75.8 million) and 30 % probability of being cost-effective at the same threshold.

Conclusion: ROTARIX vaccination had a substantial public health impact in Mozambique between 2016 and 2020. ROTARIX is currently estimated to be the most cost-effective product, but the choice of vaccine should be re-evaluated as more evidence emerges on the price, incremental delivery cost, wastage, and impact associated with each of the different rotavirus vaccines.

1. Introduction

Globally, diarrhea is the third leading cause of mortality in children under five years of age [1]. Rotavirus (RV) is the most common cause of severe diarrhea in young children worldwide, with most hospitalizations and deaths occurring in low- and middle-income countries (LMICs) [2,3]. Despite efforts to reduce the global burden of RV, in 2019 it was responsible for approximately 150,000 deaths among children under five years of age, most of them (81 %) in sub-Saharan Africa [4]. Prior to the introduction of ROTARIX® (GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium) in 2015, the annual mortality rate in Mozambique was estimated to be

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https://doi.org/10.1016/j.vaccine.2022.07.044
0264-410X/

around 48 (19 – 90) per 100,000 children under five years of age [5].

Vaccination is one of the most effective ways to prevent RV gastroenteritis (RVGE). There are currently four RV vaccines prequalified by the World Health Organization (WHO) for global use: the pentavalent RotaTeq® (Merck & Co., USA), the monovalent ROTARIX, the pentavalent ROTASIIL® (Serum Institute of India Pvt. Ltd. India), and the monovalent ROTAVAC® (Bharat Biotech, India) [6]. These vaccines have been reported to be effective in numerous countries in reducing the number of RV cases, hospitalizations, and deaths [7–10].

Mozambique introduced ROTARIX in September 2015 through the Expanded Program on Immunization (EPI) as a strategy to reduce the burden of RV infections and hospitalizations. The vaccine has already had a positive impact on gastroenteritis hospital admissions in children < 5 years of age, showing a reduction in the RV-positive proportion from 40.5 % in pre-vaccine period to 13.5 % in post-vaccine period [11].

As of October 2021, RV vaccines have been introduced in 110 countries [12]. Several studies have shown that RV vaccination is a cost-effective intervention for prevention of severe diarrhea, especially in countries with a high child mortality rate [13–18]. However, there are no known published data on the impact and cost-effectiveness of ROTARIX or other available RV vaccines in Mozambique. The country currently benefits from financial support from Gavi, the Vaccine Alliance (Gavi). However, as the economic situation of the country improves, this support will gradually decrease to the point where the government will have to fully self-finance vaccine costs [19]. From 2018 to 2020 Mozambique had an average Gross National Income (GNI) per capita of US $470 [20]. Upon reaching the eligibility threshold (average GNI per capita of US$1630 over a three-year period), the country will begin a five-year transition towards full self-financing [21]. Cost-effectiveness analyses can provide important evidence to decision-makers about the health and cost consequences of the current use of ROTARIX, both in the context of financial support from Gavi and in the absence of such support. It can also be used to compare ROTARIX to alternative RV vaccines (e.g., ROTAVAC and ROTASIIL) with different product characteristics. This should help to support national strategic planning and priority setting in the context of a constrained budget for public health interventions.

This study aims to assess the health and economic impact of the recently introduced ROTARIX into Mozambique's EPI and to calculate and compare the cost-effectiveness of three products (ROTARIX, ROTAVAC, and ROTASIIL) that could be used in future.

2. Methods

2.1. Study design and model

For this analysis we used the universal vaccine cost-effectiveness and impact modelling framework (UNIVAC) proportionate outcomes decision-support model (version 1.4.16). This was developed in Microsoft Excel (Excel, Microsoft Corp, Redmond, WA, US) to allow transparent assessment of the cost-effectiveness of different vaccines, including RV vaccines [22]. The model has a user-friendly interface and was specifically designed for use by national multidisciplinary teams in LMICs [23].

We ran two separate analyses. In the first, the cost-effectiveness of ROTARIX was compared to no vaccination over the five-year period 2016–2020. In the second, we calculated the cost-effectiveness of ROTARIX, ROTAVAC, and ROTASIIL compared to no vaccination, and to each other, over the ten-year period 2021–2030. We also estimated the cost-effectiveness of the three vaccines as if they had the same health impact. ROTATEQ was not included in this analysis because it is not available for Gavi-supported countries [6].

For each birth cohort included in the evaluation, RV cases, visits, hospital admissions, deaths, vaccine program costs, and healthcare costs were calculated over the first five years of life. Disability-adjusted life-years (DALYs) were calculated over the lifetimes of all cohorts evaluated. DALYs account for both years lost due to early death and years lived with the disease, which facilitates comparison with other potential public health interventions [24].

The primary outcome measure was the cost (US$) per DALY averted [24]. We used 2018 US$ (United States Dollars) for all costs. Both future health outcomes and costs were discounted at 3 % to reflect the time preference for immediate benefits and the opportunity of investing present capital, as recommended by WHO [25]. All results were calculated from a government healthcare cost perspective. This excludes any costs borne by households when seeking treatment at public or private health care providers, e.g., out-of-pocket medical expenses, travel costs, lost earnings of caregivers, etc. The government perspective also excludes the sizable contribution paid by Gavi to the EPI. A separate 'what-if' scenario was evaluated to calculate the cost-effectiveness assuming the government was fully self-financing the program.

A willingness-to-pay (WTP) threshold, which is a value used to represent "an estimate of what an individual might be prepared to pay for one year lived healthily," allows cost–effectiveness ratios (US$ per DALY averted) to be interpreted [26]. Mozambique has not yet defined a country-specific WTP threshold, thus we assumed a threshold of 0.5 times (x) GDP per capita [15,27]. However, we produced outputs that would allow interpretation of our results at different WTP thresholds.

2.2. Data collection and consensus building

In 2016, the population of Mozambique was 27,829,930 [28]. Demographic projections for cohorts born in the period 2016–2030 were obtained from United Nations Population (UNPOP) projections and included an average population size of 990,221 (cohort from 2016 to 2020) and 1,094,020 (cohort from 2016 to 2021)by age/year, life-expectancy by age/year, and under-five mortality rates by year [29]. For all other parameters (e.g., RVGE disease burden, vaccine coverage, timeliness, efficacy, use and costs of health services, and RV vaccination program costs), a national multidisciplinary working group on RV was convened to identify and agree on the most appropriate data (and uncertainty ranges) to populate the model. This working group was convened to provide updated evidence to the National Immunization Technical Advisory Group (NITAG), known in Mozambique as *Comité de Peritos de Imunização* (CoPI), whose role is to make health policy and strategic decisions based on scientific evidence. The RV working group was composed of members from the Ministry of Health (MoH) of Mozambique namely the EPI, experts in RV diarrheal disease from the National Institute of Health (*Instituto Nacional de Saúde* – INS), and members from non-governmental organisations such as United Nations Children's Fund, John Snow Inc., WHO, and Village Reach. The group met four times in 2021 (July, Aug, Sept, Dec) to build consensus on the input parameters and scenarios included in the model.

2.3. Disease burden

To estimate the incidence of severe symptomatic RVGE cases (per 100,000 per year, aged < 5 years), we combined regional estimates of the rate of all-cause severe gastroenteritis with the mean RV-positive proportion in Mozambique, as estimated by three international sources, namely the Global Burden of Disease (GBD) study, WHO, Centre for Disease Control, and the Maternal and

Child Epidemiology Estimation Group [15]. The definition of the severity of diarrhea is based on Vesikari Score which was developed to help access the effectiveness and efficacy of rotavirus vaccine on 20 points which allows combine different symptoms such as diarrhea and vomit episodes, dehydration status, type of treatment and others [30]. The incidence of non-severe RVGE cases was then calculated by subtracting the incidence of severe RVGE cases from the incidence of any symptomatic RVGE cases, obtained from a systematic review and meta-analysis of LMICs from the African region [31]. The rate of RVGE outpatient visits was taken from a modelling study by Debellut et al [15]. To estimate the rate of RVGE hospital admissions, we calculated the number of hospital admissions due to diarrhea in children aged < 5 years based on data from Horn et al [32] and Farthing et al [33] and then multiplied this by the RV-positive proportion (38.5 %) for Mozambique [11]. We assumed that only severe cases would progress to hospital admission. The RV mortality rate (for the pre-vaccination era, i.e., 2015) was obtained from the GBD study [5] and the disability weights were gathered from Salomon et al. [34]. All the disease burden input values are shown in Table 1.

RV disease age distribution data were adapted from a study based on the national diarrhea surveillance in the pre-vaccine period (2014–2015) [11]. A parametric curve (Burr distribution) was fitted to a standard set of age distribution data points to allow more granular estimation of the proportion of RVGE disease occurring in each week of age < 5 years. Methods for age fitting have been described elsewhere [35,36].

For all parameters where there is perceived uncertainty in the data, we provided a low and high range for sensitivity analyses. If 95 % confidence intervals were not available, we assumed a wide range by subtracting or adding 25 % of the base case input value [37,38].

2.4. Vaccine coverage and timeliness

For the 2016 to 2020 cohorts, coverage of the first and second dose of ROTARIX vaccine was assumed to be 90 % and 88 %, respectively. This was based on the reported coverage of the last dose in 2019 (88 %) and allowing for expected drop-out between the first and second doses [39].

For the cohorts from 2021 to 2030, the coverage of all doses administered within the two-dose (ROTARIX) and three-dose (ROTASIIL and ROTAVAC) RV vaccines was assumed to be the same as diptheria, tetanus, and pertussis (DTP1) (93 %), DTP2 (91 %) and DTP3 (88 %), since these vaccines are provided at the same time. We used 2019 coverage rates of DTP1 and DTP3 [39] and assumed that the average between DTP1 and DTP3 would correspond to DTP2 coverage.

The timeliness (coverage by age) of DTP1, 2, and 3 vaccinations was used as a proxy for the timeliness of the first, second, and third dose of RV vaccines. A gamma curve was fitted to the Demographic and Health Survey (DHS) data for 2015 to allow estimation of timeliness by week of age < 5 years.

2.5. Vaccine efficacy

In the absence of head-to-head data from the same trial population, we assumed equivalent vaccine efficacy and waning for all RV vaccines. According to a meta-regression of randomised controlled trials, efficacy two weeks after the first dose is 49.9 % (38.2–65.3 %) and efficacy two weeks after the final dose is 78.9 % (75.5–82.3 %). This analysis calculated the efficacy of live oral RV vaccines in countries with high under-five mortality, including Mozambique. Substantial declines in vaccine protection over time were also assumed, based on the same analysis [40]. We assumed the same level of efficacy and the same rate of waning protection after the second and third dose. This assumption therefore favoured the vaccines with three doses as this schedule delays the onset of waning protection. However, due to substantial uncertainty about this assumption, we also showed the results with the assumption of equal overall impact irrespective of the vaccine product used (Supplementary file I - Fig. 1). Since UNIVAC is a static proportionate outcomes model, any herd effect of the vaccine was not considered in the analysis.

2.6. Vaccination cost

Because Mozambique is eligible for vaccine financial support from Gavi, the government only co-finances part of the vaccine cost, which is currently US$0.40 per course for any vaccine [21].

Table 1
Input parameters for estimating the burden of diarrhea in Mozambique.

Parameter	Central value	Scenarios		Source
		Lower bound	Higher bound	
Incidence (per 100,000 under-five children)				
Non severe RVGE cases	7,473	5,224	10,870	[31]
Non severe RVGE visits	685	239	2,489	[15]
Severe RVGE cases	2,527	1,776	3,130	[15]
Severe RVGE visits	2,315	1,627	2,867	[15]
Severe RVGE hospitalizations	807	605	1,009	Adapted based on [11,32,33]
Severe RVGE deaths	48	19	90	[1]
Disability weights				
Non-severe RVGE	0.19	0.13	0.26	[34]
Severe RVGE	0.25	0.16	0.35	[34]
Mean duration of illness				
Non-severe RVGE	5	2	6	Assumption [17]
Severe RVGE	7	5	9	Assumption [17]
RVGE age distribution	**Cumulative percentage**			
<1 month	0 %	–	–	Adapted based on [11]
<2 months	1 %	–	–	Adapted based on [11]
<3 months	6 %	–	–	Adapted based on [11]
<6 months	28 %	–	–	Adapted based on [11]
<1 year	70 %	–	–	Adapted based on [11]
<2 years	94 %	–	–	Adapted based on [11]
<3 years	98 %	–	–	Adapted based on [11]
<4 years	99 %	–	–	Adapted based on [11]
<5years	100 %	–	–	Adapted based on [11]

This value has been used in the model for the base-case scenario and is assumed to be fixed over both periods evaluated (2016–2020 and 2021–2030). However, the full per-course price of the vaccines (US$ 4.66 for ROTARIX, US$ 3.42 for ROTAVAC, and US$ 2.85 for ROTASIIL), assuming no support from Gavi, was used for scenario analysis [6], again assuming the price would be fixed over the entire period of the analysis.

The EPI team chose to analyse ROTASIIL in its two-dose vial, lyophilised presentation (US$0.95 per dose), ROTAVAC in its five-dose vial, liquid presentation (US$1.14 per dose), and ROTARIX in its one-dose vial, liquid presentation (US$ 2.33 per dose) after careful consideration of the price per dose, wastage, volume, and storage conditions.

The vaccination cost per child was calculated based on the vaccine price, wastage [6], international handling (procurement process) [41], international delivery (transportation), and immunization delivery cost (Table 2). The immunization delivery cost is the additional cost to the health system that would be involved in adding the vaccine to the current vaccine delivery system and represents expenses related to supply chain, capital, labour, and other service delivery to implement the vaccination in the country [42].

2.7. Healthcare costs

Country-specific estimates of healthcare treatment costs borne by the government for clinic visits and hospital admissions were obtained from a systematic review of literature published between 2006 and 2018 on the cost of childhood diarrhea across 137 LMICs [43] (Table 3).

