UMEÅ UNIVERSITY

Health economic evaluation for evidence-informed decisions in low-resource settings.

The case of Antenatal care policy in Rwanda.

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TABLE OF CONTENTS

TABLE OF CONTENTS ..... **i**
LIST OF TABLES ..... **iii**
ABSTRACT ..... **iv**
ENKEL SAMMANFATTNING PÅ SVENSKA ..... **vi**
ABBREVIATIONS ..... **viii**
ORIGINAL PAPERS ..... **ix**
1. INTRODUCTION **1**
1.1. Point of departure 1
1.2. Evidence-based public health 2
1.3. Cost-effectiveness of maternal health interventions in LMIC 15
1.4. Maternal health in Rwanda 22
1.5. Knowledge gap and contribution of this thesis 24
1.6. Aim and objectives 27
2. MATERIALS AND METHODS **29**
2.1. Study setting 29
2.2. Primary data sources 33
2.3. Ethical consideration 39
2.4. Data analysis 40
3. RESULTS **51**
3.1. Socio-economic and demographic characteristics, HRQoL and ANC utilization of participants 51
3.2. Cost of ANC–Current practice and 2016 WHO ANC recommendations 53
3.3. ANC and Health Outcomes 57
3.4. Incremental cost-effectiveness 59
3.5. Results of the systematic review of cost and cost-effectiveness of ultrasound during pregnancy 60
4. DISCUSSION **63**
4.1. The cost of current (2015) ANC practice in Rwanda 64
4.2. What would be the incremental cost if Rwanda implements the 2016 WHO ANC recommendations? 65
4.3. ANC effectiveness in Rwanda 65
4.4. Is it worth it for Rwanda to implement the 2016 WHO ANC recommendations? 68
4.5. Reflections on methods 70
5. CONCLUSION AND RECOMMENDATIONS **75**
5.1. Conclusion 75
5.2. Recommendations 76
6. EPILOGUE **77**
7. ACKNOWLEDGEMENT **79**
8. REFERENCES **81**

LIST OF TABLES

Table 1. Progress of key maternal, newborn and child health and mortality indicators 23
Table 2. Cost data collection process and sources of information 41
Table 3. Distribution of women by socio-economic and demographic categories (N=922)..... 52
Table 4. Description of selected health facilities 54
Table 5. Societal cost of ANC..... 55
Table 6. Association between health-related quality of life and ANC utilization: Regression analysis using the EQ-5D and EQ-VAS 58
Table 7. Incremental health benefits 59

LIST OF FIGURES

Figure 1. Typical graphical presentation of incremental cost and outcomes in health economic studies..... 2
Figure 2. Evidence, transparency and voice: steps in priority setting. (Adapted from Terwindt et al, 2016)..... 12
Figure 3. Prevalence of the dimensions of quality of life (N=922) 53
Figure 4. Simulation of ANC attendance..... 56
Figure 5. Incremental costs 57
Figure 6. Incremental cost-effectiveness of the 2016 WHO ANC recommendations for Rwanda..... 59
Figure 7. Screening process of papers 61

ABSTRACT

Introduction

The general aim of this thesis is to contribute to the use of health economic evidence for informed health care decisions in low-resource settings, using antenatal care (ANC) policy in Rwanda as a case study. Despite impressive and sustained progress over the last 15 years, Rwanda's maternal mortality ratio is still among the highest in the world. Persistent gaps in health care during pregnancy make ANC a good candidate among interventions that can, if improved, contribute to better health and well-being of mothers and newborns in Rwanda.

Methods

Data used in this thesis were gathered from primary and secondary data collections. The primary data sources included a cross-sectional household survey (N=922) and a health facility survey (N=6) conducted in Kigali city and the Northern Province, as well as expert elicitation with Rwandan specialists (N=8). Health-related quality of life (HRQoL) for women during the first-year post-partum was measured using the EQ-5D-3L instrument. The association between HRQoL and adequacy of ANC utilization and socioeconomic and demographic predictors was tested through bivariate and linear regression analyses (Paper I). The costs of current ANC practices in Rwanda for both the health sector and households were estimated through analysis of primary data (Paper II). Incremental cost associated with the implementation of the 2016 World Health Organization (WHO) ANC recommendations compared to current practice in Rwanda was estimated through simulation of attendance and adaptation of the unit cost estimates (Paper III). Incremental health outcomes of the 2016 WHO ANC recommendations were estimated as life-years saved from perinatal and maternal mortality reduction obtained from the expert elicitation (Paper III). Lastly, a systematic review of the evidence base for the cost and cost-effectiveness of routine ultrasound during pregnancy was conducted (Paper IV). The review included 606 studies published between January 1999 and April 2018 and retrieved from PubMed, Scopus, and the Cochrane database.

Results

Sixty one percent of women had not adequately attended ANC according to the Rwandan guidelines during their last pregnancy; either attending late or fewer than four times.

