University of London
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The development and use of evidence in the context of vaccine introductions

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Statement of Originality

I declare that all work presented in this thesis is my own, completed under the supervision of Dr Lesong Conteh and Prof Timothy Hallett. Any ideas or quotations from the work of other people, published or otherwise, or from my own previous work are fully acknowledged in accordance with the standard referencing practices of the discipline.

The work presented in Chapter 3 has been published in an altered form in:

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Abstract

Infectious diseases are among the leading causes of death and disability globally, disproportionately affecting people in low- and middle-income countries (LMIC). Vaccines have made a significant contribution to reducing the global burden of infectious diseases, preventing an estimated 5.1 million deaths annually. However, with changing infectious disease epidemiology, other competing health challenges, and new vaccine products and technologies, the decision-making environment for vaccine introductions is becoming more complex. To progress towards elimination goals, programmes that promote immunisation access and health equity need to be implemented. To this end, evidence, in its many forms, can inform policies and programmes. To date, how specific forms of evidence are used at specific moments in vaccination programme introductions in LMIC remains opaque. Understanding how the perspectives of stakeholders in science and policy development can be integrated into evidence development and how this evidence can be translated to support immunisation programmes, is vital to improving health outcomes.

The aim of this thesis is to contribute to the global evidence base by exploring knowledge translation in the context of vaccination programmes at the global and national levels, with a particular focus on evidence generated with mathematical models. Through integrating the perspectives of decision-makers in modelling the human papillomavirus vaccine impact in Mozambique, this thesis reflects on how evidence can be shaped for health policy and programmes. This work reflects on how mathematical models of infectious diseases can contribute to reducing health disparities in settings with limited resources. It is envisioned that the findings of this research will support operationalizing evidence-informed decision-making in immunisation programmes, and will thereby contribute to more evidence-informed actions to advance global health.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome.
CC	Cervical cancer.
CHE	Catastrophic health expenditure.
CISM	Centro de Investigação em Saúde de Manhiça.
CoPI	Comite de Peritos para la Imunizacao.
DAH	Donor assistance for health.
DALY	Disability-adjusted life years.
EBM	Evidence-based medicine.
EC	Evidence consumer.
ECEA	Extended Cost Effectiveness Analysis.
EDU	Evidence development and use.
EP	Evidence producer.
EPI	Expanded Program on Immunization.
EVIPNet	Evidence-Informed Policy Network.
FDC	Fundação para o Desenvolvimento da Comunidade.
FDI	Foreign Direct Investment.
FIGO	International Federation of Gynecology and Obstetrics staging system.
FRP	Financial risk protection.

FTE	Full-time equivalents.
Gavi	Gavi, The Alliance.
GHO	Global health organization.
GRADE	Grading of Recommendations, Assessment, Development and Evaluation.
HIV	Human immunodeficiency virus.
HPV	Human papillomavirus.
HQ	Headquarter.
HTA	Health Technology Assessment.
IARC	International Agency of Research on Cancer.
IHME	Institute for Health Metrics and Evaluation.
IMF	International Monetary Fund.
IO	International organization.
LIC	Low-income country.
LMIC	Low- and middle-income countries.
MCDA	Multi-criteria decision analysis.
MEF	Ministry of Economy and Finance.
MINEHD	Ministry of Education and Human Development.
MoH	Ministry of Health.
N	National.
NCD	Non-communicable diseases.
NGO	Non-governmental organization.
NICE	National Institute of Health and Care Excellence.
NITAG	National Immunization Technical Advisory Group.

P	Provincial.
PAV	Programa Alargado de Vacinacao.
PIE	Post introduction evaluation.
PRIME	Papillomavirus Rapid Interface for Modelling and Economics.
R	Regional.
RENAMO	Portuguese Resistência Nacional Moçambicana.
SAAJ	Adolescent and Youth Friendly Services.
SELV	Electrónico de Logística de Vacinas.
SIVAC	Supporting Independent Immunization and Vaccine Advisory Committees.
SMART Vaccines	Strategic Multi-Attribute Ranking Tool for Vaccines.
SNA	Social Network Analysis.
SORT	Strength of Recommendations Taxonomy.
UICC	Union for International Cancer Control.
VIA	Visual Inspection with Acetic Acid.
VIMC	Vaccine Impact Modelling Consortium.
WHO	World Health Organization.

Contribution Statement

In order to conduct this research, I independently established a collaboration with the Mozambican research institute, Centro de Investigação em Saúde de Manhiça (CISM). For this purpose, I set up a memorandum of understanding and a data sharing agreement with the partners in Mozambique. This strategic partnership offered an opportunity to go beyond the descriptive and inform a more analytical, empirical testing environment. I received ethical approval from the Institutional Review Board of the Manhica Health Research Centre in Mozambique and Imperial College London. I benefited from the co-supervision of Dr Neusa Torres in Mozambique. I received financial support from LISS DTP (ESRC) and the MRC Center at Imperial College London through competitive seed funding.

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Chapter 1

Introduction

Infectious diseases are among the leading causes of death and disability globally, disproportionately affecting people in LMIC [37]. Vaccines have made a significant contribution to reducing the global burden of infectious diseases, preventing an estimated 5.1 million deaths annually [85]. However, with changing infectious disease epidemiology, other competing health challenges, and new vaccine products and technologies, the decision-making environment for vaccine introductions is becoming more complex. To progress towards elimination goals, programmes that promote immunisation access and health equity need to be implemented [246]. To this end, evidence, in its many forms, can inform policies and programmes. To date, how specific forms of evidence are used at specific moments in vaccination programme introductions in LMIC remains opaque. Understanding how the perspectives of stakeholders in science and policy development can be integrated into evidence development and how this evidence can be translated to support immunisation programmes, is vital to improving health outcomes.

Vaccination programmes provide a compelling case for a number of reasons. First, factors associated with an era of global change in technology, demographics, and climate favour the emergence, evolution, and spread of new pathogens [22]. Further, lack of immunisation access has been pronounced as coverage targets for safe, efficacious, and cost-effective vaccines remain unmet [291]. This underlines the need for research in implementation science for immunisation programmes.

One method that can inform decisions around vaccination programmes is evidence generated

with mathematical models. With mathematical models, experimental hypotheses that would otherwise be expensive, difficult, or unethical to explore can be tested efficiently [43]. They have been used to assess disease risk, forecast health and economic outcomes of diseases, evaluate public health interventions on their impact, and allocate resources [202, 218]. However, on the one hand, they are often developed by scientists distant from the political decision-making space to which their work could contribute [43]. Thus, their evidence may not have been developed with critical current and future policy questions in mind, using assumptions that are open to criticism. On the other hand, policymakers may not have communicated their evidence needs and have unrealistic expectations of scientific potential. A lack of engagement between stakeholders can lead to evidence being undervalued or overvalued. This disconnect can, in the worst cases, be to the detriment of public health.

Thus, understanding how evidence is developed and used in the context of vaccine introductions is of high priority for researchers, funders of research and immunisation programmes, as well as policymakers. Probing evidence development and use (EDU) at the global and national level, it is envisioned that this thesis will help inform approaches to operationalize EDU, which integrate the perspectives of policymakers and scientists.

1.1 Objectives

This thesis aims to understand how evidence is developed and used in the context of vaccine introductions. More specifically, the thesis aims to explore how the integration of different stakeholders in EDU can be operationalized. With a focus on evidence development and the use of estimates from mathematical models, the thesis compares and contrasts perspectives (a) of evidence consumers and evidence producers; (b) at global and national decision-making arenas; and (c) in political and organizational environments.

1.1.1 Rationale for objectives

Objective 1: Investigate perspectives on EDU at global and national decision-making arenas, and in political and organizational environments.

The introduction of vaccines in the context of infectious diseases involves decision-making processes that occur at various levels, ranging from global health organization (GHO), such as the World Health Organization (WHO), to national governments, public health agencies, and local communities. Each level of decision-making is influenced by specific political, social, and organizational dynamics that shape the context in which evidence is developed and used. Power dynamics in health policy environments as well as research environments, i.e., where much of the evidence is produced, have been lamented. Critiques have emphasized inequities in global health decision-making environments, funding, and the need for more transparent decision-making processes [2, 382]. These issues are hypothesized to have spillover effects on EDU in the context of vaccine introductions.

By investigating perspectives across different decision-making arenas and environments, this thesis aims to provide a nuanced understanding of how evidence is perceived, valued, and utilized within diverse contexts. It seeks to explore how global and national decision-making processes differ in terms of evidence requirements. Additionally, it aims to uncover the influence of political factors, such as power dynamics, interests, and ideologies, as well as organizational factors, such as institutional structures, on EDU.

Objective 2: Compare and contrast perspectives of evidence consumers and evidence producers.

Evidence consumers, such as policymakers and decision-makers, can rely on evidence produced by researchers and other experts to inform their decisions regarding vaccine introductions, policies, and programmes. However, these two groups often have distinct perspectives, priorities, and levels of expertise, which can potentially influence how evidence is perceived, interpreted, and used.

By comparing and contrasting the perspectives of evidence consumers and evidence producers, this objective aims to explore the factors that shape the understanding and decision-making processes of both groups, including their knowledge, values, political considerations, and organizational contexts.

Objective 3: Explore how the integration of different stakeholders in EDU can be operationalized.

The question of how different stakeholders, such as researchers, policymakers, public health officials, and community representatives, can effectively collaborate and contribute to EDU has been at the core of the knowledge translation literature. Participatory approaches that seek to foster stakeholder engagement to attune evidence to their policy context have been discussed in the literature more recently [4]. However, to date, this approach has not been researched in the context of the mathematical modelling of vaccine-preventable infectious diseases.

By exploring the operationalization of stakeholder integration in EDU, this thesis aims to shed light on the dynamics and mechanisms that facilitate effective collaboration. It seeks to identify the challenges and opportunities associated with stakeholder engagement, and coordination in the context of vaccine introductions. This knowledge can contribute to the development of strategies and frameworks that enhance the integration of diverse perspectives, expertise, and interests, ultimately leading to more robust and contextually relevant evidence.

1.2 Thesis Overview

This thesis offers several novel contributions to the existing literature on knowledge translation in public and global health. Chapter 2 presents a narrative literature review, building on the considerable research on knowledge translation. To allow for more focus, the review concentrates on the research approach underpinning the assumptions, the research questions investigated, the analyses conducted, and the framing of findings.

In Chapter 3 I examine the use of a specific type of evidence, global epidemiological and economic research commissioned by GHOs using an organisational science perspective. Chapter 4 builds on this research, with a broader perspective on the meaning of evidence in policy development and programme implementation processes and the human papillomavirus (HPV) vaccine as a national tracer in Mozambique. Specifically, findings from in-depth, semi-structured interviews with evidence producers and its consumers, i.e., political and programmatic decision-makers, are presented and critiqued. The first section depicts participants' narratives of the chronology of the HPV vaccination programme policy development and implementation in Mozambique with reference to the policy stages cycle. In the second section, the study populations' perspectives on how evidence was used throughout this process are compared. The findings are compared with those from the preceding chapter. In Chapter 5, the evidence needs of actors in the issue network around the HPV vaccination programme in Mozambique are captured. In this explorative piece, the focus is on identifying evidence gaps that can be addressed with mathematical models to formulate policy-relevant research questions and define how each outcome is measured. In the discussion, approaches to addressing evidence gaps with mathematical models in other contexts are discussed. In Chapter 6, a mathematical model, which was previously developed by Goldie et al. [166] is applied and extended to quantify the impact of current HPV vaccination from a population health, health system, and societal perspective, based on findings from the previous chapter. In the final results chapter, Chapter 7, reflections on the approach to developing evidence and on how the evidence could be used by decision-makers in Mozambique are presented. The thesis concludes with a chapter (Chapter 8) in which the main findings from the thesis are tied together and potential policy implications as well as future research directions and recommendations are depicted.

In the remainder of this chapter, the author reflects on her positionality (Section 1.3), and she introduces the study setting of the research conducted.

1.3 Positionality statement

The following reflective stance provides a self-critical and self-conscious analytical account of the researcher's positionality and potential influence on the methods used, data collection, and interpretation of the data. Inspired by Savin-Baden and Howell Major's [356] suggestions of what a comprehensive positionality statement should entail, the following reflects on:

1. Potential influences on the research approach
2. The researcher's chosen or pre-determined position about the participants
3. The research project context and an explanation as to how, where, when and in what way these have influenced the research process
4. The researcher's lens, i.e., philosophical, personal, and theoretical beliefs and perspectives that have influenced the research approach

The author is a social scientist and epidemiologist, having taken a first degree in Management at Bayes Business School and two Masters, one in Business Analytics and one in Epidemiology, both from Imperial College London. In a lecture on Network Analytics in 2016, the author was introduced to the field of epidemiology, specifically the mathematical modelling of infectious diseases. In her thesis for the Masters in Business Analytics, she evaluated mathematical models of Ebola on their accuracy. Further, as a research assistant at the Centre for Health Economics & Policy Innovation, Imperial College Business School, she conducted a systematic literature review on the economic impact as a result of environmental hazards (e.g., air pollution, noise pollution, etc.) on health to support work for Public Health England. In her thesis for the Masters in Epidemiology, the author researched the effect of endemic equilibrium assumptions on estimates of yellow fever burden. Through these experiences, the author became increasingly interested in how different methods, specifically mathematical models of infectious diseases, are developed and used to inform policy and programmes.

During the COVID-19 pandemic, the author was part of the COVID-19 Response Team at Imperial College London, where she contributed to the development of tools and evidence,

including a mathematical model, to support the public health response. In a nine-months consultancy to the Advanced Analytics Team at the UK Health Security Agency, she contributed to translating findings from mathematical models to formulate policy recommendations for the cabinet of the UK. Due to these applied mathematical modelling experiences, and education in epidemiology, for parts of this research, she assumes an 'insider perspective'; the author has a lived familiarity with and a priori knowledge of mathematical modelling and knowledge translation for policy.

The author decided to focus on the development and use of evidence in settings with limited resources (e.g., countries that are classified as low-income country (LIC) by the World Bank), as most mathematical modelling research on infectious diseases that are predominantly prevalent in low-income settings has been published by the scientific community in Europe and North America. This thesis has been influenced by critical thinking about who sets global health research priorities and to what extent research processes may still inherently be colonial.

Learning from discussions about the HPV vaccination programme with national researchers in Mozambique and preliminary desk review findings, the author identified an opportunity to do primary data collection here. Thus, PC reached out and independently established relationships with Mozambican researchers at Centro de Investigação em Saúde de Manhiça (CISM), set up a memorandum of understanding, obtained ethical approval from the Institutional Review Board of the Manhica Health Research Centre and Imperial College London, set up a data sharing agreement (Appendix B), and secured competitive funding. This enabled the establishment of a new strategic partnership with a Mozambican-based research team and offered an opportunity to go beyond the descriptive and inform a more analytical, empirical testing environment. Further, through data collection support by the Mozambican-based research team, the data could be collected in person, which was not otherwise possible because of travel restrictions imposed due to the COVID-19 pandemic. Moreover, working with the research team, coding data together, and discussing translations helped interpret and understand the data.

The researcher's lens changed over the course of the thesis from assuming a positivist lens, i.e., the objective and value-neutral nature of scientific inquiry and knowledge translation

in policy to a more post-positivist lens, i.e., appreciating epistemological pluralism. For example, decision-making around vaccine introductions and their implementation is subject to juggling various political interests at the global, national, sub-national and individual level, while challenged with various resource shortages. Such considerations cannot be factored into mathematical calculations and is beyond the scope of optimization algorithms.

The author's change in perspectives was influenced by the research findings that emerged in each chapter as well as the researcher's work to support the work in response to the COVID-19 pandemic and a recent workshop that focused on the reflections of a diverse and global group of leading mathematical modellers and public health decision-makers. The author's first Masters degree and early lay theoretical knowledge of epidemiology shaped her initial hypothesis and assumption that results from mathematical models are likely to directly inform programmatic action, such as resource allocation decisions, and thereby can inform optimal decision-making processes to improve population health outcomes. During her PhD, this notion changed as the author learned more about the standpoints, assumptions, and political contexts of public health and policy decisions. In this process, the author acknowledged that a mixed-methods research approach is most appropriate for this research as it allows to triangulate quantitative and qualitative data and to probe underlying reasons for how specific forms of evidence are useful (or not). This shift in understanding is also traceable in the thesis; having looked at the use of burden of disease and vaccine impact estimates at the global level, the thesis pivots to research on how evidence is defined in its broadest sense for national health policy decisions. This is further discussed in Chapter 8 considering the findings presented in this thesis.

1.4 Study setting

The description of the study setting begins with sections reflecting on 1) the context for the research conducted at the global level and 2) the HPV vaccine as an intervention against cervical cancer (CC). This is followed by a country profile of Mozambique at the time of the study. In the country profile section, Mozambique's political system, the organization of the public health

sector, the main public health concerns, the burden of HPV and CC in Mozambique, as well as the country's public health capacities are described.

1.4.1 Vaccines, global health organizations and evidence

GHO, including the Bill and Melinda Gates Foundation and partnerships like Gavi, The Alliance (Gavi), have a prominent role in immunization programs in LMIC, in addition to their domestic efforts. Over the period of 1990 to 2016, donor assistance for health (DAH) provided by global, bilateral, and multilateral partnerships and agencies specifically targeting immunization amounted to $34.5 billion [141]. This financial support has contributed to remarkable improvements in health outcomes. However, despite efforts to achieve universal immunization for all children, as initially outlined by the WHO through the Expanded Program on Immunization (EPI) in 1974, disparities in access to immunization still persist both between and within countries [242].

GHOs collaborate closely with researchers to address the effects of long-standing, emerging, and re-emerging infectious diseases on public health. For example, epidemiologists are commissioned by these organizations to estimate the impact of vaccines at a global and national level using mathematical models of infectious diseases [282, 355, 395]. Through epidemiological models, it is possible to estimate the transmission of infectious diseases within a specific population and quantify the lives saved or deaths prevented through public health interventions. By determining the estimated number of deaths caused by a particular disease, this information can be used to calculate other metrics such as disability-adjusted life years (DALY). These metrics aid in measuring the burden of disease and evaluating the impact of vaccines. One notable example of this collaborative work is the Vaccine Impact Modelling Consortium (VIMC), which has conducted studies estimating the burden of disease, deaths, and DALYs associated with ten pathogens across 98 LMIC [233]. Such evidence has the potential to provide insights into policy questions [56], assist in addressing complex policy issues, and guide decision-making regarding resource allocation [112, 183]. This is further explored in Chapter 3.

1.4.2 The HPV vaccine as an intervention

HPV is a non-enveloped deoxyribonucleic acid (DNA) virus that infects skin or mucosal cells. Of more than 200 identified HPV genotypes, HPV16/ 18/ 31/ 33/ 35/ 39/ 45/ 51/ 52/ 56/ 58/ 59 are high-risk HPV genotypes according to the International Agency of Research on Cancer. These can cause cancer of the cervix and are associated with other anogenital cancers and cancers of the head and neck. The two most common high-risk HPV genotypes (HPV 16 and 18) cause approximately 70% of all CC [247]. Other genotypes (HPV 6 and 11) can cause genital warts. CC remains a global health issue, disproportionately affecting women in countries in the African region, where 85% of global mortality from CC occurred based on 2020 estimates [199].

Globally, three prophylactic HPV vaccines against persistent infection with HPV vaccine genotypes and high-grade cervical intraepithelial neoplasia are currently licensed. In 2006, the quadrivalent vaccine, GARDASIL® (Merck & Co. Inc.), which targets HPV genotypes 16, 18, 6, 11, was licensed in Europe, followed by the bivalent vaccine, Cervarix® (GlaxoSmithKline Biologicals), which targets HPV genotypes 16 and 18 in 2007 [46]. In 2015, a third vaccine, GARDASIL-9 (Merck & Co. Inc.), which targets an additional five oncogenic genotypes was licensed [208]. According to a UNICEF report (2020), 27 new generation vaccine candidates are under development of which 60 % are in discovery or preclinical stage, with the other 40 % being in other clinical development phases [111].

The vaccines are most efficacious (100 %) in those who have not had exposure to HPV. The WHO recommends HPV vaccination of girls of age 9 – 13 prior to sexual debut [338].

WHO updated its recommendation for the HPV vaccine to be administered following a one or two dose schedule. Previously, it was recommended to follow a two to three dose schedule. The updated recommendation is based on a systematic review, which showed high rates of seropositivity for vaccine-type HPV genotypes regardless of the number of doses received [285]. Immunocompromised individuals should receive two or more doses where possible [285].

Small-scale pilots, known as demonstration projects were conducted in several LMIC between

2007 and 2012. In this period, vaccines were provided through the GARDASIL® Access Program (GAP), Merck & Co., the Bill & Melinda Gates Foundation through PATH, and other means. These pilots were called "demonstration programmes" and were conducted to gain experience at delivering a vaccine to adolescents, a cohort outside of the usual immunization schedule for children. To support access to the HPV vaccine globally, Gavi confirmed its support for HPV immunization programmes in eligible countries (with gross national income per capita greater than US$1580) in 2011 [181]. In 2012, Gavi commenced support for 2-year demonstration projects as well as national introductions. National programmes were supported if a country had experience of vaccinating the target age group and achieved 50% vaccination coverage [159]. Gavi's support encompassed the entire cost of the vaccine, injection consumables, and some delivery costs. In the first year, Gavi covered either US$ 4.80 per girl or US$50,000 for delivery (whichever was largest) [159]. This was reduced to US$4.40 per girl or US$25,000 in the second year respectively [159].

The pilots have led to a plethora of scientific research, learnings, and international guidelines [39, 191, 220, 411], which recommend the integration of the HPV vaccine in national plans to fight CC. In many countries, the scale-up of the vaccination programme took place over a long period of time, or is yet to happen. As of March 2022, only 8 of 29 (28%) countries classified as LIC by the World Bank have introduced the HPV vaccine to their national routine immunisation schedules. In comparison, 43% of LMIC, 64% of upper-middle-income economies, and 89% of high-income countries have introduced the vaccine [323]. Global demand for the vaccine has increased in recent years; as of 2019, 115 countries had begun the immunisation programme, with some high-income countries implementing "gender neutral" policies. This may be the reason for the global supply shortage, with manufacturers unable to meet global demands [15]. Furthermore, the COVID-19 pandemic led to supply chain disruptions of the vaccine [111]. Yet, with the one-dose schedule of the vaccine and new vaccine candidates on the market, the global demand for the HPV vaccine is more likely to be met [417].

In Mozambique, CC is one of the leading causes of cancer death among women. In 2020, the country was among the countries with the highest estimated age-standardized CC incidence rate of 50.2 per 100,000 [199], Figure 1.1. This incidence rate is 3.7 times higher than the

estimated global average of 13.3 per 100,000 and 2.4 times higher than the estimate for the southern African region of 20.6 per 100,000 [379].

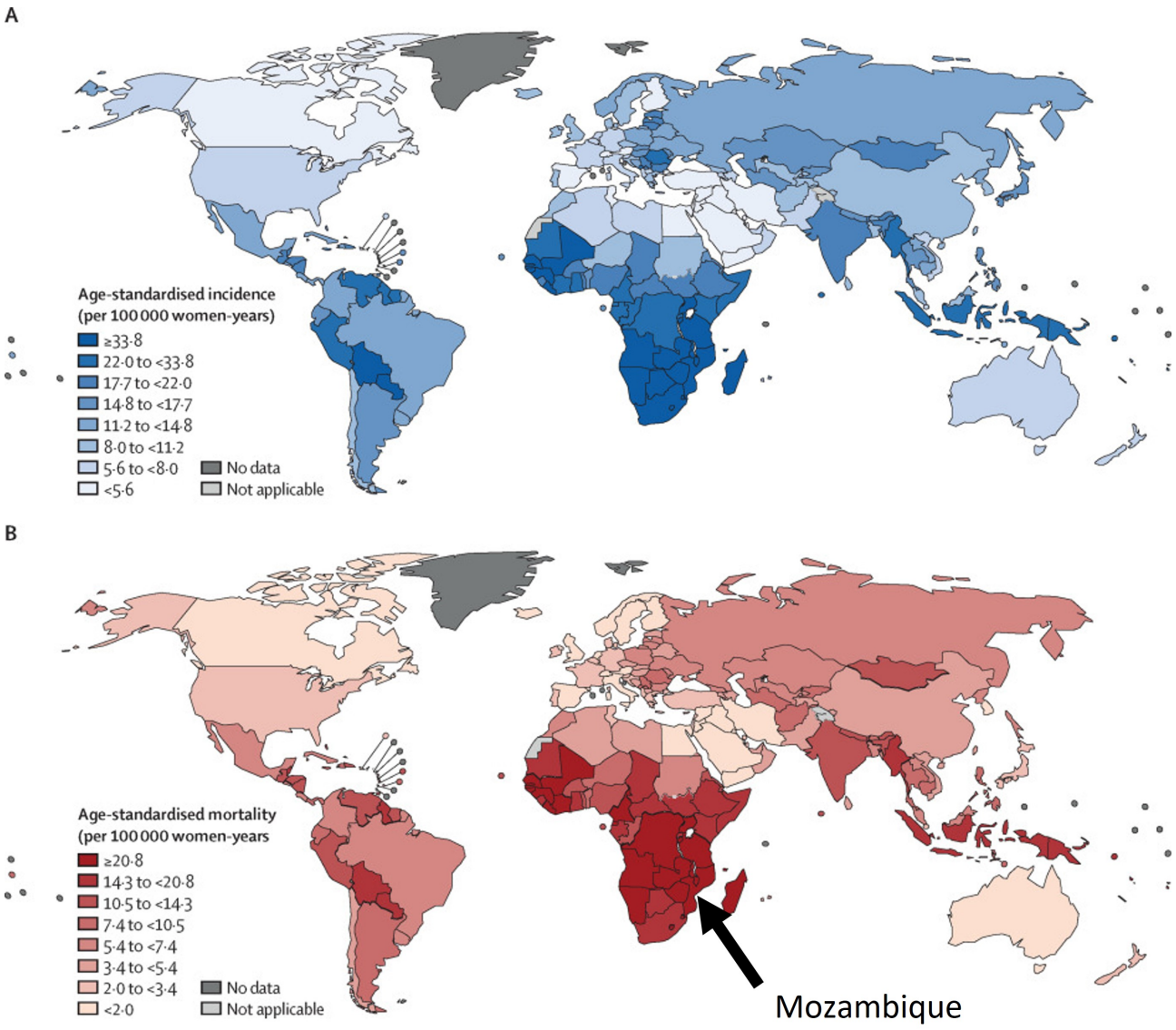
In Mozambique, radiotherapy treatment has only been available since 2019 at Maputo Central Hospital, with a capacity to treat 75 patients per month [333]. Access to CC screening and treatment in Mozambique is very limited. The CC screening programme based on Visual Inspection with Acetic Acid (VIA) and cryotherapy in selected health facilities through other treatment programmes since 2009 [18, 266]. Radiotherapy has been provided since 2019 at two facilities in Mozambique (the Maputo Central Hospital and the Central Private Hospital), both located in Maputo [333]. CC treatment is not covered by Mozambique's health coverage benefit package [107]. Before radiotherapy services were available in the country, less than 1% of patients received optimal guideline-adherent therapy and less than 3% received therapy with major deviations from guidelines [172]. Case-fatality rates are also high due to a lack of timely, safe, and affordable surgical care [253]. Cancer treatment is not covered by Mozambique's health coverage benefit package [107] and therefore poses a significant financial burden on the individual.

In 2021, Mozambique eventually introduced the HPV vaccine following a lengthy policy development. Since 2021, GARDASIL® (Merck & Co. Inc.) has been administered following a two-dose schedule. The political decision-making and programme development processes are analyzed in depth in Chapter 4.

1.4.3 Country profile

Research conducted in Chapters 4 - 7 is set in the sub-Saharan African country, Mozambique. Mozambique is classified as a LIC by the World Bank. The country has a population of over 33 million (in 2022) [27]. Geographically, Mozambique stretches along the south eastern coast of Africa and is divided into 11 provinces (Figure 1.3). The capital, Maputo City, a province by itself, is located in the south.

Figure 1.1: Age-standardised incidence (A) and mortality rates (B) of cervical cancer by country in 2020. (Arrow added to original map) [365]



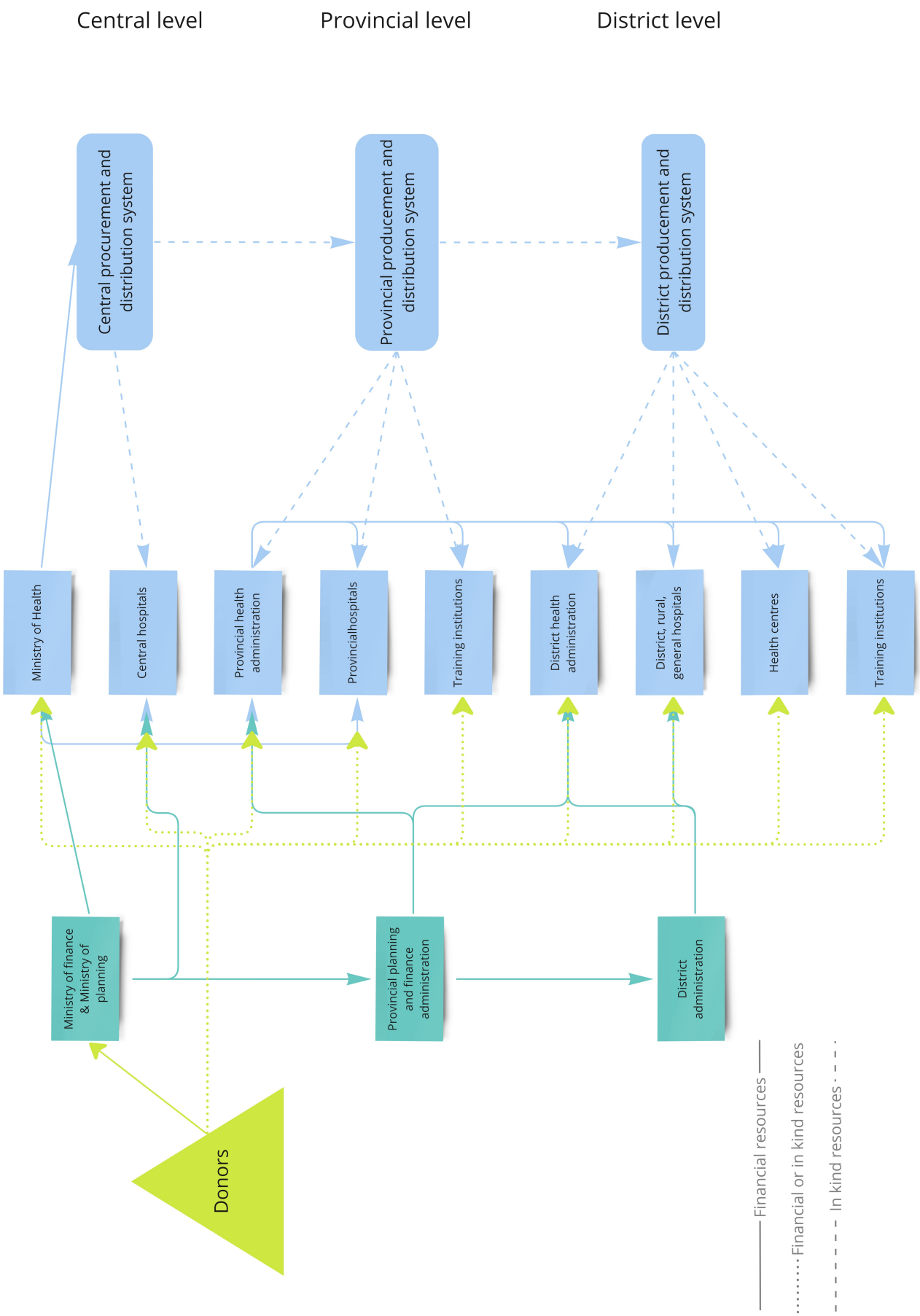


Figure 1.2: Health system structure in Mozambique. [13]

Following its independence from Portugal in 1975 and a long civil war, a peace agreement was signed in 1992 [35]. In the post-war period, the country experienced economic growth, increasing school attendance rates, and a decreasing number of people living below the poverty line until the early 2000's [288]. Between 2005 and 2013, the country attracted significant donor funding (up to 39.5% of GDP in 2013) [25] and became one of the three most attractive economies for Foreign Direct Investment (FDI) in sub-Saharan Africa [89]. However, the "hidden" loan crisis, which was uncovered through the Kroll report and an independent forensic audit taken up in 2013, led to a protracted economic downturn [288]. Corruption and a decline in growth rates also led to a loss of confidence among international investors [288].

Since 1975, the Frelimo party has ruled Mozambique, winning all general elections [35]. The party exercises its power by appointing staff at the central and local state levels, as well as most public institutions. In northern and central Mozambique, violent conflicts persist through an Islamist insurgency linked to the Al-Shabaab, and the self-proclaimed Military Junta linked to the major opposition party, the Mozambique Nacional Resistance (the Portuguese Resistência Nacional Moçambicana (RENAMO)). Since 2017, this has led to a surge in internally displaced people, with over 13% of the population having migrated [234, 245]. The timeline of political events since Mozambique's independence up to 2015 is illustrated in Figure 1.4. These political events have collided with various natural disasters, such as Cyclone "Ida" (Figure 1.5). Most recently, Mozambique was heavily affected by the severe tropical storm "Freddy" [100].

The current most prevalent issues of violence, poverty, the debt crisis, inflation, inequality, and environmental problems are largely interrelated and affect the country's public health profile and the progress of public health programmes [288].

The average life expectancy of 59 years in 2021 in Mozambique is comparable with those in other sub-Saharan African countries [26]. Mozambique's infant mortality rate from 70.6 deaths per 1000 livebirths in 2020 is comparable with the average of 73.3 deaths per 1000 liverbirths in sub-Saharan Africa but high in comparison to the global average of 3.66% and the global aspirational target of 2.5% [347].

The country experiences a high burden of preventable and curable communicable and non-

Figure 1.3: Map of Mozambique. [152]



communicable diseases (NCD). Mozambique is among the countries with the highest prevalence

Figure 1.4: Historical timeline of political events in Mozambique since its independence from Portugal until 2020. Drawn based on data from [288]. Abbreviations: MAM: Mozambique Asset Management

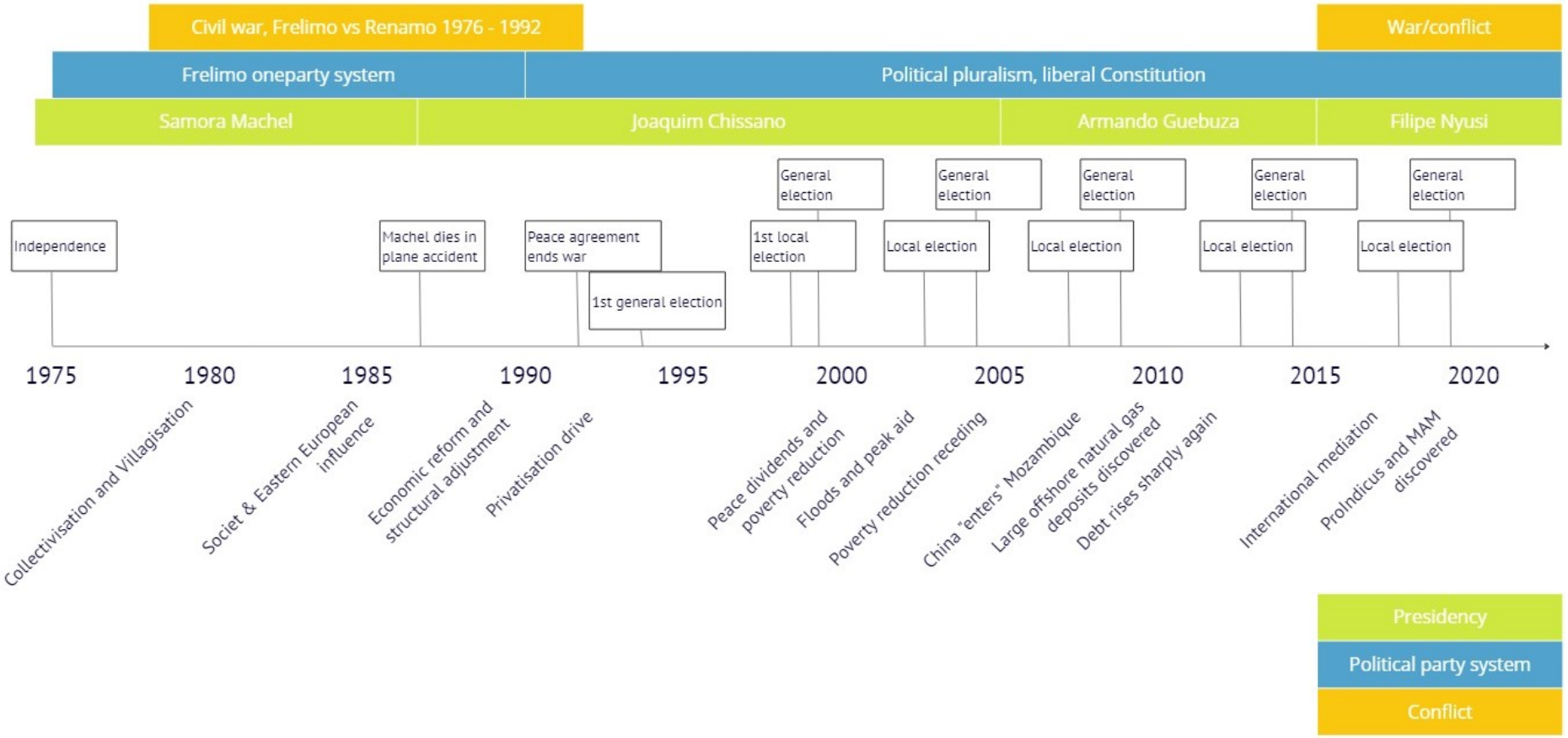
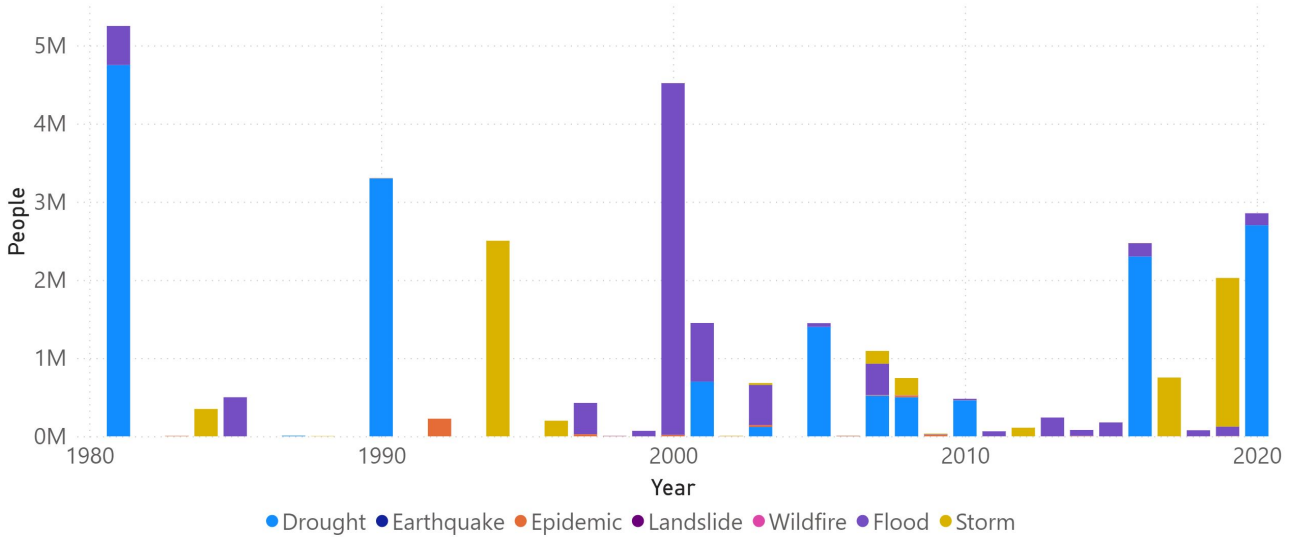


Figure 1.5: Key Natural Hazards [28]



of malaria and HIV, Acquired immunodeficiency syndrome (AIDS) in the world [346]. Further to that, internal migration due to natural hazards and violence has led to severe cholera outbreaks, especially during the hot and rainy seasons [418]. Surveillance data for NCD in Mozambique are sparse. However, regional surveillance data indicates a surge in NCDs due to the increasing incidence of risk factors, e.g., unhealthy diets, reduced physical activity, hypertension, obesity, diabetes, dyslipidaemia, and air pollution [38]. It is likely that Mozambique is following this trend. Weak surveillance systems are argued to slow down the development of policies for diseases such as cancer [240]. Yet, a recorded increase in human resources for health since 2016 indicates some progress [151]. But the estimated average number of health workers of 88 per 100,000 in 2018 [151] is still considered critically low by the WHO [413].

Health policies, health promotion, and supervision of national health sector activities are defined at the central level by the MoH [14]. However, the engagement of provincial and district-level stakeholders in policy development and health promotion has also been observed more recently [14, 363].

Financing of the healthcare system follows a top-down hierarchical approach from the central to provincial levels. The flow of financial and in-kind resources through these levels is presented in Figure 1.2. Notably, a majority of funding for public health programmes goes to North American non-governmental organization (NGO) [327]; conditionalities and austerity programmes

set out by donor organizations, and specifically the International Monetary Fund (IMF) have crippled the progress of Mozambique's national health system, e.g., through limitations on state budget growth [327].

With the aim to reduce child mortality and morbidity through the provision of immunisation services at all levels, the EPI, locally known as Programa Alargado de Vacinacao (PAV) was introduced by the Ministry of Health in 1979. The programme receives funding from various stakeholders, with the most prominent one being Gavi. This public–private global health partnership funds 64% of the EPI; 36% of funding is provided by the government of Mozambique [88]. The immunization service is part of the primary health service in Mozambique and is provided through health facilities and outreach services [88]. By 2019, all recommended childhood vaccinations had been adopted into the national routine immunisation schedule [88].