2.8. Deterministic and probabilistic sensitivity analysis

To assess the impact of uncertainties introduced by each parameter provided in Tables 1, 2, and 3, one-way sensitivity analysis was performed to understand the variation of the cost-effectiveness results in scenarios that are less or more favourable to the vaccine [24,25]. For **less favourable scenarios,** we considered: upper bound of incremental delivery cost per dose, vaccine price without Gavi support, lower bound of disease burden parameters, lower bound of vaccine efficacy, and lower bound of healthcare cost. For **more favourable scenarios,** we considered: upper bound of disease burden parameters, upper bound of vaccine efficacy, lower bound of incremental delivery cost per dose, and upper bound of healthcare costs. We also looked at ROTARIX cost-effectiveness with equivalent impact of three-dose vaccines, and at ROTAVAC and ROTASIIL with equivalent impact of two-dose vaccines, to assess how the number of doses impacts the cost per DALY averted. Furthermore, a probabilistic sensitivity analysis (PSA) was performed by varying all parameters simultaneously within their ranges, with 1,000 iterations of a Monte Carlo simulation to yield a range of possible values for costs and outcomes. For simplicity, a transparent Beta-PERT distribution was assumed for all parameters and their ranges. The proportion of probabilistic runs with ICERs below different WTP thresholds reflected the probability that RV vaccination would be cost-effectiveness at these thresholds.

3. Results

3.1. Cost-effectiveness of ROTARIX from 2016 to 2020

Under the **base-case scenario**, from 2016 to 2020, we estimated that use of ROTARIX in Mozambique prevented 963,701 RVGE cases, including 269,784 severe cases (42 % reduction) and 4,628 deaths (42 % reduction). This corresponds to 286,178 discounted DALYs averted and around US$3.1 million avoided (45 % reduction) in RVGE treatment costs from the government perspective (Table 4).

The cost of vaccine implementation with Gavi support was projected to be around US$12.3 million over the 5-year period, representing an average of US$2.5 million annually. However, it was partially balanced by the health care costs averted. Annually, an average of US$622,659 in treatment costs was averted from the government perspective (42 % reduction).

We calculated a cost of US$70 per DALY averted (95 % UI, 36–159) for ROTARIX vaccination, from the government perspective, compared to no vaccination. This was below the WTP threshold of 0.5x the national GDP per capita. Further, scenario analysis showed that the cost-effectiveness was below this threshold in most scenarios. ROTARIX was not below the WTP threshold in the scenario of vaccine price without Gavi support (US$259 per DALY averted) (Fig. 1).

3.2. Cost-effectiveness of ROTARIX, ROTAVAC, and ROTASIIL from 2021 to 2030

ROTAVAC and ROTASIIL were estimated to prevent more RVGE health outcomes and RVGE treatment costs than ROTARIX (Table 4), because we assumed the same vaccine efficacy after the second

Table 2
Input parameters for estimating ROTARIX, ROTAVAC, and ROTASIIL program costs.

Parameter	Central value	Scenarios		Source
		Lower bound	Higher bound	
Vaccine price per dose (US$) – with Gavi support				
ROTARIX	0.20	–	–	[6]
ROTASIIL	0.13	–	–	[6]
ROTAVAC	0.13	–	–	[6]
Vaccine price per dose (US$) – without Gavi support				
ROTARIX	2.33	–	–	[6]
ROTASIIL	0.95	–	–	[6]
ROTAVAC	1.14	–	–	[6]
OTHER COSTS				
Wastage rate (% of vaccine)				
ROTARIX	4.00 %	2.00 %	6.00 %	[6]
ROTASIIL	9.00 %	7.50 %	9.40 %	[6]
ROTAVAC	13.00 %	7.50 %	9.40 %	[6]
International handling (all vaccines)	3.00 %	1.40 %	4.50 %	[41]
International delivery (all vaccines)	6.00 %	2.00 %	15.00 %	[41]
Safety box/bag per dose (US$) - all vaccines	0.02	0.02	0.03	[47]
Incremental delivery cost per dose (US$) - all vaccines	1.17	0.39	2.78	[42]

Table 3
Input parameters for estimating health service costs (2018 US$).

Parameter	Central value	Scenarios		Source
		Lower bound	Higher bound	
Non-severe RVGE				
Government cost of RVGE outpatient visit (US$)	4.47	2.23	6.70	[43]
Severe RVGE				
Government cost of RVGE outpatient visit (US$)	4.47	2.23	6.70	[43]
Government cost of RVGE hospitalization (US$)	19.62	9.81	29.44	[43]

Table 4
Projected impact and cost-effectiveness of RV vaccination in cohorts vaccinated over the period 2016–2020 and 2021–2030 (DALYs discounted), government perspective.

	2016–2020	2021–2030		
	ROTARIX	ROTARIX	ROTAVAC	ROTASIIL
HEALTH OUTCOMES				
Non-severe cases averted	693,917	1,568,970	1,800,582	1,800,582
Severe cases averted	269,784	624,120	700,037	700,037
Outpatients' visits averted	321,253	715,515	833,589	833,589
Hospitalizations averted	86,972	199,326	225,676	225,676
Deaths averted	4,628	8,067	9,198	9,198
DALYs averted	286,178	522,905	595,410	595,410
ECONOMIC OUTCOMES				
Health treatment costs averted (US$)				
Healthcare treatment costs	3,113,296	7,106,570	8,078,406	8,078,406
Vaccination programme cost (US$)				
With Gavi support	12,251,605	31,030,830	40,791,230	40,449,222
Without Gavi support	35,395,396	84,744,515	85,318,192	75,785,017
Cost per DALY averted (compared to no vaccine) (US$)				
With Gavi support	70	102	122	121
Without Gavi support	–	330	295	259
Proportion of the GDP per capita (US$448)	16 %	23 %	27 %	27 %
Cost per DALY averted compared to ROTARIX (US$) (with Gavi support)				
ROTAVAC compared to ROTARIX	–	–	20	–
ROTASIIL compared to ROTARIX	–	–	–	19

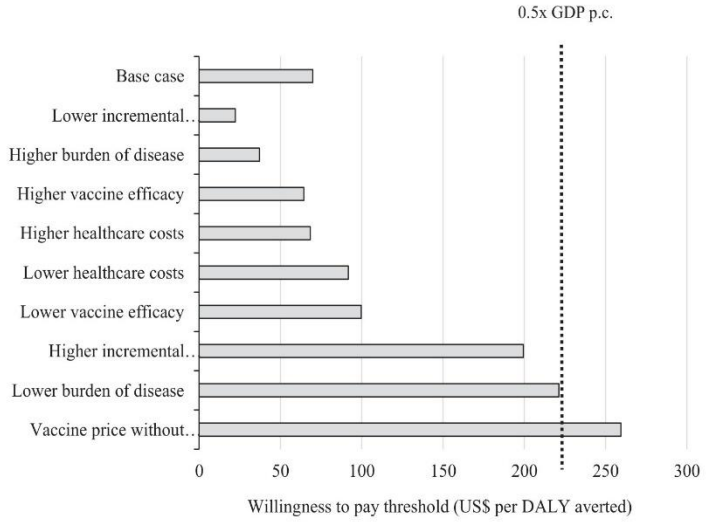

Fig. 1. Scenario analysis results, showing incremental cost-effectiveness ratio (US$ per DALY averted) of ROTARIX, compared to no vaccination.

and third dose. However, there is substantial uncertainty about this assumption, as explained above. With Gavi support, the vaccine program cost was lowest for ROTARIX (US$31 million) compared to ROTASIIL (US$40.4 million) and ROTAVAC (US$40.8 million). Without Gavi support, the vaccine program cost was lowest for ROTASIIL (US$75.8 million) compared to ROTARIX (US$84.7 million) and ROTAVAC (US$85.3).

With Gavi support, the cost-effectiveness of the lowest cost product (ROTARIX) was US$102 per DALY averted (95 % UI, 40–221), compared to no vaccination. Both ROTAVAC and ROTASIIL were

dominated because they provided similar benefits at greater cost (Fig. 2).

Table 4 also shows that without Gavi support, the cost-effectiveness of the lowest cost product (ROTASIIL) was US$259 per DALY averted (95% UI, 147–466), compared to no vaccination. In this scenario both ROTARIX and ROTAVAC were dominated because they provided similar benefits at greater cost. Additional information on the cost-effectiveness of vaccination from 2021 to 2030 with and without Gavi support is presented in the Supplementary file - Fig. 2.

With Gavi support, the only non-dominated product is ROTARIX, and there is a 98 % probability it will be cost-effective at a WTP threshold set at 0.5x GDP per capita. Without Gavi support, the only non-dominated product is ROTASIIL, and there is 30 % probability that it will be cost-effective at the same threshold (Fig. 3).

3.3. Scenario analysis

As shown in the Supplementary file - Fig. 1, all three vaccines were cost-effective at a threshold of 0.5x GDP per capita (US $224) in most of the scenarios evaluated when compared to no vaccination. At the Gavi-subsidized price, ROTARIX has the most favourable cost per DALY averted (US$102). At the vaccine price without Gavi support, ROTASIIL was the most cost-effective vaccine at US$259 per DALY averted. The most influential parameters identified in deterministic scenario analyses were the burden of disease, the incremental delivery cost, and the vaccine price.

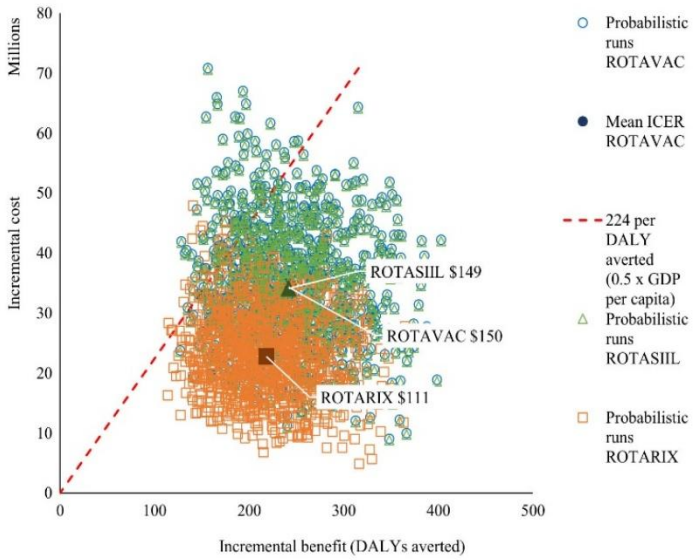

Fig. 2. Cost-effectiveness plane showing the incremental costs and benefits of vaccination with ROTARIX, ROTAVAC, and ROTASIIL, compared to no vaccination.

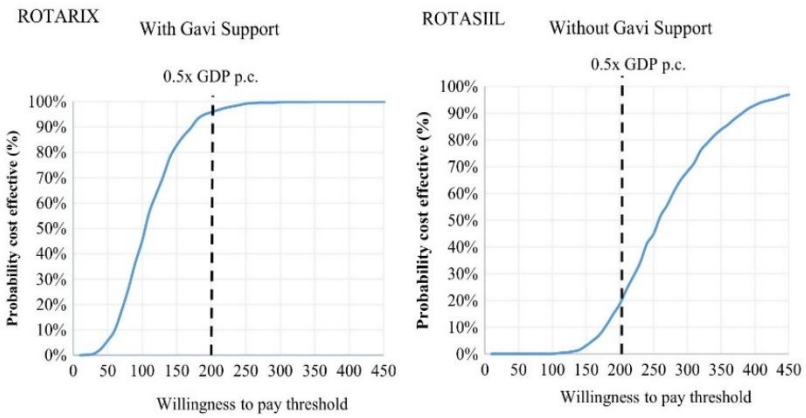

Fig. 3. Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis of ROTARIX (with Gavi support) and ROTASIIL (without Gavi support) over the period 2021–2030.

When we estimate the cost-effectiveness of ROTAVAC, ROTASIIL, and ROTARIX as if they have the same health impact, the rank order did not change, ROTARIX still represented the best option with Gavi support. When doing the same exercise using vaccine price without Gavi support, we observed that ROTASIIL was the best option.

4. Discussion

We estimate that ROTARIX vaccination may have prevented over 4,500 deaths between 2016 and 2020. This more than 40 % reduction in deaths is broadly consistent with the real-world impact of ROTARIX observed in Mozambique. When comparing the pre-vaccine and post-vaccine period, de Deus *et al.* [11] found that the vaccine halved the RV-positive proportion among diarrhea hospital admissions. We also found similar reductions in severe RV disease cases, clinic visits, and hospitalizations.

Compared to no RV vaccine, the use of ROTARIX with Gavi support in Mozambique's immunization program from 2016 to 2020 was cost-effective (US$70 per DALY averted). Even in scenarios with the least favourable incremental delivery cost and the lowest vaccine efficacy (49.9 %), the cost-effectiveness results were still favourable (US$199 and US$100 per DALY averted, respectively). ROTARIX would continue to be cost-effective from a government perspective if Gavi support were to continue throughout the period 2021–2030. Our modelling found that ROTARIX was the most cost-effective option despite averting fewer RVGE disease events than ROTAVAC and ROTASIIL. When we assumed the same impact for all three vaccines, the cost per DALY averted for ROTARIX was only slightly more favourable (US$89 vs US$102). This difference in health benefits occurs because we assume that all three vaccines confer a similar level of protection at the final dose, and after that, the protection declines over time. Since the last dose of ROTARIX is given earlier, at 4 months of child's age, the decline in protection begins earlier than with the other vaccines, which have the last dose given at 6 months. This results in lower overall modelled health and economic benefits, which may not reflect real-world differences in vaccine impact [40]. Higher modelled impact for three-dose courses is not based on a head-to-head product comparison. Rather, this finding is the result of a later time point for the final dose for the three-dose products and should be interpreted cautiously.

With Gavi support, vaccination program costs with ROTASIIL and ROTAVAC are higher than with ROTARIX by almost US$1.0 million per year. This is because the former two vaccines are administered in three doses, increasing overall immunization delivery costs by additional US$1.17 per complete vaccine schedule compared to the two-dose ROTARIX. Another important driver of this difference is the wastage rate per dose, which is higher for ROTASIIL and ROTAVAC (9 % and 13 %, respectively) compared to ROTARIX (4 %) [6]. The lower costs calculated for ROTARIX resulted in this vaccine having the most favourable cost-effectiveness ratio (US$102 per DALY averted). This finding is consistent with a previous analysis that aimed to compare the cost-effectiveness of the same vaccines in Bangladesh, Ghana, and Malawi, where ROTARIX was the most cost-effective [44]. Later analysis demonstrates that this finding is sensitive to context and assumptions [45].

In the absence of Gavi support, ROTASIIL was estimated to have the lowest costs and would have the most favourable cost-effectiveness, driven by the lower price of this vaccine. This result differs from the findings in Bangladesh, Ghana, and Malawi, where ROTARIX remained the most cost-effective product even in the absence of Gavi support. This is because the system cost for vaccination was lower than the other vaccines, which made the ratio between costs and gains better for ROTARIX [44]. We found a relatively low probability (around 30 %) that the most favourable product without Gavi support (ROTASIIL) would be cost-effective from a government perspective based on the current WTP threshold set at 0.5x the national GDP per capita. However, when the country reaches Gavi's fully self-financing phase and utilizes a higher anticipated threshold (e.g., 0.5x US$1,630), the probability for ROTASIIL to be cost-effective is higher than 95 %.