Adequate utilization of ANC was significantly associated with better HRQoL after delivery measured using EQ-VAS, as were good social support and household wealth. The most prevalent health problems were anxiety or depression and pain or discomfort. The first ANC visit accounted for about half the societal cost of ANC, which was $44 per woman (2015 USD) in public/faith-based facilities and $160 in the surveyed private facility. Implementing the 2016 WHO recommendations in Rwanda would have an incremental national annual cost between $5.8 million and $11 million across different attendance scenarios. The estimated reduction in perinatal mortality would be between 22.5% and 55%, while maternal mortality reduction would range from 7% to 52.5%. Out of six combinations of attendance and health outcome scenarios, four were below the GDP-based cost-effectiveness threshold. Out of the 606 studies on cost and cost-effectiveness of ultrasound during pregnancy retrieved from the databases, only nine reached the data extraction stage. Routine ultrasound screening was reported to be a cost-effective intervention for screening pregnant women for cervical length, for vasa previa, and congenital heart disease, and cost-saving when used for screening for fetal malformations.

Conclusions

The use of health economic evidence in decision making for low-income countries should be promoted. It is currently among the least used types of evidence, yet there is a huge potential of gaining many QALYs given persistent and avoidable morbidity and mortality. In this thesis, ANC policy in Rwanda was used as a case to contribute to evidence informed decision-making using health economic evaluation methods. Low-income countries, particularly those that that still have a high burden of maternal and perinatal mortality should consider implementing the 2016 WHO ANC recommendations.

Key words

Antenatal, maternal, cost, cost-effectiveness, ultrasound, EQ-5D-3L, Low-income countries

ENKEL SAMMANFATTNING PÅ SVENSKA

Inledning

Syftet med avhandlingen är att bidra till användning av metoder som kan generera ekonomisk ”evidens” inför beslut om hälso- och sjukvård i resurssvaga miljöer. Det exempel jag använder för att demonstrera metoderna är mödrahälsovård i Rwanda. Trots stora och ihållande förbättringar under de senaste 15 åren, är fortfarande Rwandas mödradödlighet bland de högsta i världen. Bestående brister i hälso- och sjukvård under graviditet gör att mödrahälsovården är ett viktigt förbättringsområde för beslutsfattare som vill förbättra hälsa och välbefinnande för mammor och nyfödda i Rwanda.

Metoder

I avhandlingen används både primär- och sekundärdata. Primärdata är dels en tvärsnittsstudie som omfattade 922 intervjuer med hushåll, dels en insamling av data som gjordes med sex olika vårdgivare. Båda dessa studier genomfördes i Kigali och den norra provinsen. Den tredje primära datainsamlingen var enkäter till en expertpanel bestående av gynekologer.

Hälsorelaterad livskvalitet för kvinnor under ett år efter förlossning mättes med EQ5D-3L. Sambandet mellan hälsorelaterad livskvalitet och determinanter som deltagande i mödrahälsovård, och socioekonomiska/demografiska faktorer undersöktes bivariat och multivariat (artikel I). Kostnaden för mödrahälsovård i Rwanda, både för hushållen och hälso- och sjukvården, beräknades genom analys av primärdata (artikel II). Tillkommande kostnader för mödrahälsovård, ifall WHOs nya riktlinjer (2016) skulle implementeras, beräknades genom en simulering av troligt utnyttjande och en skattad kostnad per besök (artikel III). Förbättrad hälsa till följd av WHOs nya riktlinjer (2016) bedömdes av expertpanelen och kvantifierades i termer av vunna levnadsår på grund av minskad mödra- och perinataldödlighet (artikel III). Avhandlingens fjärde artikel är en systematisk översikt av kostnader och kostnadseffektivitet vid rutinbruk av ultraljud under graviditet (artikel IV). Vi fann 606 studier publicerade mellan januari 1999 och april 2018 i databasena PubMed, Scopus och Cochrane.

Resultat

Sextioen procent hade inte ett adekvat deltagande i mödrahälsovården enligt de Rwandiska riktlinjerna. Somliga hade gjort sitt första besök för sent och andra hade färre än de fyra besök som riktlinjerna stipulerar. Adekvat deltagande i mödravård, socialt stöd och hushållens inkomst hade ett signifikant samband med hälsorelaterad livskvalitet om den mättes med EQ-VAS. De vanligaste hälsoproblemen var oro eller depression, och smärta eller obehag.

Det första besöket i mödrahälsovården svarade för ungefär halva totala kostnaden i ett samhällsperspektiv, lika med 44 dollar (2015 års prisnivå) i offentlig vård och lika med 160 dollar i privat vård.

Att implementera WHOs nya riktlinjer från 2016 skulle kosta mellan 5,8 miljoner dollar och 11 miljoner dollar beroende på deltagarfrekvens. Perinatal dödlighet skulle minska med mellan 22,5 och 55 procent, medan mödradödligheten skulle minska med mellan 7 och 52,5 procent. Kostnadseffektivitetskvoter beräknades för sex olika kombinationer av deltagande och hälsoeffekter, och fyra av dessa var lägre än ett BNP-baserat tröskelvärde.

Endast nio av de 606 studier av kostnader och/eller kostnadseffektivitet vid rutinbruk av ultraljud under graviditet uppfyllde alla krav för att ekstrahera data. Rutinultraljud rapporteras vara kostnadseffektiv för screening av livmoderhalsens längd, vasa previa och medfödd hjärtsjukdom samt kostnadsbesparande för screening av fostermissbildningar.