1.4.4 Country selection

Mozambique was strategically chosen for this research due a window of opportunity and national interest in the research. Initially, the researcher set out to work with stakeholders in Pakistan, India, Nigeria, and Ethiopia, which the VIMC proposed. However, due to the COVID-19 pandemic, stakeholders in these countries were not approachable for this research. Thus, the focus of the research pivoted to Mozambique, as at the time of the study's conception (December 2020), the HPV vaccine policy development and programme planning were ongoing and the country was not (yet) affected by the COVID-19 pandemic. Thus, the research team thought it would be possible for most of the data collection to be done in person. A perfectly placed partner, CISM was identified as a collaborator. There was mutual interest in the collaboration. The Mozambican research institute saw particular value in the research question as they are core evidence producers in Mozambique and collaborate with the MoH. They have significantly contributed to evidence development for the HPV vaccination programme. Further, through CISM, identifying and reaching out to a wide spectrum of stakeholders would be possible.

Chapter 2

Theoretical perspectives on evidence-informed decision-making in the context of vaccine introductions

2.1 Preface

This thesis explores EDU at different levels in public health systems (global to national level), with the foci of analyses varying by type of evidence (from burden of disease and vaccine impact estimates to uncodified policy and programme learnings). The research approach, including the assumptions made, research questions investigated, analyses conducted, and framing of findings, was informed by the knowledge translation literature.

As such, the next section begins with explaining the origins and meanings of evidence and evidence-informed decision-making. The review draws on theories from various disciplines in which knowledge translation has been researched, including public health, and political science. Then, frameworks that conceptualize the meanings of using evidence, i.e., how evidence can inform policies and programmes, are summarized with reference to Weiss' foundational knowledge translation framework. Weiss' framework was used for analyses presented in Chapters 3 and 4. Following, evidence-informed decision-making concepts are discussed in view of public health policy perspectives. Then, knowledge translation interventions are discussed. With respect to the focus of this thesis, chapter concludes with a section presenting a review of the literature on what evidence is used in vaccine introductions, and a section on how evidence

from mathematical models is defined and what evidence from mathematical models may be useful.

2.2 The origins and meanings of evidence and evidence-informed decision-making

The movement around knowledge translation in policy was born out of the field of evidence-based medicine (EBM), in which the focus is on optimising clinical care for the individual patient. The underlying motivation in EBM is that scientific, empirical evidence on interventions replaces tradition, anecdote, and theoretical reasoning [170]. Evidence of generalizable cause-and-effect relationships is sought for decision-making in clinical settings [364]. In this discrete decision-making context, randomized controlled trials, systematic reviews, and meta-analyses are considered the gold standard as evidence, sitting at the top of the 'hierarchy of evidence' [318, 364]. Such research is characterised by its robustness, which is achieved through large and representative sample sizes, control for experimenter and participant bias, control for external variables, and value-neutrality [260, 319]. As a result, such experimental pieces of evidence demonstrate 'what works' [277]; EBM is built on the premise that the volume of evidence leads to an increased likelihood of its use [318]. Based on the hierarchy of evidence, various frameworks have been developed. To name a few, these include the UK's National Institute of Health and Care Excellence (NICE) grading framework used for recommendations of interventions, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria to evaluate biomedical evidence [168], and the Strength of Recommendations Taxonomy (SORT) [123]. Across all of these frameworks, non-experimental research receives the lowest grading. Further, the concept of appraising and synthesizing evidence systematically has been institutionalised through organizations such as the Cochrane Collaboration, which, based on systematic literature reviews, sets global standards for developing and updating clinical practice guidelines [186].

The interpretations of 'evidence' and 'evidence use' are broad and subjective, inherently subject

to social construction [318]. Therefore, they should be unpacked and operationalized in research [280]. With respect to the Aristotelian framework on types of knowledge, evidence can be categorized as 1) *episteme* (facts or explicit knowledge, including notably research evidence), 2) *techne* (skill or practice), and 3) *phronesis* (situation-specific practical wisdom) [104, 171]. This broad epistemological framework appreciates that research is only one form of evidence, and evidence is one source of knowledge [277]. For example, "lived experience", in combination with other forms of evidence, has been identified as a significant contributing piece of evidence to decisions [185]. Depending on the context, other forms of relevant evidence can include surveillance data, personal experience, clinical expertise, or other informal knowledge [281].

Further, rather than implying "evidence use" to be dichotomous, i.e., 'used' versus 'not used' or 'taken up' versus 'not taken up', in reality, evidence use is on a spectrum [318]. As stated by Nutley et al.: 'Policymakers say that while research is often interesting and helpful... it most often "informs" policy rather than providing a clear steer for action' [277]. Among others, evidence can be developed or used:

- To generate knowledge on the effectiveness of a solution, e.g., [12]
- To prompt attention and exhort an appropriate response [63]
- To exercise power [62]
- To deprioritize issues by portraying them as technical and/or resolvable via evidence
- Anecdotally to demonstrate success
- To understand what is feasible [1, 169]
- To help clarify the aims of policymakers
- To measure how well policy is working
- To evaluate pilot projects [324]
- To legitimise political actions [316]
- To make decision-makers sound more authoritative or credible [316]

Thus, in recognition of the unlikely case that political decisions are based on one particular piece of evidence, scholars have advocated for the term 'evidence-informed decision-making' in which knowledge translation from science to policy takes place. A commonly cited definition of

knowledge translation, initially proposed by the Canadian Institutes of Health Research, is "the exchange, synthesis, and ethically sound application of knowledge - within a complex system of interactions among researchers and users - to accelerate the capture of the benefits of research for [citizens] through improved health, more effective services and products, and a strengthened health care system" [19]. The principle idea is argued to date back to as far as Aristotle, who put "forward the notion that different kinds of knowledge should inform rulemaking" [318]. Today, various synonyms for and derivations of knowledge translation exist, including research transfer, knowledge transfer, knowledge-to-action, evidence-based action, evidence-informed action, and knowledge utilization.

Similar to decision-making in clinical settings, public health policy decisions should be informed by evidence on what works, as demonstrated by research, rather than relying on decisions justified by ideology, political or moral beliefs, or tradition [270]. Despite also striving for health and welfare of society, evidence-informed public health policymaking is qualitatively different to EBM [41, 217]. As described by Easton, political processes are subject to the "allocation of social values and relative weights to multiple social, political, or economic concerns" [319]. Public health policy decisions are subject to a myriad of questions, posed by a variety of stakeholders [326], with varying understandings and interests of the policy instrument in question. Respectively, Pettricrew and Roberts [326], and Parkhurst [319] argue that the relevance of a type of evidence (and scientific research) is determined by whether it answers the decision-maker's question (evidence appropriateness). WHO's Evidence-Informed Policy Network (EVIPNet) summarized common research questions and appropriate research methods to answer these based on preceding research and the GRADE framework [283]. The framework appreciates the breadth of questions that could be addressed with observational studies, experimental studies, qualitative research, and systematic reviews. For example, surveys, an observational study, and qualitative research are considered more suitable to explore the satisfaction of users of an intervention. Yet, again, across all other research questions, systematic reviews are considered the 'best' evidence.

As opposed to the dyadic knowledge translation in clinical settings (from healthcare provider to healthcare recipient) (EBM), policy development is defined by the involvement of multi-

ple stakeholders, diffused authority, institutional hierarchies, vested interests, and partisan considerations [144]. In this context, knowledge translation is more likely to be conceptual, incremental, and non-specific [280] than attributable to specific evidence as observed in clinical decision settings. An important step to move "beyond oversimplistic treatment of evidence use is to understand the different interests of stakeholders holding varying power and influence over a given policy decision" [316].

Stakeholders engaged in health policy can include policymakers at different ministries (e.g., health, finance, or education), research groups, organizations in the third sector (e.g., NGO), population groups that are affected by an intervention or policy, pharmaceutical companies, donor organisations, knowledge brokering organisations [243] and other types of businesses [148]. These stakeholders have different interests, assume different positions, and exhibit varying degrees of power in the policy environment around public health policy development [23]. This diverse network of actors can be described as an 'issue network', a term coined by Heclo's research [213]. An issue network is formally defined as "a shared knowledge group that can be populated by a wide and unpredictable number of actors who are devoted to the issues and not each other" [385]. Specifically, an issue network describes stakeholders who are devoted to the issues and not each other [385].

2.3 Frameworks of evidence-informed decision-making

In the knowledge translation literature across multiple disciplines, various frameworks have been conceptualized to make sense of the different aspects of the process of EDU [20, 48, 87, 198, 216, 229, 238]. These have been compared and synthesised in systematic reviews [44, 180, 289, 388]. Most of them are adaptations of the fundamental theory of knowledge utilization by Weiss, who outlined different routes by which evidence use can occur [406]. These routes (also referred to as explanatory models) can be ascribed to three overarching categories of evidence use: instrumental, conceptual, and symbolic [409] (Table 2.1). Weiss' framework was chosen to be used for this research as it appreciates the spectrum of 'evidence use'; more recent

Table 2.1: Definitions of explanatory models to evidence use. Previously published in [97].

<table>
<tr><th colspan="2">Instrumental</th></tr>
<tr><td colspan="2">Instrumental evidence use describes the production and use of evidence in a linear process. This type of evidence use assumes the most rational approach [386]. Scientific evidence is assumed to be instructive to the decision such that the impact is concrete and visible [277]. Evidence use falls under the instrumental use category when decisions are based on evaluation results [386].</td></tr>
<tr><th>Knowledge-driven</th><th>Problem solving</th></tr>
<tr><td>• Evidence leads policy and decision-making.
• New technologies or innovations that result from scientific evidence are adopted by decision-makers.
• Evidence producers “push” their evidence towards the decision-maker. As a result, new policies emerge.</td><td>• Evidence aims to reduce the decision-maker’s uncertainty around a specific problem by suggesting a specific solution [277].
• Decision-makers consult evidence when needed (research antedates the problem), or evidence producers are commissioned by evidence consumers to find solutions to problems [277].
• The policy goal is pre-determined [277].</td></tr>
<tr><th colspan="2">Conceptual</th></tr>
<tr><td colspan="2">Evidence influences actions, but in less specific, more indirect ways. Research evidence permeates the action generation.</td></tr>
<tr><th>Enlightenment</th><th>Interactive</th></tr>
<tr><td>• Evidence use happens incrementally, leading to changes in the status quo in light of political realities as well as other factors and sources of evidence.
• Evidence may be used indirectly [277].</td><td>• An advancement of the enlightenment model, giving rise to disorderly interconnections, networks, and relationships among stakeholders to enable the understanding of different paradigms and viewpoints.
• Continuous back-and-forth among stakeholders [277].
• Recognition of decision-making processes being complicated as stakeholders have different experiences with the evidence and diverging political insights, pressures, and judgements [415].</td></tr>
<tr><th colspan="2">Symbolic</th></tr>
<tr><td colspan="2">Evidence is used to legitimize and support existing positions by evidence users. Evidence is used as ammunition to support predetermined positions or to delay decisions strategically.</td></tr>
<tr><th>Tactical</th><th>Political</th></tr>
<tr><td>• The evidence is not necessarily used as intended by its producer [406].
• The fact that evidence is being produced is used as a supporting argument by organizations for their responsiveness to an issue.</td><td>• The evidence consumer is uncontested and pre-determined [407].
• Evidence is used to support the decision-maker’s standpoint.</td></tr>
</table>

frameworks and theories were revisited to interpret the findings of each chapter. Notably, the models discussed in the following sub-sections are not specific to policymaking. They have also been used to research phenomena such as action generation in organization science [36].

Instrumental forms of evidence development and use

Instrumental evidence use follows a rational, prescriptive and systematic approach [6]. This form of EDU is most positivist. Instrumental evidence use can be described with the problem-solving model and the knowledge-driven model.

Knowledge-driven model. In this model, problems are identified through research evidence and then receive political attention. Based on natural science, this model suggests that research drives policy linearly. As such, this model is most likely to be applicable in clinical settings, e.g., in the development of clinical practice guidelines.

Problem-solving model. A specific piece of evidence is applied to a pending decision [406], which would not have been made otherwise [10]. For example, specific pieces of research may be commissioned to find a solution to a problem or an answer to a question.

Both of these models have been criticized for being overly simplistic as they do not account for the wide range of other factors that influence decisions, especially in the context of public health (e.g., social values and economic considerations) [10]. Thus, they are generally unlikely to be applicable to describe EDU in isolation. Moreover, these two models are based on the assumption that evidence, especially evidence from scientific research that was produced using rigorous methods, is objective and therefore presents the best solution to a problem. This assumption presupposes appropriate synthesis of evidence, e.g., through meta-analysis, when evidence is being used. This time-intensive process is unlikely in the context of policy decisions, which often need to be made at a fast pace within political windows. Further, much of the information that may be relevant for public health, e.g., surveillance data, is social science, i.e., it is abstracted through subjective interpretation [153]. Evaluating the robustness of such evidence can be particularly challenging. Grimshaw et al. emphasise that findings from individual studies may also be misleading due to random variation and the higher potential for

bias in their conduct [173].

Conceptual forms of evidence development and use

Conceptual evidence use can be described with the enlightenment [399] or the interactive model [180]. Within the category of conceptual evidence use, decision-makers consider multiple sources of evidence and other contextual factors that could impact the decision [399]. This reflects the complexity of decision-making processes, arguably more realistically. In this model, EDU are not bound to a linear but a dynamic process.

Enlightenment model. In the enlightenment model, evidence 'creeps' into decisions, shaping them incrementally over a longer period of time [339]. Thus, evidence may indirectly shape (and change) the status quo and lead to a change in perceptions. The use of evidence may be observed as a more subtle form of deliberation. Scholars consider this model to be more realistic than instrumental forms of evidence use in that it considers various pieces and types of evidence to be influential on decisions [48]. As opposed to naïve perspectives of political decision-making contexts, which assume narrow views of gold standard evidence [280], this model appreciates that various forms of evidence can be mutually informative and relevant for policy development and programme planning and concurrently mobilized [3, 40, 104, 180, 182].

Interactive model. This model is an extension of the enlightenment model in that it is based the same assumptions but, more specifically, focuses on the existence of collaborations among stakeholders [406].

Symbolic forms of evidence development and use

Lastly, symbolic evidence use can be further described through the political model or the tactical model [180].

Political model. In the political model, evidence is used as a supportive device for a position that has already been taken. Decision-makers use evidence selectively and strategically for decisions that have already been made. Evidence is used to support an argument, for example, by demonstrating benefits or success in other contexts.

Tactical model. In the tactical model, the content of the evidence is negligible, as the fact that scientific research is being conducted in the field is used as an argument. Thereby, the lack of evidence may be used as a means to buy time and deflect criticism.

Research on knowledge translation and its various derivatives in different fields has been challenged on theoretical underpinnings, assumptions, methods, and focus [280]. Firstly, critical policy scholars have lamented that analyses of knowledge translation are mostly divorced from the inherent features of political processes and political realities [69]. Oliver et al. [280] critique that research and policy processes are rarely made explicit. Rather than focusing on moments in the policy development process when researching knowledge translation, the process as a whole, beginning with the inception of a research idea, should be considered. Further, the use of evidence may be observed throughout the entire process of policy development and implementation [318].

Public policy theories, frameworks, and approaches have been developed to find reasoning for the many meanings of EDU. These include the advocacy coalition framework [157], multiple streams theory, narrative frameworks, punctuated equilibrium theory, social constructivism, and studies of policy transfer or diffusion [403]. These frameworks provide further explanatory perspectives to explain how and when evidence is used. Yet, such theories on the contested nature of policymaking are often not integrated into EDU research, but should contribute to the discussion of EDU research findings [280]. Frameworks such as the narrative policy framework or contribution mapping [215] help explore cognition and emotion, or rational and irrational shortcuts taken by decision-makers in their daily lives and activities that shape policy [63].

Hence, it is worth unpacking narratives of policy development and viewing this as a dynamic process, i.e., a series of actions or decisions taken to achieve a particular end, unfolding dynamically in time. In the interest of understanding the interactions of stakeholders, their ideas, and their interests in a policy environment, the chronology of a policy's development can be systematically unravelled. To structure a chronological analysis, the policy cycle, or stages heuristic, has been adopted as a framework in the literature [52, 225, 398]. With regards to this framework, the policy process can be aggregated into four main stages, each entailing a

number of sub-processes [192]:

1. Agenda setting/problem identification
    - Identifying and defining the problem or issue that requires attention from policymakers.
    - Prioritizing issues based on their significance and urgency.
    - Building support and consensus among stakeholders to include the issue on the policy agenda.
2. Policy Formulation
    - Develop evidence for potential policy options and solutions.
    - Engaging in debates, negotiations, and deliberations to secure support for the proposed policy.
3. Policy implementation
    - Developing detailed plans, regulations, and procedures to put the policy into action.
    - Allocating resources, such as funding and personnel, to support the implementation process.
4. Policy Evaluation
    - Assessing the effectiveness and efficiency of the policy in achieving its intended goals.
    - Collecting and analyzing data to measure the outcomes and impacts of the policy.
    - Deciding whether to maintain, revise, or terminate the policy based on its performance and evolving needs.

While the framework portrays policymaking as a fluid course of action, it has been criticised for being too simplistic and lacking an explanation of what it describes [187]. Nonetheless, the framework is useful as an approach to structuring narratives and bringing order to data [31]. Further, other explanatory theories and frameworks, including the advocacy coalition framework and multiple streams analysis, build on the concept of policy as a process [351].

The literature has presented numerous case studies of how evidence has informed policy [215]. Seminal work by Parkhurst [316–319], Smith [366], Nutley [277], Fafard [144], Cairney [63–69, 77] and other scholars focusing on knowledge translation in public health policymaking has advanced our knowledge of how evidence informs policy in LMIC. Yet, measuring the impact and contribution of science remains a significant challenge. Relevant metrics for evidence contribution to health programmes, policies, and health outcomes have been contested. Thus, frameworks that aim to facilitate the evaluation of knowledge translation are broad and inclusive of the many ways in which impact is manifested. Based on a systematic review of methodological impact frameworks, Cruz Rivera et al. [101] categorize the impact of research evidence across five dimensions: primary research-related impact; influence on policymaking; health and health systems impact; health-related and societal impact; and broader economic impacts. However, most of the metrics proposed to measure research impact in these frameworks are quantitative and often focus on aspects of academic performance rather than its externalities [248, 280]; only a few methodologies, such as 'contribution mapping' [215] rely on qualitative methods, employing a more 'naturalistic approach using empirical methods to study participants *in vivo*' as suggested by Oliver et al. [280]. More recently, Reed et al. summarized, which evaluation approaches and methods can be employed considering the subjective nature of impact [340].

2.4 Knowledge translation interventions

Furthermore, scholars have extensively explored knowledge translation interventions, i.e., the "effort to increase the chances that those who have the power to make binding decisions about public health policy have the opportunity to consider all the relevant evidence" [144]. However, none of the approaches explored in the literature promise the use of evidence to be good [397].

The 'two communities' theory is potentially the first theory that led to a discourse on strategies that can facilitate communication between stakeholders in policy and science [75]. With the aim of bringing stakeholders together, e.g., policymakers and scientists, *push*, *pull*, *exchange/ bridging strategies* have been proposed in the literature [226]. While the 'two communities'

theory has significantly shaped strategies to improve EDU, it has also been criticised for focusing on policymakers and scientists only and presenting them as two monolithic and distinct communities [93]. In reality, the relationship between stakeholders of various types, including non-academic actors as evidence producers and non-traditional actors as policymakers and decision-makers, is fluid and porous.

Push strategies are motivated by evidence producers, e.g., through the dissemination of evidence in accessible formats [173]. Importantly, the communication strategy should be chosen with regard to the target audience. Push strategies can be concrete communication strategies through which science is presented in an accessible format to policymakers (e.g., policy briefs [16]).

Pull strategies are invoked by decision-makers. Such interventions include educational training programmes, such as workshops, and building and institutionalizing capacities to use and appraise scientific evidence.

Exchange strategies are defined by collaborations between evidence producers and consumers. Interventions include interdisciplinary partnerships and networks that bring different types of stakeholders together. Bridging strategies can be facilitated through knowledge brokerage to inform decision options [165] as well as using participatory research methods [227]. Through these approaches, different perspectives aim to be aligned, and the chances that evidence contributes to policy increase [366].

In 2022, a protocol for a Cochrane review, which aims to systematically determine the effectiveness of knowledge translation interventions for facilitating evidence-informed decision-making amongst health policymakers was published [384]. This indicates that best practices for enabling knowledge translation in health policymaking contexts have not been identified.

As part of the knowledge translation intervention research efforts common barriers and facilitators to the use of evidence by policymakers have been identified [105, 281, 289]. As summarized by Oliver et al. [281], knowledge translation is influenced by:

- Contact and collaboration, e.g., relationships between stakeholders

- Organisation and resources, e.g., availability and access to research evidence
- Evidence and evidence producer characteristics, e.g., clarity, relevance, and reliability of research findings
- Policymaker characteristics, e.g., policymakers' research skills
- Policy characteristics, e.g., importance of policy

In Appendix A, Table A.1, facilitators and barriers to EDU that have been identified in literature reviews [105, 281, 289] are summarized.

2.5 Use of evidence in the context of vaccine introductions

From funding for research on a new vaccine to scaling it nationally, regionally, or globally, various types of evidence inform decisions [59, 60, 115]. Multi-criteria decision analysis (MCDA) frameworks provide a structured approach to assessing and comparing the different criteria that are essential in evaluating a vaccination programme. MCDA consolidates codified evidence and takes into account different perspectives. In a literature review, Burchett et al. [59] identified nine broad categories of criteria on which vaccines are evaluated: vaccine characteristics; the importance of the health problem; financial and economic issues; consideration of alternative interventions; the decision-making process; the impact of vaccination; programmatic considerations; acceptability; accessibility, equity and ethics. Additionally, Guillaime et al. [174] identify two further decision criteria: communication and sociocultural considerations. A more recent literature review of criteria that affect vaccine policy decisions [115] showed that, for each one of the broad categories, national frameworks most commonly draw evidence on the burden of disease, vaccine efficacy/effectiveness, vaccine safety, economic evaluation, the vaccine impact on health and non-health outcomes, and the cost-effectiveness of the alternatives.

Vaccines can be evaluated from different perspectives, quantifying health and non-health outcomes. The "Value of Vaccination" framework broadly suggests evaluating a vaccine from (1)

the payer perspective (e.g., health gains for the vaccinated, direct medical costs) and (2) the societal perspective concepts (e.g., indirect health/economic gains to caregivers/households, productivity in vaccines) [30]. Other novel societal concepts (e.g., financial risk protection (FRP), peace of mind, societal health gains, healthcare system security, political stability, social equity, and macroeconomic gains) are also considered relevant broader vaccine benefits that should be evaluated [30]. Wilder et al. [412] point to two key phases in the vaccine development process: the pre-licensure and post-licensure phases. With regard to these phases, what is considered relevant evidence changes. Respectively, the authors argue, the methods for evaluating a vaccine should be adopted. For example, to quantify broader vaccine benefits, Wilder-Smith et al. suggest an Extended Cost Effectiveness Analysis (ECEA) approach. Thereby, outcome- and behaviour-related productivity gains, community health externalities (e.g., improved health outcomes in unvaccinated community members), improved economic outcomes at the household and societal levels, and reduced health system disruption adn impact on other diseases can be estimated [412].

Yet, what Wilder-Smith et al.'s opinion piece fails to address is how the evidence ought to be developed for specific audiences. They mention 'regulatory' decisions, however, it should be explained who the potential evidence consumers are (i.e., the stakeholders that are that are engaged in this decision-making process), and how their evidence needs may differ. Further, Wilder-Smith et al. point to the role of funding organizations (e.g., global health organizations, prominent donor organizations such as the Gates Foundation, and public health agencies) in commissioning evidence development post-licensure. The extent how these organizations use commissioned evidence is yet unknown.

Further, based on empirical research [115], other influencing factors are the political priority of the vaccine introduction, vaccine delivery issues, vaccine supply, funding sources, and the procedures and stakeholders involved in the vaccine introduction.

Despite varying efforts for transparent, evidence-informed and rational decision-making around vaccine introductions, the processes are inherently political. In their systematic literature review, Burchett et al. [59] identified the lack of research on the actual process of decision-

making. Beyond the technical decision criteria, Donadel et al's review [115] identified enabling factors for vaccine-related policymaking, which highlight that vaccine-related policy decisions are subject to social, institutional, economic, and political factors [60, 246]. These include recommendations made by global and national organizations (e.g., WHO, UNICEF, Gavi and National Immunization Technical Advisory Group (NITAG)), country ownership, policy dialogues, public-private partnerships, vaccine introduction processes in place, integration of EPI within the health system, lessons learned from other countries, and immunization law. Burchett et al. conducted one of the first qualitative research studies exploring new vaccine adoption decision-making processes qualitatively across seven LMICs [60]. This research showed that the political decision to a vaccine is mostly motivated by funding opportunities, political prioritization of vaccination and the burden of disease.

Burchett et al.'s and Donadel et al.'s research also points to various actors and initiatives that have been established to support vaccine introductions. To support evidence-informed vaccine policy decision-making in national contexts, NITAGs have been established [361]. Their role in vaccine introductions has been extensively studied in the literature for specific policy instruments and vaccines. NITAGs are mandated to provide independent recommendations to national decision-making bodies. For a specific policy question, a small working group of NITAG members is established and responsible for gathering, analyzing, and preparing information, which is then presented to the wider group for decision-making. Conflicts of interest are possibly unconsciously affecting discussions due to the ongoing working relationships of NITAG members. As these cannot be avoided, the main aim is to manage conflicts of interest in a transparent and ethical fashion.

Additionally, various regional and international initiatives have supported NITAGs, national decision-making bodies and other stakeholders engaged in vaccine introductions by developing evidence in the form of research, guidelines, and in-kind support. Examples include ProVac Global Initiative in the WHO Region of the Americas, established in 2004 and Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative. The SIVAC Initiative has been established with the WHO and other partners [5] to promote, accelerate, and systemize the establishment of NITAGs in LMICs. Moreover, decision support tools are

also available. For example, the SMART Vaccines, which was developed by the US Institute of Medicine, is an online tool that allows to synthesise evidence across multiple dimensions and weight decision-making criteria.

Further, Donadel et al.'s literature review emphasised that the role of Health Technology Assessment (HTA) agencies has increased in importance over the past ten years. HTA agencies evaluate the properties and effects of a vaccine. While HTA agencies can facilitate evidence-informed decision-making (Text box 2.5), they are rarely formally established in LMIC [21, 57, 190], or are currently in the process of being institutionalized, e.g., in Kenya [251].

Text box 2.5.1: Health technology assessments.

A Health Technology Assessment (HTA) aims to support/enable evidence-informed decisions for or against a vaccine introduction. HTAs have been developed on the basis of multi-criteria decision-analysis frameworks and aim to synthesise perspectives on "whether the technology works, for whom, at what cost, and how it compares with the alternatives" [375]. This approach is firmly rooted in research. A prominent example of a HTA agency is the Health Intervention and Technology Assessment Program (HITAP), a semi-autonomous research unit under Thailand's Ministry of Public Health.

2.6 Evidence from mathematical models

The literature review of knowledge translation research has highlighted that various types of evidence are developed for and used in political decision-making. In the previous section, the various types of evidence that play a role in vaccine introductions in LMIC are outlined. However, our knowledge about the development and use of specific types of evidence, such as epidemic models, a specific type of mathematical model, is still in its infancy.

Mathematical models can be used as a method to develop scientific evidence. Broadly, mathematical models are an abstract depiction of a complex system. They can describe the behaviours of components in the system, explain why these occur, and predict future behaviour and re-

sults. In the context of health research, mathematical models can be used to generate and test scientific hypotheses and inform the design of practical strategies. Experimental hypotheses that would otherwise be expensive, difficult, or unethical to explore can be tested efficiently [43]. For example, at a population level, projections of the trajectory of substantial Ebola epidemics in Liberia and Sierra Leone, despite not materializing due to interventions, prompted the mobilization of humanitarian aid [256, 262]. During the H5N1 (avian) influenza pandemic, mathematical models projected the catastrophic costs of failure and prompted investments in containment efforts and antiviral pharmaceuticals globally [150].

""Epidemic modelling" describes a set of approaches where mathematical, statistical, and computational tools are used to study the spread of communicable pathogens in host populations." [368] They can be used to quantify conditions and changes in demographic processes, environmental characteristics, transmission opportunities, health consequences, and mitigation efforts. Various model forms exist; their appropriateness depends on the complexity of the research and/or policy question being posed. *Compartmental models* allow to explore disease transmission dynamics, considering average interactions among individuals that are assumed to be homogeneous. In *static cohort models*, a single cohort, i.e., a closed population, is modelled. Transitions between states are modelled with regards to average characteristics. Transmission risk is not affected by the number of infectious people [204]. *Individual-based models*, or agent-based models, require more data and computing power but allow to account for individual's characteristics [344]. These examples of epidemic models attempt to depict underlying biological or epidemiological mechanisms. Statistical model types, such as regression models in which relationships between variables are explored, may also be useful to research associations between phenomena.

In the context of vaccines, mathematical models can provide evidence for some of the key decision criteria presented in Table 2.2. Different modelling approaches to quantify the impact of vaccination on population health are further discussed in Chapter 6.

2.7 Conclusion

These considerations informed the research approach taken and the knowledge gaps filled with this thesis. Key terms underpinning the research in this thesis are summarized in text box 2.7. The extent to which the findings in this thesis align with the literature and the applicability of frameworks are discussed in each results chapter as the focus of analysis changes throughout the research.

Table 2.2: Vaccine introduction decision categories (adopted from Burchett et al. [59]), criteria (adopted from Donadel et al. [115], example scientific evidence (Ex.), and the type of model(s) used to develop the example scientific evidence.

Category	Criteria	Ex.	Type of model(s) in example
Vaccine characteristics	Efficacy and effectiveness	[131]	Cox proportional-hazards model
	Vaccine safety		
	Delivery issues		
Importance of the health problem	Political priority		
	Costs of disease	[54]	Micro-costing approach
	Perceptions of importance	[416]	Hierarchical linear modeling regression analysis
Financial and economic issues	Economic evaluation	[250]	Various
	Incremental costs	[203]	Cost effectiveess analysis (based on transmission model)
	Funding sources		
	Vaccine price	[228]	Cohort model
	Financial sustainability	[197]	Financial model
Considerations of alternative interventions	Cost-effectiveness of alternatives	[95]	Epidemic models coupled with cost-effectiveness analysis
	Effectiveness of alternatives	[53]	Epidemic models
Decision-making process	Evidence sources and quality of evidence		
	Stakeholders involved		
	Procedures		
	Cues to action		
Impact of vaccination	Impact on health outcomes	[341]	Various
	Impact on non-health outcomes	[332]	Static cohort model and extended cost-effectiveness analysis
	Effects of co-administration		
	Risks of serotype replacement	[404]	Regression analysis
Programmatic considerations	Feasibility		
	Vaccine supply	[96]	Supply chain model
Acceptability	Acceptability of vaccine	[146]	Deep learning model
Accessibility, equity and ethics	Accessibility, equity and ethics	[200]	Epidemic model

Text box 2.7.1: Key terms underpinning this research.

Evidence. With regards to the Aristotelian framework on types of knowledge, the definition of evidence is kept broad throughout the thesis unless otherwise specified. As such, evidence can range from tacit (colloquial) knowledge, such as informal accounts of opinions, to scientific (codified) evidence, such as peer-reviewed systematic reviews. Moreover, evidence can be on a spectrum from sub-national or national to international or global. Sub-national evidence asserts context-specific observations, whereas global evidence is generalized evidence, often presented in the form of guidelines. International evidence refers to evidence sought from a foreign country. National evidence may be an assembly of multiple sources of evidence from one country or evidence covering the entire population of that country.

Evidence use. The meaning of "using evidence" is broad and subjective. Rather than implying "evidence use" to be dichotomous, i.e., 'used' versus 'not used' or 'taken up' versus 'not taken up', in reality, evidence use is on a spectrum and can be described using explanatory models as summarized by Weiss [406] and other scholars (Table 2.1).

Evidence development. Evidence development refers to the process of generating and gathering information, data, or knowledge to support or validate a claim, hypothesis, or decision. It encompasses intentional and commissioned efforts where individuals or institutions actively seek to explore and document evidence to address specific questions or objectives. Additionally, evidence development can occur unintentionally, such as through informal learning or exploration, without a deliberate documentation process. It can also stem from academic curiosity, where researchers or scholars engage in rigorous investigation to expand existing knowledge. Evidence development can take both systematic and non-systematic approaches, with the former emphasizing structured methodologies and rigorous data collection, while the latter may involve more informal or ad hoc methods. It can be carried out by individuals or institutionalized within academic institutions, as well as government bodies, reflecting diverse settings where evidence is sought and cultivated.

Mathematical models. Mathematical models are a tool to develop evidence. Specifically in the context of infectious disease epidemiology, epidemiological models can estimate the spread of infectious diseases in a given population and quantify the number of lives saved or deaths averted through public health interventions. The estimated number of cases and deaths due to a disease can be used to derive other generic metrics, e.g. disability-adjusted life years.

Chapter 3

Evidence development and use at the global level: mathematical models

3.1 Preface

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This chapter, which is the first results chapter, explores how a specific form of evidence, burden of disease and vaccine impact estimates are used by stakeholders at the global level that commission this type of research and what actions are generated following the commissioning of evidence production.

3.2 Methods

The research in this chapter was informed by a conceptual framework, which addresses possible types of evidence use throughout different organizational processes [36]. This conceptual framework is rooted in organization science, particularly derived from Beyer and Trice's comprehensive examination of research utilization in organizations [36]. I explicitly focus on the organizational process of action generation. Within the action generation process, evidence utilization aligns with Weiss' three overarching categories: instrumental, conceptual, and symbolic [409]. Chapter 2 provides an in-depth

exploration of these categories, further summarized in Table 2.1. Importantly, the models of evidence utilization complement one another rather than present contradictions [10].

I conducted in-depth, semi-structured interviews to explore how global burden of disease and vaccine impact estimates are used by global health organizations as recommended by Hanney et al to study research utilization [180].

Beyer and Trice identify two primary stakeholder categories involved in research utilization: those who generate evidence (evidence producer (EP)) and those who consume it (evidence consumer (EC)). In the context of this study, individuals specializing in mathematical modeling, specifically commissioned to produce global burden of disease and vaccine impact estimates, assume the role of EP. Producers were initially identified as individuals, who are specialized in the mathematical modelling of a vaccine-preventable disease and were commissioned to produce the specific type of research evidence, global burden of disease and impact estimates by global health organizations.

On the other hand, EC are employees at global health organizations responsible for commissioning research, aiming to guide global resource allocation decisions and strengthen global immunization strategies. Consumers were initially identified by researching profiles of individuals employed at global health organizations that grant funding to EP and provide donor assistance for health to countries to support global vaccination initiatives. Notably, EC do not need be the ultimate decision-makers; instead, they may occupy various positions along the path from receiving evidence to disseminating it to higher-level decision-makers within the organization, such as board members overseeing organization-wide decisions. This nuance is significant, considering previous research indicating that decisions are seldom the sole prerogative of a single individual [235], and individuals often do not perceive themselves as ultimate decision-makers [405].

I acknowledge that line between EP and EC is blurred [366]. Frequently, individuals in the role of consumers may have previously served as producers in their past professional roles or may concurrently function as EP within their current organizational positions. Consequently, I attribute the informant's classification to the organization where they are currently employed at the time of the interview. It is acknowledged that the production of burden of disease and vaccine impact estimates may also occur within the organizations where EC are employed. To address this, I specifically inquired with informants about the utilization of globally commissioned burden of disease and vaccine impact estimates intended for external audiences.

Data were collected from purposively sampled individuals between March and September 2020. Snowball sampling was employed to broaden the study's participant pool, encompassing individuals who met the specified eligibility criteria but had not been previously identified. All interviews were conducted through the telecommuting platform Zoom. Prior to each interview, informed consent was secured from every participant. The interviews followed a pre-written interview guide with open-ended questions (Appendix C), with further questions introduced as needed to elucidate information or delve deeper into specific topics. Recordings of the interviews were made, and intelligent verbatim transcripts were generated from the audio files. All study participants' identities were pseudonymized to ensure confidentiality. The storage, organization, search, and coding of the transcripts were performed using NVivo 12 Pro [335].

The data were analyzed using the Framework method developed by Ritchie and Lewis [343], allowing for the comparison of pre-defined study population groups [158]. Emergent themes were identified through initial coding. Initial coding was succeeded by focused, selective coding borrowing concepts from the theoretical framework following a deductive approach. The information was aggregated by theme and sub-theme with respect to the two pre-defined study population groups. The approach allows to explore the specific use cases of evidence, while leaving space to discover unexpected or further emerging themes and relate findings to organizational theories and processes.

The results focus on how global burden of disease and vaccine impact estimates are used and what actions are generated by GHO as a result of receiving this evidence, with respect to the research utilization spectrum and associated explanatory models and draw upon key themes identified in the analysis.

Ethical approval was obtained from Imperial College London (ICREC reference: 20IC5841) (Appendix B).

3.3 Results

A total of 21 potential participants were approached for the study. Out of these, two individuals declined to participate, and six individuals did not respond. The interviewees consisted of seven EPs, including six epidemiologists and one health economist. Additionally, there were six ECs, comprising

of four senior programme officers, one team lead of the department of immunization, and one medical epidemiologist in the same department. All the EPs held positions as postdoctoral fellows, assistant professors, or professors. The ECs had qualifications such as PhDs (n=4), Master of Science (n=1), Master of Public Health (n=1), and/or medical doctor (n=2). The interviewees were primarily based in Europe (n=5) or North America (n=7), except for one EP who was located in Asia.

3.3.1 Instrumental evidence use

The concept of instrumental evidence use refers to the structured creation and application of evidence in a sequential manner, suggesting that burden of disease and vaccine impact estimates would directly impact a decision or serve as a remedy for a particular issue. Following this viewpoint, there was a consensus and critique among those who produce and utilize evidence that the generation of burden of disease and vaccine impact estimates is determined by ECs, who explicitly establish research priorities by providing funding for specific forms of evidence. However, no explicit connections could be found between specific research findings and decisions made by GHOs.

Knowledge-driven model

In order for this framework to be applicable, the generation of research evidence that is intended for use by consumers of evidence should be motivated by academic curiosity. EPs and consumers agreed that this is rarely the case; however, opportunities exist for more of the processes along the evidence use route to be more knowledge-driven.

Setting the research agenda

An EP emphasized that it should be their responsibility to take the lead in determining 'what should be done' that would be of value to ECs. Consequently, research priorities should be established for each pathogen and for multiple mathematical models pertaining to the same pathogen. The interviewee described the research agenda as being determined by ECs:

> EP: "We aren't answering any questions about really what is actually happening at the policy level whether it is country-level policy and decision-making or global [...] level decision-making. [...], we are handed the demographics, we are handed the coverage

> assumptions and it is just running it through a population [pathogen] model, by age and time, to say what the impact of those assumptions would be. We are not really doing anything in terms of the research agenda" [133].

Changes in evidence production

Both ECs and EPs expressed their disagreement with following the knowledge-driven route to evidence use. Informants emphasized that making changes to well-established mathematical models can pose a hindrance to the utilization of evidence. One EC specifically highlighted this concern:

> EC: ".... for the most part, we are always a little cautious about dramatic changes in models because we're really trying to translate observed changes in coverage, which is what [a GHO] has been investing in and understanding what that means for deaths averted [rather than] new modelling assumption" [124].

Furthermore, EPs [134, 139] mentioned the delicate balancing act of responding to specific commissions for prescribed global burden models while simultaneously seeking funding for models driven by their personal academic interests related to knowledge gaps and advancements in methodologies:

> EP: "It's sort of a little like a chicken and egg thing, I think. Like, you want to have those discussions, but [...] I think people don't feel that they should give you the time, or why would they give you the time if you haven't done some work already?" [134].

There was a consensus that a linear evidence production and consumption process, when initiated by EPs, is rare and unrealistic due to their hesitance towards innovation and embracing changes in evidence. A linear evidence production and consumption process would imply changes in evidence are not questioned further by evidence consumers.

Problem-solving model

During the interviews, participants discussed certain principles of instrumental evidence use that align with the problem-solving model, albeit indirectly. This is achieved through the practice of commissioning EPs and establishing specific deliverables through contractual agreements.

Evidence use through the commissioning of research

Both EPs and consumers emphasized that evidence production is primarily driven by ECs, who commission and fund the production of evidence. As a result, ECs are seen as having a significant influence on evidence production, shaping its direction and structure [127]. They have the power to predefine research questions and act as "technical agencies" that determine the research agenda, as mentioned by one of the interviewees:

> EC: "When you, as an academic institute get funding, you will not argue with your donors, which are funding you. So, you follow the donor, you follow the money. [...] [The funding organizations] are not only funding, they are doing more and more technical assistance, they are very much involved in the model set up, in everything from contracting to implementing" [127].

Another concern raised by an EP is that the research agenda and problem definition are determined by ECs. Grant deliverables, which set the research agenda, are established in advance, while discussions regarding progress, goals, and activities take place [139]. Both EPs and consumers acknowledged that this approach overlooks the expertise of the EP, who often have a better understanding of what areas require further research [127, 134]. However, an EP highlighted the importance of commissioned research being the outcome of discussions in order for the evidence to be considered "usable" by decision-makers:

> EP: "I'd say that the questions need to be applicable, usable, and so [the decision-makers] very much should be in the discussion of setting those questions" [138].

It is evident that the interviewee recognizes the importance of increased interaction among stakeholders, as emphasized in the interactive model (section 3.3.2).

Problem-definition

The questions posed by decision-makers when commissioning research may not necessarily be the 'right' questions or lead to decisions that are 'right' [134]. An EP expressed concerns that when aggregating the impact of all mathematical models and projecting results on a global scale, insufficient attention is given to specific national and sub-national questions. For instance, assumptions that all children who receive the first vaccine dose will also receive the required second dose can result in misleading outcomes [133].

3.3.2 Conceptual evidence use

In the following subsection, I explore how evidence indirectly influences actions, resulting in gradual changes in the knowledge, understanding, and/or attitudes of ECs through the utilization of burden of disease and vaccine impact estimates.

Enlightenment model

As per the interviewees, evidence gradually shapes the organizational agenda over time. The understanding of which vaccines have the most impact becomes deeply ingrained in people's knowledge, as they have encountered these estimates on multiple occasions [125]:

> EC: "Our management isn't using the numbers in a one-to-one way to make trade-offs. But it's more that this is really foundational information for us to understand what the most important areas for us are to invest in. And then that drives more on an underlying fundamental basis, what we invest in immunizations" [125].