The eligibility threshold for graduation from Gavi support is currently US$1,630 GNI per capita. Similar to other studies [15,44,46], a re-evaluation of the cost-effectiveness of RV vaccines and comparison to updated thresholds will be needed before Mozambique starts this process. Budget impact analysis will also be important to show the financial resources that may eventually be required to graduate from Gavi support.

In a situation of scarce resources, as observed in most low-income countries such as Mozambique, ROTARIX represents good value for money for the government while the price is heavily subsidised by Gavi. If Mozambique begins to transition away from Gavi support, then ROTASIIL may be a preferable option, but still may not be as cost-effective from a government perspective at today's threshold. However, in addition to the cost-effectiveness result, the selection of vaccine product should also consider other aspects as affordability, feasibility, and other country-specific factors [24,25].

Cost–effectiveness analysis in health is used to compare the costs and outcomes of alternative interventions and is measured by the incremental cost to obtain a unit of health gain [27]. The assessment of whether the intervention is cost-effective is made based on a WTP threshold that represents a good value for money [24]. The WHO Commission on Macroeconomics in Health recommended that the cost-effectiveness thresholds corresponds to up to 3x a country's per-capita GDP [25]. However, the use of GDP-based thresholds in a decision-making process is less country-specific. Together with uncertainties in the model, their use can lead to the wrong decision on how to choose the intervention and spend health-care resources [24,25].

Our study had some limitations. First, some of the parameters were based on global estimates or assumptions. To mitigate this aspect, we were able to share these estimates with a national team of experts to ensure consensus around the inputs that were selected, including many context-specific inputs such as vaccine coverage, wastage, system costs, and prices. Second, WHO no longer recommends using generic GDP per capita thresholds to interpret cost-effectiveness results [26]. However, Mozambique has not defined a country-specific WTP threshold, so we used 0.5x GDP per capita to help put our results in context. Third, we have made several assumptions to differentiate the current RV vaccine products on the basis of price, system costs, wastage, and efficacy. These influential parameters are likely to be updated over time, and this analysis should be updated with more relevant data when possible. Fourth, we excluded costs borne by households such as out-of-pocket medical expenses, travel, 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. Finally, UNIVAC is a static model and does not take the herd immunity effect into account. There is currently limited evidence to suggest a substantial herd effects in LMICs; nevertheless, our results should be interpreted as a conservative estimate of the potential health benefits of RV vaccination.

5. Conclusion

Vaccination with ROTARIX has already had a substantial public health impact in Mozambique, preventing over 4,500 deaths between 2016 and 2020. With continued Gavi support, ROTARIX

remains the most cost-effective product. However, if Mozambique were to fully self-finance the program, ROTASIIL would be preferred but may not be as cost-effective based on current prices and assumptions. The choice of vaccine product should be continually re-evaluated as more evidence emerges about their prices, health system costs, wastage rates, relative health impacts, and also as Mozambique's Gavi eligibility status and WTP thresholds change.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the EPI and the NITAG, from Mozambique for their support and commitment to the present analysis. We also thank PATH team for the technical support and Laura Kallen (from PATH) for linguistic revision of the manuscript.

Funding statement

The authors received funding from Bill and Melinda Gates Foundation (OPP1147721), through PATH subaward number: GAT.2111-01707508-SUB.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.07.044.

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2.2. Study 2. Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study

Reference: Guimarães, E.L.; Chissaque, A.; Pecenka, C.; Debellut, F.; Schuind, A.; Vaz, B.; Banze, A.; Rangeiro, R.; Mariano, A.; Lorenzoni, C.; Carrilho, C.; Martins, M.d.R.O.; de Deus, N.; Clark, A. Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study. Vaccines 2023, 11, 1058. https://doi.org/10.3390/vaccines11061058

vaccines

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Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study

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Abstract: Mozambique has one of the highest rates of cervical cancer in the world. Human papillomavirus (HPV) vaccination was introduced in 2021. This study evaluated the health and economic impact of the current HPV vaccine (GARDASIL® hereafter referred to as GARDASIL-4) and two other vaccines (CECOLIN® and CERVARIX®) that could be used in the future. A static cohort model was used to estimate the costs and benefits of vaccinating girls in Mozambique over the period 2022–2031. The primary outcome measure was the incremental cost per disability-adjusted life-year averted from a government perspective. We conducted deterministic and probabilistic sensitivity analyses. Without cross-protection, all three vaccines averted approximately 54% cervical cancer cases and deaths. With cross-protection, CERVARIX averted 70% of cases and deaths. Without Gavi support, the discounted vaccine program costs ranged from 60 million to 81 million USD. Vaccine program costs were approximately 37 million USD for all vaccines with Gavi support. Without cross-protection, CECOLIN was dominant, being cost-effective with or without Gavi support. With cross-protection and Gavi support, CERVARIX was dominant and cost-saving. With cross-protection and no Gavi support, CECOLIN had the most favorable cost-effectiveness ratio. Conclusions: At a willingness-to-pay (WTP) threshold set at 35% of Gross Domestic Product (GDP) per capita, HPV vaccination is cost-effective in Mozambique. The optimal vaccine choice depends on cross-protection assumptions.

Keywords: cervical cancer; papillomavirus; vaccination; modelling; UNIVAC; cost-effectiveness; Mozambique

Citation: Guimarães, E.L.; Chissaque, A.; Pecenka, C.; Debellut, F.; Schuind, A.; Vaz, B.; Banze, A.; Rangeiro, R.; Mariano, A.; Lorenzoni, C.; et al. Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study. *Vaccines* **2023**, *11*, 1058. https://doi.org/10.3390/vaccines11061058

Academic Editor: Pedro Plans-Rubió

Received: 30 January 2023
Revised: 14 March 2023
Accepted: 16 March 2023
Published: 2 June 2023

1. Background

Cervical cancer is the fourth most diagnosed cancer among women globally, with an estimated 342,000 deaths worldwide in 2020 [1,2]. Around one in five cervical cancer deaths are estimated to occur in sub-Saharan Africa [1,3]. Mozambique had the eighth highest age-standardised cervical cancer mortality rate (38.7 per 100,000 women) in the world, with 5325 new cases and 3850 deaths, in 2020 [4]. This accounted for 21.4% of all female cancer deaths in the country.

Cervical cancer is caused by persistent high-risk human papillomavirus (HPV) infection, which is mainly spread through sexual contact [5]. In Mozambique, cervical HPV infections have been identified in almost two-thirds of women aged 18–24 years. Screening for pre-cancerous lesions and vaccination against HPV infection prior to sexual debut are safe and effective ways to prevent cervical cancer [6,7]. In 2009, Mozambique started the National Screening Program for Cervical Cancer, using the visual inspection with 3-4% acetic acid (VIA) method, targeting women aged 30–55 years of age every five years [8–11]. However, in 2014/2015, the self-reported coverage of cervical cancer screening uptake using cytology and VIA among women aged 30–55 years was estimated to be only 3.5% [8]. From April 2018 to September 2019, Mozambique performed a hospital-based pilot screening demonstration project using primary HPV DNA testing, but it was never implemented at the national level [12].

In addition to cervical cancer screening at older ages, HPV vaccination is the primary prevention measure that can benefit pre-adolescents or adolescents. HPV vaccines have now been introduced in over 100 countries worldwide [13], with several studies demonstrating favorable cost-effectiveness [6,14,15]. Four vaccines are currently pre-qualified by the World Health Organization (WHO): CECOLIN®, CERVARIX®, GARDASIL® (referred to hereafter as GARDASIL®-4), and GARDASIL®-9. All four vaccines cover HPV genotypes 16 and 18. GARDASIL-4 covers additional two types (6 and 11) that are responsible for anogenital warts. GARDASIL-9 covers an additional seven types (6, 11, 31, 33, 45, 52, and 58), but is not eligible for external funding from Gavi, the Vaccine Alliance (Gavi). All vaccines were indicated to be administered in two doses given six months apart to pre-adolescent girls aged 9–14 years [16,17]. However, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recently recommended a single-dose schedule, since it provides similar efficacy to the two or three-dose regimens [18,19].

In 2014 and 2015, Mozambique performed a school-based HPV vaccine demonstration project in the districts of Manhiça, Manica, and Mocímboa da praia using CERVARIX [20]. In November 2021, with support from Gavi, the country introduced GARDASIL-4 into the national program on immunization. In the first phase, the vaccine was administered to girls aged 9 years via community outreach brigades (28%), health centres (22%), and schools (50%) [21].

An economic evaluation is required to assess the health and economic impact of the recently introduced GARDASIL-4 vaccine and the cost-effectiveness of two alternative vaccines that are currently eligible for funding by Gavi (CECOLIN and CERVARIX). This also provides an opportunity to explore the potential costs and benefits of different strategies, e.g., a single-dose schedule or multi-age-cohort [MAC] campaign. This will provide important evidence to decision-makers about the value for money of the current HPV vaccine and alternative products and strategies that could be used in the future.

2. Methods

2.1. Study Design

From a government perspective, we evaluated the cost-effectiveness of three HPV vaccines (CECOLIN, CERVARIX, and GARDASIL-4), each compared to no vaccination (and no change in screening practices) and to each other. In our base case scenario, we evaluated the lifetime costs and benefits of vaccinating nine annual cohorts of 9-year-old girls (routine vaccination 2022–2031) and five cohorts of girls aged 10–14 years (catch-up MAC campaign conducted in the year 2022) at the national level.

A multidisciplinary group of experts was invited to a stakeholder consultation workshop (10–11 May 2022) to provide feedback on the inputs and assumptions used in the analysis. This included stakeholder representatives from the Expanded Program of Immunization (EPI), the National Immunization Technical and Advisory Group (known in Mozambique as Comité de Peritos de Imunização), the National Cancer Control Program, WHO, and the United Nations Children's Fund.

2.2. Modelling Approach

We used the UNIVAC decision-support model (version 1.54), an Excel proportionate outcomes static cohort model [22]. UNIVAC is populated with the United Nations (2019 revision) population estimates of the number of girls alive in each year and calendar year of life over the lifetimes of all birth cohorts included in the analysis [23]. Numbers of girls alive in each single year/age of life are multiplied by age-specific rates of cervical cancer cases and deaths to estimate the number of cases, deaths, and disability-adjusted life years (DALYs) expected to occur with and without vaccination over the lifetimes of each cohort of vaccinated girls. The model also estimates the costs of vaccination and the healthcare costs associated with treating cervical cancer cases, with and without vaccination.

In addition, the model requires estimates of age-specific cervical cancer incidence and mortality by stage, rates of access to healthcare and associated treatment costs, vaccination program costs, and the expected coverage and efficacy of each vaccine.

The primary outcome measure was the cost (2021 USD) per DALY averted from a government perspective. DALYs were used because they combine both years lost due to premature death and years lived with disease and allow health effects to be compared consistently across diseases. Future health and cost outcomes were discounted at 3% per year to reflect the time preference for immediate benefits and the opportunity of investing present capital [24].

Mozambique has not yet defined a country-specific WTP threshold to determine whether an intervention is cost-effective. A previous study recommended that countries with a low human development index should use a threshold below 100% of the GDP per capita based on the revealed WTP of many low- and middle -income countries [25]. However, for Mozambique, others studies have recommended a threshold of 16 to 35% of the GDP per capita [26]. Given the uncertainty around this threshold, we calculated the probability that HPV vaccination would be cost-effective for WTP thresholds ranging from 0% to 35% of the GDP per capita. This is equivalent to USD 175 based on a national GDP per capita of USD 500 in November 2022 [27].

2.3. Disease Burden

Input data for disease burden are summarized in Table 1. We used age-specific rates of cervical cancer cases and deaths estimated for Mozambique by Globocan for the year 2020 and assumed these rates would remain constant over time in the absence of vaccination or any changes to current screening practices [28]. We assumed cases were distributed into 18.6% local, 72.9% regional, and 8.5% distant cervical cancer, based on a cancer stage distribution previously estimated for countries in the low-income/lower–middle-income strata [29]. Cancer stage definitions are based on the surveillance, epidemiology, and end results (SEER), as well as the International Federation of Gynecology and Obstetrics (FIGO) staging system [30]. Disability weights represent time lost, while living with local, regional, and distant cancer were taken from the Global Burden of Disease project [31].

The percentage of women alive five years after diagnosis was estimated for each stage based on the data from a recent study of survival rates from several sub-Saharan African countries [32]. In this study, Mozambique's three-year survival percentage from all stages was very similar to Kenya's (both around 55%). Data on five-year survival was not reported for Mozambique, so we assumed the five-year survival reported for Kenya (44%) [32]. To estimate survival by stage (local, regional, and distant), we applied the ratio between all-stage survival and stage-specific survival, as recently reported in the United States of America [30]. The resulting five-year survival rates (61%, 39%, and 12% for local, regional, and distant cervical cancer, respectively) are broadly consistent with estimates for the low human development index [32]. For all parameters without uncertainty ranges, we varied the central estimate by±20% to generate a plausible range for use in uncertainty analysis [33,34].

Table 1. Input parameters for estimating cervical cancer disease burden.