Slutsatser

Hälsoekonomisk ”evidens” borde spela en större roll i låginkomstländers beslut om hälso- och sjukvård. Idag är hälsoekonomisk ”evidens” sällsynt i dessa länder, och ”priset” i termer av förlorade möjligheter att undvika dödlighet och sjuklighet blir högt. I den här avhandlingen har mödrahälsovård i Rwanda använts som ett exempel för att demonstrera hur hälsoekonomiska utvärderingsmetoder kan bidra med ”evidens” för beslutsfattande. Låginkomstländer, i synnerhet sådan som fortfarande har hög barn- och mödradödlighet, bör överväga att implementera WHOs nya riktlinjer från 2016.

Nyckel ord

Prenatal, förlossning, kostnad, kostnadseffektivitet, ultraljud, EQ5D-3L, låginkomstländer

ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome
ANC: Antenatal Care
CET: Cost-effectiveness thresholds
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CHW: Community Health Workers
CONSORT: Consolidated Standards of Reporting Trials
DALYs: Disability Adjusted Life Years
DHS: Demographic and Health Survey
EQ-5D-3L: EuroQol 5 dimensions, 3 levels
GBP: Great Bretain Pound
GDP: Gross Domestic Product
HIV: Human Immunodeficiency Virus
HRQoL: Health-Related Quality of Life
LICs: Low income countries
LYS: Life-Years Saved
MatHeR: Maternal Health Research in Rwanda
MDGs: Millenium Development Goals
NCDs: Non Communicable Diseases
NICE: National Institute for Health and Care Excellence
OECD: Organization of Economic Cooperation and Development
QALY: Quality-Adjusted Life years
RCTs: Randomized Controlled Trial
SD: Standard Deviation
TB: Tuberculosis
UK: United Kingdom
UN: United Nations
UNFPA: United Nations' Population Fund
WHO: World Health Organization

ORIGINAL PAPERS

1. Hitimana R, Lindholm L, Krantz G, Nzayirambaho M, Condo J, Semasaka S.JP, Pulkki-Brännström A-M. **Health-related quality of life determinants among Rwandan women after delivery: does antenatal care utilization matter ? A cross-sectional study**. Journal of Health, Population and Nutrition; 2018; 37(1), 12.

2. Hitimana R, Lindholm L, Krantz G, Nzayirambaho M, Pulkki-Brännström A-M. **Cost of antenatal care for the health sector and for households in Rwanda**. BMC Health Services Research. 2018;18:262. doi:10.1186/s12913-018-3013-1

3. Hitimana R, Lindholm L, Mogren I, Krantz G, Nzayirambaho M, Semasaka S JP, Pulkki-Brännström A-M. **Incremental cost and health gains of the 2016 WHO antenatal care recommendations for Rwanda: results from expert elicitation.** (submitted)

4. Hitimana R, Lindholm L, Krantz G, Nzayirambaho M, Pulkki-Brännström A-M. **Systematic Review of Cost and Cost-effectiveness of Routine Ultrasound during pregnancy**. (Manuscript).

1. INTRODUCTION

1.1. Point of departure

I was one of four PhD students recruited in 2013 for the project "Maternal Health Research in Rwanda (MatHeR)". Each of us had a unique research angle, and mine was health economics, since I am trained in a related discipline: business administration. The working title for my thesis was "Cost-effectiveness of maternal health interventions in Rwanda". I applied a standard health economic framework (Figure 1), with resources measured on the horizontal axis and health outcomes (e.g. QALY) on the vertical axis. The curve in the figure shows this relationship. Research questions which naturally follow from this framework are the costs for a sequence of visits (Paper II), and the increment in QALYs when the number of antenatal care (ANC) visits is increased (Paper I). Two years down the road, a new WHO recommendation for ANC was launched (November 2016), and influenced the last part of the thesis (objectives three and four).

This kind of analysis is common in many countries, but not in Rwanda. My ambition, therefore, was, and still is, to consider maternal healthcare as a pilot case, followed by many more analyses of interventions relevant for Rwanda. My main interest is the method (health technology assessment) and the system necessary for using it at a larger scale.

Countries which have gone down this path, such as the United Kingdom, Sweden, Norway, New Zealand, etc., seem to systematically use almost the same criteria when ranking interventions [1]. Typically, there are four criteria: magnitude of the health problem, effectiveness in treatment, cost-effectiveness and affordability and equity analyses [2]. A valid estimate of cost-effectiveness requires evidence for effectiveness in treatment. During recent decades, scholarly views on ideal evidence have drifted from the large single randomized controlled trials (RCTs) to systematic reviews and meta-analyses of RCTs. This is helpful for low-income countries (LIC) like Rwanda, since the country cannot afford large trials. Systematic reviews as a part of economic analyses have a great potential for countries like Rwanda. In the background section, I therefore first discuss the idea of evidence use in public health more theoretically, as well as the role of health economics in the evidence base. Secondly, cost-effectiveness in maternal health in Rwanda and other LIC is introduced.

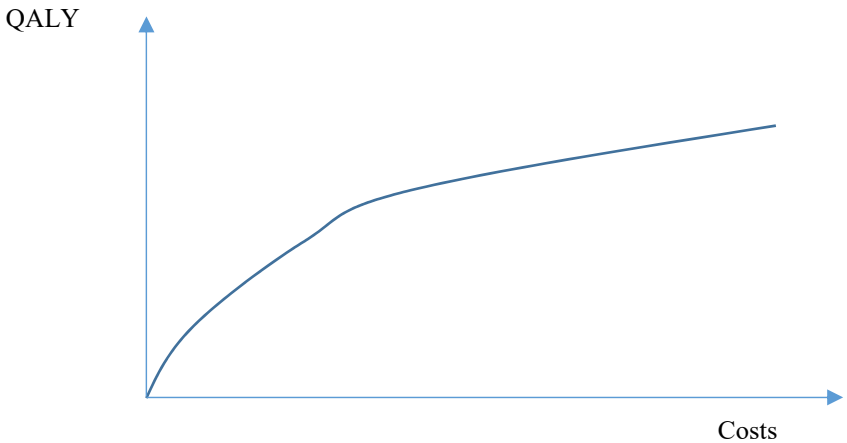


Figure 1. Typical graphical presentation of incremental cost and outcomes in health economic studies.