Another EC highlighted that the evidence is not used at a high level by decision-makers to understand details of the impact of pathogen-specific interventions that are modelled mathematically (e.g., which age groups are affected or the specific immunity gaps within countries) [128].

Additionally, investment decisions made by an organization's management have an impact on the work carried out by all other departments within the organization [125]:

> EC: "So [burden of disease and vaccine impact estimates are] not the only thing that we would factor in, but it would be something that helps us to prioritize which countries we will most focus on investing in. And then that trickles down to all the rest of our work" [125].

Consequently, research evidence is gradually and subtly influencing decisions, aligning with the principles of the enlightenment model of evidence use. The relevance and applicability of the enlightenment model are further examined in specific sub-themes.

Argument generating evidence

One of the sub-themes associated with the enlightenment model in relation to evidence use is that evidence often leads to the generation of arguments. The interviews conducted in this study revealed several recurring questions posed by ECs after receiving burden of disease and vaccine impact estimates, as presented in text box 3.3.2. The presence of argument-generating elements in the evidence utilization process suggests that social interaction is essential for facilitating the use of evidence in generating actionable outcomes (further discussed in section 3.3.2). If the evidence fails to support the beliefs of the EC and unanswered questions persist (e.g., those listed in text box 1), the EC tends to perceive the evidence itself as the problem [129, 139].

According to interviewees' accounts, the dissemination of burden of disease and vaccine impact estimates is often formally set out through reporting channels. This poses a challenge to the applicability of the enlightenment model, which characterizes the process of evidence dissemination as unguided and indirect. The existence of tools for disseminating evidence implies a more guided process of evidence use. However, the presence of argument-generating questions suggests that understanding evidence cannot always be facilitated solely through these means.

Interactive model

Relationships among stakeholders

Social interaction plays a crucial role in enabling evidence to be produced in an iterative process that aligns with the information needs of ECs [127]. Consequently, it is important to involve ECs in the early stages of evidence development, including the establishment of the model structure and the

definition of desired outcomes [127, 128]. Furthermore, social interactions are essential for addressing questions, such as those outlined in text box 3.3.2.

Text box 3.3.1: Argument generating questions oftentimes posed by evidence consumers after receiving burden of disease and vaccine impact estimates

EC: What are the mathematical model differences in comparison to the previous year or reporting period? [126]

EP: How well has the model done at predicting things that we know have happened in the past? Why are model estimates not meeting the consumers' expectations? Can estimates be trusted? [136]

EC: What explains changes in the mathematical model which affect the estimated impact? [124, 126]

EC: Do we believe that these are good changes or are they going to end up going the other direction the next year when the modellers update their assumptions again?' [124]

EC: Is a change in burden of disease and vaccine impact estimates the result of something that happened in the world? Did the coverage decrease? Did the production not happen? Did something in the model change? Did the understanding of the epidemiology of a pathogen evolve? [125]

EC: What drives differences in impact estimates from different models? [125, 126]

EC: Are the multiple models valid for the same pathogen? Is there an error in one of the models? [125]

EP: What can models do and cannot do? What improvements may be needed? With the aim of eliminating specific diseases, how does the mathematical model need to be aligned or changed? [133]

EP: What is the population level impact that go beyond direct protection (herd immunity effect) in lower income settings where data is limited? [137]

EC: How can estimates be additive in terms of not just using them in a vacuum, but using them to better understand and validate admin data estimates that come out? [128]

EP: How do you interpret the relative contribution of different source of vaccination to the overall burden? I.e. routine immunization programs (multiple doses), pulse national campaigns or national or subnational campaigns, outbreak response. [135]

EC: What are the assumptions around the treatment for a disease? [124]

Both EPs and consumers have emphasized the importance of interactions in various aspects of evidence utilization. These interactions are necessary to ensure a clear understanding of the research possibilities, limitations, and caveats of the evidence, as well as to allow ECs to provide improvement suggestions [133]. Longstanding relationships between stakeholders contribute to smoother transitions when evidence evolves over time, particularly if new conclusions differ from previous ones and require reallocation of resources [135, 139]. Changes in mathematical models and evidence supply are crucial

discussion points in interactions between EPs and ECs. Over time, established foundational knowledge held by ECs may be challenged if new evidence fails to meet their expectations [136]. Lack of relationships can pose challenges in obtaining buy-in from stakeholders to utilize the evidence effectively [134, 139].

Overall, there is a consensus among EPs and consumers that the interactive model should be adopted as the framework for evidence utilization. However, it may not fully explain the current state of evidence use within stakeholders' organizations. Interactions, particularly in the early stages of evidence production, are crucial to ensuring that evidence, along with its limitations and caveats, is understood, thus promoting its utilization and preventing it from being ignored by ECs.

3.3.3 Symbolic evidence use

In the symbolic evidence use category, which stands in stark contrast with instrumental evidence use, evidence is strategically employed to justify decisions that have already been made. The symbolic use observed in this study corresponds to the political explanatory model, wherein evidence is utilized to reinforce the stance of the evidence user. None of the participants mentioned the tactical model, in which the mere existence of research being conducted is employed in the actions of evidence users.

Political model

An EC interviewee refers to 'meta-questions', which should be addressed by EPs [128]:

> EC: "But [EPs are] answering kind of a more existential question rather than a specific programmatic question" [128].

Probing revealed that evidence derived from mathematical models primarily serves strategic thinking and planning purposes [126]. Additionally, it is used for accountability and advocacy when engaging with external funding partners of ECs [124, 138]. Burden of disease and vaccine impact estimates play a crucial role in securing funding for subsequent rounds from donor partners [124]:

> EC: "The impact numbers are probably the most important numbers that we use for replenishment efforts and for reporting to donors, so for high-level kind of accountability"

[124].

Sometimes, evidence is used for framing the setting or as contextual information for anyone trying to make the case for why the organization should invest in a particular project over another one [125]. Evidence on vaccine impact comes into play when someone needs supporting evidence for their argument [125] or to track the organizations' progress [128].

One EP pointed out that despite significant variations in estimates from different models for the same pathogen, the main conclusions remain consistent [136]. Specific details about burden of disease and vaccine impact estimates are of less interest to ECs [127]. Instead, ECs focus on the overall direction of impact to support their arguments [127].

Overall, the political model best describes the use of evidence once it has become ingrained in the understanding of decision-makers and the organization's agenda. ECs agree that research evidence is often used to inform and communicate targets to donors and to support an argument when wanting to receive more funding. However, EPs did not provide any information indicating the applicability of the political model.

3.4 Discussion

This chapter aimed to examine how global burden of disease and vaccine impact estimates are utilized by GHOs to strengthen global immunization programmes. The findings indicate that burden of disease and vaccine impact estimates are not directly translated into the actions of GHOs, specifically in terms of vaccine resource allocation decisions. Instead, these estimates are used for accountability purposes and to solicit funding from external partners. While burden of disease and vaccine impact estimates partially influence the actions of GHOs, the evidence is primarily used in an anecdotal manner.

In terms of the conceptual framework used in the analysis, both the conceptual model and the political model best describe how evidence is utilized by GHOs. Previous studies have shed light on evidence use in various contexts, such as maternal and child health [389] and drug policies [269]. However, this study is the first to focus on the use of global epidemiological and economic research commissioned by GHOs from an organizational science perspective.

GHOs operate in a competitive environment [261], with IOs primarily reliant on fulfilling their mandates for support, while philanthropic organizations are less dependent on donor partners [55]. Burden of disease and vaccine impact estimates serve three purposes in this context: validating short-term funding objectives, strategically planning mid- to long-term actions based on potential global health impact, and securing financial support from donor partners. Donor partners assess the impact of their budget allocations through initiatives like the Multilateral Organizations Performance Assessment Network [261]. Therefore, GHOs invest heavily in commissioning research evidence, such as burden of disease and VIE, to demonstrate their impact and gain support from donors.

Burden of disease and vaccine impact estimates also play a role when individuals within the organization require supporting evidence for their arguments. As GHOs are political organizations with multiple stakeholder groups and potentially conflicting interests [261], burden of disease and vaccine impact estimates are used to promote specific causes internally, such as decisions on vaccine investments.

The study reveals that the use of research evidence by GHOs occurs over a prolonged period, during which many individuals within the organization become acquainted with the evidence. Over time, evidence on disease burden and vaccine impact becomes ingrained in people's knowledge. From organizational theory, we learn that organizational norms and objectives are entrenched in employees' minds [325]. Actions are admixtures of scientific evidence and nonrational premises [359] and embrace the ideas of their founders. Stinchcombe et al. highlight that values are often preserved, and interests are protected by those who possess and retain power [376]. With respect to this explicit role of agency and power within GHOs, burden of disease and vaccine impact estimates competes with other factors influencing organizational decisions. I found that organizational actions follow pre-set pathways established by executives' opinions, interests and organizational norms rather than burden of disease and vaccine impact estimates forging new paths. The study suggests the need for further research on how GHOs benefit from the accumulated knowledge and experiences of their employees. Further empirical research on organizational learning processes as suggested by Langley [224] was beyond the remit of this research, in part to protect respondents' confidentiality.

Interactions between EPs and consumers are crucial for facilitating understanding of the evidence, including its caveats and limitations [49, 226]. Trusted relationships contribute to trust in evidence and the acceptance of new evidence, even if it challenges established beliefs. Previous studies suggest

that ECs, who participate in earlier phases of research react favourably to results [349]. However, rather than ECs prescribing the research agenda, I found agreement among respondents that the problem definition should result from dialogues between EPs and consumers. To facilitate these dialogues and to enable the reflection of societal concerns, Beran et al. advocate for platforms for exchange and the institutionalization of a multi-stakeholder approach [34].

Consistent with findings of previous studies, this study showed that trusted relationships can lead to trust in evidence and the acceptance and adoption of new evidence, which may otherwise be regarded as controversial or "negative" evidence [280, 345, 408]. This may be the case, if foundational knowledge, that has entrenched within ECs over time, is being challenged, not meeting their expectations. Early organizational studies showed that "negative" research evidence can actively threaten the beliefs and worldviews of ECs [6, 36]. All ECs interviewed for this study had extensive prior education in infectious disease epidemiology, yet they were still reluctant to use findings from commissioned burden of disease and vaccine impact estimates, if these deviated too far from previous burden of disease and vaccine impact estimates or strongly held beliefs. Therefore, this study shows that organizational norms, objectives, and/or other factors prevail direct, demonstrable use of evidence in this context. While the benefits of interactions among EPs and consumers became obvious through this and other research, this process can also jeopardize the objectivity of the scientific community. The objectivity of the scientific community may be questioned if the political interests of research commissioners inhibit knowledge production. While this was not voiced by ECs or EPs interviewed for the purpose of this study, evidence-informed decision-making interventions that aim to enhance the dialogue between stakeholders need to reflect on the role of power and politics in the process of knowledge production [94].

Mathematical models of infectious diseases have gained popularity in global health, complementing other epidemiological studies (e.g. clinical trials [330]) and are less cost-intensive. They offer high-level perspectives on global issues and allow for quick scenario testing. Despite their caveats and limitations, mathematical models provide valuable insights. However, when communicating results to external stakeholders, point estimates are often used, overlooking the important aspect of uncertainty [189]. This study suggests both ECs or EPs share an honest assessment and understanding of the underlying uncertainties and caveats of mathematical models. Yet, when communicating results to external constituencies (e.g. donor partners), point estimates are used to simplify messages and the

important aspect of uncertainty is lost. This further supports the conclusion that evidence is used anecdotally when mobilizing resources from donor partners, thereby serving a strategic purpose [106].

The global health system is heavily influenced by a few entities headquartered in high-income countries [188]. Mathematical models are predominantly used by GHOs to demonstrate accountability and legitimacy when soliciting funding. It is important to recognize that this study focused on a specific type of commissioned knowledge output. Different types of research, particularly explorative and innovative studies, may contribute differently to organizational actions. Further research is needed to explore the broader portfolio of evidence used by GHOs and compare evidence use across this portfolio. Additionally, this study primarily examined the use of burden of disease and vaccine impact estimates by philanthropic organizations and organizations with procurement mandates and may not fully apply to advisory GHOs like the WHO, where such evidence may be used for strategic guidance.

3.4.1 Limitations

This study has several limitations that should be acknowledged. Firstly, there is the possibility of social desirability bias in the responses provided by the study participants. They may have expressed idealistic views of evidence use rather than accurately representing their actual practices. Secondly, the interviews were originally intended to be conducted in person, but due to circumstances, they were conducted via video calls. This may have made it more challenging to fully capture participants' voices, opinions, and non-verbal communication. However, video calls are considered a viable alternative for collecting primary data when face-to-face interviews are not feasible [236].

Thirdly, the study had a small sample size and only represented the perspectives of a subset of employees from GHOs that commission evidence and researchers. However, considering the concentrated nature of stakeholders involved in global vaccine resource allocation, the findings are likely to be qualitatively robust within the sampled institutions. Nonetheless, it is important to recognize that the findings may not generalize to GHO based in LMIC or national government bodies, which may have different dynamics. Further research should explore how evidence produced by researchers affiliated with LMIC institutions is used by GHOs based in LMICs or national government bodies.

Lastly, it is worth noting that all EPs and consumers in this study were affiliated with institutions in high-income countries. Therefore, the findings may not fully capture how evidence from LMIC-

affiliated EPs is utilized by GHOs. This highlights the need for future research in this area. While the sample in this study reflects those most involved in this type of evidence production and consumption, it raises awareness of the challenges associated with the "foreign gaze" and the entrenched power asymmetries in global health partnerships. These issues are being increasingly questioned by both the study participants and the wider literature [2, 382].

3.5 Conclusion

In summary, this chapter revealed that GHOs utilize burden of disease and vaccine impact estimates to showcase their impact and accountability on a global scale, often to secure funding for global immunization initiatives. To maximize the value of burden of disease and vaccine impact estimates, GHOs involved in research evidence production should maintain continuous engagement throughout the research process. Similarly, EPs should be involved when GHOs utilize their research outputs. While burden of disease and vaccine impact estimates have been influential in demonstrating organizational legitimacy and may have indirectly influenced vaccine resource allocation decisions at various levels, their full potential remains underutilized. These estimates have the potential to significantly enhance organizational decision-making, including guiding vaccine resource allocation decisions across countries, going beyond mere progress tracking and measuring organizational success.

Chapter 4

Evidence use at the national level: The HPV vaccine introduction in Mozambique

4.1 Preface

Evidence, in its many forms, their use, and their relevance in national policy development and programme implementation are multidimensional, construed by the nature of the evidence, the policy problem, the moment and who is engaged throughout the process. Previous literature reviews have summarized the decision criteria that are commonly considered in the process of introducing vaccines in frameworks. This research builds on Burchett et al.'s [59, 61] and Guillaume et al.'s [174] work (which had previously been discussed in Chapter 2, in which theoretical concepts of knowledge translation were outlined), exploring how evidence was used the HPV vaccine introduction process in Mozambique. Such findings could be useful to justify which forms of evidence should be developed and communicated at which stages of policy development and implementation. The aim of this chapter is to explore how and why various forms of evidence, documented and uncodified, have been developed and used in the context of the HPV vaccine policy development and programme implementation in Mozambique.

In this chapter, which is the second results chapter, the focus is on how evidence is used at the national level throughout the policy development and programme implementation process, i.e., the process of EDU. Following the methods section, the results section first presents the policy development process of the HPV vaccination programme in Mozambique. Second, the results from the social network

analysis are presented. Then, the analysis of how different evidence was used throughout the vaccine introduction process is presented, followed by a discussion of results with reference to previous studies.

4.2 Methods

4.2.1 Study design and sampling

The research in this chapter followed a mixed-methods approach to collecting and analyzing data. Data from a (1) literature and desk review was triangulated with data collected via (2) semi-structured interviews to (a) trace the HPV vaccination policy development and programme implementation, (b) analyse how different evidence was used throughout this process, and (c) reflect on stakeholders and their relationships in the issue network around the HPV vaccine policy development and programme implementation in Mozambique.

Literature and desk review

Documents relevant to or providing information about the HPV vaccination policy development and programme implementation were searched for in the peer-reviewed and grey literature. The purpose of the narrative literature and desk review was to:

1. Map the landscape of different types of codified evidence, which may have informed the HPV vaccination programme development in Mozambique
2. Explore the features of the different types of evidence
3. Understand, which stakeholders and organizations formed in the issue network
4. Identify key stakeholders for interviews
5. Inform the interview guide
6. Identify references to specific pieces of evidence made

This process also helped the researcher to familiarise herself with general public health priorities in Mozambique and the context in which the HPV vaccination programme was developed.

The literature and desk review were conducted continuously by PC and Mozambique-based research assistant MM from April 2021 to January 2022. PC did a supplementary review in January 2023 to learn about new evidence and more recent vaccination programme developments.

In the desk review, documents directly related to the HPV vaccination programme in Mozambique and available in the public domain were sourced. For this, a search for documents on the websites of the Mozambican MoH, Gavi, and WHO was performed. These websites were searched for documents outlining decisions and providing information on stakeholders engaged in the vaccination programme and their relationships, e.g., meeting reports. Websites with search functions were searched for the terms "HPV", "Cervical cancer", and "Mozambique", as well as their Portuguese equivalent. The search was expanded by consulting the websites of partner organizations, which were named on any documents found on the MoH, Gavi, and WHO websites. This process was repeated until no new documents could be identified. Further, interview participants were asked to share internal documents, such as documents from meetings, reports, or any other pieces of evidence that were recalled during interviews and related to the interview content that they had on file and felt comfortable sharing. The interviewer asked for such supporting documentation to be shared via email with PC following the interview. Documents were searched for references to specific pieces of evidence as well as decisions and recommendations for the HPV vaccination programme.

The desk review was complemented by a narrative literature review. The search strategy borrowed from systematic review methodologies to reduce bias in selecting publications for review. The literature was searched for publications on CC and HPV in Mozambique. The review strategy was bibliographic. One electronic database (PubMed) was accessed and searched with a combination of two search terms using AND. The following query with a filter on being published before January 2022 (the time of the first interview) was used: ((human papillomavirus) OR (cervical cancer)) AND (Mozambique). The search was repeated in Portuguese with the search terms "virus del papiloma humano" and "cáncer de cuello uterino". The database was searched on article titles, abstracts, and keywords. Duplicates were removed.

Publications and documents that were only available in Portuguese were reviewed and partially translated into English by MM.

For each document identified through the desk review, the year of writing, a short summary, the language, the type, and references made to specific pieces of evidence were recorded. Similarly, for each study published, its title, year of publication, key findings, language in which the research was published, type of research, scope (district or hospital, national, regional, international, or global), and information on the authors were extracted from the abstract.

In-depth interviews

In-depth, semi-structured interviews with purposefully sampled study participants, who have or had been employees at organizations that have been engaged in the decision to introduce the HPV vaccine in Mozambique and/or the program planning as decision-makers or evidence producers. Interviews were conducted to learn about stakeholders' perspectives on the HPV vaccine policy development and programme implementation, and evidence development and use within this process.

Study participants were identified through suggestions from Mozambican colleagues in the research team, the initial desk review, and snowball sampling. Thereby, participants were purposefully sampled with regards to whether they were in the issue network around the HPV vaccination programme in Mozambique. Thus, study inclusion criteria were loosely defined as programme planning, policy development, and evidence development are often diffused across many levels and types of government and shared between public and private actors [213].

Study participants were categorized as evidence producers, evidence consumers, or as hybrid, depending on their engagement with the HPV vaccine policy development and programme implementation. *Evidence consumers* were stakeholders who were influential on the HPV vaccine policy development and programme planning. Stakeholders were regarded as influential if they engaged with the vaccination programme through financial investment, technical support, or decision-making power. The study population included stakeholders at:

1. Government departments (Ministry of Health (MoH), Ministry of Education and Human Development (MINEHD), Ministry of Economy and Finance (MEF)) at the national and sub-national/provincial level;

2. Sub-nationally/provincial, nationally, regional, or globally operating NGOs and IOs;

3. Donor partners and organizations providing financial support for vaccination programmes

Evidence producers included stakeholders, whose engagement with the HPV vaccination programme was defined by producing any form of evidence that could have been relevant to programmatic decisions. As such, this included researchers who produced scientific evidence on HPV in Mozambique, systematically produced evidence (e.g., surveillance data) outside of the research context, as well as individuals, who developed evidence unsystematically (e.g., by gaining experience with other health programmes).

Hybrid study participants. Stakeholders can be both *producers* and *consumers*. If study participants held multiple functions throughout the policy development, they were labeled as 'hybrid' (H). For example, an individual may have been engaged in the HPV vaccination programme demonstration programme (as an evidence producer), and later be engaged in the decision-making around the programme planning.

Interviews were conducted in English or Portuguese in person or via the telecommunication software Microsoft Teams (due to travel restrictions related to the COVID-19 pandemic) between January 2022 and May 2023.

Prior to interviews, study participants received a Participant Information Sheet and were asked to sign an informed consent form. Interviews lasted between 25 and 120 minutes and were audiotaped.

Study participants were pseudonomyzed to protect their identity; their type of affiliation and institution were their defining characteristics. This was done to make people feel more comfortable to speak more candidly.

The interviews followed a pre-written, semi-structured interview guide probing the policy development process and development, use, and demand of evidence in the context of the HPV vaccination programme specifically. Open-ended questions were co-developed and piloted with Mozambique-based research assistants, AL and MM (Appendix C). The guide was inspired by similar studies [180, 210, 215], elements of the theoretical frameworks presented in Chapter 2, and the method of contribution mapping [215] in which study participants are encouraged to tell their narratives from personal experience. The interview schedule probed stakeholders' involvement in the HPV vaccination programme planning process or policy development, followed by asking for examples of specific pieces of evidence

and how these may have been influential on the HPV vaccination policy and programme development. It was not assumed that mathematical models were the study participants' preferred type of evidence. Instead, the interview inquired about any form of evidence that could have been useful to stakeholders throughout the policy development and programme implementation process (Appendix C). A timeline of key events supported interviewees as a recall aid (Appendix C). Additional questions were asked to clarify any information or go into further depth on a topic.

Interview observations and informal interview summaries were discussed in weekly team calls. After four months of data collection, the research team members (PC, AL, and MM) read, independently coded with reference to the theoretical frameworks (the policy cycle and Weiss' framework of evidence use (Chapter 2)), and compared preliminary findings from a subset of five interviews to explore if data saturation had been achieved. Saturation was achieved when ideas and/or opinions were repeated by multiple stakeholders. Discussions were held at length over a period of one week during a country visit by PC in March 2022. The data analysis is outlined in detail in the following section (4.2.2)

From the audio recordings, intelligent verbatim transcripts were produced. Interviews that were conducted in Portuguese were translated into English by MM. Personal or organizationally identifiable information shared during the interview was masked through pseudonyms to ensure confidentiality or excluded if pseudonymization was not possible. Transcripts were shared with study participants after the interview for them to clarify information or correct any transcription mistakes that arose due to low audio quality.

Storage, organization, searching, and coding of transcripts were performed using NVivo 12 Pro [335].

4.2.2 Data analysis

Data was triangulated to map the chronology of the HPV vaccine programme and policy development in Mozambique, to map stakeholders in the issue network around these processes, and to explore evidence development and use in this context.

The data was first coded deductively with reference to the stages of the policy cycle and Weiss' theoretical framework of evidence use (Chapter 2). Second, the data was coded inductively, through which sub-themes for each framework dimension were identified. The approach allowed to explore the

specific use cases of evidence, while leaving space to discover unexpected or further emerging themes and relate findings to other frameworks on evidence use in vaccine introductions (e.g., [59, 61, 174]. The analysis followed the framework method developed by Ritchie and Lewis [343], allowing for the comparison of predefined study population groups [158].

Further, a Social Network Analysis (SNA) was conducted. SNA aims to dismantle complex network structures and explain social phenomena that result from structural and relational attributes of a system. The approach can be used to identify who the actors/stakeholders in a system are, what their position is, and what their relative influence on decisions are. Connections between actors/stakeholders are mapped out to understand which relationships are present and which ones could be value-adding for a more harmonized, evidence informed decision-making process [147, 164, 214]. Networks and actors'/stakeholders' position in a network can be analysed using centrality measures. For example, the measure *betweenness* measures the number of times a node lies on the shortest path between other nodes in the network. By comparing the betweeness of all nodes in the network, the most influential actors in the network can be identified. The purpose of this mapping exercise was to illustrate a qualitative assessment of the decision making environment and interconnectedness of stakeholders engaged in the HPV vaccine introduction in Mozambique.

Each interview participant and organization named during interviews was characterised. For each organization with which study participants were affiliated at any point throughout the vaccine introduction or others that were named during the interview, the type of organization, their collaborations, and responsibilities in the HPV vaccination programme introduction were documented. A tie, i.e., a connection between two actors, was defined by whether they collaborated throughout the process of the HPV vaccine policy development or programme implementation. The time, moment of collaboration, and intensity could not be derived from the data. The data was aggregated at the organizational level, i.e., one network node is one organization. Thereby, results could not be traced back to individuals. The centrality measure, *betweeness* was calculated for each node.

In the SNA, study participants were classified as either consumers or producers (rather than being hybrid). Participants were assigned the role that they assumed most of the time throughout the policy development process.

4.2.3 Ethical clearance

Ethical approval was obtained from Imperial College London (ICREC reference: 21IC7033) and the Institutional Review Board of the Manhiça Health Research Centre (CISBS-CISM/076/2021) (Appendix B). Approval from the Bioethics Committee in Mozambique was not required for this study.

4.3 Results

Of the 50 individuals that were attempted to be contacted, 28 (56%) individuals who have or had been stakeholders in the issue network around the HPV vaccine introduction in Mozambique took part in the research. 78% of study participants were based in Mozambique during their involvement in evidence development and/or HPV vaccination policy development and programme planning. 21% of study participants were based in North America or Europe. Two participants (1%) were based in a regional office, which covers Mozambique. At the time of involvement in the vaccine introduction, study participants were employees at organizations that had been engaged in the decision to introduce the HPV vaccine in Mozambique, the programme planning, and/or implementation. These components of the policy development and implementation process are further discussed in Section *Chronology of HPV vaccination programme introduction in Mozambique*, page 65. In addition to their full-time occupation, four study participants had been members of the Mozambican NITAG, locally known as Comite de Peritos para la Imunizacao (CoPI). Study participants were categorized by the level at which their organization or office is operated: headquarter (HQ), regional (R), national (N), provincial (P). The distribution of interview participants across types of organizations is summarized in Table 4.1.

In addition to interviews, data from the literature and desk review was used throughout the analyses. Figure 4.1 presents a flow chart of the article selection process. 50 documents were identified in the narrative literature review (Table 4.3). 50% of these were cross-sectional studies of HPV conducted in Mozambique. Figure 4.2 depicts the evolution of scientific evidence development over time. PC received 16 documents from the interviews (Table 4.2). The content and type of pieces of evidence that were shared by participants following interviews are summarized in Table D.1 (Appendix D).

Table 4.1: Overview of interview participants by type of organization and engagement in the issue network (either as an evidence producer (EP), evidence consumer (EC), or hybrid (i.e., both) (H)). Count of National Immunisation Advisory Group (NITAG) members by type of organization are presented separately. National: Mozambique-based.

Type of organization	**Evidence producers (EP)**	**Evidence consumers (EC)**	**Both (H)**	**Total**	**NITAG**
Government department					
National level			4	4	1
Province level	2			2	
Non-governmental organization (NGO)/ International organization (IO)					
NGO/IO based in North America or Europe	1	1	4	6	
Nationally operating office of IO	2	2	1	5	
Regional operating NGO		2		2	
Mozambican NGO	2		3	5	2
Research capacity					
International			1	1	
National	2		1	3	1
Total	**9**	**5**	**14**	**28**	**4**

4.3.1 Chronology of the HPV vaccination programme introduction in Mozambique

The HPV vaccination policy development and programme planning is presented by the stages of the policy cycle in Figure 4.2 [52, 225, 398]. The following subsections depict each stage in more detail.

Agenda Setting

Small-scale pilots of the HPV vaccine in a few LMIC between 2007 and 2012 marks the beginning of the policy development. These pilots were called “demonstration programmes” and were conducted to gain experience at delivering a vaccine to adolescents, a cohort outside of the usual immunization schedule for children. According to interviewees, this coincided with the Mozambican Ministry of Health engaging with partner organizations and other ministries to galvanize their interest in the vaccine introduction as a public health intervention against CC in 2009 [303, 305, 308].

Figure 4.1: Flow diagram of the selection process for including studies in the narrative literature review. Abbreviaions: CC - cervical cancer; HPV - human papillomavirus; LMIC - low and middle income countries

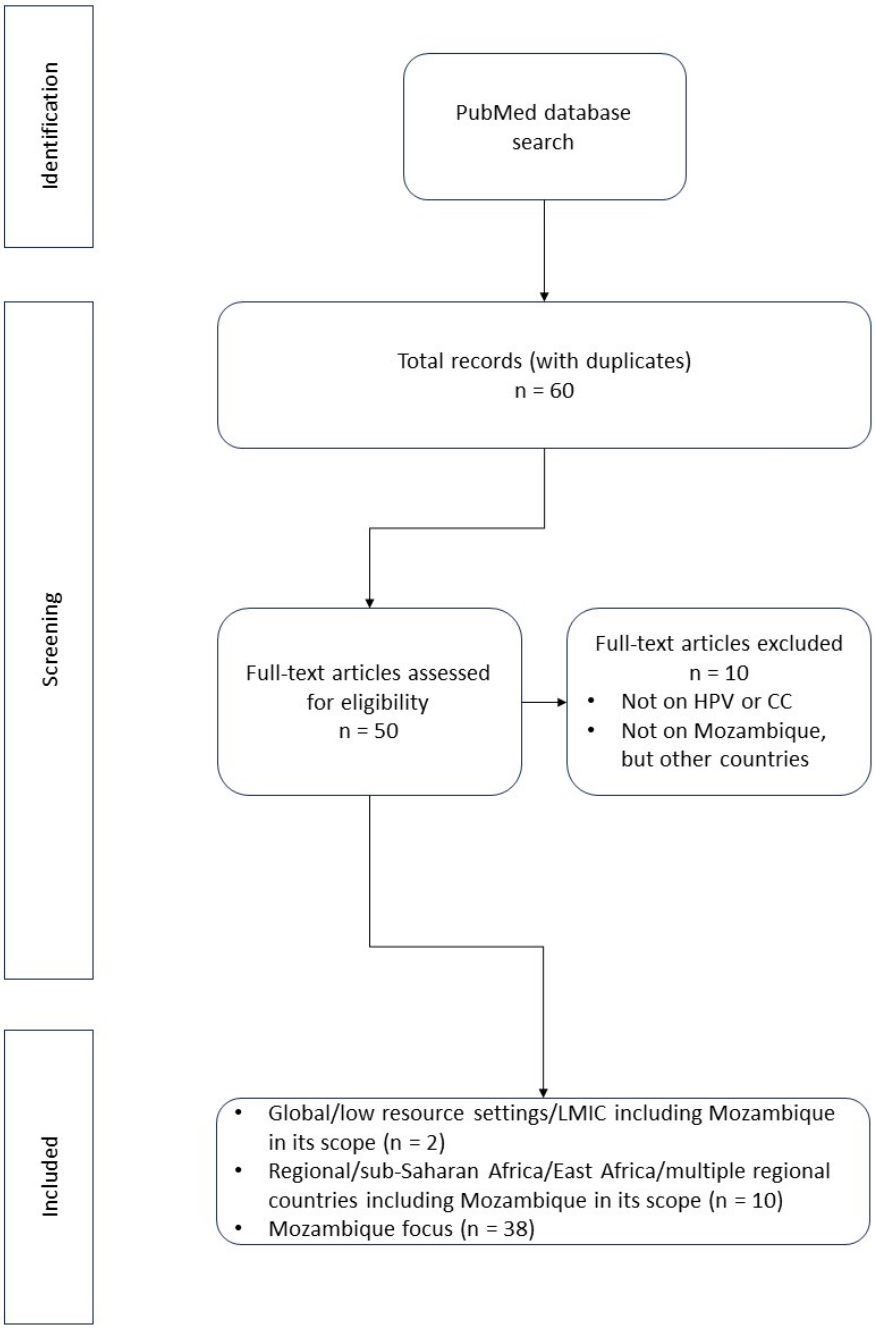


Table 4.2: Summary of evidence shared by study participants following interviews by type of evidence and language.

Type of evidence	English	Portuguese	Total
Email exchange	2		2
Excel tool		1	1
Meeting report	3		3
Presentation	4	1	5
Report	4	1	5
Total	**13**	**3**	**16**

Table 4.3: Publications identified in narrative review by type of study and scope.

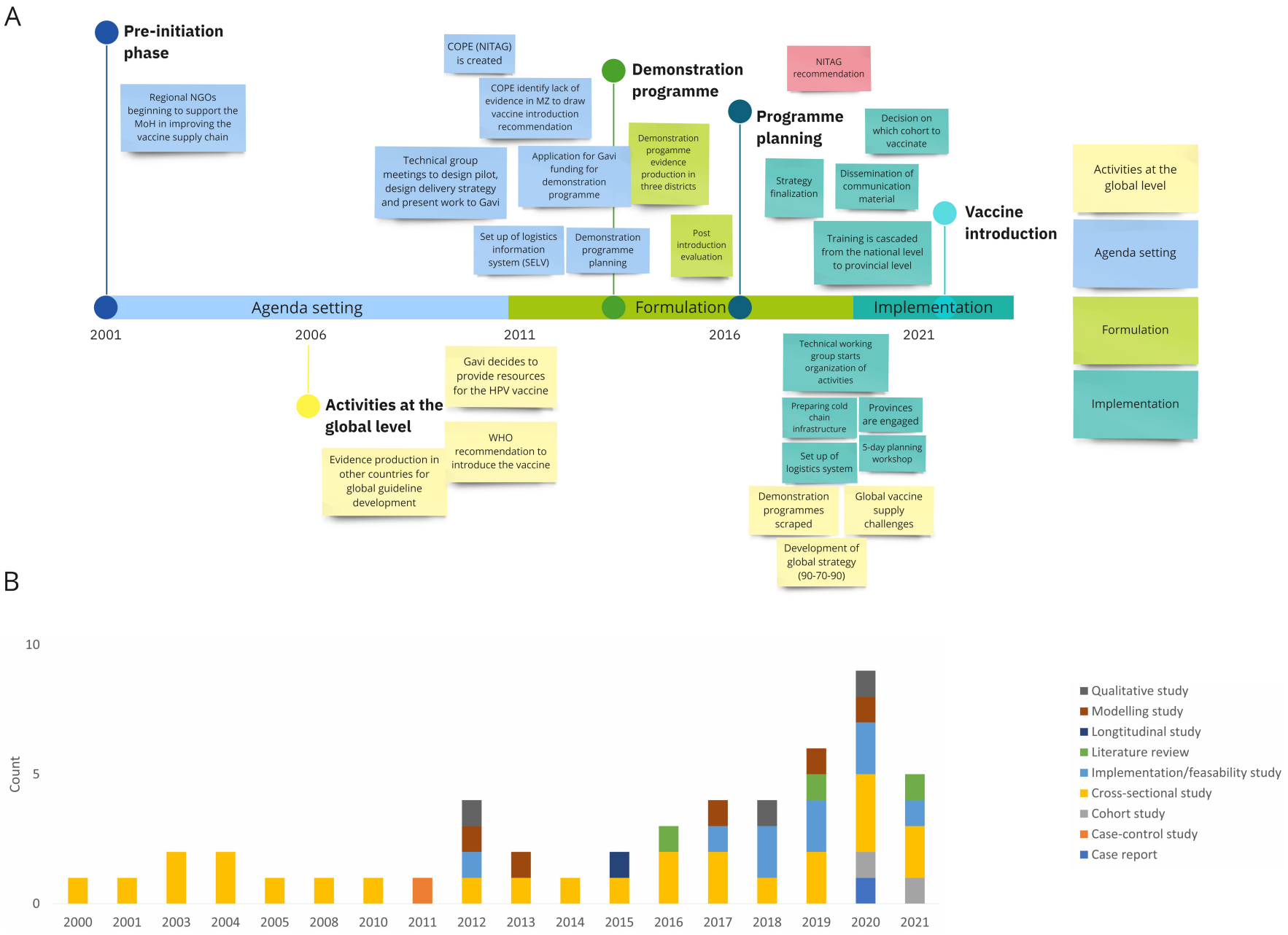
Type of study	Global	Regional	(Sub-)national	Total
Case report			[98]	1
Case-control			[274]	1
Cohort		[172]	[353]	2
Cross-sectional	[7, 8]	[223, 249, 275]	[50, 79, 84, 130, 348] [11, 42, 78, 81, 83, 91, 221] [58, 80, 82, 90, 241, 259, 273, 328]	25
Implementation		[113]	[222, 267, 352, 354] [266, 321, 369, 370]	9
Literature review		[231, 290]	[329]	3
Longitudinal			[239]	1
Modelling		[71, 211, 360]	[9, 178]	5
Qualitative			[18, 29, 258]	3
Total	**2**	**10**	**38**	**50**

Further, the engagement of global and regional stakeholders (Cervical Cancer Action, Union for Union for International Cancer Control (UICC), Forum-Africanas African First Ladies [72], PATH [142]), advocacy work, the recommendation to introduce the vaccine by WHO [410] as well as more knowledge of the CC epidemiology in Mozambique (evident through the number of cross-sectional studies of HPV condcuted in Mozambique, Figure 4.2) led to increased interest in the HPV vaccine in the Ministry, mostly the Ministry of Health.

The slow adoption of the policy, and why it gained momentum, was influenced by political factors. The attention to HPV and CC and interest in the vaccination programme seems to have been driven by the interests of high-level national or global stakeholders, e.g., Gavi and WHO. Political influences were a key concern for most study participants. One informant hypothesised:

> "The actual introduction on the date to introduce etc. was entirely political, so it was taken by the minister because I think they needed a win. And also because the First Lady

Figure 4.2: A. Chronology of HPV vaccination programme introduction in Mozambique with key events categorized by policy cycle stage. B. Peer-reviewed evidence identified in the literature review on HPV and CC in Mozambique categorised by research type over time.



> had been contacted and had specified her availability. [...] And so that just meant that regardless of readiness, regardless of arguments to delay it, the introduction went ahead." [313]

This was also critiqued by a study participant at the national ministry:

> "what happened for this and other vaccines that we introduced is that the WHO has a goal that is in the coming years the countries starting to introduce. It's our sequence that they first come from the North, then sub-Saharan, those things they do. They have their goal of introducing a vaccine. After that, the headquarters with Gavi are organized there, lobbying between them and this is my point of view and the point of view of all of us. They are lobbying among themselves, organizing the money who will receive the money for the purchase of the vaccine, those things that they do and organize themselves well. Once they get organized, they really start this movement." [293]

Formulation

The *formulation phase* encompasses the transformation from problem identification in the agenda-setting phase into a government programme. In the context of the HPV vaccine introduction, this phase covers the demonstration programme and the programme planning phase.

From 2012 to 2016, Gavi provided financial support to countries to conduct these small-scale demonstration projects, with the aim of determining effective and sustainable vaccine delivery strategies, and national introductions [309, 312]. Gavi's engagement led to significant vaccine price reductions (from USD 100.59 per dose to USD 5.00 per dose for Gavi-eligible countries) [72]. With the HPV vaccine demonstration programme and national introductions receiving support by global funding organizations, the vaccine got on the political agenda in Mozambique.

A programme task force team was formed and led by the EPI to consolidate the application to Gavi to receive demonstration programme funding [309]. CISM conducted research on the awareness of cervical cancer and willingness to be vaccinated against HPV [29], and drafted the application.

Mozambique was among 25 countries for which Gavi had approved demonstration project funding [191]. The Gavi funding was for the demonstration programme at one site in Mozambique, Manhica

[311]. The Mozambican government's decision to finance the pilot in two additional districts located in the North and the Centre of Mozambique (Manica Village and Mocimboa da Praia) indicated that the HPV vaccine became a priority for the government. Eventually, the demonstration programme took place from 2014 until 2015 [380]. Cervarix® (GlaxoSmithKline Biologicals) was used for these pilots. The pharmaceutical's engagement in these trial is undocumented and was not elaborated by study participants.

Through the demonstration programme, various pieces of evidence were generated. CISM conducted the post introduction evaluation (PIE) [311, 336]. These led to the following reflections and recommendations:

- The government of Mozambique, together with stakeholders, should introduce the HPV nationally through three delivery modalities:
    1. Health facilities: provided through Adolescent and Youth Friendly Services (SAAJ);
    2. School: periodic school-based campaigns for girls, initiating with a year one catch-up for girls 10-13 years and subsequent 10-year-old immunization target group. Also allow for non-school attending girls access at schools;
    3. Community: periodic outreach campaigns in low school attendance areas, and supported with involvement of community leaders.
- Use viable community structures for registration and proof of age;
- Implement active community search for girls who miss school on vaccination days;
- Work with the education sector to understand the causes of withdrawal and recover dropout girls; and
- Keep in touch with members of the community that maintains the connection with the school.

In 2017, the Mozambican NITAG formally recommended the Mozambican government to introduce the vaccine at national scale [299, 303]. Shortly after, in 2018, the Mozambican government filed the application for Gavi funding [268]. Gavi approved the application to support the introduction in 2020 [307].

Following, the EPI organised three sub-teams: communications, logistics and cold chain, service provision [296]. Various technical workshops were held to plan the introduction. According to workshop documentation [110], the strategy was finalized in 2018.

Implementation

The plan to introduce the vaccine at national scale in 2019 was disrupted by natural disasters, including cyclones Idai and Kenneth as well as the COVID-19 pandemic [313]. Finally, the First Lady of Mozambique formally introduced the vaccine in November 2021 [294], at a time when schools were closed (as an intervention against the COVID-19 pandemic) [293]. The country decided for GARDASIL® (Merck & Co. Inc.). The rationale behind the decision to use this particular vaccine is unknown. Global shortage of the HPV vaccine led to the decision to vaccinate a single-age cohort (9-year-old girls) rather than a multi-age cohort (9- to 14-year-old girls) in the first year as originally planned. The 10- to 14-year-old girls were reached through a catch-up campaign in May 2022 [174]. Over the first year, the vaccination was introduced through community brigades (28%), health centers (22%), and schools (50%) [175].