Parameter	Base Case	Uncertainty Range		Source
		Low	High	
Age-specific rates, 100,000 per year, cervical cancer cases				
10–15	0.6	0.4	0.7	[28]
15–20	2.7	2.2	3.3	
20–25	17.8	14.3	21.5	
25–30	34.9	27.9	41.9	
30–35	55.1	44.1	66.1	
35–40	76.5	61.3	91.9	
40–45	99.8	79.8	119.8	
45–50	120	96.1	144.1	
50–55	131.5	105.3	157.7	
55–60	136.5	109.2	163.9	
60–65	130.7	104.7	157.0	
65–70	120.6	96.4	144.7	
70–75	107.6	86.0	129.0	
75–80	92	73.6	110.4	
80–85	72.1	57.6	86.6	
85–90	53.5	42.8	64.2	
90–95	53.5	42.8	64.2	
95–100	53.5	42.8	64.2	
Percentage of cervical cancer cases in each stage				
Local cancer [a]	18.6	17.9	22.3	[29]
Regional cancer [b]	72.9	70.0	87.5	
Distant cancer [c]	8.5	8.2	10.2	
Age-specific rates, 100,000 per year, cervical cancer deaths				
10–15	0.4	0.3	0.5	[28]
15–20	2.8	2.2	3.4	
20–25	8.3	6.6	10.0	
25–30	16.8	13.4	20.2	
30–35	28.7	23.0	34.4	
35–40	43.6	34.9	52.3	
40–45	65.3	52.2	78.4	
45–50	87.2	69.8	104.6	
50–55	107.2	85.8	128.6	
55–60	122.9	98.3	147.5	
60–65	126.4	101.1	151.7	
65–70	123.3	98.6	148.0	
70–75	113.1	90.5	135.7	
75–80	96.8	77.4	116.2	
80–85	75.9	60.7	91.1	
85–90	48.7	39.0	58.4	
90–95	48.7	39.0	58.4	
95–100	48.7	39.0	58.4	
Percentage of healthy time lost while living with disease				
Local cancer [a]	28.8	19.3	39.9	[31]
Regional cancer [b]	45.1	30.7	60.0	
Distant cancer [c]	54.0	37.7	68.7	
Average 5-year survival rate (% alive after 5 years)				
Local cancer	60.7	72.8	48.6	Assumed based on [32,35]
Regional cancer	38.3	45.9	30.6	
Distant cancer	11.9	14.3	9.5	

[a] Local cancer refers to FIGO stage 1 and 2. [b] Regional cancer refers to FIGO stage 3. [c] Distant cancer refers to FIGO stage 4.

2.4. Health Service Utilization and Costs

We assumed that all women captured in the Globocan incidence rates would be diagnosed and that 91% of these women would go on to receive treatment [36]. Therefore, estimates of the average cost of cervical cancer treatment were only applied to women who were both diagnosed and treated. Since there are no data on cervical cancer treatment costs in Mozambique, we used data from a cost of illness study performed in Tanzania from a government perspective. This included direct medical costs for labor, supplies, equipment, and patient hospital accommodation/admission (Table 2) [37]. These costs were originally in 2013 USD, so we converted them to 2021 USD [38].

Table 2. Input parameters for estimating health service costs from the government perspective (2021 USD).

Parameter	Base Case	Uncertainty Range		Source
		Low	High	
Local cancer				
% of diagnosed receiving treatment	91%	86%	96%	[36]
Cost per treated woman [a]	1,188	950	1425	[37]
Regional cancer				
% of diagnosed receiving treatment	91%	86%	96%	[36]
Cost per treated woman [b]	692	553	830	[37]
Distant cancer				
% of diagnosed receiving treatment	91%	86%	96%	[36]
Cost per treated woman [c]	691	553	829	[37]

[a] Local cancer refers to FIGO stage 1 and 2, of which treatment includes curative radiotherapy, chemotherapy, and surgery. [b] Regional cancer refers to FIGO stage 3, which treatment includes palliative radiotherapy only. [c] Distant cancer refers to FIGO stage 4, which treatment includes palliative radiotherapy only.

2.5. Vaccine Coverage and Efficacy

Vaccine inputs on vaccine coverage and efficacy are presented in Table 3. The first and second dose coverages were estimated to be 93% and 17%, respectively, for 2022, based on coverage reported by the EPI program for the current HPV vaccine [21]. For the period of 2023–2031, we assumed 93% and 73%, respectively, based on measles coverage in children aged 10–14 years in 2018 [39]. The same coverage (93 and 73%) was assumed for the catch-up campaign in the first year.

Some studies have indicated potential cross-protection against HPV genotypes not covered by the vaccines [40,41]. However, there is uncertainty about how much cross-protection should be assumed for each vaccine. We, therefore, modelled the cost-effectiveness of each vaccine with and without cross-protection. The efficacy of the complete (two dose) vaccination schedule was taken from clinical trials of efficacy against high-grade lesions, i.e., cervical intra-epithelial neoplasia [42–44]. An overall weighted efficacy value was calculated by multiplying the efficacy assumed for each HPV type by the proportion of cervical cancers caused by each type in Mozambique. The type distribution for Mozambique was taken from the HPV Information Centre. The top three HPV types in Mozambique were 18 (43.0%), 16 (20.4%), and 45 (11.9%) [9]. The overall weighted efficacies of CECOLIN, CERVARIX, and GARDASIL-4 were estimated to be 63% [42], 63% [43,45,46], and 62% [47,48], respectively, without cross-protection, and 64% [42], 83% [43,45,46], and 63% [47,48], respectively, with cross-protection. The influential cross-protection assumptions for CERVARIX were taken from the study by Wheeler et al. [43]. For all vaccines, we multiplied the two-dose efficacy values by 0.8 (range 0.7–1.0) to estimate the efficacy of one dose.

Table 3. Input parameters for estimating the health impact of HPV vaccination.

Parameter	Value	Uncertainty Range Low	Uncertainty Range High	Source/s
Coverage for routine vaccination and catch-up campaign (2022–2031)				
1st dose (2022–2031)	93.0%	74.0%	98.0%	[21]
2nd dose (2022)	17.0%	13.6%	20.4%	
2nd dose (2023–2031)	73.0%	58.4%	87.6%	[39]
Vaccine efficacy (all types combined) with cross-protection				
CECOLIN				
Dose 1	51.4%	30.2%	51.6%	Assumption (80% of 2 doses)
Dose 2	64.3%	37.8%	64.5%	[42]
CERVARIX				
Dose 1	66.1%	48.3%	67.9%	Assumption (80% of 2 doses)
Dose 2	82.7%	60.3%	84.9%	[43,45,46]
GARDASIL-4				
Dose 1	50.4%	45.4%	51.3%	Assumption (80% of 2 doses)
Dose 2	63.0%	56.7%	64.1%	[47,48]
Vaccine efficacy (all types combined) without cross-protection				
CECOLIN				
Dose 1	50.7%	29.9%	50.7%	Assumption (80% of 2 doses)
Dose 2	63.4%	37.4%	63.4%	[42]
CERVARIX				
Dose 1	50.1%	40.7%	50.7%	Assumption (80% of 2 doses)
Dose 2	62.7%	50.8%	63.4%	[43,45,46]
GARDASIL-4				
Dose 1	49.7%	45.0%	50.4%	Assumption (80% of 2 doses)
Dose 2	62.1%	56.3%	63.0%	[47,48]

Note: We have assumed a type distribution based on Information Centre on HPV and Cancer. We assume lifelong protection from vaccination. Cross protective efficacy was assumed against HPV types 31, 33, 45, 51, 52 and 56 for CERVARIX [43,45,46], and against type 31 for GARDASIL-4 [47,48]. We further assumed the same cross-protection against type 31 for CECOLIN.

2.6. Vaccination Program Costs

Mozambique is currently eligible for vaccine financial support from Gavi. This means the majority of the manufacturer's vaccine price is paid for by Gavi, and only USD 0.20 per dose is paid for by the government [49]. However, we also presented our results without Gavi support to show how the cost-effectiveness would be impacted if the government were to pay the full manufacturer's vaccine price over the full ten-year period. We assumed that the prices would be fixed for the entire period of the analysis. In both scenarios (with and without Gavi support), the government is expected to cover all the costs associated with wastage, procurement related charges, and integrating the vaccine into the current immunization program. In the first year of vaccine implementation, Gavi provides a vaccine introduction grant (VIG) equivalent to USD 2.40 per girl aged 9 years (USD 1,327,040) and USD 0.65 per girl aged 10–14 years (USD 1,793,700), and all MAC vaccines (10–14 years) are provided at no cost [50].

HPV vaccination program costs were calculated by combining the United Nations estimates of the number of girls in the target ages/years with estimates of HPV vaccine coverage and the input data presented in Table 4, namely the vaccine price, wastage, international handling (procurement process), international delivery, and immunization delivery cost (which comprises the additional cost to the health system that would be involved from adding the vaccine to the current vaccine delivery system and representing expenses related to supply chain, capital, labor, and other service delivery costs to implement the vaccination in the country).

Table 4. Vaccination cost inputs.

Parameter	Base Case	Uncertainty Range Low	High	Source
Price of vaccine doses (USD)				
CECOLIN	0.20	-	2.90 *	
CERVARIX	0.20	-	5.18 *	[16]
GARDASIL-4	0.20	-	4.50 *	
Handling and delivery (% of price)				
% International handling	3.0	2.4	3.60	[51]
% International delivery	10.0	8.0	12.0	
Wastage percentage (%)				
CECOLIN	5.0	3.8	6.3	
CERVARIX **	10.0	3.8	6.3	[16]
GARDASIL-4	5.0	3.8	6.3	
Other costs				
Syringe price per dose (USD)	0.05	0.04	0.06	[16]
Syringe percentage wastage (%)	10.0	8.0	12.0	[20]
Costs of safety box per dose (USD)	0.01	0.01	0.01	[16]
Incremental Cost for delivery (USD) ***				
Costs per dose (2023–2031))	3.76	3.0	4.5	[52]

* Vaccine price without Gavi financing. ** CERVARIX wastage was assumed to be higher than the other vaccines, due to a multi-dose vial presentation. *** Includes Cold chain, planning and training, social mobilization, supervision, and service delivery, which was the biggest ingredient accounting for 24% of the total incremental delivery cost.

2.7. Uncertainty Analysis

We ran univariate (one-way) deterministic scenario analyses to estimate the influence of several model assumptions and input values on the cost-effectiveness results [24]. One scenario evaluated the cost-effectiveness of a single dose of HPV vaccination (with full protection assumed for one single dose), consistent with a recent study from Kenya [10]. We ran one additional scenario for CERVARIX (with cross-protection) excluding any cross-protective benefits for types HPV-52 and HPV-56 because a study by Wheeler et al [43] has suggested any reported health benefit for these types might be due to chance observations. Other scenarios unfavourable to vaccination included low vaccine coverage, low average treatment costs, discount rate at 10%, low disease burden, and no MAC. Scenarios favourable to vaccination included high vaccine coverage, high average treatment costs, and high disease burden. In addition, we ran a probabilistic sensitivity analysis (PSA), varying all parameters simultaneously within their uncertainty ranges, assuming simple BETA-Pert distributions for each parameter [53]. Prices were assumed to be fixed within the PSA. We ran separate PSAs for each vaccine, with and without cross-protection, with 1000 runs per vaccine/scenario. PSA results were presented on a cost-effectiveness plane and used to estimate the probability that each vaccine would be cost-effective at different WTP thresholds.

3. Results

3.1. Base Case Analyses

Without HPV vaccination in Mozambique, we estimate there could be 342,246 cases of cervical cancer, 282,687 deaths, and 1,695,103 DALYs lost over the lifetimes of 14 cohorts of preadolescent girls (Table 5).

With Gavi support, each of the three vaccines would cost around USD 37 million (USD 42 million undiscounted), compared to no vaccination (Tables 5 and 6). Without Gavi support, vaccine program costs are estimated to be USD 60 million for CECOLIN, USD 73 million for GARDASIL-4, and USD 81 million for CERVARIX (Table 7).

Table 5. Lifetime effects and costs of vaccinating 14 cohorts of preadolescent girls over the period 2022–2031 in Mozambique (with Gavi support, without cross-protection).

OUTCOMES	No Vaccine	CECOLIN	GARDASIL-4	CERVARIX
HEALTH OUTCOMES				
Cervical cancer cases (local)	63,637	29,299	29,527	29,719
Cervical cancer cases (regional)	249,451	114,852	115,744	116,496
Cervical cancer cases (distant)	29,158	13,425	13,529	13,617
Cervical cancer cases with treatment	311,443	143,394	144,508	145,446
Cervical cancer deaths	282,687	130,159	131,170	132,021
DALYs (discounted *)	1,695,103	786,204	792,228	797,304
ECONOMIC OUTCOMES				
Healthcare treatment costs (USD)	65,657,026	30,464,253	30,697,492	30,894,019
Vaccination programme cost (USD)				
Discounted (3%)	-	37,450,569	37,450,569	37,581,339
No discount	-	42,074,184	42,074,184	42,224,497
Cost (USD) per DALY averted (compared to no vaccine) *				
Cost	-	2,257,796	2,491,034	2,818,332
DALYs averted	-	908,898	902,875	897,799
Cost per DALY averted (with Gavi support)	-	2.5	2.8	3.1
Cost (USD) per DALY averted * (compared to next least costly non-dominated ** option)				
Cost	-	2,257,796	Dominated **	Dominated **
DALYs averted	-	908,898	Dominated **	Dominated **
Cost per DALY averted	-	2.5	Dominated **	Dominated **

* Future costs/effects were discounted at a rate of 3% per year. ** A product is dominated if at least one other product provides greater benefits at lower cost.

Table 6. Lifetime effects and costs of vaccinating 14 cohorts of preadolescent girls over the period 2022–2031 in Mozambique (with Gavi support, with cross-protection).

OUTCOMES	No Vaccine	CERVARIX	CECOLIN	GARDASIL-4
HEALTH OUTCOMES				
Cervical cancer cases (local)	63,637	20,187	28,828	29,527
Cervical cancer cases (regional)	249,451	79,132	113,004	115,744
Cervical cancer cases (distant)	29,158	9,250	13,209	13,529
Cervical cancer cases with treatment	311,443	98,798	141,088	144,508
Cervical cancer deaths	282,687	89,685	128,065	131,170
DALYs (discounted *)	1,695,103	550,289	773,729	792,228
ECONOMIC OUTCOMES				
Healthcare treatment costs (USD)	65,657,026	21,342,264	29,981,215	30,697,492
Vaccination program cost (USD)				
Discounted (3%)	-	37,581,339	37,450,569	37,450,569
Undiscounted	-	42,074,184	42,074,184	42,224,497
Cost (USD) per DALY averted (compared to no vaccine) *				
Cost	-	−8,273,533	1,774,758	2,491,034
DALYs averted	-	1,184,261	921,373	902,875
Cost per DALY averted	-	Cost saving	1.9	2.8
Cost (USD) per DALY averted * (compared to next least costly non-dominated ** option)				
Cost	-	−8,273,533	Dominated **	Dominated **
DALYs averted	-	1,184,261	Dominated **	Dominated **
Cost per DALY averted	-	Cost saving	Dominated **	Dominated **

* Future costs/effects were discounted at a rate of 3% per year. ** A product is dominated if at least one other product provides greater benefits at lower cost.

Table 7. Lifetime effects and costs of vaccinating 14 cohorts of preadolescent girls over the period 2022–2031 in Mozambique (without Gavi support, without cross-protection).