1.2. Evidence-based public health

1.2.1. Key concepts

Public health is one of the disciplines that have promoted the concept of evidence-based practice [3]. It has formally emerged in the early 1990s [3], following the success of the evidence-based medicine movement [4–6]. The term "evidence" has its origin in western legal settings [7][8]. It broadly refers to the facts or proof that is used to conclude whether a statement or an assertion is true or false [9,10].

In public health science, evidence refers to any type of information comprised of quantitative (including epidemiologic data) and/or qualitative data used in making judgements or decisions [7]. Evidence-based public health is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of communities and populations in the domain of health promotion, disease prevention, health maintenance and improvement" [6][9]. This definition underlines two important aspects of evidence-based public health: (1) the use of a specific type of evidence (current best evidence) to make decisions aiming at improving public health; and (2) the importance of using logical and objective methods of appraisal and interpretation of evidence [9].

The use of evidence in medicine and public health has spectacularly increased over the last three decades [3], and it is credited to have contributed to the achievements in improvements of populations' health.

The use of evidence in public health helps in identifying the real health problems and distinguishing what interventions are most effective compared to others. Ideally, public health policies should be informed by evidence because the society pays a high opportunity cost when the interventions with the highest return on investments are not implemented [7].

Evidence-based public health has inherited the hierarchization of evidence from evidence-based medicine, which consists of ranking evidence according to how strong the internal validity is [11]. According to the common classification, at the top there is evidence from systematic reviews of randomized controlled trials (RCTs), followed by single RCTs, then cohorts, case controls, cross-sectional studies, and, at the bottom, case studies and expert opinion [11].

Applying a hierarchy of evidence in health policy decisions has attracted criticism from many scholars. They argue that evidence from highly ranked sources, such as randomized trials that measure the effect on a specified and limited number of outcomes, is suitable to serve the needs and realities of clinical medicine, but not necessarily public health policy, given the complexity that it presents [12][13][14].

There are three main types of scientific evidence, based on the main questions they address [10,15]. The first category includes evidence that describes the health problem in the society, as well as its magnitude, distribution, and risk factors and recommends that action should be taken to deal with the problem. The second type is concerned with suggesting a specific intervention and measuring its impact on the population's health and well-being [3][15]. The third type is comprised of evidence that responds to the question of how interventions should be implemented. It shows the conditions in which the intervention is implemented, the factors that lead to its success or failure, and how it is received by the intended beneficiaries [15].

The big part of evidence can be considered as part of the second type of evidence, since I am trying to show to which extent an intervention (ANC) can improve Health-Related Quality of Life (HRQoL) and reduce maternal and perinatal mortality in a specific context. The part of this thesis that is considered as type 1 evidence is the report on the prevalence of HRQoL among postpartum women (Paper I). My work will be complemented by the work of my colleagues, such as Jean Paul Semasaka Sengoma, who is reporting on the prevalence of pregnancy and delivery-related complications in Rwanda (type 1 evidence) [16] and Andrew Rurangirwa Akashi, whose work is focused on ANC attendance, prevalence of intimate partner violence, and non-psychotic mental health disorders among postpartum women in Rwanda.

Actors involved in evidence-based public health are categorized in four main groups, namely, the public health practitioners, the policymakers at local, national, and international levels, stakeholders, and researchers [10,15].

a. Public health practitioners who work at the frontline of the application of evidence in their daily activities have executive and sometimes managerial responsibilities [10,15]. They have a narrow range of options from which to choose, but they seek the best available evidence to make rational choices.

b. Policymakers have responsibilities of making policies on public health issues and allocating resources to implement those policies at the local, regional, state, national, and international levels [10].

c. Stakeholders, including citizens, interest groups, other non-governmental organizations, who support or seek to change specific public health policies.

d. Researchers on the population's health issues who are concerned with evaluating the impact of specific health policies, programmes, or interventions.

1.2.2. Limitations of evidence and challenges to its application

First, the use of evidence for public health policy is limited by the unbalanced availability of evidence itself. While a lot has been published in terms of distribution, severity, and risk factors for the world's health problems, little evidence is available in terms of effective intervention to address those problems [17,18]. Another concern with regards to availability of evidence is related to the limited generalizability of effectiveness from one context and population to another [15]. Furthermore, the evidence that is supposedly available is dispersed in a multitude of journals that continue to increase in numbers [15], and many healthcare providers who are needed to apply the evidence have difficulties in accessing it, in interpreting it, as well as applying it in their practice [10].

Second, it is often said that there is an apparent disconnection between the research community and the decision makers, and that the two groups do not understand each other's cultures, methods, or needs [17], even though they are supposed to complement each other. Some decision makers accuse researchers of being naïve about the policy environment and consequently generate "policy-free evidence", the kind of research that does not answer any specific policy question [18].