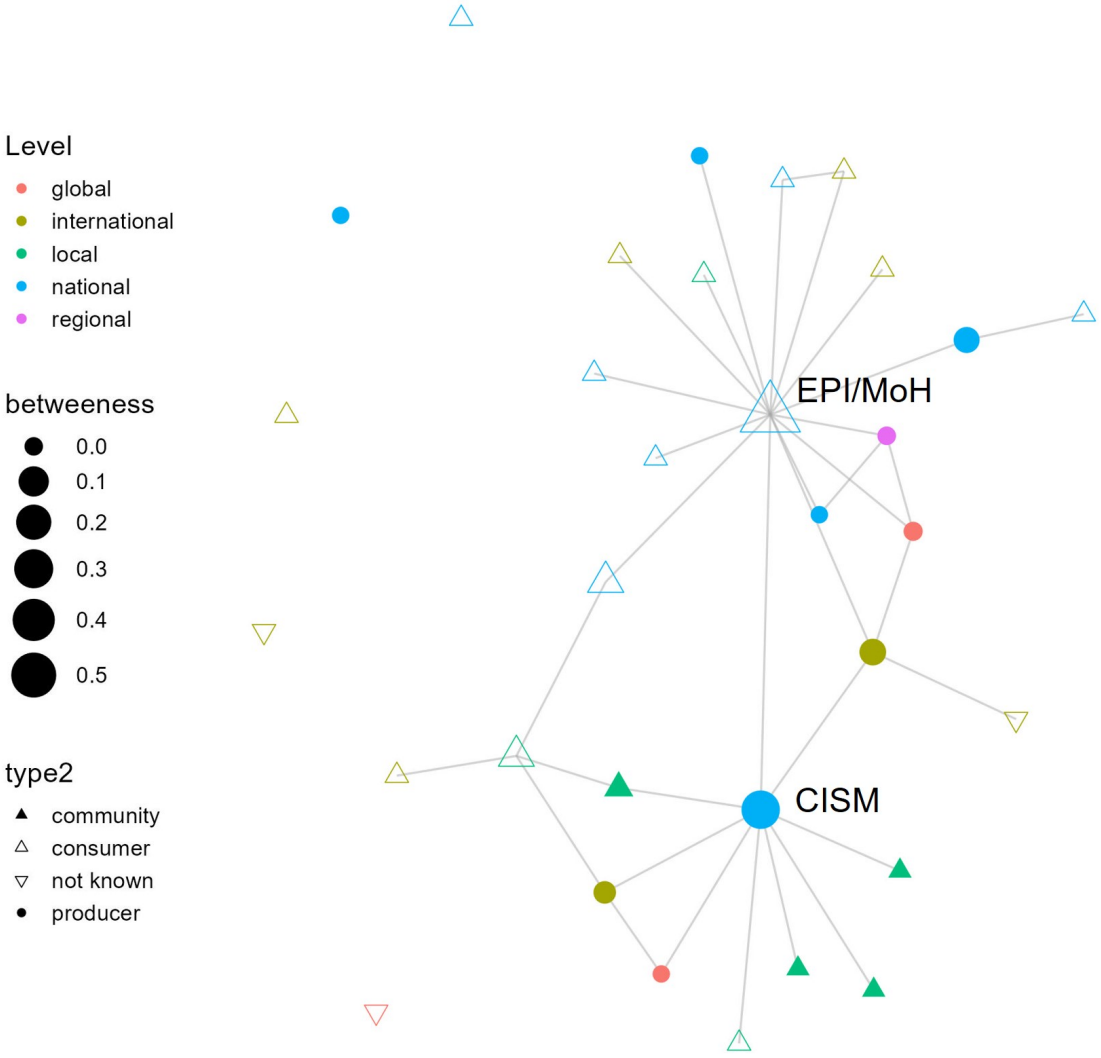
4.3.2 Issue network around the HPV vaccination programme policy development and programme planning

Figure 4.3 illustrates the composition of the issue network around the HPV vaccine policy development and programme implementation. The network graph depicts the even mix of evidence consumers and producers, and high number as well as diversity of types of stakeholders in the network. Two organisations, the EPI and CISM exhibit the highest betweenness, shown by the relative node size, and appear to be hubs of the network.

The EPI is leading all immunization programmes [298, 305]. Throughout the vaccination programme introduction, the EPI had oversight of activities and led all group discussions with other stakeholders in the issue network. Their overarching responsibilities included taking budget allocation decisions [315] and developing the vaccine delivery strategy, e.g., the organisation of the cold chain, vaccine demand, defining project costs [304]. For this purpose, the EPI engaged with partners that specialised in certain tasks providing technical assistance (further elaborated below) [295, 296, 300, 305]. The network graph indicates that the EPI was mostly engaged with stakeholders at the national level and evidence consumers.

CISM is a research institute, which specialises in research on transmissible diseases prevalent in

Figure 4.3: Issue network around the HPV vaccination programme introduction in Mozambique. Each node is one organization. Abbreviations: EPI: Extended Programme for Immunisation; MoH: Ministry of Health; CISM: Centro de Investigação em Saúde de Manhiça



Mozambique, with particular focus on malaria, HIV/AIDS, tuberculosis and bacterial diseases. Researchers from CISM's social science unit have been working closely with the EPI and communities throughout the entire vaccination programme introduction process (Timeline 4.2) [309]. CISM's contribution to the HPV vaccination programme included research on the awareness of the vaccine [29], then writing the Gavi funding application, and reviewing social mobilization materials that was developed by technical partners (Table E.1) [309]. The network graph shows that the research institute is the organization that engages most with stakeholders at the local level. In comparison to the EPI, CISM has significantly more connections to community members, which include adolescents, their guardians, matrons, and teachers.

Despite scoring low betweenness, the WHO (at all levels) also appears to be an influential stakeholder in the network. The WHO has been providing technical support for micro planning, training, and the development of training materials for community leaders [297].

All other organizations are peripheral to the network of the vaccination programme introduction collaborating with two or less other organizations. Isolated nodes were mentioned but could not be assigned to any specific collaboration. Yet, despite some organizations only having a few connections, interviewees emphasized their significant importance in the network. For example, Fundação para o Desenvolvimento da Comunidade (FDC) had community engagement specific tasks, an area in which the organization is specialized [303]. A second example is VillageReach. This organization became the focal point for the development of the logistics system, Electrónico de Logística de Vacinas (SELV), according to an evidence producer:

> "SELV is the [...] electronic vaccine logistics system. This system advised the ministry as well, on data, on vaccine usage at the last mile. And during the HPV, [...] we provided data that we captured at both provincial and district levels on stock levels, stock usage, consumptions and losses." [304]

Thus, a seemingly peripheral position in the network does not correlate with the level of engagement in the vaccination programme introduction. Key responsibilities held by each of the organizations are presented by policy stage in more detail in Table E.1 (Appendix).

4.3.3 Forms of evidence and their utilization

Over time, different forms of evidence were developed (Figure 4.2) and contributed to the policy development and programme implementation in different ways. In the following section, how and which evidence was used by whom throughout the HPV vaccination programme development in Mozambique is discussed with reference to the evidence use models (Chapter 2).

The interpretation of "evidence" was broad across interviewees. By probing what specific evidence contributed to actions taken, interviewees recalled various forms of technical and scientific information (*episteme*), e.g., hospital research on the incidence of CC in Mozambique, as well as intangible knowledge (*phronesis*), e.g., learnings and experiences acquired from other programmes targeting adolescents in Mozambique, other vaccine introductions in Mozambique, and HPV vaccine introductions in other countries. Specific examples are provided in each sub-section. An overview of how each form of evidence that was recalled is presented in Table 4.4. The table structure mirrors how the results presented in Chapter 3, which concerned the use of burden of disease and vaccine impact estimates by GHO were structured.

Instrumental evidence use

Instrumental evidence use describes the systematic development and use of evidence in a linear process, implying that specific evidence would directly influence a decision or action as a solution to a specific problem. Surprisingly, there are numerous examples of where this model applies throughout the policy and programme development (Figure 4.2). Yet, evidence was not found to drive the agenda setting, formulation (demonstration programme and programme planning) and implementation. Rather, evidence was responsive to specific questions of programme planners and decision-makers. Hence, the *problem-solving model* is found to be more applicable than the *knowledge-driven model* to describe evidence use in this context.

Knowledge-driven model

For this model to apply, production of evidence considered for use by its consumers should be driven by academic curiosity. According to informants, this model of EDU does not apply in the context of the HPV vaccination programme development. Instead, the inaptness of this model highlights that

Table 4.4: Forms of evidence used in the context of the HPV vaccination programme in Mozambique.

Instrumental Production and use of evidence happen in a linear process. Scientific evidence is assumed to be instructive for the decision, such that the impact is concrete and visible. Decisions are based on evaluation results.	**Conceptual** Evidence influences actions, but in less specific, more indirect ways. Research evidence permeates action generation.	**Symbolic** Evidence is used to legitimise and support existing positions of evidence users. Evidence is used as ammunition to support predetermined positions or to delay decisions strategically.
Episteme • Evidence from the demonstration programme highlighted where capacity support was required for further evidence production. • Sub-national evidence (from demo programmes) verified that the vaccination programme should be scaled up to the national level. • Sub-national evidence from varying locations emphasized the need to develop culture- and religion-specific communication strategies. • Sub-national evidence highlighted that evidence had to be communicated in lay terms to community leaders. *Phronesis* • Planning benefited from the experiences of other programmes.	*Episteme* • Global guidelines, research from other countries, evidence collected nationally and sub-nationally (hospital data on prevalence of HPV) shaped the issue network's understanding of HPV as a public health issue. *Phronesis* • Experience leads to confidence in the programme. • Learnings from other countries are used to reduce uncertainties and can guide on how to combat challenges (e.g., vaccine hestitancy) or mitigate programme failures.	*Episteme* • Global evidence was used to support the programme advocacy, when demonstrating the need for the intervention to the Ministry. • Potential impact of the vaccine on national CC mortality rates served as an important component of the investment strategy.

especially the agenda-setting phase of the policy development was influenced by other factors than evidence, which are further discussed in the *Enlightenment model*, page 78.

Problem-solving model

Decision to introduce the HPV vaccine. In the decision-making process around the demonstration programme (agenda setting, c. 2012, Figure 4.2), research was sought or developed to address specific questions posed by Gavi in the application process for demonstration project funding. Specifically, informants recalled CISM conducted research on the vaccine acceptability to understand if the population would understand why the vaccine is introduced. Learnings from Angola and Tanzania were sought to have examples of countries that had already introduced the vaccine. Even though a question on the worth of the vaccine was posed, no health economic evaluation of the vaccine was recalled by interviewees.

The political commitment to the vaccination programme seemed to have been very influenced by specific nationally produced evidence (*episteme*). Early in the policy development (agenda setting), interviewees mostly wanted to learn about the magnitude of CC in Mozambique and therefore sought evidence on the epidemiological profile as well as the availability of oncology doctors and treatment capacities for CC patients. For this purpose, the number of women who were being treated for lesions was considered as a proxy [293]. Additionally,the national disease surveillance system and sub-national studies on prevalence were considered useful [308]. This evidence was also critical for the NITAG recommendation to introduce the vaccine (formulation), according to an evidence consumer at a nationally operating NGO [295]. Even though there were no records of a formal HTA process in place, according to this study participant [295], the vaccine was evaluated systematically by collating the best available evidence.

All studies that were identified in the literature review (Table 4.3) used surveillance data that was collected in the South of Mozambique, either in rural areas or at the Central Hospital in Maputo. This suggests that the scope of epidemiological evidence or generalizability was not necessarily an important feature to evidence consumers.

Structuring of information for programme planning and implementation. For the demonstration programme (formulation), the task force was organized in three teams: communications, logistics and cold chain, and service provision. Each of these teams highlighted relevant metrics on or tasks for which

evidence was sought during the programme planning. For the communications team, relevant evidence concerned communities' acceptability of the vaccine. Information from the acceptability study conducted during the demonstration programme, and coverage surveys highlighted heterogeneity in acceptability across communities. Respectively, there was consensus that communication materials had to be developed in light of different religions that are practised in communities [122, 309]. The study participant also highlighted the need to engage political and community leaders to overcome barriers, as also pointed out in the recommendations summarized in the PIE (page 70). While this form of evidence (*episteme*) appeared to be an important analytical piece, experience from other countries that are similar to Mozambique was considered critical to overcome programme challenges, such as vaccine hesitancy [298].

However, according to a hybrid study participant at a nationally operating NGO, in this case learnings from other interventions are not transferable as HPV has delayed consequences on the individual's health. This was found particularly difficult to communicate to women, as a hybrid study participant recalled:

> "because cancer is a silent disease there are many people who end up dying without ever knowing about cancer. So it's very challenging to do this kind of social mobilization. It is different, for example, from malaria in which the person gets sick." [303]

For the logistics and cold chain team, learnings and experiences (*techne* and *phronesis*) from other vaccines and interventions are considered highly relevant evidence that reduces the risks and uncertainties associated with the intervention, e.g., deploying an ineffective vaccine delivery strategy. According to a hybrid study participant at the national ministry, experience from planning other vaccine introductions meant that no new processes had to be established:

> "We already had previous experiences introducing vaccines to Mozambique. So HPV wasn't something new because in terms of planning almost not much has changed." [315]

The service provision team consolidates the planning activities. For these planning exercises, prescriptive application forms (e.g., the Gavi financing application), global guidelines (e.g., Guide to introducing HPV vaccine into national immunization programmes [284]) and templates (e.g., materials for community engagement) were considered useful. These helped structure information. Deviations from any of the guideline metrics were viewed as insightful and helpful to develop a bespoke vaccination

programme in Mozambique according to a hybrid study participant at a nationally operating NGO [297]. Additionally, micro-planning that was done virtually during the pandemic led to the consensus view among all programme planners that the vaccine should not be introduced at the time.

Conceptual evidence use

If evidence use follows the conceptual model, evidence diffuses incrementally into the knowledge base and thereby leads to evidence-informed decisions and possibly changes in evidence consumers' attitudes and/or understanding.

Enlightenment model

Existence of evidence prior to political interest and slow adoption. As the timeline shows, the introduction of the vaccine was a lengthy process. Scientists were ahead of the policy development (Figure 4.2). Between 2001 and 2013, 11 cross-sectional studies of HPV types, and one case-control study had been published. In all of the scientific publications produced in Mozambique the introduction of the vaccine was recommended. Additionally, regional evidence demonstrated the cost-effectiveness of the vaccine [211]. In 2012, the first qualitative study and implementation research studying the awareness of CC in rural areas [18, 266] was published. Epidemiological studies and prevalence data were used to convey the importance of this public health issues in communities, according to a hybrid study participant at a nationally operating NGO:

> "[Epidemiological studies are] important so that we understand the severity of the problem because when we look at a community, when we want to make it clear that this health problem is worrying or is serious for the health in the community, it is necessary to bring a little of this data, to have a sense of the dimension. Because without this data, communities already have their health priorities. [...] So we need to first see where the community places this health problem within its pyramid and we look at the data to see if this placement is being made due to lack of knowledge of the size of a problem and how based on that information in that data, we can clarify the weight of this disease in the health of the community itself. So it's from this perspective that data is important when the data can't speak." [297]

By the time of the vaccine introduction, many study participants appeared to be aware of the evidence developed for and supporting the vaccine introduction.

Adoption of experiences. It was thought crucial to have both formalised and deeply entrenched understandings of the context in which this vaccination would be introduced. Global evidence was considered relevant but had to be localized to be useful. For example, in the absence of data on the prevalence of HPV in Mozambique, one hybrid study participant seemed to particularly appreciate the fact that a 'script' provided by the WHO could be shaped to the local contexts in Mozambique [297].

Interactive model

Interest in more evidence and more transparency. Both evidence consumers and producers in Mozambique voiced the lack of transparency in research production. For example, one evidence producer at a research institution in Mozambique criticised the fact that a lot of evidence and data is not publicly disseminated:

> "People work, put things in drawers, statistics are not made, nothing is done, when statistics are made, it is reported in the institutions, it is not published. So the general public and researchers in general they do not have access. So many representative epidemiological data are lacking, for example, what is the incidence of cervical cancer or HPV in the country as a whole." [314]

This was echoed by a study participant at the national ministry. The study participant at the Ministry voiced that there was little knowledge on what research was generally conducted in Mozambique. Thus, even in the interest of taking evidence into consideration, they need to be taught or informed about it, which implies interaction:

> "All the work, every year you are producing something, it would be good to share so that we would have the flavour of having our own scientists in Mozambique." [294]

An evidence producer highlighted that much of the social science research was co-produced with stakeholders at ministerial departments. This ongoing relationship meant transparent data sharing and collaborative evidence production:

> "[CISM was] engaged in all processes and in all plans, [the MoH] always shared whether there was a workshop, if there was information, if there were interactions at the HPV level and until now in the post-introduction, CISM was invited. [...] All publications were made in collaboration with the Ministry, they were also co-authors of our publications and one of the most interested parties in the above publications." [309]

Similarly, according to an evidence producer at a nationally operating NGO, who is on the logistics team, engagement with the Ministry on how data should be presented has led to the creation of interactive dashboards, which visualize key performance indicators of vaccination programmes, e.g., the vaccination coverage [304].

Study participants voiced the importance of engaging different types of stakeholders in the process of programme planning and implementation. Different ministries should also be engaged to identify and reach influential stakeholders that work in the communities. For example, the Ministry of State Administration needs to be involved because it is trusted by community leaders. The Ministry of Education is relevant for creating the link between health and education personnel. The evidence producer suggests a holistic, integrated approach of these different perspectives in the implementation:

> "So, the other participants are also extremely important, because each one has a little to give in the process. So to say that, even in the future, in the next introductions, regardless of the type of vaccine, whenever there is an introduction of a new vaccine, it is important that there is coordination of several stakeholders before the introduction." [308]

Symbolic evidence use

Under the symbolic evidence use category, which stands in stark contrast with instrumental evidence use, evidence is used to support arguments, politically or tactically. In the context of the HPV vaccine introduction, evidence was used politically, i.e., to support stakeholders' standpoints. The tactical model was not applicable to any of the examples of evidence use.

Political model

Evidence was mostly used to frame the public health issue of HPV and CC. Regional and sub-national prevalence data, projections of how many lives could be saved, and the vaccine's cost-effectiveness were

used by stakeholders at the EPI to demonstrate the need for and worth of an intervention. Thereby, the evidence played an advocacy role; its consumers built a case for why this issue should receive attention at higher political levels. In this instance, the quality and accuracy of the evidence were of less interest.

Moreover, even though it was less frequently discussed across the study population, evidence on the low rate of adverse effects of the vaccine was used in the communication strategies. Arguably, this is another example of the applicability of the political model.

4.4 Discussion

This study set out to examine what, how, when, and by whom (Text box 4.4) evidence is used in the context of a vaccine introduction at the national level. The research was conducted by exploring the perspectives held by stakeholders engaged in the national policy development and implementation of the HPV vaccine in Mozambique.

In the long time frame from the agenda setting phase in 2009 to the programme implementation in 2021 a variety of evidence was developed and used. Stakeholders actively sought evidence; this conveyed stakeholders in Mozambique have a positive attitude toward the concept of using evidence. Which evidence was considered relevant depended on the stage of the policy and programme development. First, there was a need for situational evidence, i.e., on HPV and CC epidemiology, as well as vaccine acceptability. Then, following the demonstration programmes, the demand shifted to evaluation evidence on the vaccination programme, specifically, coverage rates achieved, reasons for gaps between targets and coverage reached, and acceptability. Throughout this process, sub-national granular evidence was identified as critical to addressing stakeholders' questions. Evidence provided by global stakeholders and evidence from other countries was useful as verification, guidance, and support for sub-national decisions as well as structuring evidence needs. Specifically, experience with the HPV vaccine introduction in relatable countries (e.g., Angola), other vaccines introduced nationally, as well as other interventions that target adolescents in Mozambique allowed to foresee and plan for challenges and reduce uncertainty. These findings suggest that the dimensions in the frameworks by Burchett et al. [59] and Guillaume et al. [174] may change over time. Overall, the development and use of evidence appeared systematic and orderly, while contextual factors led to surprising turns in

this process.

Text box 4.4.1: What, how, when, and by whom is evidence used in the context of a vaccine introduction at the national level

How: Evidence is used to inform policy development and implementation. The development and use of evidence appeared systematic and orderly, although contextual factors led to unexpected turns in the process, e.g., introducing the vaccine nationally through a different delivery strategy than decided on in previous planning meetings.

When: The research revealed that stakeholders actively sought and utilized a variety of evidence throughout the long timeframe of agenda setting and program implementation. The relevance of the evidence depended on the specific stage of policy and program development.

What: Situational evidence, such as epidemiology and vaccine acceptability, was initially needed, followed by evaluation evidence on program coverage and acceptability. Sub-national/provincial-level and more granular evidence was deemed critical in addressing stakeholders' questions, while global evidence served as verification, guidance, and support for national and sub-national decisions. Stakeholders emphasized the importance of tailoring global evidence to the sub-national context and engaging with community leaders and teachers.

By whom: The study identified two hubs in the evidence issue network: the Expanded Program on Immunization (EPI) and the Manhiça Health Research Centre (CISM) as core evidence consumers and producers. Additionally, the study also highlighted the need for technical capacity among decision-makers in Mozambique and the importance of bottom-up program planning for achieving higher vaccination coverage rates. The study participants recognized the influence of street-level bureaucrats in policy implementation and emphasized the value of their engagement.

In contrast to how evidence is used by GHOs, the problem-solving model is surprisingly applicable to describe the development and use of evidence in the issue network in Mozambique. Specific pieces of evidence could be recalled by their consumers and identified as having been influential in the desk review, e.g., the email exchange. In the knowledge translation literature, the applicability of the linear model has been generally contested. The scientific community has been called out for their positivist assumptions around evidence use; policy scholars frequently emphasise, researchers need to think more realistically about political realities and competing priorities [378]. While this research

shows that, indeed, political interference led to decisions that were not evidence informed, programme implementers and public health decision makers had the intentions to use evidence to the best of their ability.

High value was placed on global evidence that was localized. The tailoring of global evidence, and evidence triangulation is common and have been widely discussed in other public health policy topics [201, 272]. To use the words of one key informant "it is necessary to work with local languages... local evidence helps to understand how the regional and international strategies can be adopted" [294]. Thus, for the effective translation of international health policy recommendations to national contexts, in-country technical capacity among decision-makers is required [105, 389]. More recently, integrative or automated analysis tools and reporting pipelines, such as dynamic meta-analysis [362] and living HTA [383], have been suggested in the literature to make the evidence adoption process more dynamic. Thokala et al. define a living HTA "as a full HTA that is planned from the outset to be updated at regular intervals or at specific trigger points (e.g., in light of new evidence and/or feedback from stakeholders)" [383]. Whether these tools are useful and can be implemented to support the introduction of vaccination programmes and other interventions in LMIC should be subject to further research.

Systematically mapping out which evidence was perceived relevant over time also helped identify which evidence did not inform the vaccination programme. Notably, to the surprise of the researcher, throughout the policy development and programme implementation, there was no demand for quantitative evidence on the potential impact of the vaccine in terms of population health, e.g., generated through mathematical models forecasting relevant programme outcome measures. Surprisingly, none of the quantitative evidence that appeared policy relevant to the researcher, PC [9, 211] was recalled by study participants. More recently, another research estimating the impact of the HPV vaccination in Mozambique has been published [175]. However, this was published after the literature review and data analysis had been completed. To my knowledge, how mathematical models as a form of evidence has informed vaccination programmes and policies at national level has not been researched.

Further, evidence producers and consumers placed a high value on engagement with street-level bureaucrats, e.g., community leaders and teachers; this signals recognition of the power these stakeholders have over the implementation of policy. Purposeful community engagement in research for policy and programme implementation has been advocated for extensively in the literature in the context of the

HPV vaccine [177, 209] and other interventions [120]. Possibly, the diversity of stakeholders that contribute to and are central to the evidence issue network in Mozambique is what positively shaped the development and use of evidence here.

Further, questions posed at the ministry define research objectives. Rather, in the context of national policy development, the problem definition should result from dialogues between evidence producers and consumers. This is in line with the findings from the study on the development and use of evidence at the global level [97] (Chapter 3). Further, stakeholders at the MoH and the National Institute of Health lamented that much of research is not made accessible to the public or in relevant formats more generally. Echoing this finding, the scoping review on the barriers and facilitators of translating health research findings into policy in sub-Saharan Africa by Damba et al. [105] found that research is published in journals, which is not an accessible format for policymakers. Further SNA may be conducted to identify strategies on how to increase connectedness and thereby get "to hear critical voices that challenge the dominant discourse on the programme planning and policy" [147].

Moreover, the SNA could be advanced by exploring the types and intensity of relationships, e.g., by drawing on frequency of engagement, and how this changed over time.

Cairney and Oliver also question what the responsibility of scientists in the network of stakeholders is [68]. All literature reviews of the barriers and facilitators of EDU conclude with the recommendation that evidence dissemination and communication needs to be improved [105, 281, 289]. Thus, to get decision-makers' attention to specific evidence, scientists are encouraged to communicate their work more strategically by drawing on the knowledge of mental short-cuts. For example, while this is not advised, scientists can decorate evidence with manipulative emotional appeals to persuade decision-makers [68]. But, concealing evidence in the interest of persuading decision-makers of policy options thwarts scientific objectivity and can lead to an ethical dilemma as scientific credibility is undermined [68].

This is the first time the policy process has been documented in such detail in Mozambique. Considering the complexity of vaccine introduction processes, the integration of political science with public health helps understanding the change in evidence needs over time [144]. This depiction can be considered as a reference point for the introduction of other vaccination programmes.

It was difficult to discern differences in perceptions across evidence consumers and producers as many

stakeholders assumed hybrid roles. The responsibilities of the variety of study participants that were identified through the snowball approach often included evidence production, translation, and decision making. There was no dedicated stakeholder, who would assume the role of a knowledge broker. Considering the knowledge translation literature, it is advisable to introduce dedicated knowledge brokers. In the context of vaccine introductions, where stakeholders have vested political interests, and many lack impartiality, a knowledge broker could objectively synthesize recommendations stemming from research as well as facilitate the dialogue between the scientific community and the decision makers. Thus, the knowledge broker would require experience of how robust research is developed, have understanding of decision-making processes in organizations in the issue network around a vaccine introduction, and frequently engage with both parties. The knowledge broker may be positioned inside the epicentre of decision-making processes, in a senior position with decision-making power so that evidence-informed decision-making can be institutionalized.

4.4.1 Limitations

This study is subject to several limitations. Firstly, interviews conducted in Portuguese had to be translated. While this is best-practice, to mitigate the risk of misinterpretation or distortion of data in the process of translating the interviews, the translator, MM familiarized herself with topic-specific concepts in the areas of new vaccine introductions and evidence-informed decision-making.

Secondly, the 42% of individuals, who were invited to participate in this study did not respond to the invitation. With the exception of 9% of the people (n=2), who were invited but did not participate, individuals did not reply to the invitation to participate. Thus, the study population may be subject to a selection bias. It is possible that the invitation never reached these individuals as their engagement was early in the policy development and they moved to a new organization since. To mitigate the effect of this potential bias on the study, PC ensured the number of participants engaged was balanced over different time points throughout the policy development. The two remaining participants, who did not partake in the study asked someone else in their organization to talk on their behalf. Thus, at least institutional experience informed this study.

Thirdly, there was a potential recall bias as there was a long latency between some interviewees' engagement and the time of data collection. To reduce recall bias during interviews, the recall aid in

form of a timeline of key events was provided by the interviewer.

Fourthly, while global level constituencies interviewed for this study were in part from the same institutions as in Chapter 3, they were not the same individuals. Further to this, interview schedules had slightly different emphases with this Chapter exploring the definition and use of different types of evidence. Thus, comparisons in conclusions should be made carefully as individuals reflected on their personal views on evidence use.

Lastly, this research reflects on the views held by a subset of individuals in the issue network around the HPV vaccine introduction. High-level political decision-makers, e.g. the Minister of Health, and individuals, who were influential spokespeople of the vaccine, e.g. the First Lady, would have enriched the findings of this research. Additionally, the study population did not include community leaders and other key influential actors, who are directly engaging with girls in the target groups and their guardians. As they have also been engaging with different forms of evidence and policy development, their perceptions should be subject to future research.

4.5 Conclusion

In examining the development and use of evidence in the policy development and programme implementation of the HPV vaccine, stakeholders' high value placed on situational (e.g., the current epidemiology of HPV and CC), and retrospective science (e.g., evaluation reports) as evidence for policy and programme development was identified. This study highlights the difference in the role evidence plays at the national policy level compared to the global, organizational level. Further, this study focused on the HPV vaccination programme rather than immunisation programmes more generally. The scope of the evidence was also not confined to evidence developed with mathematical models, but rather considered all forms of evidence.

In the context of national policy and programme development, the value of evidence is contingent upon the perspectives, priorities, and interests of different stakeholders involved in the political and programmatic decision-making process. While many different types of evidence were identified as policy-relevant during the policy development, mathematical models were not used as a tool to develop evidence for the HPV vaccination programme to date. Further, none of the evidence identified was

developed using a participatory approach. Thus, in the following three chapters (Chapters 5 - 7), a participatory approach to developing and using evidence, specifically, generated with mathematical models, is explored for future policy and programme decisions at national level.

Chapter 5

Identification of policymakers' and programme planners' knowledge gaps

5.1 Preface

Early knowledge translation scholars have conceptualized the "gap" between scientists and policymakers in terms of a "two communities" logic, with actors coming from different cultures and not speaking the same language [176]. The co-production of evidence, for example, through participatory modelling, has been suggested as a solution to "bridge" the gap between scientists and policymakers [24, 402]. One way of co-producing evidence is the co-designing of research questions together with potential evidence consumers [279].

The aim of this third results chapter is to capture the evidence needs of actors in the issue network around the HPV vaccination programme in Mozambique. The focus of this exploratory study is on identifying evidence gaps that can be addressed with mathematical models to formulate policy-relevant research questions and define how each outcome is measured. Following the methods, findings are summarized, and approaches to how the evidence gaps have been addressed with mathematical models in other contexts are discussed.

5.2 Methods

5.2.1 Study design

An exploratory qualitative study was conducted through the collection and analysis of data from in-depth, semi-structured interviews. The data that informed the research presented in this chapter was collected during the same interviews as those in Chapter 4, which concerned the exploration of evidence use and development throughout the vaccination program planning process. The final section of the interview guide (Appendix C) contained open-ended questions to elicit stakeholders to reflect on and describe the aspects of the HPV vaccination programme in Mozambique that they believed to be less understood, known, or conceptualized. During the interviews, mathematical models as a method to develop evidence were not mentioned so that interviewees' responses would not be preempted. Instead, the interview inquired about any form of evidence that could help stakeholders in the future.

The data was managed following the same steps as outlined in Chapter 4.

5.2.2 Data analysis

Interview data were analyzed inductively. Thereby, emergent themes were identified. Knowledge gaps were categorized by theme. Knowledge gaps that could be addressed using mathematical models were extracted and translated to sets of research questions by PC.

To compare knowledge gaps across types of study participants, participants were characterized by the type of organization (M: ministry; NGO: non-governmental organization; IO: international organization) they were affiliated with, and the level at which their organization was operating (HQ: global; N: national; P: provincial).

5.3 Results

Five broad themes were identified in the interview responses of 28 study participants (Table 4.1): (1) Vaccine delivery strategy; (2) Distributional impact of the vaccine programme; (3) Vaccine economics; (4) Comparison to other CC prevention methods. Table 5.1 presents interview extracts which helped

Table 5.1: Policymakers' questions about the HPV vaccine in Mozambique that can be addressed using mathematical models. Abbreviations: M: ministry; NGO: non-governmental organization; IO: international organization; HQ: global; N: national; P: provincial.

Interview extract	**Knowledge gap translated to research question**	**Potential outcome measure(s)**
1. Vaccine delivery strategy		
N, IO: "Also the issue of sex. Because there was a lot of discussion about whether we could introduce to boys or give it only to girls, because boys can also transmit the disease and may have the disease and can transmit it to others it is true that they will not have cervical cancer because they do not have a cervix, but they can transmit the disease." [308] *P, M: "We are now vaccinating nine-year-old children. But we want to understand why it's only nine years old and why just the girls and not the men. Are men not a source of HPV transmission?" [302]*	1.1 What would be the impact on population health if boys were also vaccinated?	Population-level burden of disease
N, IO: "For me it is more in relation to the broad target groups in terms of age group, because we only covered 9-year-old girls, but we also wanted to cover more. [. . .] So in our context of sexual intercourse in some parts of the country it starts very early, we have premature marriages, so how do we align that with what we want." [296]	1.2 What impact does sexual debut prior to vaccination have on the population health benefit (e.g., if older age groups are included in the target group)? How should the target group be defined with respect to sexual intercourse behaviour?	Optimal target group that maximizes the population-level impact in terms of burden of disease
N, NGO: "Practically we're not getting vaccines for the age group that we had initially intended. We're just getting a single cohort. We're going to do nine-year-old girls. So these are the things that we need to think about. These are the things that we need, structuring it like you would. And I think this is where the technical assistance needs to bring in these kinds of good practices into the ministry." [313]	1.3 What implications does the change in target cohorts from a multi-age-cohort strategy to a single-age-cohort strategy have?	

Continued on next page

Table 5.1: Policymakers' questions about the HPV vaccine in Mozambique that can be addressed using mathematical models. Abbreviations: M: ministry; NGO: non-governmental organization; IO: international organization; HQ: global; N: national; P: provincial. (Continued)

Interview extract	**Knowledge gap translated to research question**	**Potential outcome measure(s)**
2. Distributional impact of the vaccine programme		
HQ, IO: "Then, going through with the programmatic people is what the potential delivery modes are and identify where girls at high risk are in the country. Is it in urban settings, in slum areas, so the issue is always to identify the high risk, and these are often in difficult-to-reach communities, literally in terms of geographic, but also just you can't identify them because they are in the informal sector or yeah. And that is more of a problem compared to high income countries, right due to roll out of the vaccine." [301] *HQ, IO: "Hard-to-reach populations. We seem to be very bad at. We sometimes call them out of schoolgirls in southern Africa, for example. The programme is really school based, and it's not very clear whether a very active attempt is made to deliver out of school. So, you know, some girls, including those in private schools, may just miss out on the vaccine because they're not part of the public programme. That is quite well, you could call it unacceptable, but that's a shortcoming. So I think, who we are reaching remains a black, you know, a grey zone. Nomadic populations in some parts of Africa, you know, so research is needed in that direction." [310] N, IO: "The issue of access to rural-urban vaccines I still cannot see this in the data I access. if we were seeing that the coverage is only in urban areas and the rural areas is not having anything, we have to do to change the strategy. So I can't understand whether it's urban or rural." [296]* *HQ, IO: "So I think some kind of modelling around looking at socioeconomic inequity indicators against HPV coverage." [312]*	2.1 How do inequalities in access to education and infrastructure reflect in vaccination programme impact?	Distributional impact of the vaccination programme across population subgroups
3. Vaccine economics		
N, R: "We do not know yet what the cost effectiveness of this vaccine is here in Mozambique. So, doing this analysis now will allow us to say whether the vaccine that was introduced will be cost-effective during this implementation period and in addition we will not only analyze Gardasil, the one that was introduced, we will also analyze the other two vaccines for Cervarix and Gardasil 9. So this will allow us to know in the medium to long term if we make the decision to change vaccines and how to adopt it. Not because we are going to propose to change this vaccine that has already been introduced, but perhaps in the medium and long term the other vaccines give us more advantage or we have reached the conclusion, making sure that the vaccine that was introduced last year is more cost-effective compared to the others." [314]	3.1 What is the cost-effectiveness of the different vaccine candidates?	Cost-effectiveness ratio

Continued on next page

Table 5.1: Policymakers' questions about the HPV vaccine in Mozambique that can be addressed using mathematical models. Abbreviations: M: ministry; NGO: non-governmental organization; IO: international organization; HQ: global; N: national; P: provincial. (Continued)

Interview extract	**Knowledge gap translated to research question**	**Potential outcome measure(s)**
HQ, IO: "And then particularly for costing is whether countries have access to Gavi prices or not. That often also makes a huge difference when it comes to economic impact for the product itself." [301] *N, M: "There is the aspect of the price of vaccines for us as managers and so we are taking into account that until now almost all the vaccines that we are using in our system are financed by partners and there always comes that fear of: what will happen if one day the partners do not want to pay for these vaccines." [293]*	3.2 What costs does the vaccination programme imply following the transition from Gavi funding? or What financial resources/budgets are required for the HPV vaccination programme over time?	Vaccination programme costs
N, IO: "If you reduce the number of women with cancer, you are also reducing the economic burden and investment in the area of treatment, so this is important to demonstrate." [296]	3.3 What is the wider economic benefit of introducing the HPV vaccine?	Resource savings; financial risk protection provided
N, IO: "I think that in the future, when there are projects of this nature, it is necessary that we can not only secure funds for the purchase of equipment, but we also have to secure funds for customs clearance, because if we do not deliver, if we sometimes look at those that are state budget funds, the Ministry of Health use it to clear it if it's not available so it takes time. Then it is also necessary in the budgets to make planning, to make forecasts in order to have the budget to cover this expense" [306]	3.4 What financial resources/budgets are required for the HPV vaccination programme over time?	Financial resources required
4. Comparison to other CC prevention methods		
N, NGO: "It would also be important to have vaccination data and what is the level of immunization done so far, the question related to safe sexual practices, what is the tendency for condom use among adolescents and young people to also have this information about what the probability would be in a scenario where low vaccination and low rate of condom use, so what would that mean from the point of view of the incidence rate and prevalence of cervical cancer in these communities when trying to cross-check that data and see how it can work." [297]	4.1 How does the vaccine introduction relate to/interact with/compare with other public health interventions and safe sex practices (e.g. condom use)?	Comparison of CC elimination strategies and combinations of these

identify knowledge gaps, and, respectively, possible research questions. The third column presents outcome measures that could be relevant to address evidence needs. Numbers in parentheses in the following paragraphs refer to question numbers in Table 5.1.

5.3.1 Vaccine delivery strategy

Based on multiple interviewee accounts, programme operationalization and the vaccine delivery strategy via schools were subject to a lengthy planning process after the HPV vaccine demonstration programme was concluded in 2015. Eventually, the Ministry introduced the HPV vaccine in November 2021, when schools were closed, against the advice of the task force team in charge of programme planning. Due to global supply chain shortages of the vaccine, only a single age cohort (9-year-old girls) were targeted in the first year of vaccination. Study participants remained wary of the decision to introduce the vaccine in November 2021 and to focus on 9-year-old girls only. The impact of vaccinating a single cohort only, should be explored in further analyses as voiced by a study participant at a nationally operating NGO (1.3):

> N, NGO: "Practically we're not getting vaccines for the age group that we had initially intended. We're just getting a single cohort. We're going to do nine-year-old girls. So these are the things that we need to think about. These are the things that we need, structuring it like you would. And I think this is where the technical assistance needs to bring in these kinds of good practices into the ministry." [313]

Further, two study participants, one at the provincial level in government, and the other at a nationally based international organization were interested in knowing the potential impact on population health if boys were also included in the target group (1.1)

Study participants highlighted that it is important to evaluate the implications of targeting an older age group, that could have had sexual intercourse already and including boys in the target group (1.2).

5.3.2 Distributional impact of the vaccine programme

Interviewees at IOs (HQ, N) flagged that the vaccination programme may not be accessible to hard-to-reach population groups, such as girls who are not attending schools or are too far away from

healthcare facilities (2.1). For example, a study participant at an IOs (HQ) highlights that access to the vaccine is likely to be limited for girls, who do not attend state-run schools:

> HQ, IO: "The programme is really school based, and it's not very clear whether a very active attempt is made to deliver out of school. So, you know, some girls, including those in private schools, may just miss out on the vaccine because they're not part of the public programme. That is quite well, you could call it unacceptable, but that's a shortcoming. So, I think, who we are reaching remains a black, you know, a grey zone. Nomadic populations in some parts of Africa, you know, so research is needed in that direction." [310]

Another study participant at an IO (HQ) voiced interest in analysing socioeconomic inequity indicators and vaccine coverage.

The concern of having varying vaccine coverage by rural and urban population sub-groups was also voiced by a study participant at a nationally operating international organization. However, according to the study participant, this information cannot be elicited from the vaccine coverage data.

5.3.3 Vaccine economics

Study participants at national and international research institutes were interested in the cost-effectiveness of the vaccine (3.1). The cost per fully-immunized girl had previously been quantified by Alonso et al. [9] and Soi et al. [370]. These cost estimates were derived from the demonstration programme experience in Mozambique. Further, a study participant at a national research institute [314] was, at the time of data collection, working on a new cost-effectiveness study, which relies on mathematical modelling. This mathematical model aims to evaluate the cost-effectiveness of three HPV vaccines (CECOLIN, CERVARIX, and GARDASIL-4) in the medium and long term [175].

Further, study participants at an IO (HQ, N) and the Ministry (N) wanted to understand how much the vaccine will cost once Gavi no longer supports the immunisation programme in Mozambique (3.2). The study participant at the Ministry voiced concerns about the sustainability of the vaccination programme:

> N, M: "There is the aspect of the price of vaccines for us as managers and so we are taking into account that until now almost all the vaccines that we are using in our system are financed by partners and there always comes that fear of: what will happen if one day the partners do not want to pay for these vaccines." [293]

Moreover, study participants at IOs (HQ), the Mozambican NITAG, and national research institutions were interested in learning about the vaccine's wider benefit in Mozambique (3.3). For example, one study participant was interested in understanding the impact of the vaccine on the health sector, e.g., in terms of resources that will be saved due to fewer CC patients, as stated here:

> N, IO: "If you reduce the number of women with cancer, you are also reducing the economic burden and investment in the area of treatment, so this is important to demonstrate." [296]

Another study participant, also at a nationally operating NGO, flagged that vaccination programme costs should also be forecasted so that budgets account for various aspects of the programme, e.g., equipment purchases (3.4).

5.3.4 Comparison to other CC prevention methods

Study participants were interested in how the HPV vaccine interacts with other primary prevention interventions, such as safer sex practices, as one study participant at an NGO (N) and a researcher at an international research institute highlighted (4.1).

5.4 Discussion

Hence, study participants would like to learn about the distributional impact of the vaccination programme on CC prevention across poorer socioeconomic and rural population subgroups.