OUTCOMES	No Vaccine	CECOLIN	GARDASIL-4	CERVARIX
HEALTH OUTCOMES				
Cervical cancer cases (local)	63,637	29,299	29,896	29,719
Cervical cancer cases (regional)	249,451	114,852	117,190	116,496
Cervical cancer cases (distant)	29,158	13,425	13,698	13,617
Cervical cancer cases with treatment	311,443	143,394	146,314	145,446
Cervical cancer deaths	282,687	130,159	132,809	132,021
DALYs (discounted *)	1,695,103	786,204	801,961	797,304
ECONOMIC OUTCOMES				
Healthcare treatment costs (USD)	65,657,026	30,464,253	31,074,244	30,894,019
Vaccination programme cost (USD)				
Discounted (3%)	-	59,745,515	72,957,335	80,987,673
No discount	-	68,017,900	83,391,954	92,734,670
Cost (USD) per DALY averted (compared to no vaccine) *				
Cost	-	24,552,742	38,374,553	46,224,666
DALYs averted	-	908,898	893,142	897,799
Cost per DALY averted (with Gavi support)	-	27	43	52
Cost (USD) per DALY averted * (compared to next least costly non-dominated ** option)				
Cost	-	24,552,742	Dominated **	Dominated **
DALYs averted	-	908,898	Dominated **	Dominated **
Cost per DALY averted	-	27	Dominated **	Dominated **

* Future costs/effects were discounted at a rate of 3% per year. ** A product is dominated if at least one other product provides greater benefits at less cost.

In scenarios without cross-protection, all three vaccines had similar health benefits (54% reduction in cervical cancer cases and deaths) and net costs, compared to no vaccination. CECOLIN had the lowest net cost and the highest estimated impact, averting 184,669 cases, 152,528 deaths, and 908,898 DALYs (Table 5). CECOLIN, therefore, dominated both GARDASIL-4 and CERVARIX. However, subtle changes in cost and efficacy assumptions could easily change the rank order. With Gavi support, CECOLIN was the most cost-effective (USD 2.5 per DALY averted). Without Gavi support, CECOLIN was still dominant and very cost-effective (cost per DALY averted equivalent to 5% of the GDP per capita).

In scenarios with cross-protection, CERVARIX had substantially more health benefits than the other two products (70% reduction in cervical cancer cases and deaths) (Table 6). With Gavi support, CERVARIX was dominant and cost-saving (Figure 1). Without Gavi support, CECOLIN was the most cost-effective product, but CERVARIX still had very favorable cost-effectiveness; the incremental cost-effectiveness of using CERVARIX (compared directly to CECOLIN, rather than no vaccination) was USD 6, equivalent to 1% of the GDP per capita (Table 8 and Figure 2), despite CERVARIX having a substantially higher vaccine program costs than CECOLIN (81 million USD versus 60 million USD).

Table 8. Lifetime effects and costs of vaccinating 14 cohorts of preadolescent girls over the period 2022–2031 in Mozambique (without Gavi support, with cross-protection).

OUTCOMES	No Vaccine	CECOLIN	CERVARIX	GARDASIL-4
HEALTH OUTCOMES				
Cervical cancer cases (local)	63,637	28,828	20,187	29,527
Cervical cancer cases (regional)	249,451	113,004	79,132	115,744
Cervical cancer cases (distant)	29,158	13,209	9,250	13,529
Cervical cancer cases with treatment	311,443	141,088	98,798	144,508
Cervical cancer deaths	282,687	128,065	89,685	131,170
DALYs (discounted *)	1,695,103	773,729	550,289	792,228

Table 8. *Cont.*

OUTCOMES	No Vaccine	CECOLIN	CERVARIX	GARDASIL-4
ECONOMIC OUTCOMES				
Healthcare treatment costs (USD)	65,657,026	68,017,900	89,421,090	83,391,954
Vaccination program cost (USD)				
Discounted (3%)	-	59,745,515	80,987,673	72,957,335
No discount	-	68,017,900	92,734,670	83,391,954
Cost (USD) per DALY averted (compared to no vaccine) *				
Cost	-	24,069,704	36,672,910	37,997,801
DALYs averted	-	921,373	1,144,814	902,875
Cost per DALY averted	-	26	32	42
Cost (USD) per DALY averted * (compared to next least costly non-dominated ** option)				
Cost	-	24,069,704	12,603,206	Dominated **
DALYs averted	-	921,373	223,440	Dominated **
Cost per DALY averted	-	26	6	Dominated **

* Future costs/effects were discounted at a rate of 3% per year. ** A product is dominated if at least one other product provides greater benefits at lower cost.

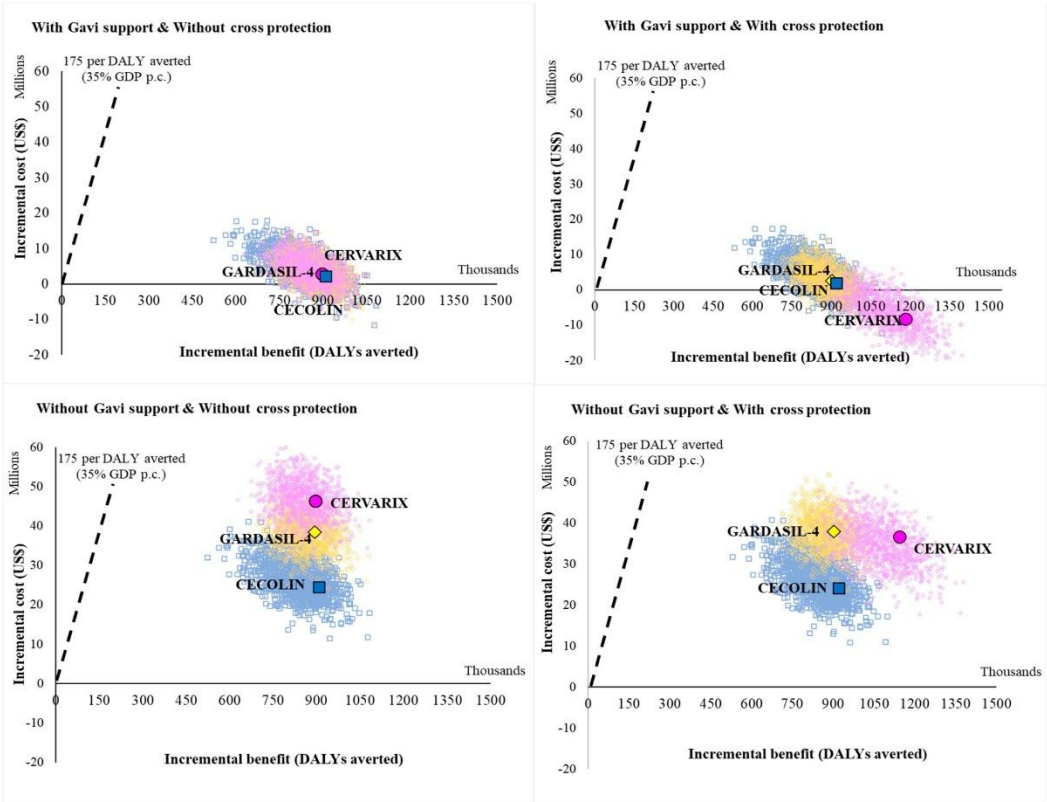

Figure 1. Cost-effectiveness plane showing the incremental costs and benefits of vaccination with CECOLIN, CERVARIX, and GARDASIL-4, considering Gavi support, cross-protection, and no cross-protection, compared to no vaccination.

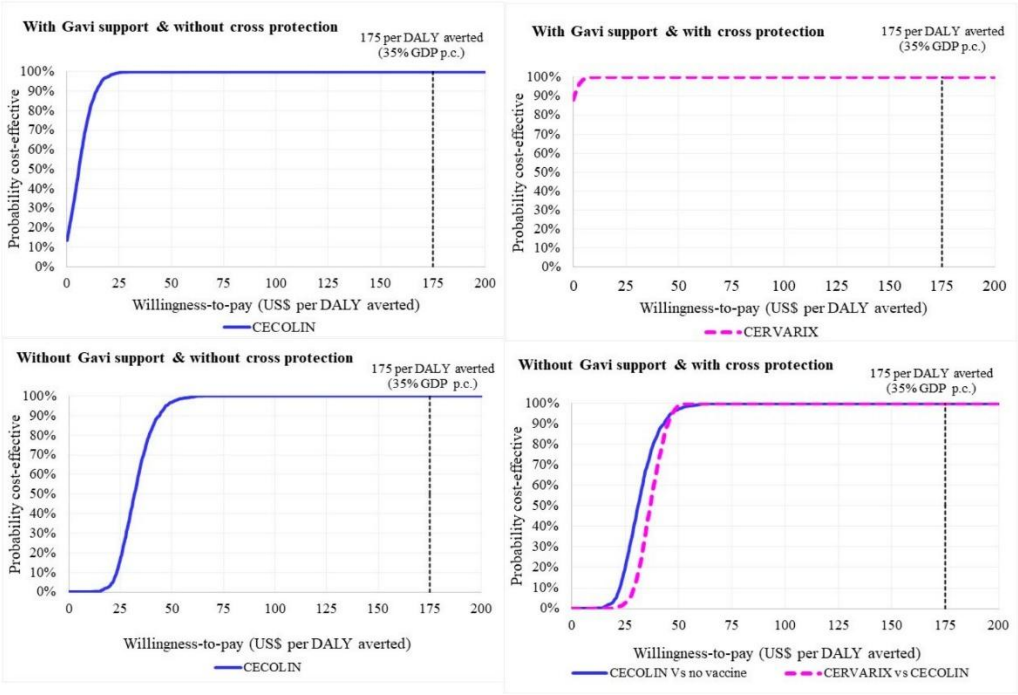

Figure 2. Cost-effectiveness acceptability curve for the vaccine with the most favorable cost-effectiveness ratio under different scenarios, over the period 2022–2031. Note: The first panel (top left) shows that with Gavi support and cross-protection all probabilistic sensitivity analysis runs reported a cost-saving result for product with the most favorable cost-effectiveness (CERVARIX), i.e., 100% probability of being cost-effective across all willingness-to-pay thresholds.

3.2. Uncertainty Analysis

One-way deterministic sensitivity analysis showed HPV vaccination with Gavi support was still cost-effective in the most unfavourable scenarios, such as higher vaccine price (no Gavi support), low disease burden rates, low vaccine coverage, low average treatment costs, and no MAC. Removing cross-protective benefits of CERVARIX against HPV-52 and HPV-56 decreased the overall weighted efficacy of CERVARIX from 83% to 81% and therefore had a minimal influence on our overall estimates of vaccine impact (70% to 69% reduction in cervical cancer cases and deaths) and cost-effectiveness. However, a very high discount rate (10%) would be influential and may change the conclusions. Under this scenario, the cost per DALY averted was equivalent to 90% (USD 448), 109% (USD 544), and 92% (USD 459) for the GDP per capita for CECOLIN, CERVARIX, and GARDASIL-4, respectively. On the other hand, none of the favourable scenarios influenced the results (Supplementary file Tables S1 and S2).

Without Gavi support, there is a 100% probability that the most cost-effective vaccine will be cost-effective at a WTP threshold set at 35% GDP per capita (USD 175). Without Gavi support, and assuming cross-protection, there was a 100% probability that CECOLIN would be cost-effective at a WTP threshold of USD 175. However, comparing CERVARIX directly to CECOLIN had a similar probability of being cost-effective in this scenario (Figure 2).

In all scenarios assuming a single-dose (assuming the same efficacy as a full dose scheme), the vaccine costs were reduced substantially (Supplementary file Figure S1) and all products were cost-saving, compared to no vaccination, even without cross-protection or Gavi support (Supplementary file Tables S1 and S2).

4. Discussion

We evaluated the lifetime cost-effectiveness of vaccinating girls 9 years of age over the period 2022–2031 with a catch-up campaign for girls aged 10–14 years in the first year. Our findings suggest that HPV vaccination could reduce the burden of cervical cancer cases and deaths by 70–53%, depending on assumptions about cross-protection. Irrespective of the scenario (e.g., with and without cross-protection, with and without Gavi support), we find that the most cost-effective vaccine would be either cost-saving or cost-effective at a WTP threshold set at 35% GDP p.c. Others have recommended a threshold of 16–35% for Mozambique, which indicates that all of our main scenarios, even those without Gavi support or cross-protection, could represent good value for the money. A similar threshold (40%) was recently used to assess the cost-effectiveness HPV vaccination in Ghana [54]. In the deterministic sensitivity analysis, we analysed the cost-effectiveness of vaccinations with one dose schedule, assuming the same efficacy as a full dose scheme, as observed in a Kenyan study and, unsurprisingly, found this was more cost-effective and less costly than using two dose schedule. Only a discount rate of 10% generated a cost-effectiveness ratio exceeding 35% of the GDP per capita. Our results were particularly sensitive to the choice of discount rate because the benefits of HPV vaccination occur many years in the future. Assigning a higher discount rate (lower value to distant events) is, therefore, unfavourable to HPV vaccination.

Mozambique introduced GARDASIL-4 in November 2021. While our analysis suggests that HPV vaccination is likely to be good value for the money, it also suggests that different products could be considered to reduce costs and/or increase health benefits. Our analysis of the optimal choice of HPV vaccine depends on influential assumptions about cross-protection and does not incorporate the benefits of GARDASIL-4 on genital warts (non-malignant) or the switching costs that would be required to replace it with either of the two alternative products. However, under scenarios of cross-protection, we find that CERVARIX could have more impact than GARDASIL-4 and is worth consideration while both vaccines are heavily subsidized by Gavi. This is despite the higher wastage that may be associated with the CERVARIX vaccine´s presentation (considering the multi versus single dose vials) [16]. Some studies have reported the impact of CERVARIX on HPV oncogenic types other than 16 and 18, demonstrating its cross-protection potential. Kavanagh and others found that, seven years after girls vaccination in Scotland, there was a decline in vaccine and cross-protective types, namely HPV 31/33/45 [41]. In addition, with data from Papillomavirus surveillance in the Netherlands, Hoes et al. showed significant reduction in cross—protective types HPV-31/45 in women and heterosexual men [40]. In contrast to other HPV vaccines using aluminum-based adjuvants, CERVARIX uses the adjuvant AS04, a combination of the traditional adjuvant alum plus the TLR4 agonist monophosphoryl lipid A, and this may enhance the immune responses [55]. If Mozambique should graduate from Gavi support, then CECOLIN should also be considered on the basis of its low cost, relative to the other two vaccines, particularly if there is uncertainty or controversy about the relative cross-protection associated with the different products.