Other frequently cited factors that limit the use of evidence in public health decision making include organizational cultures, characterized by rigid systems that are not open to changes from evidence, funding limitations and the conditions attached to it, and a limited capacity in the workforce and infrastructures in settings where it is most needed [10].

Finally the term "evidence-based public health" assumes that there is a linear relation between evidence and policy, while such a relation is rare in the real word, and it hides other realities, such as the inverse relationship in which policy influences evidence generation through funding for research [17].

Low-resource settings have specific problems in terms of generation and use of evidence in public health policy – an issue that will be explored further in the next section.

1.2.3. Public health decision making in low-resource settings

Public health decision-making in low-resource settings, including Rwanda, has, in the last three decades, been an easy task, speaking from my personal experience of four and half years in the Rwandan Ministry of Health, at the planning department. This is because of a number of obvious reasons: first, the focus on infectious, maternal, and newborn health conditions is a legitimate choice, given the fact that they are considered to be emergency problems, because they claim many lives in a short time and generally in a young category of the population [19]. Therefore, making them a priority at the international level (Millennium Development Goals) and national levels makes moral, ethical, and economic sense because more DALYS will be saved and the health maximization objective achieved. Second, different global stakeholders, including private philanthropists, UN agencies, and bilateral and non-governmental organizations, have invested huge amounts funding to deal with those problems in the most affected regions. The 2017 report on financing global health revealed that 60% of the aggregated development assistance for health was targeting maternal and newborn health, Human Immuno-Deficiency Virus (HIV), Malaria, and Tuberculosis (TB) [20]. Part of that assistance is channelled through universities and research institutions [20] to conduct research on the prevalence of these problems in the most affected countries and the cost-effective interventions to deal with those public health problems. In other words, recipient countries have received funding, along with instructions on how to use it.

Public health decision making in most low-resource countries does not follow a systematic process using pre-set criteria, and there are no institutional arrangements to support the process [19], like there are in many high-income countries.

Moreover, most of the priority settings criteria rely on epidemiological (burden of disease) and economic (cost and cost-effectiveness) data [19], which are challenging to collect and publish in many low-income settings. The recent example from Uganda, a neighbour to Rwanda, has shown that the Ministry of Health did not have a documented framework for priority setting, and that although there is a process described in the documents, it is not always followed in practice [21]. I believe that the priority setting process and framework in Rwanda are not much different from those of Uganda.

The use of evidence in health policy decision making in low-income countries is confronted with numerous challenges at the levels of research production, dissemination, and evidence use, which I describe below.

Research production

There is a persistent disproportionate global investment in health research and development, and burden of disease. The Global Forum for Health Research estimated in the early 1990s that less than 10% of the global spending on health research was allocated to 90% of the world's burden of diseases, a phenomena often referred to as "the 10/90 gap" [22]. Two decades later (in 2013), Røttingen and colleagues revealed that global spending on research and development had increased, but the gap between high- and low-income countries persisted [23]. Although there is a portion of health research generated by high-income countries that is considered to be public goods because it can be used in low-resource settings [24], many research results are not relevant to low-income countries in two ways: first, many research outputs do not align with the disease burden and priorities for low-income countries [25–27]. Second, even when they do align, the recommended interventions and treatments are sometimes not available, affordable, or feasible [24,25,28].

Research production in low-resource settings is hampered by many factors, including insufficient human and financial capacities [29], limited access to literature [28], poor research focus in education programmes [28,29], and unconducive research environments [30]. In low-resource countries, much of the research that is conducted is not published, not only because of poor quality, but also because of the bias of medical journals from high-income settings, which give less attention to problems from contexts regarded as geographically and economically distant [31,32].

Knowledge availability, translation, and use

The development of the Internet has enabled the rapid development of open access to scientific publications [33], which contributed to increased accessibility of health research outputs to many users, including those in low-resource countries. However, most, if not all, open access journals require upfront payments of publication fees, which puts a burden on low-resource users, hence deepening the gap in the publishing of research [34].
Beyond accessibility, the little evidence that is available and accessible is not adequately used by decision makers in low-income countries due to issues around dissemination and uptake. These include a lack of appreciation of the importance of research by policymakers [35], dissemination channels and unsuitable packaging that restrict access to non-academic actors to research findings [35–37], and the influence of political contexts [36]. It is evident that politicians are concerned about popularity, which increases the chances of being re-elected. In cases where the popularity-friendly choice conflicts with the evidence-recommended choice, they sometimes prioritize the former. This phenomenon is aggravated by the low literacy levels of the voters in low-resource countries, which limits their ability to judge which policy is appropriate. For example, if the aim is to reduce maternal mortality in a remote region, a politician would prefer to build new maternity infrastructures, even when they are aware that it in the end it will not be fully functional because of a lack of staff and supplies and eventually chronic underutilization.

Furthermore, the lack of resources in low-income countries reduces the power of the governments over decision making in favour of non-state actors, namely, development partners [19][21], whose interests are not always in line with those of the government [19]. Many international organizations that provide assistance to improving health in low-resource countries adopt a reductionist approach that puts an emphasis on short-term health goals, instead of helping to build strong health systems, which can respond to health challenges in the long run [38]. Such approaches often result in fragmented and inefficient health systems which are not sustainable in recipient countries [39].