This exploratory study identified knowledge gaps of stakeholders in the issue network around a recently introduced HPV vaccination programme in Mozambique. This is an important step to understand what policy-relevant evidence for further programme planning and other decision-making processes

should encompass. I found that the actors are interested in learning about (1) the impact of including boys, and multiple age cohorts in the target group on population health, (2) the impact of inequalities in access to the vaccine on population health on population health, (3) the cost implications of the vaccine, the vaccine's cost-effectiveness, and cost savings for the health sector, and (4) the extent to which benefits from multiple interventions can be attributed to the vaccination programme. The knowledge gaps were translated into research questions by PC, which are addressed using a mathematical model in subsequent research. This approach to identifying and addressing research priorities was a rich strategy, which aids the integration of different perspectives on evidence needs into the development of evidence for policy related to the HPV vaccination programme in Mozambique.

With respect to the evidence needs identified and definitions of impact elicited in this study, examples of tools or mathematical modelling approaches to estimate specific impact measures in other contexts, either in other countries or for other public health interventions, are summarized in Table 5.2. Notably, all of these approaches complement each other in determining the full value of the HPV vaccine. These findings emphasize the relevance of more recently developed frameworks, which aim to evaluate the full value of vaccines [30, 32, 70, 196, 371], but also the importance of questioning how individuals define impact. The wider impact of vaccines span from the fulfilment of societal preferences to macroeconomic gains [30]. Conventional health and economic evaluations often do not capture the salient features of vaccines that are relevant to decision-makers. In recognition of other positive externalities of vaccination, new approaches value vaccines by quantifying productivity-related individual, community, and broader macroeconomic impacts. However, these frameworks are not based on systematically evaluating evidence needs by reflecting on the perspectives of potential evidence consumers.

I found that mathematical models can be used in response to actors' evidence needs around the vaccination programme. General methods to address questions raised by actors in the issue network have been proposed in the literature, e.g., [250, 387]. Yet, I found that there were nuances in the perspective on what impact should be measured and/or with which metric across participants. On the one hand, study participants' definition of impact fall under the narrow vaccine evaluation perspectives, which are covered in conventional epidemiological and health economic models: health gains, treatment cost, treatment cost savings, and reductions in the time costs of caring associated with a vaccine. Other evidence needs fall under the broader vaccine evaluation perspective, which encompasses indirect effects of the intervention on the individual, society, and the healthcare system. Identified evidence

Table 5.2: Examples of mathematical modelling approaches applied to address identified evidence needs.

Policy-relevant research question posed by actors in the issue network	**Examples of tools or mathematical modelling approaches applied in the literature**
1.2 What impact does sexual debut prior to vaccination have on the population health benefit (e.g., if older age groups are included in the target group)? How should the target group be defined with respect to sexual intercourse?	HPV-specific, regional: [118]: Transmission-dynamic model with which the optimal age cohorts to vaccinate were identified.
2.1 How do inequalities in access to education and infrastructure reflect in the vaccination coverage?	HPV-specific, national: [332]: Economic evaluation of routine HPV vaccination quantifying distributional programme benefits following the Extended Cost Effectiveness Approach
3.1 What is the cost-effectiveness of the different vaccine candidates?	HPV-specific, global: [244]: Static models, dynamic economic models and a Markov model have been used to evaluate the vaccine on its cost-effectiveness in various contexts.
3.2 What financial resources/budgets are required for the HPV vaccination programme over time?	A variety of vaccine programme costing studies are stored in a user-friendly database here: https://immunizationeconomics.org/thinkwell-idcc
3.3 What is the wider economic benefit of introducing the HPV vaccine?	The definition of "wider economic benefit" needs to be determined together with the intended evidence user prior to identifying an appropriate modelling approach [43].
4.1 How does the vaccine introduction relate to/interact with/compare with other public health interventions and safe sex practices (e.g. condom use)?	Not HPV-specific, global: [114]: A general model is presented to compute the effect of multiple, overlapping, and targeted interventions on epidemiological incidences.

needs under this perspective include FRP for the individual and tangible resources that are saved from a health sector perspective, e.g., hospital beds and other treatment capacities required for HPV and CC patients. Table 5.3 provides a summary of which metrics can be calculated for each perspective to evaluate vaccination programme impact.

Table 5.3: Measures of HPV vaccine impact modelled in this study.

Perspective	**Metric**
Population health	Reduced CC morbidity and mortality
Health sector	Tangible resources saved by the health sector; Reduction in health inequity
Societal	Financial risk protection provided; Distribution of outcomes

The findings of this study are specific to the context of Mozambique but can also inform studies conducted in other resource-limited settings where the HPV vaccination programme has recently been introduced or is considered for introduction. However, outcome measures should be defined with actors in the issue network to be relevant, and specific to the vaccination programme that is evaluated. Other vaccine-preventable diseases may have significantly different consequences on hospital capacities, for example.

Further, findings of this study should not be interpreted without an analysis of the full value of other prevention methods. While the HPV vaccine is the most effective intervention method against CC, other prevention methods, e.g., the promotion of safe sex practices, could have a broader effect on other sexually transmitted diseases as well.

The approach used in this study is a form of participatory modelling. Research questions of previously conducted participatory modelling studies had been defined prior to engaging with participants. More commonly, in participatory modelling studies, participants engage in the process of the model development by eliciting and depicting factors that should be included [149, 337]. This study is novel in that research questions are co-designed and thereby did not take for granted what the policy-relevant research priorities in the context of a vaccination programme should be.

The participation of various types of stakeholders in the issue network contribute to valuable hypotheses about what the broader impact of the HPV vaccination programme under unexpected circumstances is. For example, there was a consensus among stakeholders at IOs, the Mozambican NITAG,

and national research institutions that evidence on the distributional impact of the vaccine across population sub-groups is very important for the issue network. Seeking the opinion from a diversity of stakeholders also allows to synthesize ideas across participants' perspectives, and thus promotes learning. In this sense, the evidence addressing elicited research questions would then become "boundary objects" [374]. Initially proposed by Star and Griesemer [372], "boundary objects" are the tangible objects that become the means to knowledge translation; notably, they are tailored to needs of the evidence consumer(s), can have different meanings, yet, maintain "a common identify across all sites" [255]. Furthermore, modelling assumptions and the status quo in the modelling environment may be challenged through the participatory approach. Thereby, advancements of models may be facilitated.

Thus, to address the elicited evidence needs, an approach that facilitates the estimation of broader benefits of vaccines is required in addition to more conventional approaches. In this context, broader benefits are tangible healthcare resources saved and the vaccination programme's effect on healthcare inequity. An approach used in studies that aimed to estimate similar broader impact measures is the ECEA [393] (Chapter 5). With this approach, broader impact measures, such as the socioeconomic distribution of outcomes and reduction in catastrophic health expenditure incidence as a result of a policy [393] are derived from products of conventional health and economic impact analyses, e.g., health gains and cost savings. Similarly, estimated averted disease burden can be translated to workforce saved using approaches such as needs-based workforce modelling [358]. For this purpose, existing models of infectious diseases, e.g., [166] with which health gains can be estimated can be extended with further outcome measures.

5.4.1 Limitations

It is also important to acknowledge two of the main challenges that I faced in this study. Firstly, participatory modelling requires a high level of trust from the study participants as they are asked to share what they were uncertain or not knowledgeable about in their line of work. The highly trained and experienced interviewers tried to obtain the participants' trust by reassuring them that their identity would be kept anonymous, and that information collected during interviews could always be revoked. Every participant had the opportunity to amend their answers post interview, in case they felt they had shared confidential information, for example. Further, questions on evidence gaps were only posed towards the end of the interview, once some form of relationship between the interviewer

and the participant had been established.

Secondly, the interviews were time constrained. This meant that study participants may have felt time pressured, when trying to think what their priority evidence gaps were. Thus, Iencouraged participants to reach out to the study team in case further questions would arise following the interview.

5.5 Conclusion

In conclusion, stakeholders in the issue network around the HPV vaccination programme were interested in determining the broader value of the vaccine, from a population health, health system, and societal perspective. This research contributes to this literature in that it probes the perspectives of potential evidence consumers on how vaccines should be valued.

With respect to question 2.1, 3.2 and 3.3 in Table 5.2, the aim of the subsequent chapter, Chapter 6 is to assess the impact of the HPV vaccination programme from a population health, health sector, and societal perspective. Question 2.1 was chosen as the topic received most traction, with four interview participants questioning vaccination programme equity. 3.3 was chosen, as the ECEA framework was amenable to be extended with other outcome measures. 3.4 was chosen to compare the costs associated with the programme to its wider impact, including healthcare treatment resources averted, and labour saved.

Chapter 6

Extension and application of a mathematical model in response to knowledge gaps around the HPV vaccination programme in Mozambique

6.1 Preface

In the previous chapter, Chapter 5 I found that actors in the issue network around the HPV vaccination programme in Mozambique are interested in learning about the programme's:

1. Health benefits as well as tangible healthcare resources (hospital beds and staff time) saved by the health sector
2. The distribution of health and financial benefits across population subgroups
3. Effect on health inequity across population subgroups

The objective of this fourth results chapter is to assess the impact of current HPV vaccination programme efforts, hypothetical scale-up scenarios, and global targets on population health, healthcare resources, catastrophic health expenditure incidence, and health disparities in Mozambique. Thereby, I aimed to quantify the value of the vaccination programme from a population health, health sector, and societal perspective. More specifically, I evaluated the magnitude and distribution of expected health and economic outcomes by hypothetically increasing coverage of the HPV vaccine and government-funded treatment coverage.

The chapter begins with an explanation of the methodology, outlining how a static cohort model was applied and extended, the data used to parameterize the mathematical model, the outcome measures, and the analysis plan. In the subsequent section the results are presented. The chapter concludes with a discussion of the model application and extension, and the method to explore vaccination programme equity.

6.2 Methods

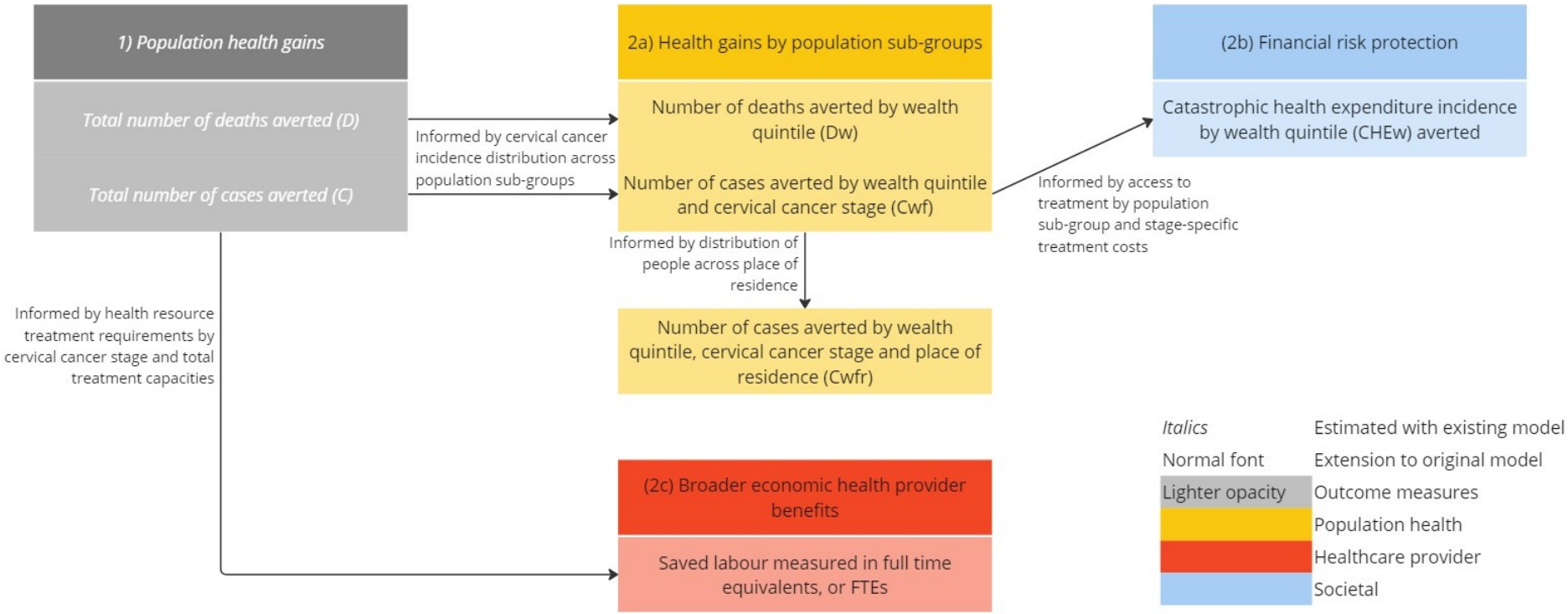
I used the ECEA approach to evaluate impact of current HPV vaccination programme efforts, hypothetical scale-up scenarios, and global coverage targets (90%) on population health, healthcare resources, catastrophic health expenditure incidence, and health disparities. Specifically, I used a previously published static cohort model [166] to estimate population health gains, which were then used as input values to estimate benefits from a health sector perspective and the level and distribution of health gains across population subgroups, and FRP provided to population subgroups (Figure 6.1). I also estimated vaccination programme costs.

6.2.1 Outline of the model to estimate health outcomes of the HPV vaccination programme

Modelling the impact of vaccination on population health can be done using either a static cohort model approach or a dynamic disease transmission modelling approach. HPV-modelling guidelines generally promote the application of disease transmission models, because they account for changes in the force of infection induced by vaccination [73]. However, static cohort models may also be applied if (1) a conservative, i.e., under-estimate, of the measure of impact and value for money is sufficient, and (2) the analysis does not compare multiple interventions with herd effects.

Using a static cohort model is subject to a number of advantages. Firstly, the model can be applied in contexts in which limited data is accessible. Key information required to parameterize the model is high-level epidemiological and demographic information. Secondly, in comparison to dynamic disease transmission models, the approach is less analytically complex and the model application does not

Figure 6.1: Schematic of the extended cost effectiveness analysis (ECEA) approach application. Population health gains (grey box) are estimated using Goldie et al.'s [166] static cohort model. All other outcomes are computed with outcomes from Goldie et al's model.



require high computing power. For example, the simulation can be executed in accessible software programmes such as Excel. On the other hand, the assumptions made by applying a static cohort model are inherently simplistic, and the model's application carries several disadvantages. Firstly, the force of infection, i.e., the instantaneous rate at which susceptible people become infected is constant over time. Thereby, the model fails to estimate indirect health impacts of vaccination on unvaccinated (herd immunity), which is unrealistic. Secondly, the model focuses on the target population (e.g., 9-year old girls in a given year) only. This is an abstract concept to communicate to policymakers, who are concerned with whole-population decisions.

I used a static cohort model previously developed by Goldie et al. [166], which had been applied in studies with similar aims in other countries [232, 332] (Figure 6.1). The model can be used to project the health impact of HPV vaccination at population level. The target cohort group(s) (e.g., 9-to-14-year-old girls) are tracked prospectively over their lifetime. In each time step, in this case *year*, the number of CC cases caused by HPV infection is simulated based on simplifying assumptions (duration and stage distribution of, and mortality from CC, HPV-16/18 serotype distribution in CC (Table 6.1)). The number of averted cases and deaths is estimated by subtracting the outcomes assuming a vaccine is introduced from the outcomes assuming no vaccine is introduced. This reduction is applied at population level, considering age-structured population prospects and background mortality. Population health outcomes (the number of averted CC cases by stage (c_f), following the International Federation of Gynaecology and Obstetrics, or FIGO, system and averted CC deaths) are then aggregated over the target cohort(s)' lifetime horizon.

6.2.2 Distributional outcome analysis

Following the ECEA approach, aggregated health gains estimated with the static cohort model can be used to quantify health gains for defined population sub-groups [393]. This approach can account for varying (1) coverage of the intervention (further discussed in section 6.2.3), and (2) distribution of disease burden across population sub-groups (d_w). An analysis conducted in five East African countries has shown that the level of education, wealth, and type of place of residence (rural v urban) are associated with the number of cancer risk factors a woman is exposed to. Similarly, in the United States, it was found that poorer living conditions, with ineffective and inadequate treatment are associated with increased incidence rate of HPV-associated cancers [33]. Moreover, Haidari et al.

Table 6.1: Parameters, values (at baseline), and variations in scenario or sensitivity analyses. Parameters, which do not have a symbol were used in the static cohort model only; they are not further referenced in the analysis.

Parameter	**Symbol**	**Value**	**Variations**	**Ref.**
Female population		Total female population as of 2022: 16,793,302		[381]
CC incidence by age		Appendix F, Table F.1		[390]
HPV-16/18 type distribution		0.51/0.49		[130]
Stage distribution of detected cancers by FIGO stage	f	Stage I: 0.09 Stage II: 0.36 Stage III: 0.47 Stage IV: 0.08		[74]
Vaccination coverage	τ	18.9%	Vaccination scenarios outlined in Table 6.2	
Vaccine wastage		5%		[320]
One-time-introduction cost per targeted girl in US$		2.00		[332]
Recurrent delivery cost per girl in US$		1.70		[332]
Vaccine price per dose in US$		4.50		[322]
Distribution of CC incidence across wealth quintiles	d_w	Q1: 29.7% Q2: 20.9% Q3: 24.7% Q4: 13.9% Q5: 10.8%	Risk of developing CC is assumed to be (a) uniformly distributed (b) linearly decreasing from Q1 to Q5.	[350]
Distribution of wealth quintiles across residence types	d_t	Urban Q1: 57% Urban Q2: 27% Urban Q3: 9% Urban Q4: 3% Urban Q5: 4% Rural Q1: 27% Rural Q2: 28% Rural Q3: 25% Rural Q4: 17% Rural Q5: 3%		[263]
Distribution of population across types of residence		Urban: 38% Rural: 62%	d_u	[264]

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Table 6.1: Parameters, values (at baseline), and variations in scenario or sensitivity analyses. Parameters, which do not have a symbol were used in the static cohort model only; they are not further referenced in the analysis. (Continued)

Parameter	**Symbol**	**Value**	**Variations**	**Ref.**
Direct medical treatment costs by FIGO stage in US$	o_f	Stage I: 2,989 Stage II: 2,999 Stage III: 1,744 Stage IV: 1,741	Varied by ±20% in sensitivity analyses.	[276]
Proportion of direct medical treatment costs covered by healthcare provider	p	0	Minimum required coverage for an effect on CHE incidence is estimated for each wealth quintile.	[107]
CHE threshold	t	10% of annual household expenditure	40% of non-food annual household expenditure	[143]
Annual household consumption by wealth quintile as a proxy for for expenditure	E_w	Estimated (see eq. 6.3)		
Average household size	h	4.78		[263]
Monthly per capita consumption in MZN (2019/20)	e_w	Q1: 224 Q2: 585 Q3: 990 Q4: 1,655 Q5: 5,022		[263]
Proportion of patients seeking treatment at Central Private Hospital	v	4.70%		[163]
Access to general care by wealth quintile	γ_w	Q1: 57.0% Q2: 67.8% Q3: 66.6% Q4: 79.9% Q5: 81.8%		[263]
Medical personnel labour cost by FIGO stage in US$	m_f	Stage I: 106.95 Stage II: 117.39 Stage III: 105.16 Stage IV: 102.24		[276]
Daily salary for medical personnel in US$	S	49.86 in 2013		[276]
Annual treatment capacity for CC patients at public hospital	r	900		[333]
Demand for CC treatment (2021)	P	5,325		[51]

showed varying access to the HPV vaccine in Mozambique as a result of significant education, healthcare, and economic within-country disparities [178].

Thus, in this analysis, health outcomes are stratified by socioeconomic population subgroup (w) and area of residence (r). To quantify health outcomes for each income group, health outcomes estimated with Goldie et al.'s model were stratified into wealth quintiles by using the distribution of CC across wealth quintiles (d_w). As a proxy for Mozambique, the distribution of CC incidence across wealth strata was informed by data collected in Tanzania [350], a country with comparable socioeconomic inequalities [76] and estimated age-standardized CC incidence (62.5 per 100,000 [199]). However, the validity of the data on the distribution of CC across wealth quintiles (d_w) is uncertain as the information is based on data collected at one hospital in Tanzania and has not been published in peer-reviewed literature. Thus, the distribution is varied in the sensitivity analysis (section 6.2.5).

When stratifying outcomes by population sub-groups living in different areas of residence, I differentiated between rural and urban populations. The distribution of people living in different types of residences by wealth quintiles was informed by data collected via the Family Budget Survey by the National Statistics Institute of in Mozambique [263].

6.2.3 Vaccination scenarios

Baseline scenario

In the baseline scenario, referred to as 'status quo', the health outcomes of the HPV vaccination programme with a two-dose schedule delivered via fixed facilities targeting 30 cohorts of 9-year old girls are estimated (i.e., every target cohort of 9-year-old girls from 2021 to 2051). In this scenario, annual vaccination coverage (τ) of 18.9% equally distributed across the population is assumed. This vaccination coverage is informed by vaccination coverage of both doses achieved over a 6-months period (April - September 2022) across Mozambique [334]. I assumed life-long 100% vaccine efficacy, i.e., complete protection against HPV-16 and HPV-18 infections and constant coverage rates over time.

All other scenarios are compared to the outcomes estimated in the baseline scenario. In each of the following scenarios, the impact of vaccinating 30 cohorts is evaluated, i.e., every target cohort of

9-year-old girls from 2021 to 2051.

Scale-up scenarios

I evaluate vaccination programme impact under two scale-up vaccination coverage scenarios (Table 6.2). In the 'global target' scenario, the Cervical Cancer Elimination Initiative coverage target of 90% is evaluated. In the 'half-way, flat coverage' scenario, I quantify programme impact with 50% vaccination coverage. In these three scenarios, I assume vaccination coverage to be uniformly distributed across the entire population of Mozambique.

Coverage distribution scenarios

I evaluate vaccination programme impact under two further scenarios in which the distribution of vaccination coverage is varied across population sub-groups (Table 6.2).

In the 'half-way, gradient coverage by quintile', vaccination coverage rates are varied by wealth quintile, with the overall coverage averaging 50% of the target population. This scenario is empirically informed by the distribution of access to general healthcare facilities across wealth quintiles. This distribution (γ_w) is informed by data collected via the Family Budget Survey by the National Statistics Institute of in Mozambique [263]. This information is considered to exhibit low validity as a proxy for access to vaccination for adolescents as the information is for the entire household and concerns the use of general care. Thus, the distribution is varied in the sensitivity analysis (section 6.2.5).

In the 'half-way, gradient coverage by residence' scenario, I evaluate the impact of the vaccination programme by area of residence. Again, while the overall average of vaccination coverage is 50%, I vary coverage by rural and urban population subgroups. Informed by the distribution of the population by area of residence and respective access to healthcare, using the Family Budget Survey by the National Statistics Institute [263], I assume that 68.4% of the target population in the urban area is vaccinated and 38.7% of the target population in the rural area is vaccinated.

Table 6.2: Vaccination programme scenarios

Scenario	Description	Coverage (τ)	Cohorts
Status quo	Informed by vaccination coverage recorded in the first year of the programme (2021).	18.9%	Single cohort and catch-up cohort
Global target	Informed by global Cervical Cancer Elimination Initiative target.	90%	30 cohorts
Half-way, flat coverage	Vaccination coverage is uniformly distributed across wealth quintiles.	50%	30 cohorts
Half-way, gradient coverage by quintile	The vaccination programme is assumed to have a gradient coverage across wealth quintiles, with an overall weighted vaccine coverage average of 50% across the population. The gradient is empirically informed by access to general healthcare (γ_w).	Q1: 41.2% Q2: 40.6% Q3: 44.7% Q4: 55.3% Q5: 68.2%	30 cohorts
Half-way, gradient coverage by residence	The vaccination programme is assumed to have a gradient coverage across populations living in different areas of residence [264], with an overall weighted vaccine coverage average of 50% across the population. The gradient is empirically informed by access to general healthcare (γ_w).	Urban: 63.9% Rural: 36.1%	30 cohorts

6.2.4 Costing and economic impact

Vaccination programme costs

I also use the static cohort model to estimate vaccination programme costs. I account for vaccine wastage, one-time introduction, and recurrent delivery costs (Table 6.1), for which assumptions made in similar research conducted in Ethiopia were adopted [332]. The HPV vaccine is acquired at US$ 4.50 per dose as per agreement with Gavi [322]. Vaccine wastage is assumed at a rate of 5% for a single-dose vial of liquid formulation [320]. As per Portnoy et al.'s assumptions [332], in the first year of the programme, vaccine introduction costs were estimated at US$2.00 per girl and a recurrent delivery cost of US$1.70 per girl thereafter. These cost estimates are derived from Gavi's standard vaccine support and vaccine introduction grant of US$2.40, which presents 80% of the total cost per girl. Thus, the total cost co-financed by Gavi and Mozambique is assumed to be US$3 on average per girl. This cost estimate includes non-recurrent introduction activities, i.e., planning, training, social

mobilization, and information, education, communication in the first year, as well as recurrent costs. Thus, the one-time-introduction cost per targeted girl is derived by subtracting the recurrent delivery cost per girl from the total estimated cost of US$3.

The recurrent delivery cost per girl is based on a literature review conducted by Gandhi and Lydon [160] as well as a costing analysis of vaccine programs across 94 LMIC by Portnoy et al. [331]. Gandhi and Lydon found that operational costs per person per dose were in the region of US$0.50 (median: US$0.33; range: US$0.03-US$0.79) and all under US$1.00. This estimate was not vaccine specific and not country specific; the estimate reflects the variance in costs by vaccine delivery strategy. The literature reviewed by Gandhi and Lydon focused on countries in Africa. Portnoy et al. estimated US$1.20 for routine delivery as a strategy. Thus, to pool these estimates, an average of US$1 as a recurrent delivery cost per girl is assumed in this model. Notably, delivery costs exhibit high variation. A research by Gallagher et al. [159] emphasized that school-based delivery was especially resource intensive, as school-based health programmes did not exist, which implies high costs for transport and staff per diems. Despite these estimates not being country specific, the estimated range for this estimate is thought to exhibit relatively high validity as it is derived from two papers that synthesized information from the region systematically.

Healthcare resource savings

Health resource requirements are derived from population health outcomes using a needs-based workforce modelling approach [17]. With this approach, the number of health professionals required to meet a population's health need is estimated based on the estimated prevalence of the disease and the appropriate standards of care for patients with the disease [17]. Other complementary analytical approaches that have informed health workforce policy and plans are demand-based, supply-based, target-based, and benchmarking [45].

A standardized metric for workforce is full-time equivalents (FTE). The metric quantifies work in hours rather than head counts. For example, if a full-time employed nurse with five working days (8 hours each) spent half of their time with CC patients, then this would account for 0.5 FTE. Thus, while this metric allows to account for the fact that employees have a variety of responsibilities across different diseases, the metric also accounts for staff working part-time.

Healthcare need is defined by the number of CC patients by FIGO stage (c_f) per year (y). Capacity is a function of labour productivity. I use labour and productivity estimates from Nelson et al.'s [276] study to derive the number of hours required to treat CC patients by FIGO stage. In Mozambique, medical staff works 210 days per year, 8 hours a day [121]. Thus, FTE required for CC patients by year are calculated:

$$L_y = \sum_{f=1}^{4} \frac{c_{fy} * \frac{m_f}{S}}{210} \tag{6.1}$$

S is the daily salary for medical personnel and m_f is the cost for medical personnel by CC FIGO stage.

Financial Risk Protection provided

Health outcomes by population sub-group are used to estimate catastrophic health expenditure (CHE) incidence. CHE is defined as out-of-pocket medical treatment costs that surpass a percentage t of household expenditure [143]. For each wealth quintile (w), CHE incidence (CHE_w) is determined by the number of CC cases by stage and wealth quintile ($c_f w$), access to CC treatment by wealth quintile (A_w), stage-specific direct treatment costs (o_f), the proportion of direct medical treatment costs covered by the healthcare provider (p_w), and annual household expenditure (E_w):

$$CHE_w = \sum_{f=1}^{4} A_w c_{fw} \mathbb{1}_w \begin{cases} 1 & if(1-p_w) * o_f > t * E_w \\ 0 & otherwise \end{cases} \tag{6.2}$$

Annual household expenditure (E_w) is derived by scaling monthly per capita consumption (as a proxy for expenditure) (e_w) multiplied by the average household size (h) to an annual average estimate:

$$E_w = e_w * h * 12 \tag{6.3}$$

I apply a stage distribution of detected cancers (f) to population sub-group specific health outcomes to estimate the number of CC cases by stage (c_f). The stage distribution is informed by regional

estimates of stage distribution at diagnosis that were derived by the Institute for Health Metrics and Evaluation (IHME) and estimated for Mozambique by Canfell et al. [74]. Empirical studies on the distribution of detected cancers by FIGO stage in Mozambique had not been published in the literature; thus, the validity of the estimated distribution cannot be ascertained.

The number of treatment-seeking CC cases by stage ($c_f w$) is assumed to vary by wealth quintile and is dependent on access to care (A_w). Access to care is a function of: (1) available resources, i.e., capacities available to treat CC patients (r); (2) people with healthcare needs, i.e., the number of people, who need CC treatment (P); (3) and a distribution of having access to care across wealth quintiles (γ_w). As of 2021, 900 CC patients (r) could be treated per year at the Central Hospital Maputo [333]. I assume that a proportion of people (v) go to the Central Private Hospital, which also has a radiology department [163] and only patients in the highest wealth quintile seek healthcare here. Therefore, with an estimate of 5,325 CC patients in 2021 [51], the probability of having access to care (A_w) can be estimated by wealth quintile:

$$A_w = \left(\frac{r}{(1-v)P}\right) * d_w * \gamma_w = \left(\frac{900}{95.3\% * 5,325}\right) * d_w * \gamma_w = 17.73\% * d_w * \gamma_w \tag{6.4}$$

The proportion of patients seeking treatment at Central Private Hospital in Maputo ($v = 4.7\%$) [163], is added to the probability of having access to care in the highest quintile. The distribution of access to treatment across wealth quintiles (γ_w) is informed by information on general care-seeking behaviour [263]. I apply this distribution to the treatment capacity for CC patients in Mozambique. These estimates are likely to be a fair representation of the access to different types of healthcare in Mozambique as they are informed by a large Household Budget Survey conducted by the National Institute of Statistics of Mozambique with a sample size of 11,480 households (58,118 individuals). The authors of the technical report in which this estimate is published have noted there is high within-country variability in access to private healthcare, mostly concentrated in the southern region. Due to this provincial level heterogeneity and potential changes since the date of the survey (2014/15) Access to treatment assumptions are varied in sensitivity analysis (see section 6.2.5). Treatment costs are assumed to be the same at both treatment facilities, the private and public hospitals.

Stage-specific treatment costs (o_f) are informed by a study conducted in Dar es Salaam, Tanzania [276]., which scored a similar Healthcare Access and Quality Index [156]. Mozambique is therefore

assumed to have comparable treatment capacities. Nelson et al. estimated average treatment costs of US$2963.60 per patient in 2022 (discounted at 3% per annum) [276]. I adopt these cost estimates as presented by Nelson et al. [276], disaggregated by labor costs (for physicians, X-ray and ultrasound technologists, laboratory technologists, radiation technologists and team planning and initial consultation), supplies and equipment costs (X-ray and ultrasound, laboratory work, curative radiotherapy, chemotherapy, palliative radiotherapy), and inpatient accommodation costs. Costs at discounted at 3% annually. Despite comparable Health Access and Quality Index, and CC prevalence, the validity of cost estimates is uncertain. Thus, cost and treatment requirement assumptions are varied in sensitivity analyses.

In the status quo baseline scenario, I assume that the total cost for CC treatment is paid out-of-pocket, as cancer treatment is not covered in the universal health coverage benefit package in Mozambique [107]. I scale annual per capita consumption [263] using average household size by wealth quintile [263] as a multiplier to approximate annual household consumption as a proxy for total annual household expenditure.

6.2.5 Analysis plan

Outcome measures

Outcome measures and sensitivity analysis are outlined in detail in the following sub-sections and summarized in Table 6.3.

Overall health benefits and resources saved attributed to the vaccination of the 9-year-old cohort. I quantify population health benefits and resources (financial and labour) saved attributable to the vaccination programme by estimating the number of CC cases and deaths, as well as vaccination programme costs saved. I also estimate these outcomes under the status quo scenario and compare estimates to health benefits estimated with the hypothetical scale-up scenarios, the 'half-way, flat coverage' and the 'global target' scenarios.

Further, I compare health benefits estimated with the 'half-way, flat coverage' scenario with health benefits estimated with the 'half-way, gradient coverage by quintile' scenario.

I examine the uncertainty induced by treatment costs and labour required by CC stage (see sensitivity analysis).

The effect on catastrophic health expenditure incidence. I quantify the difference in CHE incidence between the 'half-way, flat coverage' and status-quo scenario, and compute CHE incidence reduction attributable to the vaccination programme under different definitions of the CHE threshold.

I also estimate these outcomes under the 'half-way, gradient coverage by quintile' scenario and compared results to the 'half-way, gradient coverage by quintile' scenario. I examine how the effect is influenced by alternative assumptions about the access to treatment afforded to people in different income quintiles.

I also explored what proportion of treatment costs would have to be covered by the health sector to reduce CHE incidence, in addition to the vaccination programme. For this, two medical treatment cost coverage scenarios were explored:

1. A general percentage coverage
2. A sliding fee scale with a decrease in coverage as wealth increases

For the latter scenario, I explore what the minimum coverage would have to be to reduce CHE incidence by wealth quintile. This was done irrespective of the vaccination programme coverage as the percentage effect would be the same with or without the vaccination programme.

I analysed each scenario with the CHE threshold defined as 10% of annual household expenditure and as 40% of household non-food expenditure. These are commonly used CHE thresholds used in the literature [143]. Household expenditure data was extracted from the Budget Household Survey 2019/2020 report [263].

Sensitivity analyses

I performed one-way sensitivity analyses varying five parameters individually over plausible ranges to identify key uncertainties.

First, I explored different treatment costs by CC stage (o_f), varying these by ±20%. Similarly, labour required by CC stage (m_f) in FTE was varied by ±20%.

Table 6.3: Outcome measures, scenarios analyzed for each, and sensitivity analyses conducted. Baseline values are presented in Table 6.1.

Vaccination programme impact measure	**Vaccination scenarios analysed**	**Parameter varied in sensitivity analyses**
Population health benefits in CC cases and deaths, resources saved in financial and labour, and vaccination programme costs	Status quo Half-way, flat coverage Global target	Treatment costs (o_f): ±20% Labour required by FIGO stage (m_f): ±20%
Financial risk protection provided in CHE incidence	Half-way, flat coverage Half-way, gradient coverage by quintile	CHE threshold (t): 40% of annual non-food household expenditure
Distribution of benefits across population sub-groups	Half-way, flat coverage Half-way, gradient coverage by quintile Half-way, gradient coverage by residence	Access to treatment by wealth quintile (A_w): - Equal access to treatment at 22.4% - Gradient increase from Q1: 5.9% to Q5: 29.6% Risk of developing CC (d_w): - Equal risk of CC across wealth quintiles - Gradient decrease in risk of CC by wealth quintile

I also explored the impact of using an alternative definition for the CHE threshold (t) on CHE incidence. I changed the threshold to 40% of non-food household expenditure.

Further, I varied the distribution of access to treatment by wealth quintile (A_w). Initially, access to treatment by wealth quintile was informed by the probability of seeking (general) care as surveyed in the household budget survey [263]. In the sensitivity analysis, I explored (a) the assumption of equal access to treatment across the population and (b) a gradient increase in access to treatment from the poorest to the richest wealth quintile. The latter is a trend in breast cancer treatment access recorded in a study conducted in Nigeria and Uganda [154]. At the same average of 22.4%, only 5.9% of women in the poorest quintile, and 29.6% of women in the richest quintile would have access to treatment.

Last, I probed the distribution of CC incidence across wealth quintiles (d_w). Initially, I assumed the distribution of CC cases across wealth quintiles based on registry data collected in Dar es Salaam, Tanzania [350]. I varied this distribution, assuming (a) the same probability of developing CC by wealth quintile, (b) a gradient decrease in the probability of developing CC by wealth quintile.

6.3 Results

6.3.1 Overall health benefits and resources saved attributed to the vaccination of the 9-year-old cohort.

As a result of reaching 18.9% of 9-year-old girls between 2021 and 2051, approximately 75,000 CC cases and approximately 26,400 CC deaths (10% of expected CC cases and deaths) are projected to be averted within this cohort, compared to no vaccination, assuming 100% vaccine efficacy and lifelong protection against HPV-16/18 infections. With a flat coverage of 50% across income groups, up to 26% of expected CC cases and deaths would be averted, while, as expected due to the linear correlation between coverage and impact, 90% flat coverage would reduce expected outcomes by 46% (Table 6.4).

Total programme costs to vaccinate 18.9% of 9-year-old girls via a routine delivery strategy are estimated at US$24M. This estimate is 62% (52% - 77%) of treatment costs saved as a result of vaccinating 18.9% of girls in the target group, compared to no vaccination. Vaccinating 30 cohorts at a flat coverage of 90% is estimated to cost US$113M. Relative cost savings are proportionate to coverage and medical treatment costs saved.

The total vaccination programme-related labour saved as a result of vaccinating 9-year-old girls at a coverage of 18.9% is estimated at approximately 780 (630 - 940) medical personnel FTEs. If 30 cohorts of 9-year-old girls were vaccinated at a flat coverage of 50%, approximately 2,000 (1,700 - 2,500) and an annual median of 16.4 of medical personnel FTEs would be saved. If the 90% coverage target was reached, approximately 39,000 (31,000 - 47,000) medical personnel FTEs would be saved.

6.3.2 The effect on catastrophic health expenditure incidence.

With a 50% flat vaccination coverage and assuming no medical treatment cost coverage by the healthcare provider, the programme could avert approximately 6,000 CHE cases and more than US$100M in treatment costs paid out-of-pocket by treatment-seeking CC patients, compared to no vaccination, over the lifetime of 9-year-old girls in 30 cohorts. If it is assumed instead that the coverage is relatively higher in wealthier population sub-groups, the number of CHE cases averted would be reduced

Table 6.4: Total estimated health and non-health gains by vaccination scenario. Intervals in parentheses reflect ±20% uncertainty around direct medical treatment costs and medical personnel required. All costs are discounted at 3% annually. FTE: Full-time equivalents of medical personnel. CHE: Catastrophic health expenditure, defined as 10% of annual household expenditure. *Provide answers to question 3.2 (*What financial resources/budgets are required for the HPV vaccination programme over time?*); **Provide answers to question 3.3 (*What is the wider economic benefit of introducing the HPV vaccine for Mozambique?*); ***Provide answers to question 2.1 (*How do inequalities in access to education and infrastructure reflect in vaccination programme impact?*

Scenario	**CC cases averted**	**CC deaths averted**	**% of expected CC cases and deaths averted**	**Total medical treatment costs saved in US$**	**Vaccination programme costs in US$***	**FTEs saved****	**CHE incidence averted*****
Status quo	75,012	26,419	10%	39M (31M - 46M)	24M	784 (628 - 941)	2,284
Global target	355,322	125,141	46%	182M (146M - 219M)	113M	3,716 (2,972 - 4,459)	10,819
Halfway, flat coverage	197,401	69,523	26%	101M (81M - 122M)	63M	2,064 (1,651 - 2,477)	6,011
Halfway, gradient coverage by quintile	184,824	65,093	24%	98M (79M - 118M)	63M	1,933 (1,546 - 2,319)	5,839
Halfway, gradient coverage by residence	184,268	64,897	24%	109M (87M - 131M)	125M	1,927 (1,542 - 2,312)	6,481

by 200 persons (5,800 CHE cases in the '50% gradient' scenario vs 6,000 CHE cases in the 'half way gradient coverage' scenario).

If the CHE threshold was measured by a threshold of 40% of non-food annual household expenditure, CHE incidence would be the same as with a threshold of 10% of total annual household expenditure.

If CHE is defined as 10% of annual household expenditure and the healthcare provider in Mozambique were to cover 76% of direct medical treatment costs, CHE incidence would be reduced by 10% (Figure 6.2). 96% of direct medical treatment costs would have to be covered to avert 51% of CHE incidence in the whole population. If CHE is defined as 40% of non-food annual household expenditure, and the healthcare provider in Mozambique were to cover 26% of direct medical treatment costs, CHE incidence would be reduced by 11%. 92% of direct medical treatment costs would have to be covered to avert 51% of CHE incidence.

If CHE is defined as 10% of annual household expenditure, a sliding coverage scale with 99%, 98%, 96%, 93%, and 76% from the lowest to the highest quintile would lead to an overall 55% reduction in CHE incidence. If CHE is defined as 40% of non-food annual household expenditure, a sliding coverage scale with 100%, 95%, 92%, 83%, and 26% from the lowest to the highest quintile would lead to an overall 55% reduction in CHE incidence.

6.3.3 The distribution of benefits across population sub-groups.

Health gains by socioeconomic quintile for the 'half-way, flat coverage' and 'half-way, gradient coverage by quintile' scenario are presented in Figure 6.3. With uniform vaccine coverage (scenario: 'half-way, flat coverage'), 30% of expected benefits would accrue to the lowest income quintile. The highest number of CHE cases are averted in the lowest quintile in this coverage scenario (Figure 6.4).

In the 'half-way, gradient coverage by quintile', the distribution of benefits changes. The middle income quintile to which 23% of outcome benefits accrue ranks second after the lowest income quintile to which 26% accrue. In total, 68% of benefits would accrue to the lowest, lower, and middle income quintiles, i.e., 60% of the population. Figure 6.3 illustrates the model's sensitivity to changes in the CC risk parameter. If the risk of CC was the same across all wealth quintiles, most CC cases would be averted in the highest income group. Under both scenarios, flat and gradient coverage, when assuming

Figure 6.2: Catastrophic health expenditure (CHE) incidence with increasing medical treatment coverage for cervical cancer (CC) patients by socio-economic quintile with a threshold of (A) 10% of annual household consumption, and (B) 40% of annual non-food household consumption.