Beyond cost-effectiveness, there are other relevant aspects, such as affordability, sustainability, acceptability, and feasibility for the government, which should be discussed and contextualized [56–58]. In the absence of Gavi support, the government would need to pay the full price for the vaccine, leading to a less affordable vaccination program. Under this scenario, vaccination with CERVARIX would be the most expensive option (81 million USD), followed by GARDASIL-4 (73 million USD) and, finally, CECOLIN (60 million USD). With base case coverage assumptions, this is equivalent to undiscounted annual costs of 9 million USD, 8 million USD, and 6 million USD, respectively.

The WHO target for cervical cancer eradication is to fully vaccinate 90% of girls up to 15 years old, screen 70% of women at age 35, and again at age 45 years old, and treat 90% of diagnosed women [59]. However, in Mozambique, the only indicator currently being reached (according to a study performed in Maputo city) is the percentage of women with pre-invasive/invasive cervical disease receiving treatment (90%). However, the treatment rate in this study may not be representative of the national situation [36]. All other goals are far below the current WHO targets. Although the coverage of the first dose of HPV vaccination in 2021 was 93%, the second was only 17%, probably due to the recent introduction [21]. Furthermore, according to a national level survey, only 3.5% of the Mozambican women are screened for cervical cancer, most likely due to the lower coverage of the health service provision, lack of formal education, and low income [8]. This reinforces the need for increasing investments in health education and access to screening, to ensure socio-economic returns of the vaccination at mid-to-long-term.

Our study had a number of limitations. First, UNIVAC is a static cohort model and, therefore, excludes any potential indirect 'herd immunity' benefits of vaccination. However, these effects would only have made our results more favourable to vaccination. Second, we had limited country-specific information for some parameters and had to agree on reasonable inputs from alternative sources with the support of a national team of experts during a stakeholder consultation workshop. Third, we excluded costs borne by households, such as out-of-pocket medical expenses, travel, 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.

5. Conclusions

HPV vaccination is a cost-effective intervention in Mozambique. The optimal choice of vaccine depends on influential assumptions about cross-protection. A single-dose vaccine schedule could provide similar health benefits to two doses and may be an important way to reduce costs. The cost-effectiveness of the vaccines should be continually re-evaluated as more information emerges about their efficacy and costs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/vaccines11061058/s1. Figure S1. HPV vaccination program cost of CECOLIN, CERVARIX and GARDASIL-4, during all the analysis period, 2022–2031, including catch-up campaign. Table S1. Deterministic scenarios showing the cost (US$) per DALY averted of vaccination with Gavi support, using CECOLIN, CERVARIX and GARDASIL-4, compared to no vaccine. Table S2. Deterministic scenarios showing the cost (US$) per DALY averted of vaccination without Gavi support, using CECOLIN, CERVARIX and GARDASIL-4, compared to no vaccine.

Author Contributions: Conceptualization, E.L.G., A.C. (Assucênio Chissaque), C.P. and A.C. (Andrew Clark); methodology, E.L.G., A.C. (Assucênio Chissaque), C.P. and A.C. (Andrew Clark); software, A.C. (Andrew Clark); formal analysis, E.L.G. and A.C. (Andrew Clark); data curation, E.L.G., A.C. (Assucênio Chissaque), A.S., B.V., R.R., A.B., A.M., C.L. and C.C.; validation, C.P., F.D., M.d.R.O.M., N.d.D. and A.C. (Andrew Clark); writing—original draft, E.L.G. and A.C. (Assucênio Chissaque); writing—review and editing, A.C. (Andrew Clark), C.P., F.D., B.V., R.R., A.B., A.M., C.L., C.C., N.d.D. and M.d.R.O.M.; supervision, A.C. (Andrew Clark), C.P., N.d.D. and M.d.R.O.M.; project administration, E.L.G.; funding acquisition, C.P. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported, in part, by the Bill and Melinda Gates Foundation, through PATH subaward number: GAT.2111-01707508-SUB. Under the grant conditions of the foundation, a Creative Commons Attribution 4.0 generic license has already been assigned to the author accepted manuscript version that might arise from this submission. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill and Melinda Gates Foundation.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Instituto Nacional de Saúde of Mozambique (protocol code 001/CIBS-INS/2022, approved on 7 January 2022).

Informed Consent Statement: Not applicable.

Data Availability Statement: All the data used in this study was obtained from open platforms GLOBOCAN, UNIPOP, GAVI, manuscripts and from meetings/conversations with experts.

Acknowledgments: We thank the Expanded Programme of Immunization and the National Immunization Technical Advisory Group from Mozambique for their support and commitment to the present analysis. We also thank the PATH team for the technical support and for the linguistic revision of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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3. CHAPTER 3. GENERAL DISCUSSION AND CONCLUSIONS

3.1. General discussion

The main objective of the present thesis was to evaluate the potential impact and cost-effectiveness of vaccination against RV in children under five years of age and against HPV in pre-adolescent girls in Mozambique, using modelling. It is divided into two manuscripts. The first is focused on the assessment of the cost-effectiveness of RV vaccines from 2016 to 2030 and the other to HPV vaccines from 2022 to 2031. Both contribute to a better understanding on the long - term impact and cost-effectiveness of the interventions subsidizing decision making on the sustainable implementation of vaccine preventive strategies for RV-related diarrhoea and Cervical Cancer in the country, considering three main aspects: i) the existence of alternative strategy of HPV vaccination with one dose instead two dose schedule, ii) the availability of other vaccines that could allow sustainability of the vaccines programmes, bearing in mind shortage of the currently used vaccine (Rotarix vaccine), and iii) the potential financial limitations specially when the country starts the Gavi transition process, where the Government moves towards assuming the full cost of vaccination.

Paper I: Impact and cost-effectiveness of rotavirus vaccines in Mozambique

This study provides the first known evidence on projection of potential long-term health and economic impact of RV vaccines and its cost-effectiveness, reflected in cost to obtain one unit of health in Mozambique. The analysis was performed in two contexts, with and without Gavi subsidy. The study was equally conducted in two periods, having the first included only Rotarix in five annual cohorts from 2016 to 2020 and the second approached 10 annual cohorts from 2021 to 2030, evaluating Rotarix, Rotavac and Rotasiil.

The results show that from 2016 to 2020, the currently used vaccine (Rotarix) was potentially cost-effective and positively impacted the young children health reducing RVGE morbidity and mortality by 42%. Projections for 10 years (2021 - 2030) demonstrated that, the vaccines have potential to reduce RVGE the disease burden at 41% (Rotarix) and at 48% (Rotavac and Rotasiil). Rotarix showed a bit lower health impact than Rotavac and Rotasiil.

Regarding the cost-effectiveness, in both period analysis, at 0.5 x GDP p.c. (USD 224.3) threshold, considering Gavi subsidy, all the studied vaccines were cost-effective. From 2021 to 2030 Rotarix dominated other products. However, without Gavi support, only Rotasiil was close to the threshold, with 30% probability to be cost-effective. Similarly, in South Africa, in the absence of Gavi support, Rotarix had a higher vaccination cost, compared to Rotasiil, driving to almost 0% probability of the first option be cost-effective at a 0.53 x GDP p.c. (1). The same happened in projection from 2020 to 2029 in other middle-income countries, Eswatini, Botwana, Cabo Verde, where Rotasiil had lower vaccination cost and better ICERs than others (2).

Mozambique is currently facing Rotarix vaccine shortage (EPI 2023) due to GSK manufacturing challenges (3), which adds fragility to the current RV vaccine program.

Since Rotasiil provides better results than Rotarix and Rotavac in the absence of Gavi support there is a light for resolving the challenges that lie ahead and for a counterpart on decision making regarding the potential shifting from Rotarix to alternative guaranteed supply product that offers a balanced program cost versus health consequences, avoiding setbacks from a successful program.

Shifting from one vaccine to another is common. African countries, such as Burkina Faso, Mali, Gambia and Rwanda, had been facing challenges to sustain RV vaccine supply due to a variety of reasons, including vaccine shortage and Gavi transitioning. Consequently, some of these countries have decided to replace the vaccine with a more sustainable one (4–6).

It is also important to understand that replacement of vaccine itself will not guarantee the expected impact on child lives and cost-effectiveness. The country registered an increment of children aged 12 to 23 months who did not receive any vaccine from 5% in 2015 to 14% in 2022 (7), which represents a gap in children immunity against vaccine-preventable diseases. Although the accounted vaccines in this estimate are the most essential (BCG, poliomyelitis, DTP and measles), probably other vaccines including RV are facing a worse scenario. The higher zero dose prevalence is reported to be related to difficulties to access primary healthcare services because of long distances to reach a health facility, lack of transportation to the health facility, financial issues, and perception of lower technical quality of the provided services. In this context, besides the implementation of the EPI Recovery Plan to Restore Routine Immunization and achieve

Zero Dose for children (8), it is important to reinforce the health system capacity for vaccine provision, especially in the infancy, to increase the probability of a greater health and economic impact. Further, it's important to promote good practices and attitudes on other on breastfeeding, food and personal hygiene, improved water consume (9–11), which together with vaccination would contribute for reducing RVGE burden, following the SDG-2 "End hunger, achieve food security and improved nutrition and promote sustainable agriculture" and SDG–6 "Ensure availability and sustainable management of water and sanitation for all".

Paper II: Impact and Cost-Effectiveness of Alternative Human Papillomavirus Vaccines for Preadolescent Girls in Mozambique: A Modelling Study.

Following the previous study, on RV cost-effectiveness, this section provides a complementary view on the impact and cost-effectiveness of immunizing children with another antigen (in this case HPV), in a different age group. In turn these results together have potential to inform policy makers on decisions to benefit the population across the ages, which can contribute for healthy and productive adults, impacting other spheres, such as the country's economy.

This study results includes the evaluation of alternative strategies such as one dose schedule, instead of the currently used two doses and the catch-up multi-age-cohort [MAC] campaign covering five cohorts of girls aged 10–14 years in 2022. Further, since the country is eligible for Gavi funding, we bring evidence of analysis considering the financial support and non-support of the vaccination program. Finally considering positioning of authors about cross – protection, we provide evidence about potential of the vaccines supposing they confer cross-protection against other HPV types not covered by the vaccines.

Results revealed that without HPV vaccination the country would experience 342,246 cases of cervical cancer and 282,687 female deaths. Considering all the assumptions (with and without cross-protection, with and without Gavi support) the three vaccines showed potential on reducing burden of disease, preventing from 53 to 70% cervical cancer cases and deaths. This evidence is very important for Mozambique, especially because the prevented deaths reflect in several contexts including on reducing number of orphans

from mothers died by cervical cancer. Consequently, it reduces negative impacts of orphanhood such as vulnerable and helpless children (12–14).

All the studied vaccines were cost-effective at the threshold of 0.35 x GDP p.c. There is a potential lower vaccination cost (without Gavi support) of Cecolin, compared to Gardasil-4 (18% high) and Cervarix (26% high), at almost the same health impact as Gardasil–4 (the currently used in Mozambique). Further, the vaccination program with one dose schedule is less costly, as observed in Tanzanian (15).

The primary target for HPV vaccination are 09 to 14 years-old girls (16), however due to financial limitations Mozambique is only including 9-year-old girls.

In 2022 the Strategic Advisory Group of Experts on Immunization (SAGE) updated recommendations for HPV vaccination, including the use of one dose schedule in the same primary target girls (9 to 14 years old) and for the secondary target group (15 to 20 years -old girls) (17).

The provided evidence aligns with the current WHO position fighting cervical cancer (17), by bringing subsidies to allow decision making currently or in the future (even in the Gavi transitioning period) to successfully reduce health care costs and HPV program cost, driving to efficient resources allocation and allowing savings that would be used to reach more girls, or even expand to WHO primary target and maximize the health impact of the vaccine in Mozambique. Besides, these resources can be invested in other efficient preventable strategies, such as the cervical cancer screening, HPV testing (18) and sexual health education to promote good attitudes and practices towards the prevention of HPV infection (19).

WHO target for cervical cancer eradication is to fully vaccinate 90% of girls up to 15 years old, screen 70% of women up to 35 and again by 45 years old, and treat 90% of diagnosed women (20). However, recent national data shows only 52% of HPV vaccine coverage in 2022 (21) and only 3.5% of the women being screened for cervical cancer in 2014/2015 (22). There is not representative data on the accomplishment of the treatment goal. The available information shows that around 90% of women from Maputo City with pre-invasive/invasive cervical disease are treated (23).

Based on the evidence of positive effects of HPV vaccination, Mozambique should improve health policies to increase vaccine coverage and allow the success towards reducing incidence, morbidity and mortality of cervical cancer, aligning with vision of the National Plan of Cancer Control (18).

Integrated discussion

Model-based decision analysis is recognized as an important tool to provide a framework for understanding public health problems and improve policies to address them (24). Several countries, including African (Kenya, Uganda, Senegal) have been using ProVac Initiative's tools and methods to generate country specific evidence to support decision making on introducing vaccines (25).

Health research is mentioned it the Strategic Plan for the Health Sector (PESS) of Mozambique (26), as an important tool for evidence-based practice (EBP), ensuring that decision making is favourable to health improvements in the country. Further, studies on the impact of child vaccination against infectious diseases are currently priority of the National Research Agenda 2024 - 2028 (27), showing the relevance of the studies performed.

This thesis is aligned to Gavi recommendation of providing evidence in the context of co-funding vaccines to LIC and LMICs (28).

The presented studies are complemental, presenting subsidies for decision making towards strengthening immunization programs, to address RVGE and cervical cancer in childhood and youthful, respectively, providing foundations for long term individual and collective health and economic benefits with extended benefits to the adulthood.

These findings can potentially ensure decision making on the most health and economically impactful and cost-effective vaccines and program strategies, and consequently contribute to meet the EPI mission, on reducing morbidity, mortality and disability in children, using the best vaccines for preventable diseases (29).

The decision on the vaccine and the delivery strategy that can provide health benefits at lower costs, could bring several economic and social benefits beyond the observed in the current study, which could contribute to achieve targets of the SDG. Related to Goal-1 "End poverty in all its forms everywhere" and Goal-3 "Ensure healthy lives and promote well-being for all at all ages", savings with both diseases' treatment would improve

economic capacity of the Government and society in general, reflecting on increasing resources to improve another Health Program. Further, would increase life expectancy, improve society life quality resulted from a healthier people, where children would grow properly, have a good cognitive and academic development to contribute for country development as adult, which also. Together with out-of-pocket health care costs averted, would reduce financial toxicity to families reflected in economic empowerment for communities, whom would be able to better invest in education and income-generating initiatives (30), which besides the previous Goals aligns with SDG 4 “Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all”.