However, the emerging political trends in major western countries are favouring a shift of focus towards in-country visibility as opposed to international visibility. In the recent past, global development assistance for health has increased from 1990 to 2010, but has started decreasing again [40], and the declining trend is expected to continue, particularly for the countries that are making progress in economic growth.

On the other hand, the pressure on health sector budgets in many low- and middle-income countries is expected to significantly increase, and in particular, they will have an additional health burden to tackle: the non-communicable diseases that are becoming more and more problematic in low-resource countries [41].

Considering all of the issues mentioned above, it is expected that in the coming years, countries that are currently identified as low-income countries will have to rely more on their own resources to finance the health needs of their populations. This shift will happen – or is already is happening – concurrently with the rapid rise in demand for health care. Sustaining the gains in fighting the traditional diseases, and concomitantly addressing the increasing burden of non-communicable diseases, requires more sustained investments.

Consequently, public health decision making in current low-resource countries will no longer be easy. One can anticipate more rationalization and more demand for evidence that is relevant to decision making. The role of health economics will then become central.

1.2.4. Decision making in the Rwandan health sector

In Rwanda, the Ministry of Health holds the authority over policymaking and prioritization in healthcare, while the Rwanda Biomedical Center is the main implementation arm of healthcare policy [42]. Drawing from the Paris Declaration on Aid Effectiveness, other actors, including development partners, non-governmental organizations, and civil society organizations, are involved in policy development and prioritization through the structures called "Thematic Technical Working Groups" (at the level of unit/directorate of division, for example: Maternal and Child Health) and the Health Sector working groups (at the central ministry level) [42]. Although in theory, the ministry authorities have the final say on priorities, some development partners can easily push for their agenda, depending mainly on their financial commitments or trust in technical expertise – as is the case of the UN agencies. One recent example is the universal access to eye care to all Rwandans, which was achieved in a few years from almost nothing at the primary healthcare level, thanks to the partnership with Vision for a Nation [43]. I doubt that the Ministry of Health authorities would make the same decision if they were given all the resources that Vision for a Nation used to scale up this single intervention.

The Ministry of Health regularly establishes the list of essential medicines that should always be available in the public health system [44] and ensures registration of all other medicines based on the quality/safety criteria – not necessarily on a cost-effectiveness criteria [45].

Soon, the role will move to the newly-created institution, the Rwanda Food and Medicine Authority.

To the best of my knowledge, in Rwanda, there is no explicit appraisal of other health technologies, and there is no systematic prioritization process with pre-set criteria and institutional framework to support that process (such as an institution, a department or a committee). The decision of adding or removing from the list of services covered by the community health insurance lies in hands of two institutions – the Ministry of Health and the Rwanda Social Security Board – but the process of selection and criteria that they use are not documented.

In my experience of the Rwandan health sector, based on what I have heard in speeches of politicians and what I have read in official documents, I have the impression that there is more reliance on information from programme monitoring and evaluations (not impact evaluation), and routine information systems and cross-sectional surveys, as opposed to evidence on effective and cost-effective interventions for public health decision making. Although description of public health problems is an important element of the evidence needed for public health policy, and it should therefore not be undervalued, it is however insufficient for informed policy [17]. Decision makers need to know, in addition to the magnitude of the problem and risk factors, what works best in dealing with that problem.

"Universal health coverage" is currently the fashionable term used by actors in global health. It gained momentum during the development of the sustainable development goals (SDGs), and was reinforced by the new WHO Director General (Dr. Tedros Adhanom Ghebreyesus). Universal health coverage means that "all individuals and communities receive the health services they need without suffering financial hardship" [46]. Rwanda has made tremendous progress in that journey by introducing community health insurance [47]; however, there are still challenges related to the limited package that is covered and the high catastrophic health expenditure, especially in tertiary care level.

In conclusion, the use of evidence in decision making in the health sector is faced with numerous challenges at the levels of both production and use. In the future, more rationalization will be imperative if low-resource countries want to make progress in improving the health of their population. There is a potential to save gain more quality adjusted life years (QALYs) if the available evidence is adequately used and if more type 2 evidence is generated and used.

There is also an opportunity to produce more research that is relevant to the context; however, human capacities and the necessary infrastructure will need to be developed.

1.2.5. The role of health economics in evidence-based public health

The role of economic evaluation in public health decision making has gained attention in recent years [48–52], but it remains one of the most underutilized sets of evidence for public health decision making [50]. A number of factors have contributed to the increased importance of economic evaluation within healthcare decision making. First, the increasing demand of healthcare services has led to pressure on healthcare budgets [51,53,54] and to the need to focus on both clinical effectiveness and cost-effectiveness, rather than just on clinical effectiveness, as was the prior policy [51]. For example, in the OECD countries, the growth of total expenditure on health was much higher than the GDP growth between 1993 and 2008 [48]. In the United Kingdom, the per capita expenditure on health has increased from GBP 58 to GBP 1200 over a period of 30 years, from 1972 to 2002 [53]. Second, in many settings, decision making for funding, reimbursement, or insurance coverage has adopted explicit and transparent methods and processes that require the use of the results from economic evaluation [51][54].