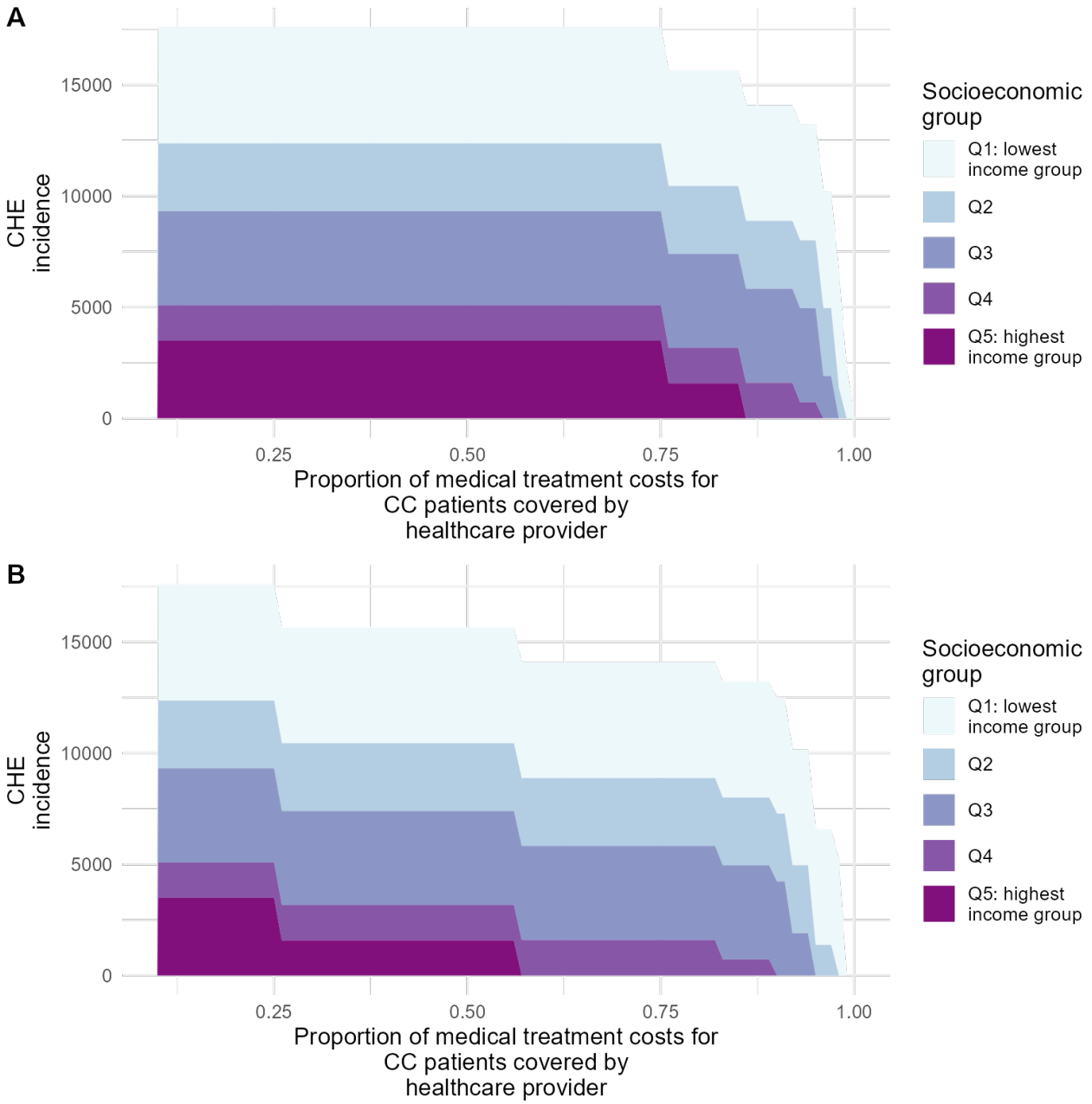
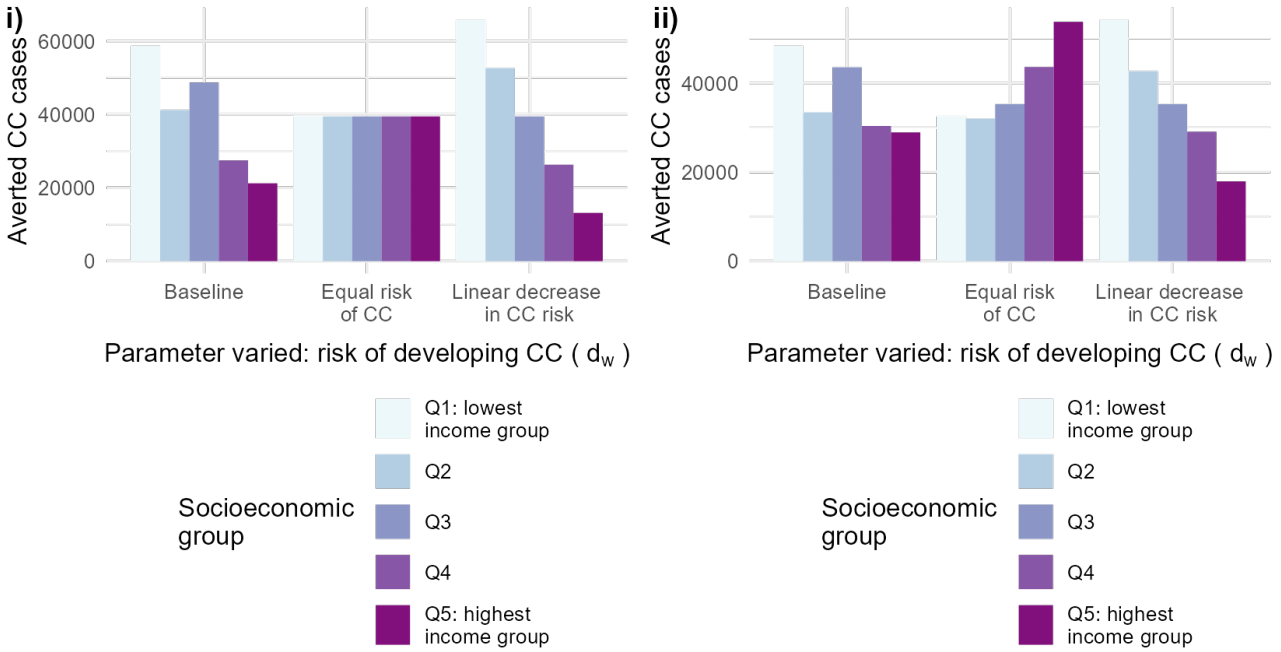


Figure 6.3: Evidence in response to question 3.1 (*To what extent is the vaccination programme equitable, given the presence of significant socioeconomic inequalities in Mozambique?*). Predicted number of averted cases by socio-economic quintile under different CC risk distributions across wealth quintiles by vaccination coverage scenario. (i) 50% coverage of the HPV vaccine across wealth quintiles, and (ii) 50% of coverage at an increasing gradient from lowest to highest socio-economic quintile.

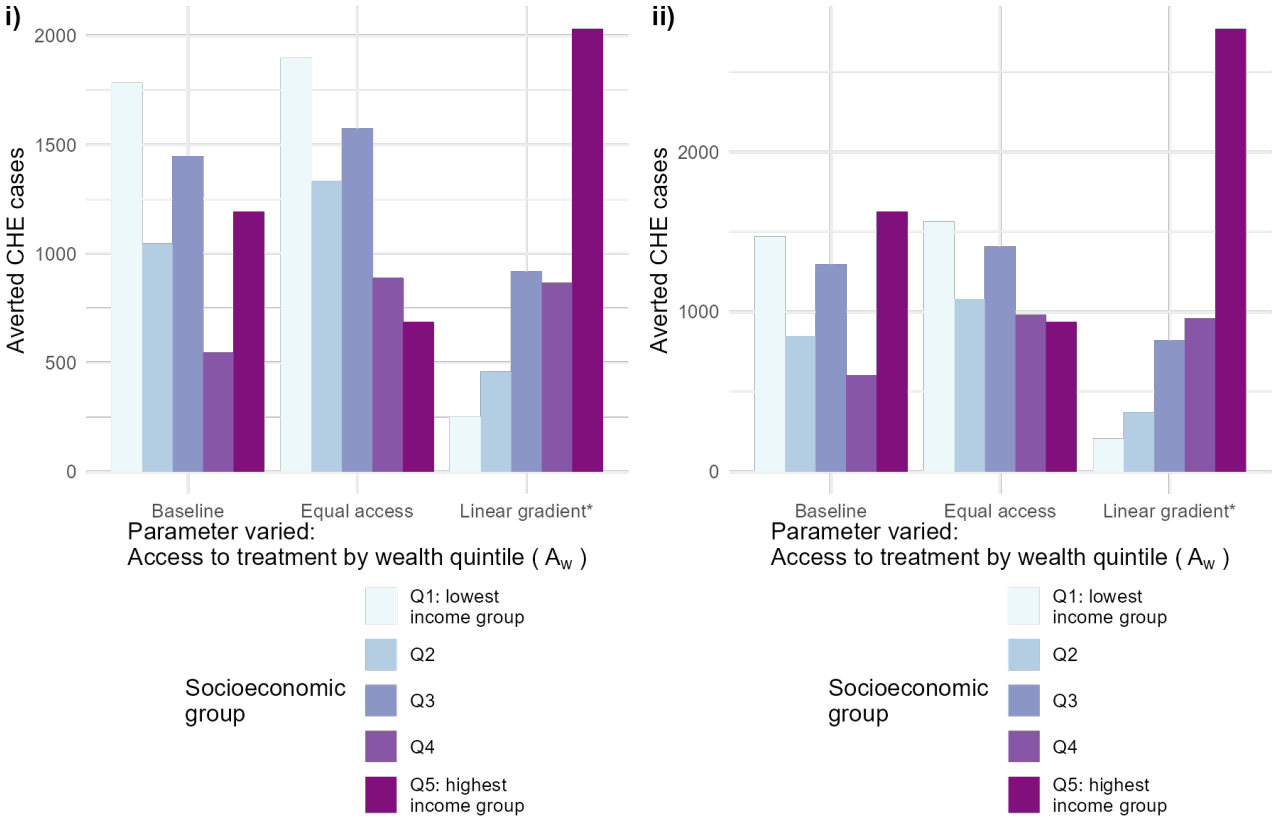


decreasing risk of developing CC by income group, health gains are most evident in the lowest income group. The highest number of CHE cases are averted in the lowest quintile in this coverage scenario (Figure 6.4).

Estimated health gains under the 'half-way, gradient by residence' scenario would mostly accrue in the urban highest income group. In this income group, 7% of expected CC cases would be averted. In the rural area, most health gains are estimated for the second lowest income group, with 3% of expected CC cases averted (Figure 6.5).

If it is assumed that people in the poorest socio-economic quintile are less able to access treatment, the highest number of CHE cases are averted in the highest income group, for both scenarios ('half-way, flat coverage', 'half-way, gradient coverage by quintile'), under both CHE threshold definitions.

Figure 6.4: Predicted number of averted catastrophic health expenditure (CHE) incidence by socio-economic quintile under different distribution to healthcare assumptions. (i) 50% coverage of the HPV vaccine across wealth quintiles, and (ii) 50% of coverage at an increasing gradient from lowest to highest socio-economic quintile. *Poorest have least access to treatment.



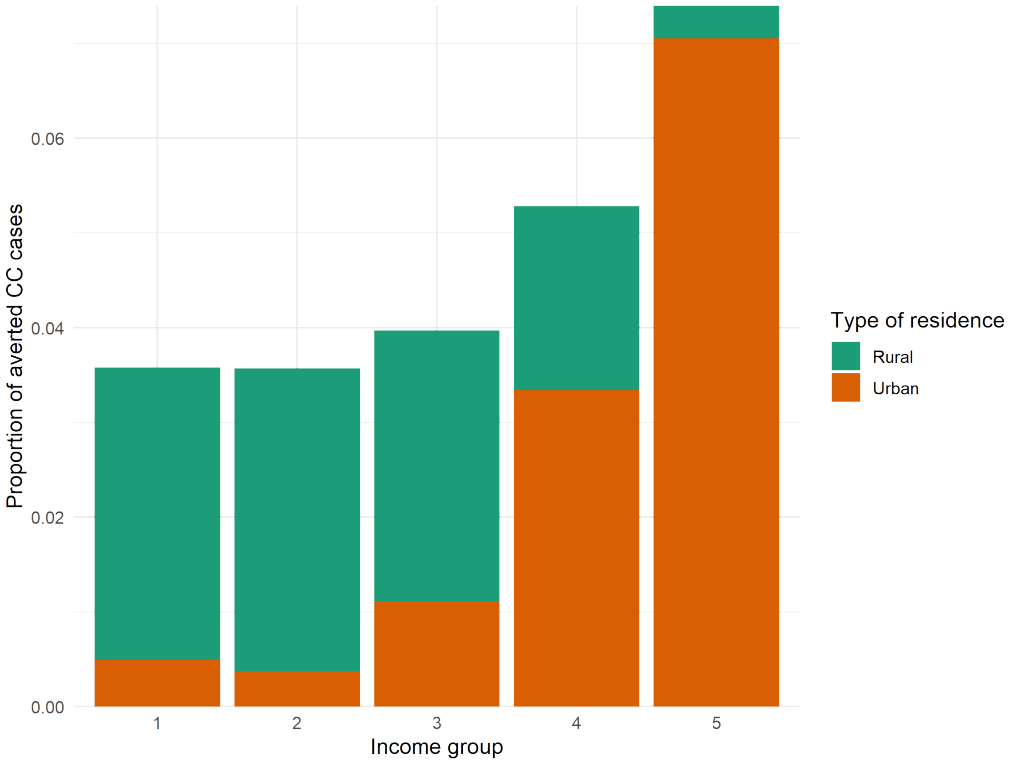


Figure 6.5: Estimated averted CC cases in percentage by wealth quintile and type of residence assuming a vaccination coverage gradient across population subgroups living in different types of residence.

6.4 Discussion

In this chapter, a static cohort model and the ECEA approach was used to quantify the value of the recently introduced HPV vaccine from a population health, societal, and health sector perspective in Mozambique. These results show that the HPV vaccination programme in Mozambique can significantly improve population health outcomes, as well as impact the human resource capacities required for cancer treatment and providing financial risk protection. However, due to entrenched inequality in income, baseline CC, and access to treatment, even with an equal distribution of the vaccine, the concentration of benefits is in the wealthier population. It would take a severe focus on the rural and poorer populations for the benefit to be evened out. CHE could be averted by reducing the out-of-pocket payments for treatment, but the treatment would have to be almost entirely paid for by the state for patients in the lowest socioeconomic quintile for CHE to be reduced by half. Answers to questions identified in Chapter 5 are summarized in an evidence brief (Appendix G).

Several limitations of this study need to be acknowledged. These relate to simplifying assumptions made around input parameters as well as the model structure. Firstly, national epidemiological information on age-specific CC incidence was available, but incidence rates are only based on the registry of two hospitals located in Beira in central Mozambique and Maputo in the south of Mozambique. The lack of data from other parts of the country and poor quality data on CC are likely to result in an underestimated number of CC cases, as also observed in neighbouring Eswatini [162]. Thus, the estimated impact of the vaccination programme is likely to be higher.

Secondly, data collected in a cohort study conducted in Dar es Salaam, Tanzania, informed the distribution of CC incidence across wealth quintiles. Therefore, varying distributions in CC incidence across wealth quintiles were probed. It was found that, when there is an equal risk of developing CC across the population and a gradient in coverage, most of the health benefits of the vaccination programme accrue to the highest income quintile. However, due to the gradient coverage favouring the highest income quintile while holding all else equal across wealth quintiles, this is the only scenario that benefits the highest income quintile most. However, the decreasing trend of CC incidence from the lowest income group to the highest income group is more likely, as it has been observed in many other countries [92].

Similarly, access to treatment across wealth quintiles was informed by the distribution of access to

general care. However, given the possibility that this distribution is different for access to CC treatment access, a gradient increase in access to treatment by wealth quintile was probed in the sensitivity analysis. Unsurprisingly, increased access to care significantly shifts the distribution of financial protection provided to the highest-income group. Yet, it is surprising that the highest quintile experiences CHE under both definitions in any case.

Thirdly, even though vaccination coverage in the status quo scenario was based on empiric data collected at the province level, this data has a high degree of uncertainty. Through interviews conducted in the previous chapter, it was found that the 2011 census data, i.e., the denominator for the coverage calculation, was inaccurate. Assuming population growth and that coverage estimates were not adjusted before they were shared with us, coverage achieved in the first year of the programme is likely to be lower. Higher coverage rates are likely as the HPV vaccine was introduced during a time in which Mozambique's healthcare infrastructure and political attention were strained with the COVID-19 pandemic. Therefore, higher coverage rates to compare the magnitude of the impact were also probed. Findings from the analysis with 50% and 90% coverage support the case for investing in scaling up the programme.

Fourthly, I adopted treatment costs and labour requirement estimates from Tanzania, which scored a similar Healthcare Access and Quality Index [156] and is therefore presumed to have comparable treatment capacities, as costs for treatment in Mozambique were not available. However, the data was not presented with any uncertainty ranges. Thus, all cost estimates were estimated with a $\pm 20\%$ interval to reflect the high degree of uncertainty for this input value. Also, direct non-medical costs, such as transportation costs, may vary by wealth quintile and type of residence.

Finally, the vaccination programme cost estimates are likely to vary with regards to the chosen delivery strategy. In the current model, a delivery strategy via fixed facilities was assumed. However, this does not account for additional efforts required to administer the vaccine to hard-to-reach populations. The cost per fully immunized girl is likely to be higher, because the denominator to estimate the economic cost per fully immunized girl at fixed facilities is likely to be lower, and outreach programmes are an additional cost factor. Thus, vaccination programme costs presented in this research are conservative estimates. To estimate the financial and economic costs associated with delivering HPV vaccination, the framework used by Alonso et al. [9] may be employed. Updated cost estimates could then be used in the vaccination coverage scenario, in which population sub-groups are differentiated by types

of residence.

A static cohort model, which does not include herd (indirect) protection or waning immunity was used. However, there is strong evidence for vaccine cross-protection and herd effects from the HPV vaccine if coverage is 50% or above [119]. Similarly, I relied on research conducted in Mozambique to inform the HPV 16, 18 type distribution to which the model is very sensitive. Global estimates suggest higher circulation of HPV 16, 18 that national sero-prevalence surveys, which were used to parameterize the model. Thus, outcomes are likely to be underestimated. Yet, the comparative impact of the different vaccination coverage scenarios would not differ. I also did not include the potential health benefits and costs associated with other preventive interventions, such as screening or treatment for precancerous lesions. Evaluations of combined strategies conducted in other countries concluded that, together, the interventions have the potential to eliminate CC [53]. Indirect costs, i.e., wages lost due to the inability of the patient or accompanying family members to work, were not estimated. These additional cost savings would further decrease CHE incidence.

Further, household consumption only accounts for goods and services, i.e., the net of expenditure. Thus, CHE incidence estimates are possibly underestimated.

Due to limited information on medical resource requirements for CC patients and demand for these resources in Mozambique, I only estimated the labour saved as an example of the value of the vaccine to the health sector. As a result of saving labour otherwise used to treat CC patients, in theory, resources can be redirected to other treatment services. In practice, I recognize that often resources are already over-committed and spare capacity may not become available. In further research, other resources saved could be estimated in terms of bed days for example.

The ECEA approach that I used to quantify the distributional consequences of the HPV vaccination programme has previously been used to value the equity impact of other vaccines as well as the HPV vaccine in other countries. These findings are consistent with those of previous research, showing that the HPV and other vaccination programmes can reduce health inequity [117, 232, 237, 332]. This analysis shows that the health impacts favour the poor while the financial benefits favour the wealthier. As such, the sliding fee coverage of out-of-pocket payments to reduce inequity is an example of how the concept of vertical equity could be employed [102]. In this sense, the method is sufficient to address the elicited evidence needs identified in the previous chapter. However, the method does not quantify the vaccination programme's impact on overall inequality in lifetime health. With this

aim, a distributional cost-effectiveness analysis [108] of the vaccination programme would complement this research to quantify other broader dimensions of the value of the HPV vaccine.

6.5 Conclusion

To conclude, this analysis on the recently launched HPV vaccination programme in Mozambique presented various forms of impact from a population health, health sector, and societal perspective. Findings on the distributional consequences of the intervention across different types of residence and income groups are relevant to the issue network and, specifically, to Mozambique's National Cancer Control Plan, which is currently under development [286]. Findings can contribute to taking fair and efficient planning decisions from various perspectives assumed in the issue network around the HPV vaccination programme in Mozambique, and at a global level. In the next chapter, I examine how stakeholders perceive results from findings that were presented in Chapter 5 and 6.

Chapter 7

The potential use of evidence from mathematical models in the context of the HPV vaccination programme in Mozambique

7.1 Preface

Mathematical modellers, specialized in infectious disease epidemiology, rarely know how their work informs or has the potential to inform decision-making processes. Commonly, they are commissioned to produce specific evidence, e.g., in the form of burden of disease and vaccine impact estimates (Chapter 3), and contribute to the academic literature by publishing their work in scientific journals. Arguably, scientists are distant from political and/or public health decisions. In recognition of this, this chapter revisits the research question posed in the research conducted in the global context in Chapter 3 *'How are mathematical models and results from mathematical models of vaccine-preventable diseases used, or not?'*. Building on the efforts of Chapter 5 and 6, this chapter focuses on the development and use of evidence in national context to inform programme and policy decisions.

This fifth and final results chapter has two main objectives. Firstly, it aims to investigate whether the formulated research questions and outcome measures (Chapter 5) align with the evidence needs of stakeholders originally interviewed. The second objective is to determine how the findings from the application and extension of the mathematical model (Chapter 6) can inform decision-making and identify the primary recipients or audience for this evidence. From here on, the evidence developed in Chapter 6 is referred to as 'vaccine impact estimates.'

7.2 Methods

7.2.1 Data collection

The research in this chapter followed a qualitative approach to collecting and analyzing data. Data was collected via semi-structured interviews with decision-makers involved in the vaccination programme planning and implementation. Interviews were conducted to investigate the utility of evidence in the form of vaccine impact estimates as presented in an evidence brief (Appendix G). Study participants from the first wave of interviews were invited for follow-up interviews in April and May 2023, a year after their original interview, if they were thought to be still engaged in the national HPV vaccination programme in Mozambique. Prior to interviews, study participants received the evidence brief, which also contains the key questions of the interview guide (Appendix C). Thereby, study participants could familiarize themselves with the content and the questions. During the interview, the evidence presented in the brief was explained in detail. The focus of the interviews was on how the evidence presented to the study participants could be used. From the audio recordings, intelligent verbatim transcripts were produced. Interviews that were conducted in Portuguese were translated into English by MM. Personal or organizationally identifiable information shared during the interview was masked through pseudonyms to ensure confidentiality or excluded if pseudonymization was not possible.

Storage, organization, searching, and coding of transcripts were performed using NVivo 12 Pro [335].

7.2.2 Data analysis

The data was coded inductively, through which emerging themes and sub-themes for each research objective in this chapter were identified.

7.2.3 Ethical clearance

Ethical approval was obtained from Imperial College London (ICREC reference: 21IC7033) and the Institutional Review Board of the Manhiça Health Research Centre (CISBS-CISM/076/2021) (Appendix B). Approval from the Bioethics Committee in Mozambique was not required for this study.

7.3 Results

Of the eight study participants that were contacted for the follow-up interview, six (75%) individuals participated in the follow-up study (5 in Mozambique; 1 at GHO)[1]. They included individuals that spanned all institution types, from global to national government departments and nationally operating NGOs. One potential interviewee declined the invitation as they felt they would not be able to answer the interview questions. The other potential interviewee did not respond to the invitation. All of the participating individuals have remained in their roles since their first interview.

7.3.1 Evidence development

To what extent have the evidence needs been mirrored in the research questions posed?

The research questions presented in the evidence brief appear to reflect the evidence needs and concerns of the study participants. Yet, study participants did not identify the evidence needs that they had initially expressed in the first round of interviews per se.

Participants reaffirmed their interest in understanding the equity implications of the programme. They highlighted the importance of reaching girls in provinces with historically low coverage and consider the trade-offs between reaching vulnerable populations and the associated costs. They suggest exploring additional indicators to strengthen the analysis of equity in the context of the HPV vaccination programme [312].

The key informant at the MOH emphasized the need to reduce the financial burden of HPV and cervical cancer on the healthcare system and families [293]. They discussed the aim of reducing cases, morbidity, and mortality from cervical cancer, as well as the potential cost savings associated with the vaccination intervention compared to the expenses of treating cervical cancer patients. The evidence brief is aligned to this concern in that it presents the vaccination programme costs and health sector costs foregone.

[1]Identifiers for study participants remained the same as in Chapter 5 in which the questions that were attempted to be addressed with the mathematical model were identified.

The key informant at the global level [312] highlighted that other globally recognised tools (e.g., the WHO Prime tool [205], the C4P HPV tool, and the HPV vaccine cost calculator) could have been used to estimate vaccination programme costs. Thus, vaccination programme cost estimates were of less interest to them. Instead, the key informant voiced their interest in the other research questions posed. The key informant highlighted:

> HQ, IO: "show[ing] how an equitable programme can create cost savings. And I think that for me is quite interesting. I think the first two research questions are quite substantiated, and we've got tools and calculators, etc. available to countries." [312]

In what format should evidence be packaged?

Probing the format revealed that the vaccine impact estimates and policy recommendations should be formatted or presented in a way that caters to different audiences and their specific needs. The communication format should be chosen considering the technical capacity of the recipient and the time to process the evidence. Generally, the presentation should be concise, clear, and actionable, while also taking into account language preferences. For national-level decision-makers in Mozambique, all evidence should be presented in Portuguese.

Beyond the academic realm, the format may require some simplification to ensure ease of understanding for a broader audience. Especially assumptions made and scenarios modelled should be clearly stated, when communicating the evidence [306]. While still providing comprehensive results, it should be visually simplified to aid comprehension and supplemented with comments on key findings. As one key informant at the MOH suggested:

> "you could try to simplify it, so that someone who... may have some difficulty in relation to what is written here... can really understand." [293]

Further, the language used in the presentation is also a crucial consideration. The format should be presented primarily in Portuguese, as English may create barriers and reduce interest in the information among national decision-makers [293]. The same informant at the MoH stated:

> HQ, IO: "everything should be in Portuguese... because English is shocking... you don't even have much interest in seeing it anymore" [293]

Notably, all key informants showed understanding of the evidence brief content, as they often paraphrased conclusions and insights from graphs during the interviews.

Parameter assumptions

All study participants criticized the coverage that served as the basis for the status quo scenario as the one major premise. The coverage, which was informed by empirical data from the first three months of the vaccination programme, is not representative of the progress made. The study participants showed interest in receiving the estimates with updated coverage assumptions, as exemplified by the key informant:

> N, IO: "the only variable to update would be the coverage. We would have more realistic things." [295]

All study participants confirmed that using data from neighbouring countries (e.g., Tanzania) was appropriate for informing parameter values used in the mathematical model. Participants did not have knowledge of other, possibly more appropriate national sources for data gaps. One participant [293] suggested speaking to colleagues at the MOH to explore national data sources that are not publicly available. This speaks to previous findings from Chapter 4, which showed that data and other information is often not accessible to the public in Mozambique.

7.3.2 Evidence use

There was consensus that the vaccine impact estimates can inform resource allocation decisions, be used for financial planning, and support advocacy work in Mozambique. Interviewees felt that the distributional outcome analysis was particularly insightful and useful, especially in relation to the zero-dose strategy. As study participants learnt about how the evidence was developed and the outcomes that were estimated, they voiced interest in refining the research, especially in its level of analysis. When probing the utility of the findings, participants mostly commented on the utility of the evidence if it was presented at the provincial level but following the same framework.

Resource allocation. Analyzing the impact estimates across different socio-economic quintiles or regions can guide decision-makers on how to tailor strategies to specific situations. The modelling

findings (as presented in the evidence brief) help determine whether more community health workers should be involved, whether vaccination should take place in health facilities or through community outreach, and how resources can be best distributed, as emphasized by a key informant at a nationally operating NGO:

> N, NGO: "looking at the different quintiles we might be able to know for sure how to tackle a situation in specific region? whether to involve more community health workers? how to best provide the vaccine, should it be via a health facility for people to come and get vaccinated? Should we go out to the communities?" [304]

This was echoed by two key informants at a global organization and the MOH, who emphasized that this can be used for micro-planning activities, in which various factors such as out-of-school girls, vulnerable populations, immunocompromised individuals, and socioeconomic distributions are considered [293, 312]. The key informant at the MOH highlighted that this is particularly useful now as coverage rates are 'inadequate' and new strategies are under development. Strategies should consider the circumstances of and disparities across population sub-groups:

> N, IO: "In addressing equity issues in the program we have identified the issue of hard-to-reach populations. The cyclone has affected different people in Mozambique differently, so there's need to tailor strategies around that?" [295]

This resonates with research question 2.1. While the evidence as presented in the evidence brief was seen as too high-level to inform programmatic decisions, the framework and outcome measures were considered policy-relevant.

Similarly, a key informant at a nationally acting IO pointed out these findings are very relevant for "strategy preparation and the elaboration of campaigns" [306]. According to the participant, in this context, these findings can influence decision-makers to take a more holistic approach, considering various relevant aspects instead of relying solely on a global checklist.

Financial planning. According to key informant [304] (N, NGO), financial planning can also benefits from vaccine impact estimates. By providing detailed information on the cost of implementing different programmes, decision-makers can have a clearer understanding of the required financial resources. This level of detail would enable better budgeting decisions and the identification of areas where adjustments

can be made to optimize resource allocation. Accurate cost estimates facilitate informed discussions on what to cut or adjust in the budgets allocated for immunization programmes. Examining the cost of vaccination per beneficiary, factors influencing these costs, and strategies to reduce them may also lead to less reliance on external funding:

> N, NGO: "thereby, we might be able to reduce donor dependency so that the government can focus on other areas." [304]

Advocacy for resources. A key informant at the global level [312] (HQ, IO) found the vaccine impact estimates served as a means to advocate for reaching under-immunized populations and promote equity in HPV vaccination. While the impact estimates demonstrate potential cost savings and the benefits of an equitable HPV vaccination programme, decision-makers need to consider the availability of human resources and domestic resources for outreach efforts. Therefore, increased domestic resources may ensure the sustainability of HPV programmes, acknowledging that Mozambique has made progress with over 50% coverage but still requires ongoing support to address the complexities of the vaccination programme.

New perspectives. A study participant affiliated with an NGO that focuses on programme implementation appeared to value the research on learning about perspectives on research agenda priorities, and specifically, the identified interest on equity. This finding speaks to the informant's organizational mission, which is to contextualize implementation work and not to assume a 'one size fits all' approach. This alignment and positive reaction to the findings is conveyed in the following interview extract:

> N, IO: "As a partner, I'm happy to see what has been said about the equity issues and also what you present in terms of cost as well as. We need to understand that the provinces will have different costs...You know, this brings out the importance of knowing the context in the different countries that you're going to work in. Do not assume that, for example, Maputo and Manhica are the same." [295]

This perspective highlights the relevance of the information for implementing partners who work directly on the ground and require a nuanced understanding of the sub-national context.

Generalizability. Key informants at NGOs that also work with other countries felt that this type of analysis is also useful for programme planning in other countries that experience low vaccine coverage [312].

To whom are these estimates relevant?

Interviewees named various stakeholders who would benefit from receiving the vaccine impact estimates, including implementing partners, technical groups, MOH, and funding organizations. Important to note is that each stakeholder is interested in different aspects of the evidence presented. Interviewees recommended having selective meetings with specific individuals, such as the head of the immunization programme, the director of research, monitoring, and evaluation, and technical experts at the MOH, COPI, and the Department for Planning and Corporation.

Further, programme managers, health system strengthening teams, and departments responsible for planning and cooperation were identified as relevant recipients of the vaccine impact estimates. This work may complement their efforts to planning activities targeting specific communities [304] (N, NGO). One participant at a nationally operating IO conveyed their enthusiasm about this work by searching for funding for a workshop on this research. This workshop would be held nationally and should engage all technical partner organizations.

At international level, it was suggested to present this evidence to forums such as ICC, which is chaired by organizations including WHO, UNICEF, and other technical partners involved in immunization programmes [296] (N, IO) and funding organizations, such as Gavi and the World Bank [295] (N, IO).

7.4 Discussion

To my knowledge, this is the first study to focus on the use of vaccine impact estimates by stakeholders engaged in the policy and programme development of a vaccination programme. Stakeholders in Mozambique who were involved in the planning of the HPV vaccination programme found evidence in the form of vaccine impact estimates to be useful in informing resource allocation decisions, financial plans, and advocacy efforts. By reflecting on the evidence generation process (model development) and potential for uptake of findings (model use) the study participants all agreed that the approach to developing this form of evidence (as done in Chapters 5 and 6) increases its relevance.

In Mozambique, programme planners consider vaccine impact estimates useful to improve programme accessibility by identifying priority target groups. This form of evidence use follows the problem-solving model by Weiss, suggesting evidence can directly inform the HPV vaccine delivery strategy. In addition

to evidence use at GHOs, which use vaccine impact estimates symbolically to mobilise resources (Chapter 3), vaccine impact estimates can support resource allocation decisions at the national MoH and may come into play more directly. This may be explained by the difference in how the objectives of decision-making bodies are defined. GHOs do not necessarily have a political mandate, whereas national ministries have to outweigh and respond to competing health priorities. At the national level, vaccine impact estimates support transparent decision-making processes; yet, as found in Chapter 4, other factors, such as global ambitions and evidence are likely to inform decisions.

Findings of the broader impact of the HPV vaccine in terms of its potential role in reducing health inequities may also be used to advocate for financial investment in the programme. Similar to the use of evidence at the global level, evidence may be used symbolically to solicit funding from external partners. Thus, for both national and global decisions, burden of disease and narrow vaccine impact estimates (e.g., cases averted and disability-adjusted life years saved) may be complemented with findings from distributional outcome analyses.

Interviewees appeared very receptive to the vaccine impact estimates and, unprompted, identified decision-makers who should learn about these findings. They could benefit from these findings when taking programmatic decisions on, for example, target groups or when mobilising resources for the vaccination programme. Equity of health programmes is a decisive criteria for donors [160] as well as nationally operating organizations. From political theory, we learn that policy decisions are subject to a diffuse, dynamic process that engages many stakeholders with vested interests [403]. In recognition of this, for evidence generated with mathematical models to lead to policy action, engagement with as many individuals who are embedded in the issue network around an intervention is advisable. Thereby, it may be possible to build momentum and bring attention to a policy issue.

Interviewees provided constructive feedback on how the evidence should be refined. There was consensus among study participants that the mathematical model should be applied at the province or district level to lead to more precise recommendations for vaccination programme planning. Similarly, detail about the vaccination programme costs was requested. The findings suggest that there is a general appetite for evidence from mathematical models and that the dialogue about findings can increase the utility of the evidence. This supply-demand dynamic is dependent on the availability of data, though through the dynamic process, more recent or unpublished data (such as new coverage data) may become available. But, to date, in Mozambique there appears to be limited demand for

evidence generated with mathematical models. Throughout the course of the HPV vaccine policy development (Chapter 4) no disease model of HPV had been developed; only recently, the PRIME model had been applied to investigate the cost-effectiveness of the one-dose schedule [175]. Further, study participants voiced the opinion that this capacity should be developed in Mozambique. Sustainable capacity-building efforts could be facilitated through, for example, leveraging national epidemiology training programmes with mathematical modelling modules [167, 394]. Thereby, evidence would naturally also be presented in the national language, and national decision-makers are likely to be more receptive to it. In the words of the study participant at the MoH, people in the Mozambican ministry "lose interest and motivation" to understand the evidence.

The usefulness of mathematical models as a method to generate evidence for health policy is potentially influenced by the type of intervention and disease. The impact of the HPV vaccine is very delayed. The forecasting horizon of 30+ years abstracts the evidence. Political decision-makers are more concerned about short-term deliverables given their legislative periods and political milestones during which they have to win votes. Resource allocation decisions for programmes whose impact will be felt in 30 or more years are therefore even more difficult to justify. Consistent with the knowledge translation literature, *timeliness* of evidence determines its use [105, 280]; in this setting, the timeliness of potential impact determines the utility of evidence. But, particularly with regards to the difficulty of demonstrating a direct impact on population health, the distributional outcome analyses may be supportive for decision-makers. In other contexts that are of more immediate concern (e.g., Mpox, COVID-19, or cholera), the utility of burden of disease and vaccine impact estimates is likely to be very different.

The approach to integrating perspectives and researching the utility of evidence was subject to a number of limitations. Study participants were interested in more refined analyses. Thus, the utility of the evidence that was identified in this chapter was hypothetical. Further iterations of the process would lead to increased value in evidence and its utility. Therefore, ideally, the development of evidence would not end at this point but be continued in light of the participants' feedback. As it stands, the model application only went through one iteration of gathering stakeholders' input on research questions. The time points between interviews and follow-up interviews were >1 year, which meant that participants could not remember their evidence needs and did not directly identify with the quotes presented in the evidence brief. Moreover, the evidence needs may have changed since the first

round of interviews, as the vaccination programme had already matured. Ideally, the development and use of evidence is continuous; this can be achieved if evidence producers are embedded in the decision-making space and evidence development methods become institutionalized, e.g., at the Ministry of Health. Further research should probe perspectives on operationalizing participatory approaches. For example, the format in which evidence was presented is only one way of communicating evidence. Other formats may be more or less interactive, e.g., through presentations, mixed media such as video formats, dashboards, or workshops. The choice of medium was made due to the possibility of engaging with the content during the interview, while providing in-depth detail on the evidence development process. Further research should be explored on the most appropriate medium to which evidence consumers are most receptive, and through which evidence is most comprehensive.

7.5 Conclusion

In conclusion, we found that evidence in the form of vaccine impact estimates can be valuable for public health policymaking, specifically to inform resource allocation decision-making, financial planning, and advocating for the vaccination programme. While the participatory approach to EDU is still in need of further refinement, the findings of this chapter suggest that adopting this approach has the potential to enhance both the process of evidence development and its use. The utility of evidence may only be identified by talking through the evidence. Similar to recommendations put forth in Chapter 3, continuous engagement throughout the research production and use process can maximise the value of this specific type of evidence. Participatory modelling as a continuous integration of perspectives is a promising approach to maximize the potential of applied research for health policy and programmes.

Chapter 8

Concluding remarks

In the context of vaccination programmes, evidence that is informed by different perspectives across public health decision-makers, funding organizations, and the scientific community can contribute to improving population health outcomes. In recognition of this, it is important to understand how evidence for vaccination programmes and policies is developed and used and where this process of knowledge translation falls short in contributing to reducing preventable mortality. Acknowledging the complex power dynamics in health systems and that evidence has many meanings in this context, this thesis probed the perspectives on EDU held by stakeholders engaging with vaccination programmes at the global and national levels. This work underscores the importance of applied research as a valuable tool in public health policymaking and highlights the potential for its utility in future vaccination programmes. To this end, this thesis makes several contributions to the knowledge translation and global health literature. This chapter reflects on these contributions and points to key recommendations for operationalizing knowledge translation in the context of vaccination programmes, as well as limitations to the research approach taken in this thesis.

8.1 Discussion of thesis findings

In the last ten years, there has been notable progress in vaccine research and development (e.g., mRNA vaccines), coupled with the emergence of technologies like artificial intelligence. These advancements hold great potential for facilitating the rapid development of prophylactic vaccines to fight the spread of infectious diseases. Yet, resource constraints across health systems at the personal, healthcare or-

ganisational, national, and research levels imperil the ability to effectively respond to health challenges associated with global change in demographics, climate, and behaviour. With widespread economic hardship and steep cuts in public health services, population health is deteriorating. In response, long-term projections as developed in Chapter 6 can support efficient programme planning efforts and resource allocation decisions, especially if province-level data on population behaviour, healthcare access, and demography is available (Chapter 7). The role of evidence in this context and how knowledge translation for public health programmes and policies can be operationalized are discussed here.

8.1.1 The role of evidence in decision-making processes

The quantitative assessment of the impact of the vaccine in Mozambique exemplifies the broad value of vaccination programmes beyond population health outcomes (Chapter 6). Recently, the impact of the single-dose HPV vaccine on population health was demonstrated with empirical population-based evidence in Rwanda [357], Sweden [230], and England [145]. Considering the recommendation of updating the dose schedules for HPV [287], the modelling framework as used in Chapter 6 can be updated and/or repurposed to evaluate the new product. In future evidence, different candidates with varying prices and schedules may be evaluated and compared on their impact from a population health, healthcare system, and societal perspective. Further, the inclusion of other target groups may be considered (e.g., boys). Despite long-standing evidence for the vaccine's efficacy and its other benefits, the majority of countries in sub-Saharan Africa had not introduced national HPV vaccination programmes at the time of conducting this research. Thus, the mathematical modelling framework may contribute to improving public health outcomes elsewhere too. A key benefit of the modelling framework used in this thesis is its flexibility. Though the extent to which such projections can inform policy change is dependent on the demand for, engagement with, and understanding of evidence.

The contributions of this thesis are relevant to other new technologies as well. For example, Mozambique recently decided to introduce the RTS,S malaria vaccine in the Northern provinces, where the disease is most prevalent. This decision was taken over malaria elimination in Mozambique's southern provinces. Considering the timeline of vaccine policy development (Figure 4.2), the need for implementation studies and forecasting studies to inform vaccine delivery strategies and related resource allocation decisions can be anticipated. Arguably, the engagement of mathematical modellers at an earlier point in this context could have supported the decision-making process. In this policy environ-

ment, transnational and regional groups, such as the E8 Alliance, which supports malaria elimination initiatives across southern African countries, and collates evidence on malaria-relevant indicators, should be integrated to explore how this research can be repurposed or used as learnings.

8.1.2 Operationalizing evidence-informed decision-making

Despite the mature knowledge translation literature in the context of health programmes, this thesis contributes to our understanding of how the use of epidemiological and economic research compares at the global and national level and in different decision-making contexts (organizational versus political).

At GHOs, burden of disease and vaccine impact estimates primarily have an advocacy function and are used anecdotally when mobilising resources from donor partners, thereby serving a strategic purpose (Chapter 3). In contrast to the use of burden of disease and vaccine impact estimates by GHOs, in the context of national vaccination programmes, evidence informs much more concrete and specific actions (Chapter 7). This may be explained by the difference in decision-making contexts and how the objectives of decision-making bodies are defined. GHOs do not necessarily have a political mandate, whereas national ministries have to outweigh and respond to competing health priorities and have broader funding priorities beyond health programmes.