Additionally, the selection of the right intervention would promote gender equity, which would particularly benefit women who commonly sustain productivity losses to take care of children or other family members, especially when they are sick (31) following the SDG-5 “Achieve gender equality and empower all women and girls” and SDG-8 “Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all” and SDG-10 "Reduce inequality within and among countries".

Lastly the studies evidence would encourage ongoing funding and advocate for added support from health investors at national and international level, contributing for cooperations among ONGs and the Government, according to SDG-17 “Strengthen the means of implementation and revitalize the global partnership for sustainable development”.

Putting all together, the provided evidence has potential to contribute for Health System and other country´s sectors strengthening and improve society well-being, following the SDG-16 “Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels”.

It is known that Mozambique have been affected by several issues such as the terrorism in North Region, the Covid-19 pandemic, the natural disasters (Idai and Kennedy cyclones and floods) (32), and at the end of 2024 the political instability (33), which possibly result in lower vaccine coverages and impairments to other health services delivery to population. However, in the light of the IA2030 strategy regarding achieving 90% coverage for essential child and adolescent vaccines (34), Mozambique needs to

reflect on mechanisms to increase coverages of both RV and HPV vaccines, which in 2023 was 63% and 52%, respectively (21). Health education based on evidence about the impact and cost-effectiveness of RV and HPV vaccines, would increase credibility of the population and the acceptability of these vaccines, which consequently would improve coverages.

Based on results of the current thesis, for RV vaccine, switching Rotarix to another favourable product considering the health and economic impact, feasibility and availability for guaranteed supply would help to improve the program. In case of HPV vaccine, changing vaccination schedule from two to one dose would cover more girls and improve the health impact of the intervention.

Overall, the thesis contributes with subsidies for a better planification and prioritization of investments in health sector, maximizing health and financial sustainability in the country. In turn it can promote improvements in the primary healthcare as one of the priorities of the Strategic Plan for the Health Sector in Mozambique (26), reducing inequalities in vaccines access, and promoting well-being for Mozambican population.

3.2.Conclusion

Both RV and HPV vaccines have a great potential for reducing burden of RVGE in children and cervical cancer in women. Equally the use of these vaccines showed to be cost-effective considering a variety of assumptions. Regarding RV vaccines, with Gavi subsidy, Rotarix was the less onerous and most cost-effective option than Rotasiil and Rotavac vaccines. Conversely, in the absence of Gavi support, none of the vaccines were cost-effective at the current vaccine price and WTP thresholds, however Rotasiil would be the best choice, considering the lower program costs and the best ICER, compared to others. In the other hand, among the HPV vaccines, the evidence of cross – protection could lead Cervarix to provide better health impact than Cecolin and Gardasil-4. All the vaccines were potentially cost-effective, nevertheless without Gavi subsidy Cecolin presents lower program costs and better value for money. The use of one dose schedule notably reduces the program costs and is cost-effective.

To maximize decision-making efficiency, since our findings are sensitive to context and assumptions, it is important re-evaluate the cost - effectiveness of the studied vaccines, using updated estimates, especially on the most influential parameters, such as, disease

burden, vaccine efficacy, program cost and WTP threshold. This analysis should be performed before starting the shifting process to allow the choice of the vaccine to be more assertive. Finally, future research on vaccine financing mechanisms and vaccine delivery may complement the present evidence by supporting more cost-efficient allocation of resources.

3.3.General discussion references

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4. ANNEXES

ANNEX I: METHODS FOR THE COST-EFFECTIVENESS STUDIES

METHODS FOR THE COST-EFFECTIVENESS STUDIES

2.1.Study design

Health economic evaluation is the comparative analysis of the costs and consequences of different strategies to identify the one that offers the most gains at the lowest cost and consequently achieve efficiency in the allocation and use of resources (1,2).

In the current thesis the cost-effectiveness analysis was used to assess the three RV vaccines (Rotarix, Rotavac and Rotasiil) and HPV vaccines (Cecolin, Cervarix and Gardasil-4). This is the most used economic evaluation type (3). It compares potential costs and health outcomes (expressed in health benefits) of interventions that can provide the same unit of outcome (1,4).

2.2.Population and Study temporal horizon

2.2.1. Population and study temporal horizon for study 1

RV vaccines cost-effectiveness study included 10 consecutive cohorts of live-born children in Mozambique, hypothetically followed for the first 05 years of life. For the Rotarix, cohorts born from 2016 to 2025 were analysed, to assess the sustainability of the vaccine in a mid-term. However, to compare the cost-effectiveness of Rotasiil and Rotavac vaccines with Rotarix, cohorts born from 2021 to 2030 were considered to assess the value of the vaccines in a long term and support future product switch decisions.

2.2.2. Population and study temporal horizon for study 2

As base-case scenario, we estimated the potential lifetime costs and benefits of vaccinating nine annual hypothetic cohorts of 9-year-old girls (as routine vaccination), from 2022 to 2031 and five cohorts of girls aged 10–14 years, as catch-up Multiple-Age Cohort (MAC) campaign conducted in the year 2022 at the national level. The MAC campaign refers to vaccinate multiple age groups simultaneously, instead of focusing only in a single age cohort (5), and was included in the analysis to provide further evidence on how to expand vaccination coverage, increase herd immunity and consequently reduce the HPV transmission and finally reduce burden of CC (6).

2.3.Model

The cost-effectiveness analysis of RV and HPV vaccines were performed using the decision analysis model, because it provides a structure for assumptions and judgements needed for decision-making and provide ways to establish the relationship between clinical variables and how their magnitude varies over time, and it can be done in a short period of time and at low cost (1).

We used a proportionate outcomes decision-support model, the Universal Vaccine Cost-effectiveness and impact modelling framework (UNIVAC) (https://www.paho.org/provac-toolkit/) (Figure 9), designed in a Microsoft Excel interface (Excel, Microsoft Corp, Redmond, WA, US) by researchers from London School of Hygiene and Tropical Medicine and Pan-American Health Organization in the context of the ProVac initiative (7). UNIVAC is a static deterministic cohort model used to generate transparent and conservative estimates of the impact and cost-effectiveness of vaccines, to support decision-making on immunization, especially in developing countries (8). This is a user-friendly tool which gives the opportunity to supplement default data with local information, provides a locally relevant assessment of cost-effectiveness in settings with limited time, capacity and resources, allows a country-led process, which increases the possibility to inform national decisions.

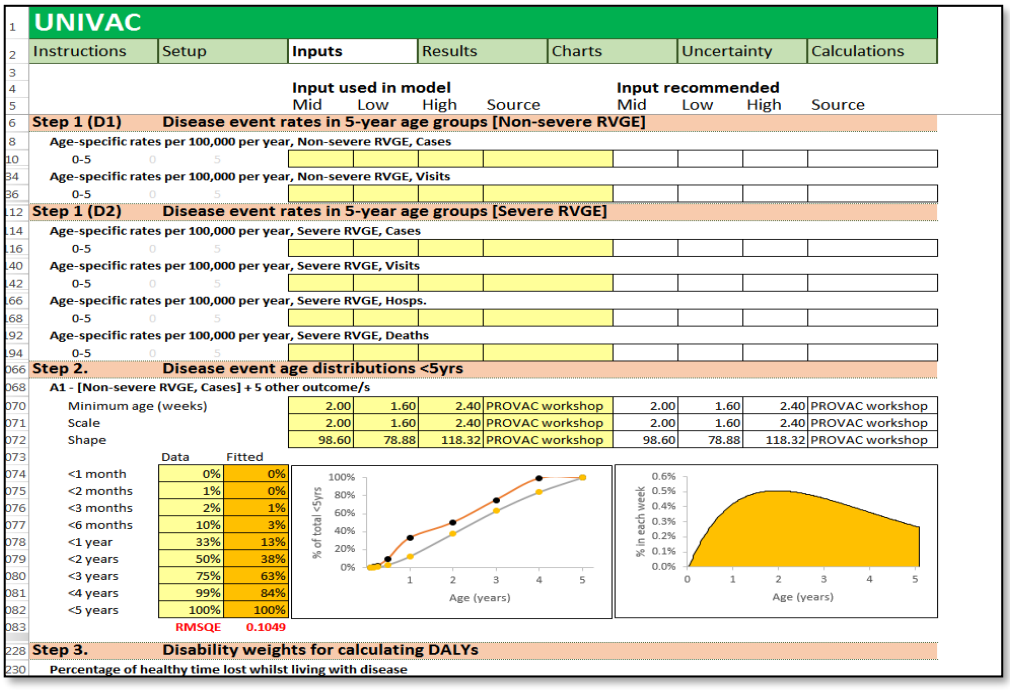


Figure 9 - UNIVAC tool – illustration of the parameters for the cost-effectiveness model. Source: (https://www.paho.org/provac-toolkit/)

2.4.Data source and consensus building

Aggregate data on disease burden of RVGE and CC by stage, estimated vaccine timeliness and coverage, vaccination and disease treatment costs were obtained from relevant literature. In cases there were no representative data, assumptions were made, followed by the validation, in several workshops, by a multidisciplinary group of experts which included investigators in diarrhoeal diseases from the Instituto Nacional de Saúde, investigators on CC field from Maputo Central Hospital and representatives from the EPI, the National Immunization Technical and Advisory Group (known in Mozambique as Comité de Peritos de Imunização), the National Cancer Control Program, the WHO and the United Nations Children´s Fund and Jonh Snow Inc.

The studies were performed in the government perspective. This perspective includes all direct costs incurred by the government, for the diagnosis and treatment of RVGE and CC RV, and RV and HPV vaccination (minus any grants received by Gavi). The complete list of parameters used to build each study model is provided in Table 3.

Table 3-List of parameters used for modelling cost-effectiveness of Rotavirus and Human Papillomavirus vaccines.

RV cost-effectiveness analysis (study 1)	HPV cost-effectiveness analysis (study 2)
Inputs for estimating disease burden	
RVGE incidence by severity and age distribution	CC incidence by stage and age distribution
Hospital visits due to RVGE by severity	Hospital visits due to CC by stage
Hospitalization by RVGE	Hospitalization by CC by stage and age range
Disability weights for RVGE by severity	Disability weights for cervical cancer by stage
Mortality by RVGE	Mortality by CC and age distribution
Duration of RVGE illness by severity	Duration of illness/ survival rate for cervical cancer by stage
Inputs for estimating vaccination parameters	
Vaccine coverage and timeliness	Vaccine coverage year1 & year-over-year change
Vaccine efficacy	Vaccine efficacy
Inputs for estimating vaccination cost per dose	
Price of vaccine dose	Cost of vaccine introduction and program start-up costs (cost per dose in the 1st year)
Cost of safety box per vaccine	Price of vaccine dose in year1 & year-over-year change
International handling and delivery fees	Costs of vaccine supplies (syringe and safety box price per dose) and vaccine wastage rate
Vaccine wastage rate	International handling and delivery fees
Costs of vaccine delivery	Costs of vaccine delivery
Input parameters for estimating health service costs	

Use and cost of health care services for RVGE treatment by severity	Use and cost of health care services for CC treatment by stage

2.5.Outcomes

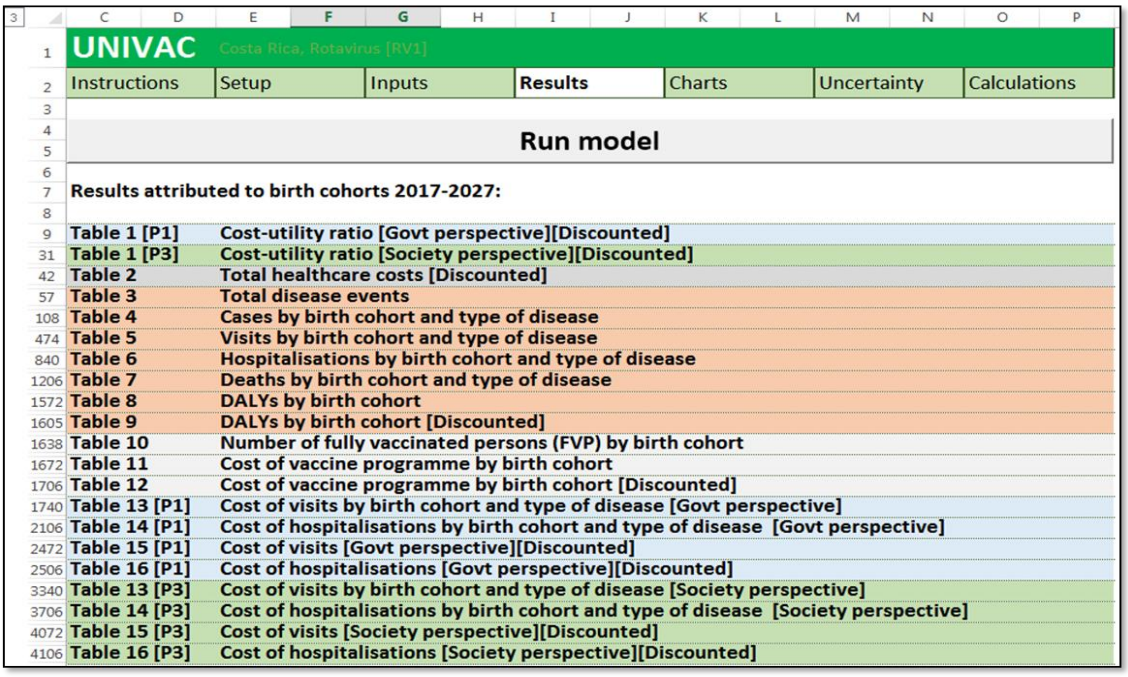
The study primary health outcome was the Disability-Adjusted-Life-Years (DALYs) averted through RV and HPV vaccination. DALYs is a single metric that measures disease burden accounting for both years lost due to early death and years lived with the disease, facilitating comparison across countries and among different diseases and injuries (1). The use of this metric is aligned with LIC´s priorities on optimizing resource allocation and reducing disease burden specially in LIC (4). Besides DALYs other outcomes were considered such as total RGVE cases by severity and total cases of CC by stage averted, total hospitalizations by RVGE and CC averted, and number of deaths associated to the diseases averted with vaccination. Additionally, economic outcomes included health care treatment costs averted in the 10 year-period.

2.6.Discount

Considering that the analysis took place over a future period of time a discount rate of 3% was used for costs and benefits to reflect the time preference for immediate benefits and the opportunity of investing present capital (3,4).