According to Drummond and colleagues, economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" [51]. Economic evaluation seeks "to identify, measure, value, and compare the costs and consequences of the alternative activities, interventions, or technologies" [51]. Economic evaluation is one component of evidence that decision makers use to optimize health with limited resources. While epidemiology data informs decision makers about key health problems and their risk factors, economic evaluation provides the type of evidence that decision makers need to understand which intervention is most cost-effective and whether the intervention at hand is feasible, scalable, and sustainable [50].

In some high-income countries, evidence from economic evaluations has been established as a requirement for decisions in the healthcare systems. In the UK, for example, the National Institute for Health and Care Excellence (NICE) assesses both clinical effectiveness and cost-effectiveness evidence for drugs, health technologies, and public health interventions before approving their use [51].

Drummond and colleagues argued that the extent to which economic evaluation is used depends on the country context with regards to healthcare financing [51].

Countries with single-payer systems, such as the UK, Scandinavian countries, Canada, and Australia, tend to have centralized decision making processes that rely more on the evidence from economic evaluations because the reimbursement decisions are made on behalf of the populations covered [51]. On the contrary, in countries with multi-payer systems, such as the United States, and many middle-income countries in Asia and Latin America, the position of health technology assessment is varied [51].

In many high-income settings, the decision to adopt a new drug or technology on the list of those reimbursed by public health insurance is based on common criteria, namely, severity and/or burden of disease, effectiveness, cost-effectiveness, and affordability (budget impact analysis), as well as equity analysis [2]. Economic evaluation provides the basis for judgement of cost-effectiveness and can be complemented by other economic analyses, such as budget impact analysis, to respond to the question of affordability. Nevertheless, geographical variations exist [54] with regard to how those criteria are explicitly and regularly followed. In addition to these traditional criteria, others, such as patient preferences and social and ethical values, are also emerging, but their inclusion in the analyses is still in the early stage [54].

Evidence should be at the centre of priority setting in the health sector [55]. The evidence that is required includes information about the magnitude and severity of the health problem, effectiveness of the interventions at hand, how much those interventions cost, the comparative analysis of cost and effectiveness among available alternatives, and documentation of acceptability and fairness [55]. Furthermore, there is a need to have transparent systems in place to appraise the evidence and collect citizen's ideas and take them into consideration in the priority setting process. The figure 2 (below) summarize by Terwindt and colleague summarizes the steps and criteria followed in priority setting [55].

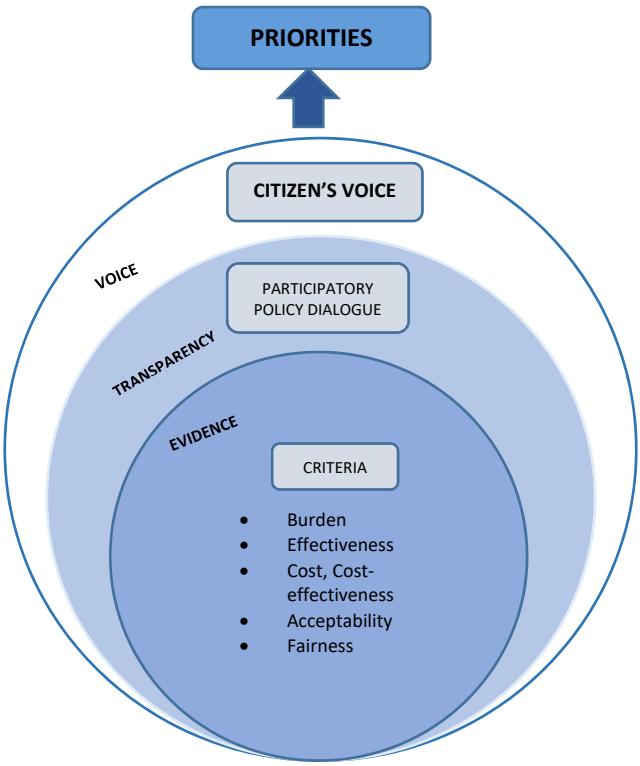


Figure 2. Evidence, transparency and voice: steps in priority setting. (Adapted from Terwindt et al, 2016).

1.2.6. Types of economic evaluation and their use in decision making

Economic evaluations can be categorized into three types according to how the consequences of alternative interventions is presented: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). The health consequences are measured in terms of unit of health outcome (such as years of life saved), utility measure (such as QALY), and in monetary unit for the first, the second, and the third, respectively [51].The two first types of evidence are used to support policy makers in deciding whether they can allocate resources to an intervention, such as scaling-up of a programme, expecting a certain amount of health benefits, and considering the opportunity cost in terms of the health benefits of other interventions within the exiting budget. By contrast, CBA seeks to help decision makers to understand whether a decision to expand the budget is justified, using measures such as willingness to pay [51].

In this thesis, we are interested in contributing to optimal use of the health sector budget with the aim of maximizing benefits. We have therefore used the first two

types of economic evaluation. We have collected utility measures using EQ-5D-3L tool (Paper I) and have also used cost per life-year saved (Paper III).

Another categorization is based on the method used to collect information. There are economic evaluations that are based on primary data of a single study (either as a stand-alone observational study or alongside a randomized controlled trial), decision analytic models, as well as systematic reviews of health economic evaluations. Although economic evaluation based on single studies still occupy a privileged position as a source of good evidence, there is a growing trend of using more decision-analytic modelling as an alternative method of generating health economic evidence for decision making in a particular context [51]. Decision-analytic modelling offers the possibility of using information from a wide range of sources to respond to a specific problem in a particular setting, hence overcoming some of the limitations of the single-study evaluations with regards to generalizability [56]. Systematic reviews of economic evaluations can bring together the best available evidence on cost-effectiveness of a given intervention in a relatively short timeframe in comparison to primary research [57]. Systematic reviews of health economic evaluation are often conducted to serve the purpose of developing a decision-analytic economic model, but they can also be used in developing clinical guidelines or in informing a given decision [58].