The literature has advanced our understanding of political processes and knowledge translation in the context of public health. Scholars have looked at this with a focus on evidence for the adoption of new vaccines and synthesized research and perspectives through systematic literature reviews and qualitative research. However, the role of different types of evidence throughout the process of introducing a vaccine had not been researched. Burchett et al. [59, 60] conducted their research focusing on the vaccine adoption decision. However, following the decision to adopt a vaccine, a vaccination programme still has to be implemented. At this point, the types of evidence relevant to decision-making processes, stakeholders engaged, and decision criteria are likely to vary [174, 412]. Further, the role of mathematical models to develop evidence for different stages in the vaccine introduction process had not been researched. Guillaume et al.'s recent literature review juxtaposes Burchett et al.'s review, but included empirical research only (i.e., not evidence from mathematical models). Understanding perspectives on evidence from mathematical models in the context of vaccine introductions benefits future knowledge translation intervention strategies, such as participatory approaches.

Participatory approaches to EDU should be fostered. Participatory approaches are still in their infancy and span varying scopes in terms of the stakeholders engaged in the process, e.g., people affected by an intervention, or stakeholders involved in decision-making and intervention development. The overarching motivation for drawing on participatory approaches is to develop 'holistic, context-specific, people-centred, and policy-relevant evidence' [219]. Kumar et al. discuss these benefits of the approach when those affected by an intervention (e.g., patients) are engaged in designing, assessing, or improving an intervention. This thesis aims to explore how the integration of the perspectives of evidence consumers and producers can ensure that evidence speaks to evidence consumers' needs while avoiding value-laden epistemic judgements. The research conducted in Chapters 5 - 7 points to the benefits of participatory EDU:

- Evidence producers' data gaps can be filled
- Data needs and ways how to strengthen (sub-)national data structures can be identified
- The utility of evidence can be identified through the dialogue of stakeholders
- Research priorities can be defined
- Policy recommendations can be elicited together
- Trust in evidence is achieved as evidence consumers have ownership in the evidence
- Capacities to interpret evidence for policy are strengthened
- Policy relevant outcome measures can be defined
- Understanding of data variables is achieved

For this reason, it is important that evidence producers understand the policy and/or organizational objectives to which the evidence may contribute. In return, evidence consumers' understanding of evidence should also be probed by evidence producers. Before acting on evidence, it needs to be fully understood in terms of what it shows, what it does not show, and why. Effectively, evidence consumers need to have confidence in using evidence and making decisions with this information. Ensuring an understanding of evidence is critical prior to decision-making. The systematic evaluation of participants' understanding of evidence was outside the scope of this research. Further, through the participatory approach, a bi-directional supply-demand relationship or dynamic and trust is created through which follow-up questions about the evidence as well as new evidence needs may emerge. The importance for this was highlighted in Chapters 3 and 7.

Notably, as presented in Chapter 6 and systematically investigated in Chapter 7, the mathematical

modelling results presented in Chapter 6 have limited utility but were considered insightful. The evidence as presented in the evidence brief (Appendix G) was considered too high-level to inform programmatic decisions (Chapter 7) and, therefore, not actionable. Thus, this process was only a starting point for developing evidence for policy in Mozambique and points to the need for continuous, iterative engagement with potential evidence consumers. While the outcome measures were considered policy-relevant, they should be estimated at the provincial level. This evidence need was not picked up in Chapter 5. Instead, the interviews only pointed towards the need for a distributional outcome analysis, which would estimate the vaccination programme impact by population sub-group. Again, the modelling framework is flexible enough that the same analysis can be conducted at the province as well as the district level, though this is often not possible due to the lack of detailed data at the province and district levels. Discussing the model's utility with interviewees on three occasions and discovering in some instances that interviewees reported priority questions had changed over time reaffirms the value of participatory research as a process with multiple exchanges rather than a one-off engagement.

The issue of unsustainable research infrastructure in LMIC has been recognised, and commitments to "addressing the decolonizing agenda in global health" [252] have been voiced. This research contributes to an understanding of how knowledge translation for health programmes in LMIC can be operationalized. To date, all published advanced analytics efforts on the HPV vaccination programme in Mozambique (Chapter 4) have been driven by researchers or organizations based in North America or Europe, with the exception of the most recent modelling work published by Guimarães [175]. To institutionalize decision-making informed by mathematical models or other forms of advanced analytics, various enabling conditions should be facilitated:

- Development of technical understanding of what evidence can and cannot be produced with mathematical models to set the right expectations
- Overview of technical capacities, which decision-making bodies can draw on (nationally and internationally) for specific purposes (e.g., organized via regional centralized hubs that have existing access and knowledge of global capacities, e.g., WHO AFRO)
- Overview of and access to mathematical modelling frameworks and code (e.g., via GitHub)
- Financial resources to support institutional capacity building (e.g., through long-term secondments of academics in policy environments and decision-makers in academic environments)

- Understanding of how surveillance systems can be improved considering the data requirements of mathematical modellers by exploring the perspectives of evidence producers, stakeholders engaged in providing healthcare services and those affected by them

Through these enabling conditions, evidence producers and consumers are sensitized to each other's environments and can contribute to sustainable capacity strengthening. As a result, the issue of helicopter research [252] could be mitigated.

Formally, such processes may be best placed at institutions that have been integrated into decision-making processes for a long period of time, i.e., the EPI, UNICEF Mozambique, and JSI. In other countries, other organizations may be closer to the decision-making space. While NITAGs convene government and academic stakeholders, they are often only instrumental in recommending new vaccination programmes. Even though CISM was at the core of the issue network around the HPV vaccination programme as an evidence-producing capacity, mathematical modelling as a tool is not institutionalized as a method. In programme implementation, decisions are taken by the EPI task force. As such, the EPI and/or research institutions such as CISM may be the most appropriate institutional units where capacities should be strengthened. With the recent publication of the PRIME model application [175], it appears that Universidade Eduardo Mondlane is developing technical capacity in this space. Though they were not identified as a core stakeholder throughout the HPV vaccination programme.

8.2 Limitations

The following section reflects on the strengths and limitations of the research approach and points to the implications of the conclusions drawn. The two main strengths of this research are that it is multidisciplinary and that it uses a mixed-methods approach to explore EDU. Drawing on the organizational perspective as well as public health policy helps to explore EDU in two different contexts; further, the theoretical framework is flexible enough to be applied in both contexts and leaves room for interpretation and synthesis of findings through both inductive and deductive analyses. This allows us to compare and contrast findings on EDU at the global and national levels.

Secondly, a strength of this research is that it reflects on the entire process, from research question

identification to evidence development, and finally to an evaluation of the utility of the research as well as the process. Through this action research, every step in the EDU could be traced and critically reflected on by the author as well as the study cohort. As a result, the mathematical model did not remain a 'black box', but could be dissected and communicated transparently in this research study and to study participants.

However, the study is subject to various limitations. Two conceptual limitations of this research offer a stimulus for further research. Firstly, the study probed perspectives held by a variety of stakeholders in Chapters 3, 5 and 7, who are decision-makers in public health at the national level. However, none of the study participants could be identified as political decision-makers. This is a common challenge in public health policy research, as policy-related decision-making is diffuse [144]. Findings from this research pointed to the fact that in Mozambique, the timing of the vaccine introduction was decided on by higher-level constituencies that were not part of the study cohort. In recognition of this, further research should be conducted focusing on the development of evidence for and use by high-level political decision-makers, e.g., the Minister of Health.

The second conceptual limitation relates to the scope of the case study (Chapters 5 - 7). The focus was on the introduction of a prophylactic vaccine, which is administered to an adolescent cohort and has a delayed impact on health. For other vaccination programme introductions, the relevant evidence is likely to be very different. For example, in outbreaks of emerging infectious diseases (e.g., cholera), policy development and, respectively, evidence development would have to be much faster and more reactive. The research approach in this thesis, which includes inductive and deductive analyses of qualitative data, a literature review of appropriate methods, the application and extension of a mathematical model, and the packaging of evidence into an evidence brief, is a lengthy process that may not be feasible in emergency situations. The evidence gap on how mathematical models of infectious diseases can be used to support pandemic preparedness has also been identified in seminal research stemming from the COVID-19 pandemic [212]. The findings of this research may contribute to operationalizing integrated disease modelling for epidemics. Further, findings on outcome measures may also be relevant to vaccines that also prevent other cancers (e.g., HepB). Notably, this study may be considered a proof of concept that helped identify the challenges and benefits of participatory modelling. If implemented in a public health response, these steps could, in part, be done concurrently and by a wider team of epidemiologists, mathematical modellers, knowledge brokers, and social scientists.

It is crucial to keep in mind that, despite the encouragement to package policy recommendations so that consumers can easily understand and digest science, scientists must also remain objective and credible. Non-epistemic value judgements can compromise the epistemic integrity of scientific knowledge [99]. At the same time, the ideal of value-free science and policy recommendations is "neither possible nor recommendable" [77] as value-based decisions need to be made throughout the production of evidence, from the decision of what evidence need is addressed to the communication of findings [400]. Instead, I propose that this process be made transparent so that epistemic and non-epistemic value-laden decisions can be subject to dialogue with evidence consumers. Through the participatory approach in this research, I tried to mitigate taking value-laden decisions throughout the research process.

Methodological limitations and their implications for conclusions have been discussed in depth in each chapter. Though it is worth reflecting on the positionality of the researcher, this directly influences how research is carried out and determines the prevailing outcomes and results. It may be argued that by writing on the topic of EDU in the context of a low resource setting, the research should be conducted by someone assuming positionality as 'outsider within', e.g., a PhD researcher from Mozambique [184, 340]. Arguably, the research presented here could be critizised for being 'helicopter science', which Stefanoudis et al. define as "international scientists, typically from higher-income countries, conduct[ing] field studies in another country, typically of lower income, and then complet[ing] the research in their home country without any further effective communication and engagement with others from that nation" [373]. The author took various actions to mitigate epistemic racism. Firstly, the author engaged the research team in Mozambique and provided a seminar on knowledge translation. Further, the research assistants actively contributed to conceptualizing the data collection tools and had full ownership of the data collection in Mozambique. The author also engaged the team in the data analysis. Lastly, the team in Mozambique has full access to all the data. However, an insider perspective in the Ministry of Health, for example, would have allowed for the collection of data via observation. This would have added 'thick' detail to the data.

The emphasis of this thesis has been to understand the drivers of vaccine model evidence production and how to better capture a wider set of perspectives in the evidence generated to inform vaccine introduction and implementation at both the global and national levels. With the overarching aim of increasing the utility and uptake of modelled vaccine estimates. This research can confidently point

to an increased understanding and appreciation of the role of modelling vaccine impact if aspects of the model are co-developed with key decision-makers at the (sub)national level. However, it remains untested (due to time constraints) if this approach translates into an increase in the actual uptake and use of the evidence by various stakeholders. There is an opportunity to work with partners in Mozambique to further refine this participatory modelling approach and explore entry points for this model to inform policy windows and implementation knowledge gaps.

Optimizing vaccine delivery programmes in a sustainable and equitable way continues to be a high priority in public health. This thesis provides insights into how evidence from vaccine impact estimates is generated and used in both technical and political environments. Increased understanding of the role and utilization of evidence is essential if we are to shape and influence policies that can maximize health outcomes.

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Appendices

Appendix A

Theory

Table A.1: Facilitators and barriers to evidence use identified in the literature and scoping reviews by Olivier et al. [281] and Damba et al. [105]

Barriers	**Facilitators**
Availability	
Lag or lack of local research production (gaps in research production)	Availability of competent in-country researchers
Research evidence frequently perceived as not available	
Lack of data needed for each step of the policy processes	
Collaboration	
Lack of researcher collaboration	Involving policymakers in research design and execution
Communication	
Poor research dissemination skills	Researchers' need to understand the limitations of their evidence and establishing a systematic approach to feeding research results to policymakers that do not rely on personal preferences of researchers
Researchers' lack of communication	Clear understanding of expected outcomes
Ultimately dissemination of research results	Soft skills to navigate the policy process and engage with policymakers
Use of jargon	
Policy understanding	
Researchers' lack of understanding of diverse political influences which drive policy formulation or policy change	
Research evidence not considered the main driver of policy decisions	
Researchers' lack of technical capacity in policy processes	
Finance	
Funder-driven research	
Relevance	
Research ill-timed, research not applicable or not well aligned with health services	Timeliness of evidence
Limited relevant evidence	A research issue that generates sufficient interest in both the research and policymaking communities (relevance of evidence)
Reputation	
	Evidence generated by credible international researchers/regional networks and consensus on research results
Generalizability	
Available evidence not generalizable	
Knowledge translation	
Lack of knowledge about knowledge translation and its processes	
Lack of skills to conduct knowledge translation activities	

Appendix B

Ethical Approval

Imperial College London

Imperial College Research Ethics Committee
Imperial College London
Room 221
Medical School Building
St Marys Campus
London
W2 1PG
Tel: +44 (0)207 594 1872

researchethicscommittee@imperial.ac.uk

06/03/2020

Dear Professor Timothy Hallett

Study Title: Is the knowledge transfer between mathematical model producers and consumers optimal to maximise the impact of vaccine resource allocation decisions on public health? – A case study of Nigeria

ICREC reference: 20IC5841

The above study was approved by your Head of Department on 10/02/20 and by the Joint Research Compliance Office on 06/03/20.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC-SETREC Application form (v1.2 04/03/2020)
- Protocol (v1.2 04/03/2020)
- Participant Information Sheet Interview (v1.3 05/03/2020)
- Participant Information Sheet Focus Group (v1.3 05/03/2020)
- Consent form (v1.3 06/03/2020)
- Recruitment Invitation (v1.1 02/03/2020)
- Interview Questions consumers (v1.1 02/03/2020)
- Interview questions producers (27/02/2020)
- Focus group discussion guide (v1.2 04/03/2020)
- Sponsorship and Insurance request

Yours sincerely

pp

Ruth Nicholson
Head of Research Governance and Integrity
Imperial College London

Imperial College London

Imperial College Research Ethics Committee
Imperial College London
Room 221
Medical School Building
St Marys Campus
London
W2 1PG
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23/11/2021

Dear Dr. Lesong Conteh

Study Title: The perception and contribution of research in vaccine introduction decision-making and program planning processes

ICREC Reference number: 21IC7033

The above study was approved by your Head of Department on 12/07/21 and by the Research Governance and Integrity Team (RGIT) on 23/11/21.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Research Governance and Integrity Team (RGIT) and Head of Division/Department, where no significant ethical issues have been identified in the protocol or ethics application, can be granted RGIT approval without requiring it to go to full committee.

Documents
The documents reviewed were:

- Local Ethics from Mozambique (8/10/2021)

Yours sincerely

Ruth Nicholson
Head of Research Governance and Integrity
Imperial College London

REPÚBLICA DE MOÇAMBIQUE
MINISTÉRIO DA SAÚDE
DIRECÇÃO NACIONAL DE SAÚDE PÚBLICA

Exmo Senhor
Director do CISM
Dr. Francisco Saúte

Nota n° 98 / 002 / DNSP/2022 **Data, 20 de Janeiro de 2022**

ASSUNTO: **Parecer sobre Carta de Pedido de Cobertura do Centro de Investigação em Saúde da Manhiça**

Em resposta a vossa carta com a Referência ***CISM/1195/05/2021*** de 15 de Janeiro de 2021, na qual solicita a carta de cobertura do Centro de Investigação em Saúde de Manhiça, vimos pela presente comunicar a V. Excia que, o Ministério da Saúde não vê nenhum inconveniente na recolha de dados, acima supra citados.

Com elevada consideração.

O Director Nacional

[redacted]

Dr. Quinhas Fernandes, MD.MPH

116/DNSP/2022

ENDEREÇO:
MINISTÉRIO DA SAÚDE
C. POSTAL
Av. Eduardo Mondlane/Salvador Allende
MAPUTO – MOÇAMBIQUE

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Telex: 6-239 MISAU MO
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cism
centro de investigação em saúde de manhiça

Ao:

Ministério da Saúde
Direcção Nacional de Saúde Pública

Maputo

Manhiça, 15 de Dezembro de 2021

Ref.CISM/1195/05/2021

Assunto: Carta de Pedido de Cobertura do Centro de Investigação em Saúde de Manhiça

Exmos Senhores,

O Centro de Investigação em Saúde de Manhiça (CISM), em parceria com a Imperial College London, pretende realizar o estudo intitulado ***"Percepção e contribuição da investigação nos processos de tomada de decisão e planeamento de programas da vacina contra o Papiloma vírus Humano (HPV) em Moçambique"***.

Para o efeito, o CISM solicita ao Ministério Saúde a emissão da carta de cobertura que autoriza a realização do estudo acima supracitado, concretamente a recolha de dados nas instituições de saúde e de educação juntos dos técnicos que trabalham em torno do Programa de Vacinação e outros afins, bem como organizações parceiras (nos seus variados níveis), envolvidas nos processos de tomada de decisão e planeamento de programas da vacina contra o papiloma vírus humano em Moçambique. Espera-se que a recolha de dados aconteça entre os meses de Janeiro e Março de 2022.

Esta pesquisa tem como objetivo identificar as evidências usadas para informar a introdução de vacinas e as decisões de planeamento. Esta pesquisa permitirá que o CISM e outras instituições compreendam a sua contribuição para a introdução de vacinas e as decisões de planeamento, bem como o valor atribuído à pesquisa e outros tipos de evidências em geral. A pesquisa é relevante em termos de tempo, dado o progresso actual do país na introdução da vacina contra o HPV.

O processo de pesquisa não põe em risco a saúde e a segurança dos participantes ou membros da equipa de estudo. Ademais, no que concerne a propagação da COVID-19, todas as recomendações e protocolos sanitários serão obedecidos pelos investigadores.

Sem mais do momento, queiram aceitar os nossos melhores cumprimentos.

Atenciosamente,

[redacted] Saúte

Director do CISM

em saúde de manhiça

The perception and contribution of research in the human papillomavirus (HPV) vaccine introduction decision-making and program planning processes in Mozambique

Memorandum of Understanding

Between

The research team at Imperial College London (Dr. Lesong Conteh, Prof. Timothy Hallett and Paula Christen)

(Partner)

and

Dr. Neusa Torres at Manhiça Health Research Centre

(Partner)

This Memorandum of Understanding (MOU) sets for the terms and understanding between the research team at Imperial College London (herein-after ICL) and the research team at Manhiça Health Research Centre (herein-after CISM) to support the conduct of the PhD research project of Paula Christen.

Background

Studies on evidence-informed decision-making (EIDM) have shown that the appropriate utilization of evidence holds the promise of leading to significant health gains and reduced uncertainties in policy decisions around public health interventions. However, there is a limited understanding of the decision-makers' and program planners' value placed on different types of evidence and the purpose of evidence in new vaccine introductions (NVI) specifically. An assessment of how and which evidence contributes to NVIs in LMICs is of interest. This research aims to identify, which evidence is used to inform vaccine introduction and planning decisions, as well as how evidence use is perceived by different stakeholders. This allows to study the perception of different influences on evidence use and to evaluate the extent to which this is an independent process. This research also leads to an understanding of stakeholders' value placed on different decision criteria at different stages throughout the vaccine introduction process. ICL and CISM indicate intention to collaborate for the purpose of conducting this research.

Purpose

This MOU will involve the mutual support of both parties in conducting the research and transferring knowledge and skills between the research teams.

The above goals will be accomplished by undertaking the following activities:

- Members of the CISM research team will contribute to this research by:
    - Presenting the research project to the Comitê Científico Interno (CCI);
    - Submitting the ethics application to the Comite Institutional de Bioética para a Saúde;
    - Identifying a research assistant in Mozambique who has the knowledge and skills of conducting and transcribing semi-structured interviews with senior individuals;
    - Scheduling interviews that are held in person by members of the CISM team in Mozambique;
    - Identifying potential study participants for the purpose of this research;
    - Ensuring that data is shared with members of the ICL team in a safe manner;
    - Supporting the arrangement of logistics, when interviews are held in person in Mozambique;
    - Co-authoring publications stemming from this research;
    - Providing induction to CISM to the ICL research team.

- Members of the ICL research team will contribute to this research by:
    - Providing training on social science methods (contribution mapping and social network analysis) to CISM employees;
    - Conceptualizing the research;
    - Conducting the data analysis;
    - Writing publications following this research;
    - Scheduling interviews that are held by members of the ICL team;
    - Providing financial resources to conduct the research activities.

Publication

- In line with good scientific practice, this collaboration will endeavour to publish its findings in international peer-reviewed scientific journals, in one or more papers;
- The authorships for each of which will have to follow the ICJME criteria and usual conventions in scientific publishing;
- In light of which, it's our expectation that the authorship will include all investigators named here and that Paula is the first author.
- The cost for publications (meeting open-access requirements) will be met by ICL.

Reporting

Principal Investigators from ICL and CISM will convene at least every three months to review the progress of the research until completed. Progress reports will be shared with both research teams at ICL and CISM on a monthly basis.

Funding
This MOU is not a commitment to funds.

Duration
This MOU is at-will and may be modified by mutual consent of authorized officials from ICL and CISM. This MOU shall become effective upon signature by the authorized officials from ICL and CISM and will remain in effect until modified or terminated by any one of the partners by mutual consent. In the absence of mutual agreement by the authorized officials from ICL and CISM this MOU shall end on 31st December 2022.

Contact Information

Partner name	Imperial College London
Partner representative	Prof. Timothy Hallett and Dr. Lesong Conteh
Position	Principal Investigators
Partner name	Manhiça Health Research Centre
Partner representative	Dr. Neusa Torres
Position	Principal Investigator

[redacted] [redacted] [redacted]

_ _____ _____

Dr. Lesong Conteh	Prof. Timothy Hallett	Dr. Neusa Torres
Principal Investigator	Principal Investigator	Principal Investigator

Appendix C

Interview guides

Imperial College London

Semi-structured interview questions with model consumers

Is the knowledge transfer between mathematical model producers and consumers optimal to maximise the impact of vaccine resource allocation decisions on public health? – A case study of Nigeria

Conducted by Paula Christen, Prof. Timothy Hallett and Dr. Lesong Conteh

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The participant will be reminded that naming other researchers or model users is beneficial for the purpose of this project. Individuals referred to during the interview will be noted down during the interview and used in the snowball sampling process when recruiting new study participants. Further, this information will be valuable to map the social network among model consumers and producers. Following the interview, participants can review the transcripts and make amendments, to exclude or add content.

A. Resource allocation decision-making practice

- What is your involvement in the VIMC?
- What kind of resource allocation decisions need to be made at BMFG?
- What is your involvement in vaccine resource allocation decisions?
- Who are other stakeholders, who you are working with when assessing estimates?
- Can you outline the vaccine resource allocation process at [the BMGF/GAVI]?
- In what ways are decisions taken around vaccine resource allocations systematically?

How are you intending to use model estimates from the VIMC or other vaccine impact model estimates?

B. The use of mathematical models in resource allocation decisions

- How do you aim to answer questions during the resource allocation decision-making process using mathematical models?
- When receiving estimates by mathematical modellers in the past, what kind of questions arose in your team?
- For most of the diseases, different modelling groups produce estimates, which aim to complement each other. In the case of receiving diverging information on the same matter, how is the information used in your decision?
- How are mathematical estimates presented to you incorporated in resource allocation decisions?

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C. Interaction with model users

- What questions have you posed to the VIMC to be answered?
- What is your experience when engaging with mathematical modellers?
- Have modellers approached you in the past to ask questions about what kind of questions they would like to answer through your models?
    - If I were to ask you the same question as the modeller in the past now, what would you reply?
- How are model results and estimates communicated or explained to you?

How do you think mathematical models could be used more effectively in the allocation of resources for vaccine preventable diseases?

D. Evidence quality

- Is there a measure of quality control of information or knowledge shared with you?
- How are you engaging with other individuals acting upon vaccine resource allocation decisions?
- What is the intensity of engagement between you and other stakeholders who are acting upon vaccine resource allocation decisions is?
- How could alignment efforts be improved in your opinion?

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Semi-structured interview questions with model producers

Is the knowledge transfer between mathematical model producers and consumers optimal to maximise the impact of vaccine resource allocation decisions on public health? – A case study of Nigeria

Conducted by Paula Christen, Prof. Timothy Hallett and Dr. Lesong Conteh

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The participant will be reminded that naming other researchers or model users is beneficial for the purpose of this project. Individuals referred to during the interview will be noted down during the interview and used in the snowball sampling process when recruiting new study participants. Further, this information will be valuable to map the social network among model consumers and producers. Following the interview, participants can review the transcripts and make amendments, to exclude or add content.

Objectives addressed by mathematical models

- When modelling a disease for the VIMC, what is your objective?
- What initiated you designing the mathematical model that has been used to inform the VIMC?
- What are the responsibilities regarding the work that you are reporting to the VIMC or that you are producing for the VIMC?
- How do you think are your estimates being used to inform policy and decision makers regarding the allocation of resources?

Interaction with model users

- What is your experience when engaging with policy and decision makers?
- Have decision makers from Gavi, BMFG or at country level approached you in the past to ask questions about your models? What were these questions about?
    - Were you able to answer their questions?
- How are model results and estimates communicated or explained to resource allocation decision makers?
- Have you discussed your model with model users?

Peer-reviewed models

Imperial College London

- Have you received feedback about your mathematical model from the VIMC through the peer-review meeting? What was the feedback? Have you amended your work respectively in the past? If so, how?
- When comparing the model with the complementary model for the same disease, what are the main differences?

Model design

- How do questions posed by policy and decision makers impact the design of your mathematical model?
- How are mathematical models scoped and tailored to specific questions by policy and decision makers?
- The most recent LSHTM model identified that updated demography data have a major impact on estimates. Apart from demography data, what do you think could be another variable that may impact your model estimates significantly?
- Which country heterogeneities have you accounted for in your model?
    - Which ones have you left out consciously?
- Would it be possible to share the model documentation with me following the interview? I.e. the review documents discussed in the model review process?

Limitations of models

- When producing model estimates, were you aware of Gavi's and the BMFG's objectives a priori? How did your model meet the VIMC's requirements? How did you have to amend the model?
- How do you account for country heterogeneities?
- Your model produces estimates for 110 countries. Do you have access to data from all these countries?
- How are the model estimates scaled up to produce global estimates?

Semi-structured interview questions

The perception and contribution of research in the human papillomavirus (HPV) vaccine introduction decision-making and program planning processes in Mozambique

Study Lead & Co Investigator: Paula Christen
Principal investigators: Dr. Lesong Conteh, Prof. Timothy Hallett and Dr. Neusa Torres

Participant ID number: __ __ __	
Did the participant read the informed consent (IC)?	
In which language was the IC explained?	☐ Portuguese ☐ English
Was the informed consent signed?	☐ Yes ☐ No
Consent form signed prior to any study questions?	☐ Yes ☐ No
Date written IC signed: |D|D| - |M|M|M| - |Y|Y|Y|Y|	
Initials of the person who explained the IC: |__|__|__|	
Does the interviewee agree to be audio recorded during the interview?	☐ Yes ☐ No
Was the interview audio-recorded? If not, Why?	☐ Yes ☐ No
Start time: |H|H| : |M|M| End time: |H|H| : |M|M|	
Initials of the interviewer: |__|__|__ |	
Place where the interview took place: ☐ Organization office ☐ Hospital office ☐ Hospital hall ☐ At home ☐ Online ☐ Other, please specify:	

Instruction for research team members

- Use this document as a guide to the interview with stakeholders
- Conduct the interview in the language with which the interviewee feels most comfortable.
- Please introduce each question separately. The interview must flow as a conversation. If you notice that the interviewee is hesitant in answering, does not give an in-depth response, or the response is not satisfactory, please probe or ask follow-up questions, but do NOT prompt any specific answer. Several probes are suggested, but you may also ask follow-up questions that are not listed in this guide but are necessary for the complete expression of the interviewee's views.
- Please record the proceedings using the tape recorder/digital recorder (if consent is provided) and state the Participant ID number.
- All responses must be treated with confidentiality. Do not discuss or share the responses with anyone outside of the study team.

Section A – Interview questions for all study participants

Every study participant will be asked the following:

1. At which organisation were you employed while engaged in the HPV vaccine introduction? Is this the same organization as you are employed at now?
2. How do you describe or define your organization?
    a. Non-governmental organisation
        i. Which department?
    b. Government/Ministry
        i. Which department?
    c. Private organisation
        i. Which department?
    d. Research organisation/Academic institute/Think tank
        i. What is the focus of your research?
    e. Other
        i. Please elaborate.
3. What is your current role?
4. Since when have you been working on the HPV vaccine introduction in Mozambique?
5. Were you involved in working towards the decision to introduce the HPV vaccine in Mozambique?
6. Were you involved in planning the national scale-up of the HPV vaccine in Mozambique?
7. In your current role, have you conducted any research yourself? [Yes/No]
    a. If "yes", what research have you conducted? Please be as specific as possible.
8. Prior to your current role, have you conducted any research yourself? [Yes/No]
    a. If "yes", what research have you conducted? Please be as specific as possible.
9. What is your educational background? What is the highest level of education you have achieved?

"In the following part of the interview, I would like to ask you more specific questions on your involvement in the process of planning the HPV vaccine introduction. Whenever you think that formal or informal reports, meeting notes or other forms of document could support your answers, please make me aware of it. I would like to get back to you regarding these documents following the interview.

I would like to encourage you to reflect on your personal views rather than institutional views when answering the interview questions. I also want to emphasise that this is not a formal evaluation of any of your work practices. Rather, this research aims to understand how decisions come about, which stakeholders have been involved and how they have been involved as well as your personal experience in any of the processes. Your name will not be revealed in any of the findings. Also, depending on what you stated on the informed consent form, we will refrain from stating the name of your organization."

In interviews with community leaders, ask the following set of initial questions:

1. As of our understanding, you are a community leader. Please explain what this role or position encompasses.
2. To which community do you relate to?/ What kind of community do you feel responsible for? For example, is this a specific religious community or is it defined by something else?
3. Since when have you been acting in the role as community leader?
4. Were you engaged in the HPV vaccine demonstration program between 2013 and 2015?

Section B – Interview questions for evidence consumers

*The following questions will be posed to evidence consumers/ study participants, who are involved in decision-making and/or planning processes. Key questions are highlighted in **bold**. Other questions listed may be asked as follow-up questions. The indented, underlined questions should be posed to evidence consumers, who were identified as community leaders, who were engaged in any vaccine introduction activity prior to the national vaccine introduction.*

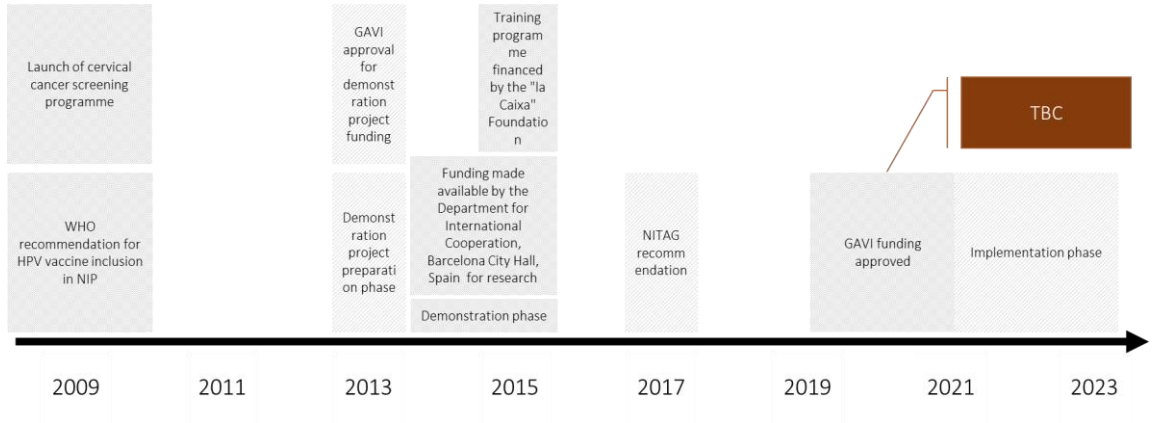
Section I: The vaccine introduction process and the interviewee's role within this

Note to interviewer: Please encourage the interviewee to explain the process from idea inception to potential contribution and what this contribution was in as much detail as possible. Probing on the responsibilities his/her role entailed may help to receive more detailed accounts of the process.

1. How are you or have you been involved in the HPV vaccine planning process?
    - How were you engaged in the HPV vaccine demonstration program between 2013 and 2015?
2. We aim to trace the full process of introducing the HPV vaccine in Mozambique, from when it was first considered up to now. Can you tell me as much as possible about the processes, which you have been involved in? Using the timeline, can you reflect on the processes which you were involved in specifically? Please be as detailed as possible.
    - What do you remember of the vaccine demonstration program at the time? Please give as much detail as possible.

    [If the interview is held in person:] Feel free to draw on the timeline.

    [If the interview is held virtually:] Show the timeline via the screensharing option and ask the participant to talk you through the processes in which he/she was engaged with.



GAVI = Global Alliance for Vaccine and Immunization

NIP = National Immunization Programme

Demonstration project = pilot projects in 3 sites in Mozambique

NITAG = National Immunization Technological Advisory Group

- What role did you play? Who else was involved or did you engage with in these process(es)? What role did others play? Who else and what else influenced actions and decisions taken?
    - What role did you play? Who else was involved or did you engage with at the time? What role did others play?
    - Were you engaged in any other processes in the vaccine introduction? If so, please elaborate, how you were engaged.
    - In the process of introducing a new vaccine, a lot of decision have to be taken. Do you remember being engaged in any decision-making processes? If so, which decisions?
    - Which organizations do you remember engaging with?
- Why were you involved in this process? Why was your role/position important in the process of deciding for the vaccine to be introduced/ in the process of planning the vaccine introduction?
    - Why was your role/position important in the process of deciding for the vaccine to be introduced/ in the process of planning the vaccine introduction?
- For other phases, in which you were not involved in, can you name other organizations, potentially specific stakeholders/individuals, who we may contact for the purpose of the study? Do you know what his/her role was?

3. Reflecting on the processes around the HPV vaccine introduction, what are the lessons learnt with respect to your role? What went well, but could have been done better in the future? For example, do you think some learnings are transferrable to the roll-out of the COVID-19 vaccine?
    - How do you think the COVID-19 vaccine introduction compared to the HPV vaccine introduction?

Section II: Sources of evidence, types of evidence and perception of evidence

4. In the process(es) which you were involved in, when and what kind of local data or other information (= evidence types) influenced actions and decisions taken? Please be specific about the type of data or other information. For example, was the data or findings sought from scientific journals?

- What shaped your knowledge on and understanding of the HPV vaccine and cervical cancer? Please be as specific as possible.
- What is your knowledge of the HPV vaccine and cervical cancer?

5. Do you remember any specific information that you made use of in the process(es) which you were involved in? (e.g. a certain report, specific study, dataset, etc.)
    - Do you remember any specific information that was communicated to you?
    - Who communicated this information to you and how (e.g. in a leaflet, report, other form)?
    - Did it matter to you, who communicated the information to you?
    - How did you perceive the information? (e.g. useful to learn more about the public health issue? Useful to spread the word about the public health issues?)
    - Do you have more questions about the vaccine and if so, what are these?
    - We differentiate types of information or evidence. Some comes from the global level, so organizations, such as the WHO or local level, so evidence from another health program in Mozambique and/or from another province. Do you think the type of information matters to you? Why does it matter to you?/ Why does it not matter to you?
6. Do you know, who produced the evidence? Did the source of evidence, for example the location of the author of the evidence or the owner of the data have an influence on your choice to use the data?
7. What motivated you to seek this information/evidence? Was the use of this information implied by external constituencies or motivated by questions you posed?
    - Did you actively request further information on the vaccine or the disease? If so, what exactly did you want to learn more about?

If the interviewee seems to have a good memory of one or multiple evidences, probe on each one stated specifically using the following questions:

8. For each one of the information types named *[refer to this by the name as stated by the interview participant, if possible]*, please clarify the following:
    - Clarify how the information was sourced
    - Clarify who produced the information – Did the source of evidence, for example the location of the author of the evidence or the owner of the data have an influence on your choice to use the data/evidence?
    - Clarify who commissioned the information to be produced
    - Was the evidence national, sub-national or global?

- What were the limitations of the information?
- Do you know more about the information production process? If this was a scientific research product, how and by whom were the objectives of the research defined? Was the organization/individual, who defined the research objectives involved in the information production?
- Did you have questions about the information?
- Did you have some form of work relationship with the information producer? Could you elaborate on this relationship and how it was established further.
- Why is the information used? (systematic use versus anecdotal use)

9. As of our knowledge, the demonstration projects were done at three sites in Mozambique. Do you think the information gathered from the three sites was enough to plan the national scale-up of the HPV vaccine?
    - How were information from the three sites generalized and applied in the national scale-up plan?
    - How could the evidence collation be improved?
    - Do you think the demonstration projects allowed to fully inform the national scale-up of the HPV vaccine?
        - Did you engage with other community leaders about the vaccine? If so, what was their perception of the vaccine and how did this differ to yours?
10. In addition to local information or when local information was not available, did you consider information from other countries or information from global health organizations?
11. What information do you perceive as more valuable, information from local settings (i.e. from Mozambique), international information (i.e. from other countries) or global information (i.e. from international/global health organizations)?
    - In which contexts do you prefer local over international or global information/evidence? And why do you prefer one over the other in these contexts?
    - In which contexts do you prefer international or global over local information/evidence? And why do you prefer one over the other in these contexts?
12. Are there certain decisions/variables/factors for which subnational, national or international evidence/information/data is preferred?
13. Has the need for subnational or national data/information/evidence emerged from what had been observed internationally? Can you provide examples for when this happened?

14. On the contrary, has the need for international/global data/information/evidence emerged from what had been observed at a national or subnational level? Can you provide examples for when this happened?

Section III: The need for evidence post-vaccine introduction

The following questions consider the future potential of evidence in the short and long term. We would like to understand whether and how results from mathematical models can support policy- and decision-makers. For this reason, we aim to find out the purpose of the evidence, in which form it should be disseminated, which outcome variables it should have (i.e., economic and/or epidemiological) and to whom this would be most useful.

1. In the next steps of the vaccine introduction (i.e., following the national vaccine rollout), what kind of evidence are you likely to be drawing on?
2. What are the greatest unknowns around the evaluation of the HPV vaccine following introduction in the national immunization program?
    - In the short-term, what kind of evidence would support your work?
        - What would the purpose of this evidence be?
        - Would this evidence be a "one-off" or routine evidence generation?
        - Who would the target audience of the evidence be?
        - In what format and through which means of dissemination would you imagine the evidence to be most useful? E.g., a tool, a paper, a policy brief?
    - In the long-term, what kind of evidence would support your work? What is the purpose of the evidence you envision to be useful?
        - What would the purpose of this evidence be?
        - Would this evidence be a "one-off" or routine evidence generation?
        - Who would the target audience of the evidence be?
        - In what format and through which means of dissemination would you imagine the evidence to be most useful? E.g., a tool, a paper, a policy brief?
    - How and what kind of vaccine impact should be measured to answer your questions and/or support your decisions?
    - Which outcome variables would you be most interested in a vaccine evaluation at a national level? For example, an economic outcome such as the cost of treating cervical cancer before and after HPV vaccine introduction or an epidemiological outcome such as the rate of cervical cancer incidence before and after HPV vaccine introduction.

- Do you have questions which could be addressed using a mathematical model?

In case of extra time, the following questions may be posed:

15. Can you remember moments in which specific information would have been helpful, but you didn't have access to the information?
    - What information would have been helpful?
    - Why would this information have been helpful?
    - What were the barriers to accessing information?
    - In these circumstances, how was the issue of having a lack of local information overcome?
    - What kind of impact did the lack of information and/or inaccessibility to information have on the stage in the new vaccine introduction process?
16. Did information conflict each other at times?
    - How did you go about it, when information with conflicting conclusions was presented to you?
17. What type of information did you find most suitable for your line of work?
    - Did you assess the quality of the information?
    - If there were multiple information sources:
        - How did you evaluate the different information?
        - Did you pick one over another information or did you merge the information?
    - What kind of decision criterion did this information support?
18. To what extent do you think was the decision to introduce the HPV vaccine informed by evidence?
19. To what extent do you think is the planning of the national scale-up of the HPV vaccine informed by evidence?

Semi-structured interview questions

Follow-up interview on the use of evidence developed with mathematical models for the HPV vaccination programme in Mozambique

Conducted by Paula Christen, Prof. Timothy Hallett and Dr. Lesong Conteh

An evidence brief, which includes these questions was shared with study participants prior to the interviews. During the interview, the interviewer explained the results in more detail. The following questions were prompted to explore the potential utility of the evidence presented.

- Whether the research questions that we posed match your evidence needs;
- Whether the evidence presented in this brief addresses your evidence needs;
- How the evidence brief could be refined in light of your evidence needs;
- For what this evidence may be useful;
- To whom this evidence may be useful;
- If this evidence should be shared with anyone else;
- If you would like to receive this evidence in another format.

Appendix D

Desk review

Table D.1: Grey literature on HPV and CC in Mozambique (MZ) written before January 2022 (beginning of qualitative data collection) with the year (Yr.) of publication/writing, a summary of the document content, its original language (Lang.), the type of evidence, evidence referenced in the document by scope (global evidence (GE), regional evidence (RE), international evidence (IE), national/local evidence (NE)). Presentation: Pres.; no specific reference: nsr.