2.7.Results of the cost-effectiveness analysis

Cost-effectiveness was measured using the incremental cost to obtain one unit of health outcome (DALY), estimated by the incremental cost-effectiveness rate (ICER) (4). The ICER is calculated through the ratio of the difference between the treatment and intervention costs and the interventions effects (3,4). The list of UNIVAC´s possible tables with results regarding impact and cost-effectiveness is shown in the figure 10.



UNIVAC Costa Rica, Rotavirus [RV1]

Instructions | Setup | Inputs | **Results** | Charts | Uncertainty | Calculations

Run model

Results attributed to birth cohorts 2017-2027:

9	Table 1 [P1]	Cost-utility ratio [Govt perspective][Discounted]
31	Table 1 [P3]	Cost-utility ratio [Society perspective][Discounted]
42	Table 2	Total healthcare costs [Discounted]
57	Table 3	Total disease events
108	Table 4	Cases by birth cohort and type of disease
474	Table 5	Visits by birth cohort and type of disease
840	Table 6	Hospitalisations by birth cohort and type of disease
1206	Table 7	Deaths by birth cohort and type of disease
1572	Table 8	DALYs by birth cohort
1605	Table 9	DALYs by birth cohort [Discounted]
1638	Table 10	Number of fully vaccinated persons (FVP) by birth cohort
1672	Table 11	Cost of vaccine programme by birth cohort
1706	Table 12	Cost of vaccine programme by birth cohort [Discounted]
1740	Table 13 [P1]	Cost of visits by birth cohort and type of disease [Govt perspective]
2106	Table 14 [P1]	Cost of hospitalisations by birth cohort and type of disease [Govt perspective]
2472	Table 15 [P1]	Cost of visits [Govt perspective][Discounted]
2506	Table 16 [P1]	Cost of hospitalisations [Govt perspective][Discounted]
3340	Table 13 [P3]	Cost of visits by birth cohort and type of disease [Society perspective]
3706	Table 14 [P3]	Cost of hospitalisations by birth cohort and type of disease [Society perspective]
4072	Table 15 [P3]	Cost of visits [Society perspective][Discounted]
4106	Table 16 [P3]	Cost of hospitalisations [Society perspective][Discounted]

Figure 10 - Univac Model – demonstration of the list of tables with the results of cost-effectiveness.

Source: (https://www.paho.org/provac-toolkit/)

2.8.Interpretation of the results

To define an intervention as good value for money, the cost–effectiveness ratios (US$ per DALY averted), must be compared to a willingness-to-pay (WTP) threshold. The WTP threshold is a monetary value which represents an estimated amount an individual or policy maker wish to pay for one year lived healthily (1,9). The intervention is cost-effective if the ICER falls below the WTP threshold (1,9).

There is no currently agreed threshold that defines a cost-effective intervention in Mozambique. In the absence of established thresholds, the interpretation of results can be done according to expert's decision based on the available literature. Based on previous studies (10–12), the present thesis used stringent WTP thresholds varying from 0 to 0.5 GDP per capita to reflect the financial constraints of the country.

2.9.Sensitivity analysis

To assess the impact of uncertainties introduced by each parameter, a sensitivity analysis was performed through the univariate deterministic scenario analyses (4). We selected

the favourable and unfavourable scenarios (10,13–15) do include in the analysis based on the most influential parameters, according to previous studies. Furthermore, the probabilistic sensitivity analyses, based on simultaneous variation of all the parameters across their uncertainty ranges at the same time, was performed to assess the robustness of the model and determine 95% credible ranges around the ICER estimates (16).

2.10. Ethical reviews and considerations

Both studies presented in the present thesis were evaluated and approved by the Institutional Bioethics Committee for Health from the National Institute of Health under the references 664/CNBS/21 and 001/CIBS-INS/2022.

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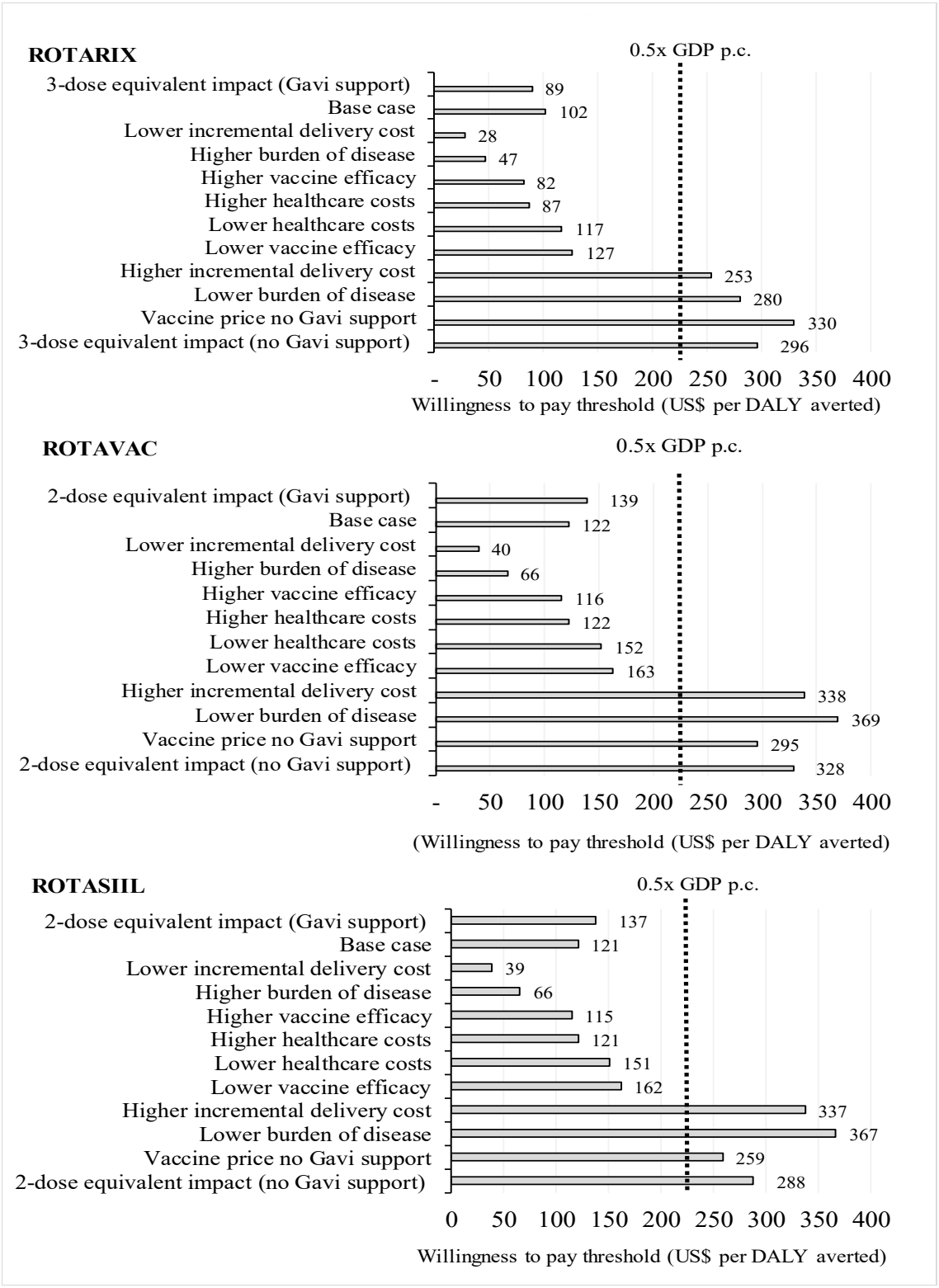
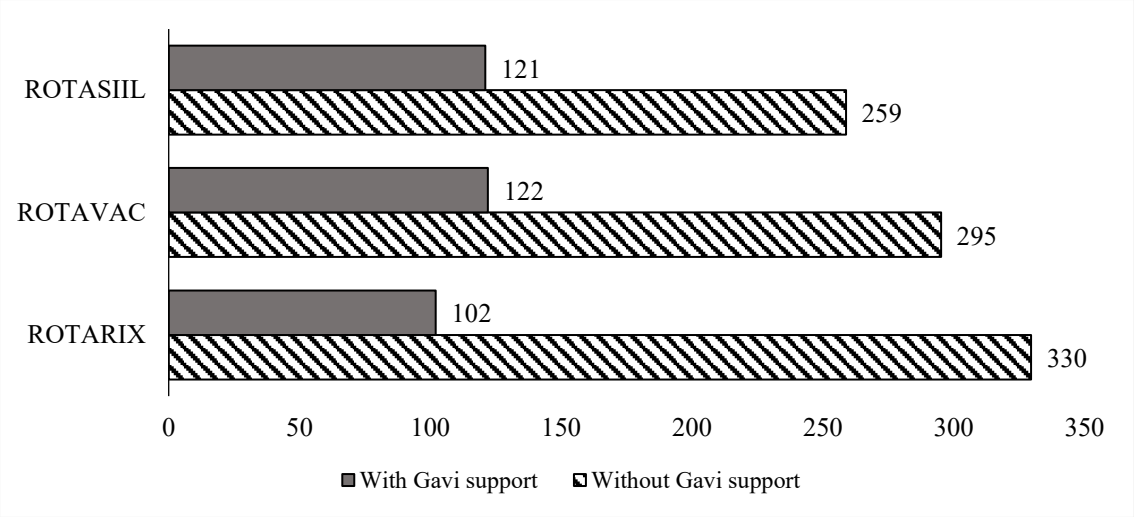
ANNEX II: FROM CHAPTER 2, PAPER I

Supplementary file I - Figure 1. Scenario analysis results, showing incremental cost-effectiveness ratio (US$ per DALY averted) of ROTASIIL, ROTAVAC, and ROTARIX, compared to no vaccination.



Supplementary file - Figure 2. Cost-effectiveness of ROTASIIL, ROTAVAC and ROTARIX vaccines, with and without Gavi support, compared to no vaccination.



ANNEX III: FROM CHAPTER 2, PAPER II

Supplementary Table 1. Deterministic scenarios showing the cost (US$) per DALY averted of vaccination with Gavi support, using CECOLIN, CERVARIX and GARDASIL-4, compared to no vaccine.

Vaccine	Scenario	Government perspective
CECOLIN	**Central inputs (US$0.20 per dose)**	**1.9**
	Vaccine price = 25% lower (US$ 2.18 per dose)	20
	Vaccine price = 50% lower (US$ 1.45 per dose)	13
	Vaccine price = Highest (US$ 2.9 per dose)	26
	Schedule = 1 dose (efficacy = 2 doses) without cross protection	0
	Schedule = 1 dose (efficacy = 2 doses) with cross protection	0
	Lower vaccine coverage	14
	Higher vaccine coverage	26
	Discount rate = 10%	448
	Disease burden rates = Low	14
	Disease burden rates = High	0
	Healthcare costs = Low	10
	Healthcare costs = High	0
	No Catch-up campaign	2
CERVARIX	**Central inputs (US$0.20 per dose)**	**0**
	Vaccine price = 25% lower (US$ 1.32 per dose)	1
	Vaccine price = 50% lower (US$ 2.64 per dose)	11
	Vaccine price = Highest (US$ 5.18 per dose)	27
	Schedule = 1 dose (efficacy = 2 doses) without cross protection	0
	Schedule = 1 dose (efficacy = 2 doses) with cross protection	0
	Lower vaccine coverage	10
	Higher vaccine coverage	13
	Discount rate = 10%	544
	Disease burden rates = Low	25
	Disease burden rates = High	0
	Healthcare costs = Low	1
	Healthcare costs = High	0
	No Catch-up campaign	18
GARDASIL-4	**Central inputs (US$0.20 per dose)**	**2.8**
	Vaccine price = 25% lower (US$ 1.13 per dose)	11
	Vaccine price = 50% lower (US$ 2.25 per dose)	21
	Vaccine price = Highest (US$ 4.50 per dose)	42
	Schedule = 1 dose (efficacy = 2 doses) without cross protection	0
	Schedule = 1 dose (efficacy = 2 doses) with cross protection	0
	Lower vaccine coverage	3
	Higher vaccine coverage	4
	Discount rate = 10%	459
	Disease burden rates = Low	15
	Disease burden rates = High	0
	Healthcare costs = Low	11
	Healthcare costs = High	0
	No Catch-up campaign	3

Supplementary Table 2. Deterministic scenarios showing the cost (US$) per DALY averted of vaccination without Gavi support, using CECOLIN, CERVARIX and GARDASIL-4, compared to no vaccine.

Vaccine	Scenario	Government perspective
CECOLIN	**Central inputs (US$2.90 per dose)**	**26**
	Vaccine price = 25% lower (US$ 2.18 per dose)	20
	Vaccine price = 50% lower (US$ 1.45 per dose)	13
	Schedule = 1 dose (efficacy = 2 doses) With Cross Protection	0
	Schedule = 1 dose (efficacy = 2 doses) without Cross Protection	0
	Lower vaccine coverage	25
	Higher vaccine coverage	29
	Discount rate = 10%	729
	Disease burden rates = Low	44
	Disease burden rates = High	14
	Healthcare costs = Low	34
	Healthcare costs = High	18
	NO Catch-up campaign	35
CERVARIX	**Central inputs (US$5.18 per dose)**	**32**
	Vaccine price = 25% lower (US$ 1.32 per dose)	1
	Vaccine price = 50% lower (US$ 2.64 per dose)	11
	Schedule = 1 dose (efficacy = 2 doses) without Cross Protection	30
	Schedule = 1 dose (efficacy = 2 doses) with Cross Protection	13
	Lower vaccine coverage	27
	Higher vaccine coverage	32
	Discount rate = 10%	753
	Disease burden rates = Low	48
	Disease burden rates = High	17
	Healthcare costs = Low	51
	Healthcare costs = High	35
	NO Catch-up campaign	43
GARDASIL-4	**Central inputs (US$4.50 per dose)**	**42.0**
	Vaccine price = 25% lower (US$ 1.13 per dose)	11
	Vaccine price = 50% lower (US$ 2.25 per dose)	21
	Schedule = 1 dose (efficacy = 2 doses) without Cross Protection	24
	Schedule = 1 dose (efficacy = 2 doses) with Cross Protection	23
	Lower vaccine coverage	40
	Higher vaccine coverage	45
	Discount rate = 10%	915
	Disease burden rates = Low	64
	Disease burden rates = High	28
	Healthcare costs = Low	50
	Healthcare costs = High	34
	NO Catch-up campaign	57

Supplementary figure 1. HPV vaccination program cost of CECOLIN, CERVARIX and GARDASIL-4, during all the analysis period, 2022 – 2031, including catch-up campaign.