Ref.	Yr	Summary	Lang.	Type	Referenced evidence, and its use as presented in the document
[254]	2012	Summary of meeting held to discuss the GAVI Demonstration Programme funding application.	En	Meeting report	
[109]	2012	Presentation of what CC is and how it can be prevented. Building the case for the demonstration programme and outlining the delivery plan for the demonstration programme.	En	Pres.	GE: • General epidemiology RE: • Prevalence figures for the sub-Saharan and comparison to epidemiology in MZ To advocate for the need of the HPV vaccine.
[194]	2014	Summary of meeting held to discuss the post-introduction evaluation, coverage survey, and HPV costing exercise.	En	Meeting report	GE: • WHO guidelines (nsr) to determine who should be included in the post-introduction evaluation To guide post-introduction evaluation.
[377]	2014	Summary of preparations for HPV Demo programme and how technical working groups are structured (communication and social mobilization; training and logistics; surveillance and monitoring)	En	Email exchange	NE: • Experience from Malaria programme on registry of bed net distribution. To understand societal behaviour towards health services.
[206]	2015	Evaluation of the demonstration programme in Manhica	En	Pres.	
[140]	2015	Brief summary of vaccination coverage progress in the district	Pt	Pres.	
[391]	2016	Workshop/ Presentation and discussion of the Demonstration Programme Results; one of the main concerns highlighted is the issue of equity. Overview of the demonstration programme timeline in MZ.	En	Pres.	GE: • WHO guidelines (nsr)

Continued on next page

Table D.1: Grey literature on HPV and CC in Mozambique (MZ) written before January 2022 (beginning of qualitative data collection) with the year (Yr.) of publication/writing, a summary of the document content, its original language (Lang.), the type of evidence, evidence referenced in the document by scope (global evidence (GE), regional evidence (RE), international evidence (IE), national/local evidence (NE)). Presentation: Pres.; no specific reference: nsr. (Continued)

Ref.	Yr	Summary	Lang.	Type	Referenced evidence, and its use as presented in the document
[195]	2015	Summary of coverage achieved and recommendations on possible next steps (e.g., the engagement of consultants, more investment in social mobilization)	En	Email exchange	NE: • Research conducted on the demonstration programme in MZ. To highlight potential vaccination programme challenges.
[207]	2016	Summary of demonstration programme.	Pt		
[110]	2018	Agenda for joint session with EPI and key partners with the aim to review the approach and methodology to be used to develop the scale-up strategy as well as clarify milestones, key activities, outputs, responsibilities of stakeholders, and to formally establish a support team.	En	Meeting report	One of the milestones on the workplan was explicitely related to the sourcing and reviewing key background documents: • Prepare a comprehensive list of information / documents required for input to the strategic process • EPI, JSI, Gavi and other partners share all required documentation (including any additional relevant information not identified on the list) with the strategy consultant • Desk review of relevant documents / information • Preparation of diagram providing an overview of all required components of the strategy (customisation based on WHO guidelines)
[292]	2018	Overview of components & considerations for development of scale-up strategy	En		GE: • WHO recommendation (nsr) • Vaccine overview and justification NE: • Country profile (key data and lessons learned) • Epidemiolgogy of CC in MZ To have an overview of evidence needs.
[292]	2018	Summary of vision and mission for the expansion strategy of the HPV vaccine in MZ	En	Report	NE: • Reference to learnings from demonstration programme To identify key action points.
[132]	2018	Update on the development of the strategic plan of the vaccination programme	En	Pres.	

Continued on next page

Table D.1: Grey literature on HPV and CC in Mozambique (MZ) written before January 2022 (beginning of qualitative data collection) with the year (Yr.) of publication/writing, a summary of the document content, its original language (Lang.), the type of evidence, evidence referenced in the document by scope (global evidence (GE), regional evidence (RE), international evidence (IE), national/local evidence (NE)). Presentation: Pres.; no specific reference: nsr. (Continued)

Ref.	Yr	Summary	Lang.	Type	Referenced evidence, and its use as presented in the document
[271]	2020	Develop a demand generation strategy to support the HPV vaccination programme in MZ	En	Report	GE: • [414] to guide formative research, specifically on key operational issues • Reference to school-based approach [396] • [103, 155] are systematic reviews, which were inconclusive about an optimal communication strategy • [278] used to back the argument that boys are benefiting from the vaccine via herd immunity, if 80% of coverage is achieved. RE: • As opposed to findings from literature reviews conducted in LMICs [103, 155], a literature review conducted in Africa concluded that health education, messages that address people's concerns, and public acceptance by gov. and health professionals can influence vaccine acceptance [367] IE: • [116] as indicator that trust in health services may be higher among those, who do not have access to it • [401] as learning that demand generation strategies should not focus on the disease, but rather make vaccination attractive with regards to different target groups NE: • Various published research and reports stemming from demonstration programme
[161]	2020	Report for GAVI reflecting on (1) the country's situation pre-COVID-19; (2) impact of COVID-19 immunisation service delivery and immunisation coverage; (3) discussion on priorities, catch-up needs, related action plan, budget, and technical assistance needs	En	Report	NE: • Evidence on data issues at local level; reflection on performance against key performance indicators, process indicators; overview of grants received for immunisation programmes (in general)
[193]	2021	Readiness assessment to identify key areas of action required.	Pt	Excel tool	

Appendix E

Stakeholders

Table E.1: Summary of of each organizations' stakeholders and responsibilities in the issue network around the HPV vaccination programme introduction in Mozambique.

Organization	Stakeholders involved	Engagement in the HPV vaccination programme
IS Global		
WHO	Global Regional National: EPI focal person; adolescent health focal person; non-communicable diseases focal person	General/throughout • Setting global targets (90-70-90) • Responding to questions posed by country, e.g., how to we customize global studies?; what targets are feasible? • Author of costing tools (WHO Cervical Cancer Prevention and Control Costing Tool (C4P)) • Guidance on how to customize global tools • Consolidating learnings about programmatic issues • Determining the value of vaccines in terms of disease and economic impact • Discussing and recommending delivery/programme options, e.g., 2-dose-vaccine schedule versus 3-dose-vaccine schedule • Communicating global and regional decisions to the MoH • Lobbying with other stakeholders Agenda setting • Set the global priority, which was then cascaded to the national level Implementation • Financial and technical support, especially for the implementation of the programme, e.g., deciding on the target group, defining vaccine eligibility criteria • Contributed to the design of the vaccine delivery strategy, especially the vaccine cold chain component
EPI (MoH)	Health system strengthening focal point	General/throughout • Leading all group discussions • Provide political technical support to other stakeholders in the issue network Formulation • Co-developing Gavi financing application Implementation • Develop vaccine strategy (cold chain, demand generation, costing of the project implementation, financial needs)
CISM		General • Publishing evidence from demonstration programmes Agenda setting • Conduct research on knowledge and acceptability of vaccine Formulation • Implementation of the demonstration programme in one district Implementation • Reviewing protocols and standards for community engagement written by UNICEF, CHAI, and JSI

Continued on next page

Table E.1: Summary of of each organizations' stakeholders and responsibilities in the issue network around the HPV vaccination programme introduction in Mozambique. (Continued)

Organization	Stakeholders involved	Engagement in the HPV vaccination programme
GAVI		General • Provision of vaccines, cash support, technical assistance for planning and preparing the programme Agenda setting • Prescribed what evidence had to be sought to receive funding (via application form/requirements) Formulation • Financing 2-year demonstration programme • Advice on demand generation activities
MoE		Formulation & Implementation • Supporting strategy development by • Consolidating data on the target group • Identifying schools • Preparing communication materials for community engagement and social mobilization
FDC		General • Working with community leaders Formulation & Implementation • Identify target group for the vaccine • Preparing communication materials for community engagement and social mobilization • Preparing training material for community leaders and guidance for community leaders on how to create demand for the pilot
Hospital Manhica		Data provider
Mothers and adolescents		
National Institute of Health	Representative from the non-communicable disease department	Formulation • Supporting the Ministry with Gavi funding application • Evaluation of pilot programme Implementation • Vaccine coverage surveys • Reviewing protocols and standards for community engagement written by UNICEF, CHAI, and JSI

Continued on next page

Table E.1: Summary of of each organizations' stakeholders and responsibilities in the issue network around the HPV vaccination programme introduction in Mozambique. (Continued)

Organization	Stakeholders involved	Engagement in the HPV vaccination programme
Community members		Study population for research on HPV in Mozambique and vaccine recipients
Teachers		Influential on adolescents' guardians
GSK, Merck		General • Provision of vaccines
UEM		• Assessment for introduction at national level
PATH		Formulation • Technical advisor for the evaluation of the pilot programme appointed by Gavi • Commissioned CISM to perform the post introduction evaluation (post pilot) Implementation • Technical and financial support for the implementation of cost-effectiveness studies
First Lady		Implementation • Pressured Ministry to introduce the vaccine
Health education department at Ministry		Implementation • Social mobilisation
EpiLinks		Implementation • Readiness assessment at national level (2019)
JSI		Implementation • Supporting quality control, e.g., functional temperature control systems in fridges • Promotion, education, creation of educational material • Production, reproduction and distribution of registration material • Revision of operational plan • Developing budget estimation for first year of introduction using the readiness assessments

Continued on next page

Table E.1: Summary of of each organizations' stakeholders and responsibilities in the issue network around the HPV vaccination programme introduction in Mozambique. (Continued)

Organization	Stakeholders involved	Engagement in the HPV vaccination programme
UNICEF		Implementation • Provision of vaccine support in terms of supplies through the UNICEF supply division • Supporting the development of communication materials • Promotion, education, creation of educational material • Production, reproduction and distribution of registration material • Service provision planning: human resources, demand estimation, demand for material resources • Supporting provinces in micro-planning • Identifying requirements for and planning the cold chain
NITAG		Formulation • Summary of scientific and technical evidence to advise the EPI

The issue network.

Social network analysis (SNA) aims to dismantle complex network structures and explain social phenomena that result from structural and relational attributes of a system. The approach can be used to identify who the actors/stakeholders in a system are, what their position is and what their relative influence on decisions are. Connections between actors/stakeholders are mapped out to understand which relationships are present and which ones could be value-adding for a more harmonized, evidence informed decision-making process. Networks, and actors/stakeholders' position in a network can be analysed using centrality measures. *betweenness* measures the number of times a node lies on the shortest path between other nodes in the network. Thereby, the most influential actors in the network can be identified.

Power

As per Bourdieu's social capital theory, actors' power can be expressed through stakeholders' (1) *economic*, (2) *cultural*, and (3) *symbolic capital* [47, 179, 342]. *Economic capital* is determined by the extent to which the stakeholder is financially invested in the network. For example, the United States government is dominating the global health network with highest investment in donor assistance for health (DAH) by financing bilateral aid agencies. *Cultural capital* is derived from education, accreditation, as well as experience. This form of power is inherently correlated with economic capital as knowledge production is reliant on funding, e.g., from philanthropic organizations such as the Gates Foundation. *Symbolic capital* is defined by the actors' reputation and how they are perceived by others in the issue network. For example, WHO guidelines are often uncontested and adopted by countries due to the reputation of the organization [179, 265]. Power can also be expressed physically, structurally, institutionally, morally, through a network, and through discourse [265].

Power dynamics in global health received increased scholarly attention in the past decade. Critical global health scholars have argued that power dynamics, especially power imbalances can widen public health inequities. But, health system complexities (at global, regional, national and local level) imply that it is not adequate to conceptualise power following the realist school, in which one stakeholder exercises power over another stakeholder to do something unintended. Instead, power may be assumed indirectly. For example, through donor funding, stakeholders may have decision-making power over the research agenda as well as a political agenda. Consequently, there may be lack of local ownership in the research, policy, or programme. Further, the research agenda is dominated by the interests of

research funding bodies. Thereby, foreign, non-state actors have influence on how and what evidence is produced, and, thus, what evidence is available for consideration in policy development. Through this dynamic, the political agenda may be indirectly shaped by the interests of stakeholders in HIC [378]. In political debates on public health policy and programmes, evidence can contribute to 'framing' an issue and facilitate democratic legitimization. As such, Parkhurt et al [316] argue, all evidence is likely to be used as ammunition in an argument for or against a particular outcome in politically charged contexts.

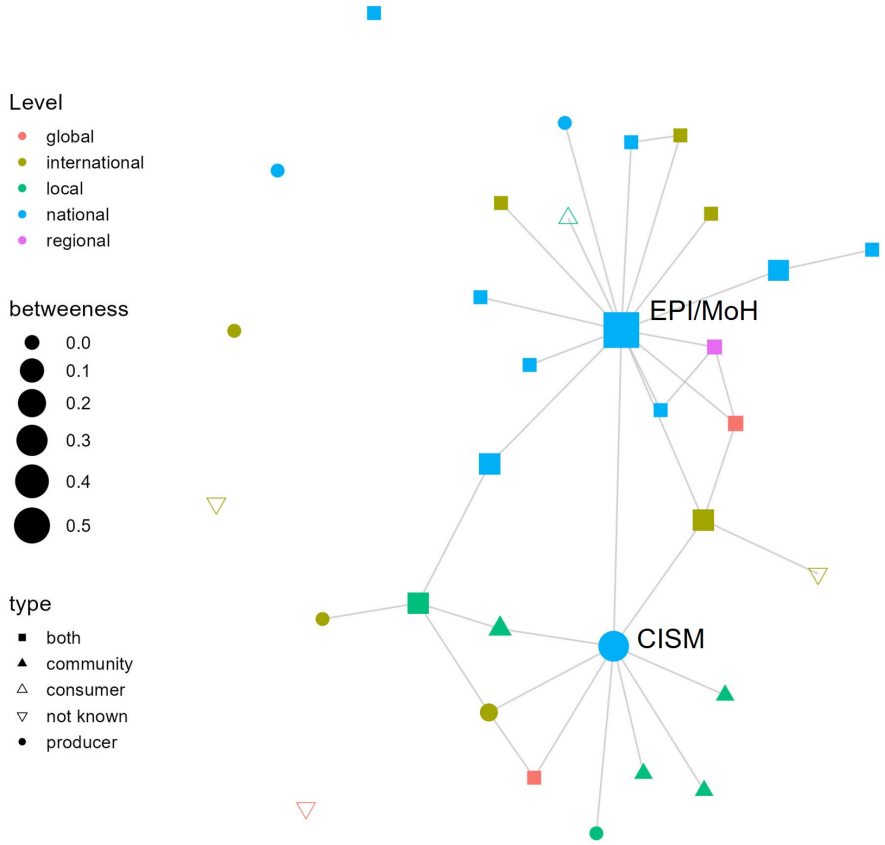
The data was analyzed to produce (1) a power map and (2) a social network graph.

The purpose of the "power map" was to provide an illustrative representation of the stakeholders in the issue network and the distribution of power across stakeholders in the issue network. The "power maps" was produced employing adapted methods used by Varvasovszky [392], the Research and Policy in Development (RAPID) team at the Overseas Development Institute [257], and Case [86]. The focus of this map is on how actors assume power, which can be expressed through stakeholders' (1) *economic*, (2) *cultural*, and (3) *symbolic capital*, as per Bourdieu's social capital theory [47, 179, 342]. *Economic capital* is determined by the extent to which the stakeholder is financially invested in the HPV vaccination programme. *Cultural capital* is derived from education, accreditation, as well as experience. *Symbolic capital* is defined by how the actor is recognized and perceived by others in the issue network.

Each study participant was scored by PC, AL, and MM on the *symbolic* capital dimension on an ordinal scale from 1 to 10, with 10 being the highest possible measure of capital. Valuations made by each researcher (PC, MM, AL) were aggregated by taking averages. Outliers were discussed in the research team. For the purpose of this study, *economic capital* is a binary variable, defined by whether the actor, or their organization is financially contributing to any stage of the policy development or not. This information was extracted from interviews as well as the desk review. Data on *cultural capital* was collected in the informative section at the beginning of the interview, in which the participant was asked about their highest academic degree, experience, and current position in their organization (see Appendix).

Further, the data was analyzed to produce a "social network graph". The purpose of this mapping exercise was to illustrate a qualitative assessment of the decision making environment and interconnectedness of stakeholders engaged in the HPV vaccine introduction in Mozambique. For this,

Figure E.1: Issue network around the HPV vaccination programme introduction in Mozambique. Each node is one organization.



interview participants were asked, who they worked with, and who collaborated in the wider network. Each interview participant and organization named during interviews was characterised. For each organization with which study participants were affiliated at any point throughout the vaccine introduction or others that were named during the interview, the type of organization, their collaborations, and responsibilities in the HPV vaccination programme introduction was documented. The data was aggregated to organizational level, i.e., one network node is one organization. Thereby, results could not be traced back to individuals. The centrality measure, *betweeness* was calculated for each node. *Betweeness* measures the number of times a node lies on the shortest path between other nodes in the network. Thereby, the most influential actors in the network can be identified.

Appendix F

Cervical Cancer incidence rate by age group in Mozambique

Table F.1: Average of cervical cancer incidence per 100,000 recorded in the Beira registry (2014-2017) and the Maputo registry (2015-2017) by age group. [390]

Age group	**Cervical cancer incidence per 100,000**
0-4	0
5-9	0
10-14	0.6
15-19	0
20-24	4.0
25-29	18.7
30-34	50.4
35-39	91.9
40-44	109.0
45-49	105.6
50-54	131.2
55-59	141.4
60-64	143.4
65-69	125.0
70-74	87.1
75-79	73.3
80-84	0
85-89	0
90-94	0
95-99	0

Appendix G

Evidence Brief

Addressing policy actors' questions about the human papillomavirus vaccination programme in Mozambique with mathematical models

Paula Christen, Agostinho Lima, Muanacha Mintade, Neusa Torres, Lesong Conteh, Timothy Hallett, Allison Portnoy



Background

The human papillomavirus (HPV) vaccine was introduced in Mozambique in Nov. 2021. However, there are aspects, which are less understood or known by those engaged with the HPV vaccination programme planning and implementation.

Aims:

1) Identify evidence needs and research questions related to the HPV vaccine programme in Mozambique, and outcome measures
2) Address evidence needs using mathematical models

We would like to know from you…

- Whether the research questions that we posed match your evidence needs;
- Whether the evidence presented in this brief addresses your evidence needs;
- How the evidence brief could be refined in light of your evidence needs;
- For what this evidence may be useful;
- To whom this evidence may be useful;
- If this evidence should be shared with anyone else;
- If you would like to receive this evidence in another format.

Selected Interview Responses

There is the aspect of the price of vaccines for us as managers and so we are taking into account that until now almost all the vaccines that we are using in our system are financed by partners and **there always comes that fear of: what will happen if one day the partners do not want to pay for these vaccines**. (P10, National Ministry)

Well, even for decision makers of the Ministry of Health, even those who make decisions in terms of the allocation of health resources, **if you reduce the number of women with cancer, you are also reducing the economic burden and investment in the area of treatment, so this is important to demonstrate**. (P13, international organization operating nationally)

At some point we need to be able to demonstrate the value of the vaccine. I think evidence as well around the communication strategy is important because that's an area where there possibly needs to be more responsiveness, **depending on what the real vaccination rates are outside of urban areas**. (P07, NGO operating nationally)

The issue of access to vaccines in rural-urban area, I still cannot see this in the data I access. […] **if we were seeing that the coverage is only in urban areas and the rural areas is not having anything, we have to change the strategy**. (P13, international organization operating nationally)

Research Questions

What costs does the vaccination programme imply in the future?

To what extent are treatment resources saved as a result of the vaccination programme in Mozambique?

To what extent is the vaccination programme equitable, given the presence of significant health inequities due to access to healthcare across wealth quintiles and types of residence in Mozambique?

Outcome metrics

(1) Reduced cervical cancer (CC) morbidity and mortality

(2) Medical personnel staff time saved; Reduction in health inequity

(3) Financial risk protection provided; Distribution of outcomes

MRC Centre for Global Infectious Disease Analysis
Imperial College London
cism centro de investigação em saúde de manhiça
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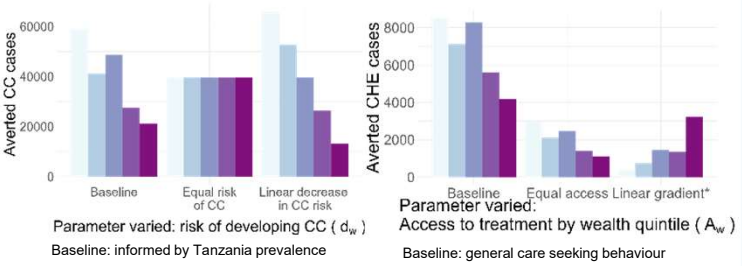
Results

- As a result of reaching 18.5% of 9-year-old girls in 2021 (status quo scenario), 9.7% of expected CC cases and deaths are projected to be averted.
- Assuming **equal access to the vaccination programme**, vaccinating 30 cohorts of 9-year-old girls, i.e., from 2021 to 2051, **at a coverage of 50%** would, between 2021 and 2120:
  - Cost US$63M (1.9% of estimated averted treatment costs),
  - Reduce the time required for treatment of CC by an amount equal to 2,064 medical personnel FTEs, and
  - Avert 33,700 catastrophic health expenditure cases.
  - Distributions of these outcomes across wealth quintiles under varying assumptions of CC risk, and access to treatment is demonstrated in A1 and A2.
- Assuming a **gradient coverage, averaging 50% across wealth quintiles**, the vaccination programme would lead to:
  - 24% of CC cases and deaths to be averted,
  - 68% of health and economic benefits accruing in the three lowest income quintile (Fig. B1 and B2).
- Assuming a **gradient coverage, averaging 50% across wealth quintiles** and **type of residence**, the vaccination programme would benefit women in the highest socioeconomic quintile in the urban area most (Fig. C).
- A sliding treatment cost coverage with 99%, 98%, 96%, 93%, and 76% from lowest to highest socioeconomic quintile would lead to an overall reduction of 55% in CHE incidence.

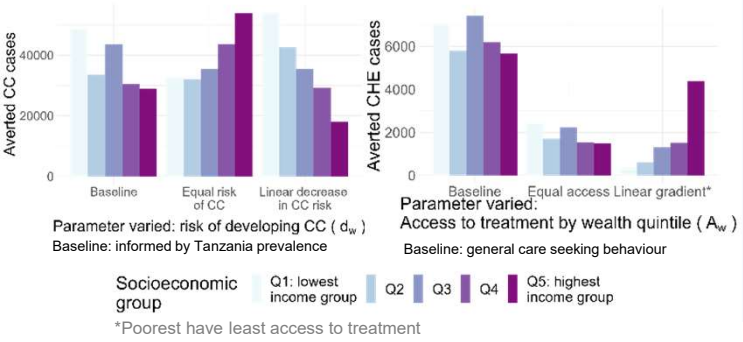
Scenario	% of expected CC cases and deaths averted	Treatment costs saved (US$)*	Programme costs (US$)*	FTEs saved
Status quo	10%	39M	24M	784

*Costs are discounted annually at 3%

(A) 50% coverage of the HPV vaccine across wealth quintiles

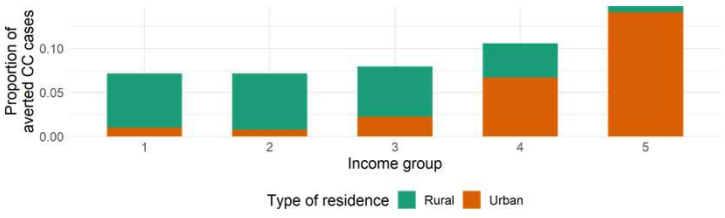


(B) *50% of coverage at a gradient across wealth quintiles*



*Poorest have least access to treatment

(C) 50% of coverage at a gradient across wealth quintiles and type of residence



Discussion

- Findings can inform fair and efficient planning decisions, e.g., in the development of Mozambique's National Cancer Control Plan, thereby, contributing to reaching Sustainable Development Goals 1 and 3.
- Results are highly sensitive to access to treatment and distribution of CC assumptions.
- The method relies on cost data, and prevalence distribution information from Tanzania; while costs are likely to differ in Mozambique, the countries have a similar Healthcare Access and Quality Index.
- The model can be refined by estimating outcomes at the provincial level.

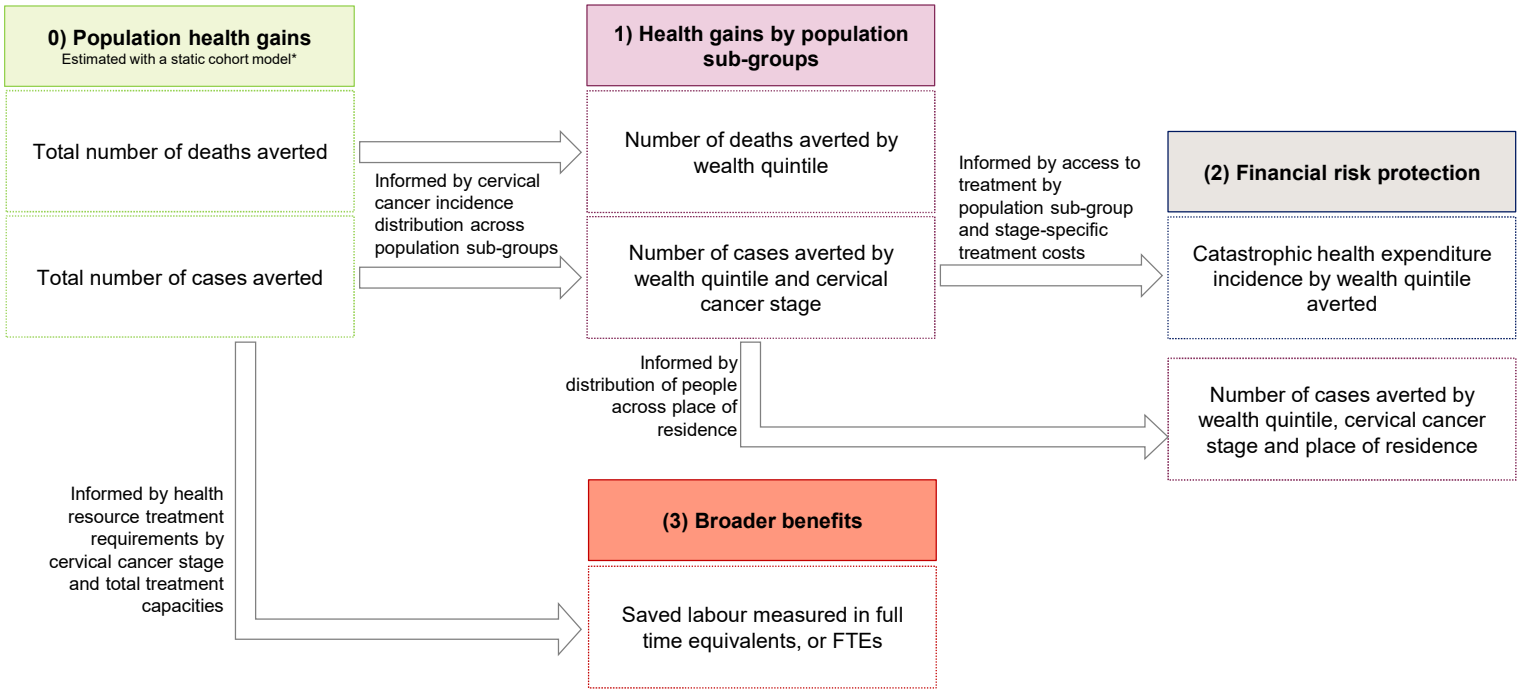
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Annex

Glossary

Term	Definition
Static cohort model	In a static cohort model the experience of a cohort of people who receive (or do not receive) a treatment is simulated. The proportion of the cohort that experiences health events or health states over time can be estimated using decision trees and Markov processes. The cohort's experience can be summarised by multiplying events, their associated costs, and utilities, as well as the expenses and utilities related to health statuses, by the appropriate fraction of the cohort.
Catastrophic health expenditure	Catastrophic health spending is defined as out-of-pocket costs that exceed a percentage of total household spending or non-food costs that lead households to forgo other essentials, sell assets, accrue debt, or fall into poverty.

Methods



Assumptions

Parameter	Value	Informed by
HPV-16/18 type distribution	0.51/0.49	Hospital cohort study
Stage distribution of detected cancers by FIGO stage	Stage I: 0.09 Stage II: 0.36 Stage III: 0.47 Stage IV: 0.08	Global
Vaccination coverage	18.5%	Empirical data (2021)
Vaccine wastage	5%	Global
One-time-introduction cost per dose in US$	2.00	Global
Recurrent delivery cost per dose in US$	1.70	Global
Vaccine cost per dose in US$	4.50	Global
Distribution of CC incidence across wealth quintile	Q1: 29.7% Q2: 20.9% Q3: 24.7% Q4: 13.9% Q5: 10.8%	Cohort data collected between 2011 and 2013 in Tanzania

Parameter	Value	Informed by
Medical treatment costs by FIGO stage in US$	Stage I: 2,989 Stage II: 2,999 Stage III: 1,744 Stage IV: 1,741	Study on cost-effectiveness of CC screening and treatment in Tanzania
Proportion of direct medical treatment costs covered by health system	0	
Average household size	4.78	Inquerito sobre orcamento familiar - IOF 2019/20
Monthly per capita consumption in MZN	As of 2019/20: Q1: 224 Q2: 585 Q3: 990 Q4: 1,655 Q5: 5,022	Inquerito sobre orcamento familiar - IOF 2019/20
Medical personnel labour cost by FIGO stage in US$	Stage I: 106.95 Stage II: 117.39 Stage III: 105.16 Stage IV: 102.24	Study on cost-effectiveness of CC screening and treatment in Tanzania
Annual treatment capacity for CC patients at public hospital	900	Presentation by International Cancer Control Partnership

*Sue J. Goldie et al. "Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries". en. In: *Vaccine* 26.32 (July 2008), pp. 4080–4093. issn: 0264410X. doi: 10.1016/j.vaccine.2008.04.053.

Responder às perguntas dos actores políticos sobre o programa de vacinação contra o papilomavírus humano em Moçambique com modelos matemáticos

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Antecedentes

A vacina contra o papilomavírus humano (HPV) foi introduzida em Moçambique em Novembro de 2021. Contudo, há aspectos que são menos compreendidos ou conhecidos por aqueles que estão envolvidos no planeamento e implementação do programa de vacinação contra o HPV.

Objectivos:

1) Identificar necessidades de provas e questões de investigação relacionadas com o programa de vacina contra o HPV em Moçambique, e co-definir medidas de resultados

2) Abordar as necessidades de provas utilizando modelos matemáticos

Gostariamos de saber de si…

- Se as questos de invetigacao
- Se as provas apresentadas neste resumo respondem às suas necessidades de prova;
- Como o dossier de provas poderia ser refinado à luz das suas necessidades de provas;
- Para o que esta prova pode ser útil;
- A quem estas provas podem ser úteis;
- Se estas provas devem ser partilhadas com qualquer outra pessoa;
- Se desejar receber estas provas noutro formato.

Respostas a Entrevistas Seleccionadas

Há o aspecto do preço das vacinas para nós como gestores e por isso estamos a ter em conta que até agora quase todas as vacinas que estamos a utilizar no nosso sistema são financiadas por parceiros **e vem sempre aquele medo de: o que acontecerá se um dia os parceiros não quiserem pagar por estas vacinas.** (P10, Ministério Nacional)

Bem, mesmo para os decisores do Ministério da Saúde, mesmo aqueles que tomam decisões em termos de atribuição de recursos de saúde**, se reduzirmos o número de mulheres com cancro, estamos também a reduzir a carga económica e o investimento na área do tratamento, pelo que isto é importante de demonstrar.** (P13, organização internacional que opera a nível nacional)

A certa altura precisamos de ser capazes de demonstrar o valor da vacina. Penso que também as provas em torno da estratégia de comunicação são importantes porque essa é uma área onde possivelmente é necessário haver uma maior capacidade de resposta, **dependendo de quais são as taxas reais de vacinação fora das áreas urbanas**. (P07, ONG a operar a nível nacional)

A questão do acesso às vacinas na zona rural-urbana, ainda não consigo ver isto nos dados a que tenho acesso. [...] **se estivéssemos a ver que a cobertura é apenas em zonas urbanas e as zonas rurais não têm nada, temos de mudar a estratégia**. (P13, organização internacional que opera a nível nacional)

Questões de Investigação

Que custos implica o programa de vacinação no futuro?

Em que medida são os recursos de tratamento poupados em resultado do programa de vacinação em Moçambique?

Em que medida é o programa de vacinação equitativo, dada a presença de desigualdades significativas na saúde devido ao acesso aos cuidados de saúde através dos quintis de riqueza e tipos de residência em Moçambique?

Outcome metrics

(1) Redução da morbilidade e mortalidade do cancro do colo do útero (CC)

(2) Poupança de tempo do pessoal médico

(3) Protecção contra riscos financeiros assegurada; Distribuição dos resultados e redução das desigualdades na saúde

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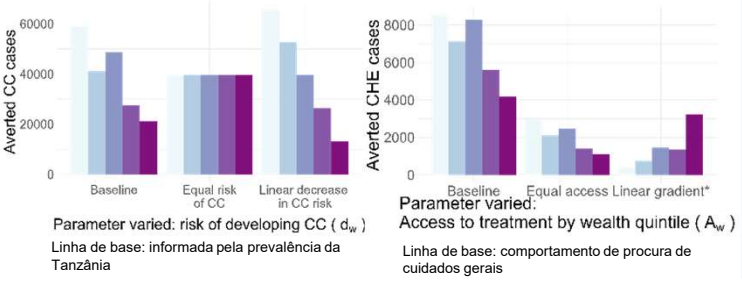
Results

- Como resultado de atingir 18,5% das raparigas de 9 anos de idade em 2021 (cenário de status quo), 9,7% dos casos de CC esperados e das mortes são projectados para serem evitados.
- Assumindo **igualdade de acesso ao programa de vacinação**, a vacinação de 30 coortes de raparigas de 9 anos, ou seja, de 2021 a 2051, **com uma cobertura de 50% seria**, entre 2021 e 2120:
  - Custou US$63M (1,9% dos custos de tratamento evitados estimados),
  - Reduzir o tempo necessário para o tratamento de CC num montante igual a 2.064 FTEs de pessoal médico, e
  - Avert 33,700 casos catastróficos de despesas de saúde.
  - A distribuição destes resultados pelos quintis de riqueza sob diferentes hipóteses de risco de CC, e o acesso ao tratamento é demonstrado em A.
- Assumindo **uma cobertura gradiente, com uma média de 50% em quintis de riqueza**, o programa de vacinação levaria a:
  - 24% dos casos de CC e mortes a serem evitados,
  - 68% dos benefícios económicos e de saúde acumulados nos três quintis de rendimento mais baixos (B).
- Assumindo **uma cobertura gradiente, com uma média de 50% entre quintis de riqueza e tipo de residência**, o programa de vacinação beneficiaria as mulheres do quintil socioeconómico mais elevado da área urbana (C).

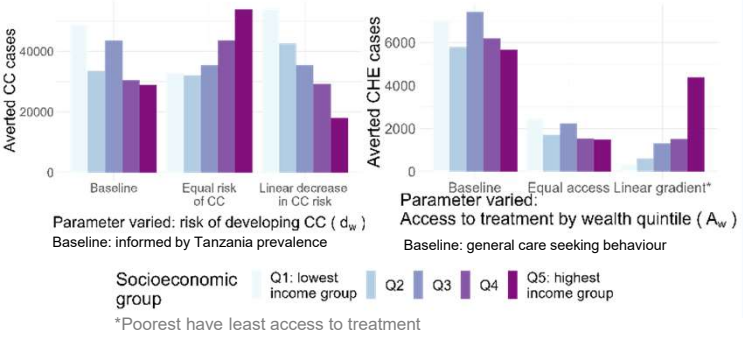
Cenário	% de casos e mortes previstos de CC evitados	Custos de tratamento evitados (US$)*	Custos do programa (US$)*	FTEs economizados
10%	39M	24M	784	10%

*Os custos são descontados anualmente a 3%.

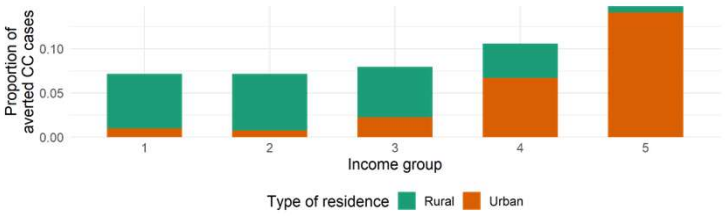
(A) 50% de cobertura da vacina contra o HPV nos quintis de riqueza



(B) 50% de cobertura a um gradiente entre quintis de riqueza



(C) 50% de cobertura a um gradiente entre quintis de riqueza e tipo de residência



Discussion

- Os resultados podem informar decisões de planeamento justas e eficientes, por exemplo, no desenvolvimento do Plano Nacional de Controlo do Cancro de Moçambique, contribuindo assim para alcançar os Objectivos de Desenvolvimento Sustentável 1 e 3.
- Os resultados são altamente sensíveis ao acesso ao tratamento e à distribuição dos pressupostos CC.
- O método baseia-se em dados de custos, e em informação de distribuição de prevalência da Tanzânia; embora os custos sejam provavelmente diferentes em Moçambique, os países têm um Índice de Acesso e Qualidade dos Cuidados de Saúde semelhante.
- O modelo pode ser aperfeiçoado através da estimativa dos resultados a nível provincial.

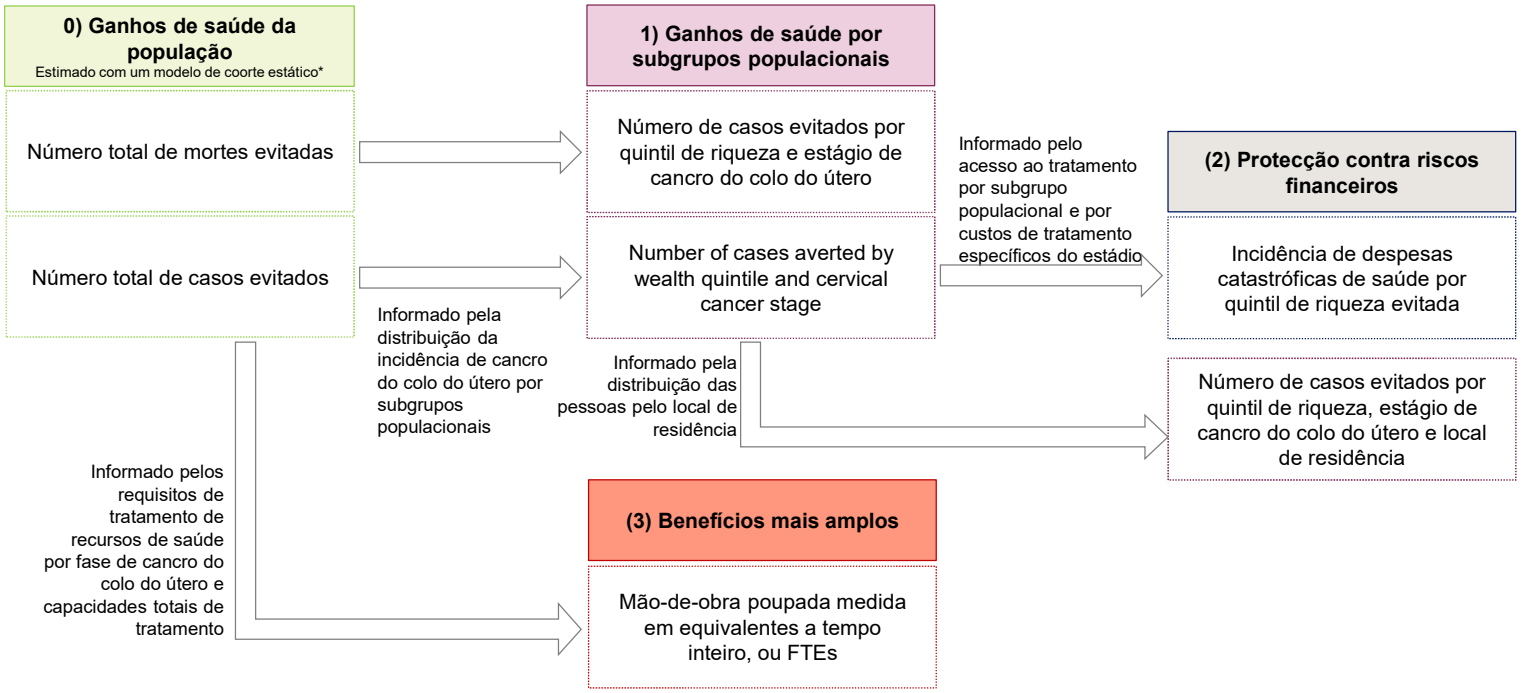
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Anexo

Glossário

Palavra	Definição
Modelo estático de coorte	Num modelo de coorte estático, a experiência de uma coorte de pessoas que recebem (ou não recebem) um tratamento é simulada. A proporção do coorte que experimenta eventos de saúde ou estados de saúde ao longo do tempo pode ser estimada utilizando árvores de decisão e processos Markov. A experiência do coorte pode ser resumida multiplicando os eventos, os seus custos associados, e as utilidades, bem como as despesas e utilidades relacionadas com os estados de saúde, pela fracção apropriada do coorte.
Despesas catastróficas com a saúde	As despesas catastróficas com a saúde são definidas como custos de saúde que excedem uma percentagem das despesas totais das famílias ou custos não alimentares que levam as famílias a renunciar a outros bens essenciais, vender activos, acumular dívidas, ou cair na pobreza.

Methods



Assumptions

Parameter	Value	Informed by
Distribuição tipo HPV-16/18	0.51/0.49	Hospital cohort study
Distribuição faseada dos cancros detectados pela fase FIGO	Stage I: 0.09 Stage II: 0.36 Stage III: 0.47 Stage IV: 0.08	Global
Cobertura vacinal	18.5%	Dados empíricos (2021)
Desperdício de vacinas	5%	Global
Custo de introdução única por dose em US$	2.00	Global
Custo de entrega recorrente por dose em US$	1.70	Global
Custo da vacina por dose em US$	4.50	Global
Distribuição da incidência de CC pelo quintil de riqueza	Q1: 29.7% Q2: 20.9% Q3: 24.7% Q4: 13.9% Q5: 10.8%	Coorte de dados recolhidos entre 2011 e 2013 na Tanzânia

Parameter	Value	Informed by
Custos do tratamento médico por FIGO em US$	Stage I: 2,989 Stage II: 2,999 Stage III: 1,744 Stage IV: 1,741	Estudo sobre a relação custo-eficácia do rastreio e tratamento de CC na Tanzânia
Proporção dos custos directos de tratamento médico cobertos pelo sistema de saúde	0	
Tamanho médio do agregado familiar	4.78	Inquerito sobre orcamento familiar - IOF 2019/20
Consumo mensal per capita em MZN	As of 2019/20: Q1: 224 Q2: 585 Q3: 990 Q4: 1,655 Q5: 5,022	Inquerito sobre orcamento familiar - IOF 2019/20
Pessoal médico custo de mão-de-obra por etapa FIGO em US$	Stage I: 106.95 Stage II: 117.39 Stage III: 105.16 Stage IV: 102.24	Estudo sobre a relação custo-eficácia do rastreio e tratamento de CC na Tanzânia
Capacidade de tratamento anual para pacientes CC em hospitais públicos	900	Apresentação por International Cancer Control Partnership

*Sue J. Goldie et al. “Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries”. en. In: *Vaccine* 26.32 (July 2008), pp. 4080–4093. issn: 0264410X. doi: 10.1016/j.vaccine.2008.04.053.