However, conducting systematic reviews of economic analyses is faced with certain limitations. The examples mentioned by Shemilt and colleagues include an insufficient number of published economic analyses comparing specific interventions. Second, many of the existing studies are of low quality because of the fundamental methodological limitations [59].

Lastly, there are problems of complexity, relevance, and transferability [52] that necessitate a good understanding of parameters in order to decide which among them vary among different settings [59]. All of these factors contribute to the limited number of economic studies that are considered in systematic reviews.

1.2.7. Conclusion

As a young discipline, health economic evaluation has already had success, as can be seen in the increase in demand and the increase in published studies, as well as improvements in the quality of methods of research and reporting [52]. The pressure imposed by healthcare demands is expected to continue, mainly due to the challenge of expensive care for an ever-aging population and increased expectations from communities [53]. In low- and middle-income countries in particular, the emerging burden of non-communicable diseases constitutes another source of pressure on national budgets. Therefore, choices will always need to be made, and the role of economic evidence will be essential [53]. The technical problems found in methods of generating, interpreting, and using health economic evidence should not distract people from the opportunities it offers by providing a rational and transparent framework for priority setting in healthcare [53].

Nevertheless, it is important to mention that economic evaluation in and of itself does not provide all the evidence that policy makers need to make decisions regarding the provision and funding of new technologies [54]. There are other considerations beyond economic evaluation, such as non-health benefits, fairness, acceptability, and feasibility [52], that are also critical to policy decision making.

This thesis will contribute to evidence for ANC policy decisions in Rwanda. This thesis is the result of two primary studies (Paper I on ANC and health-related quality of life, and Paper II on the cost of ANC), one systematic review of health economic evaluations of routine obstetric ultrasound (Paper IV), and one study that has some features of models (using inputs information on cost and health outcomes from other sources on a hypothetical cohort), but does not use typical modelling techniques (Paper III).

Before presenting the data, I will first present, in the following sections, what is known about cost-effectiveness of maternal health interventions in general and of ANC in particular (section 1.3). Subsequently, I will present the maternal health situation in Rwanda and some gaps in ANC delivery and utilization that need the attention of policymakers (section 1.4). I will conclude the introductory chapter by presenting the gap in knowledge and demonstrating the contribution of this thesis in bridging that gap (section 1.5).

1.3. Cost-effectiveness of maternal health interventions in LMIC

Globally, an estimated 303,000 maternal deaths occurred in 2015, a decline of 43% from 1990. The majority of maternal deaths occur in low- and middle-income countries: Sub-Saharan Africa (66%) and Southern Asia (22%) accounted for 86% of the global burden of maternal deaths (267,000 maternal deaths) in 2015 [60]. The majority of these maternal deaths are avoidable, but they still persist even though an enormous amount of evidence about effective and cost-effective interventions have been available to any decision maker who needs it.

Measuring health outcomes for reproductive and maternal health interventions is complicated by their complexity. The gold standard of evidence is the randomized control trial, which implies having an intervention and a control group. In terms of ethical issues, it would not be acceptable to deny access to life-saving interventions in the interest of research. Therefore, finding a control group is not possible. That is why most of the economic studies are either based on models or focus on one small component of an intervention.

The interventions packages that have been frequently referred to as most cost-effective include family planning [61–64], quality obstetric care [61–63,65–67], ANC [61,65–67], and safe abortion [61,62,66,67]. The WHO's cost-effectiveness studies have reported that for the sub-regions AFR-E[1] (where Rwanda is located), ANC, skilled birth attendance, and emergency obstetric care are the most cost-effective maternal health interventions [68]. Family planning and safe abortion have been repeatedly highlighted in many studies in low- and middle-income countries as interventions that can significantly reduce maternal mortality [61–63,67].

The importance of externalities in maternal mortalities deserve to be mentioned. The common risk factor for the majority of countries that bear the highest burden of maternal deaths is being in disaster, conflict, or post-conflict situations [60], which are factors external to the health sector decision space, and rest on the entire political leadership of those countries, regions, and the international community.

[1] AFR-E region is composed by: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

Improving maternal health cannot be limited to maternal health interventions given the importance of socio-economic determinants of maternal mortality and disability, especially in low-resource settings. The United Nations Population Fund (UNFPA) has estimated that one out ten girls from low- and middle-income countries become mothers before the age of 16, and adolescent pregnancy leads to school dropouts, with long-term consequences, including lower use of maternal health services [69]. Mothers in low-resource settings who are poor, uneducated, and live in remote places are less likely to receive adequate maternal health services, such as family planning, ANC, and skilled assistance during childbirth [69]. In addition, there are other socio-cultural factors that put girls and women at risk, such as dependency (financially and in other decisions to their partners and mothers-in-law, including seeking care), poverty, and gender inequality in low-resource settings, which contribute to exposing girls to the risk of sexual and physical abuse, exploitation, and teenage pregnancy [69]. Lastly, many low-income countries and health systems restrict girls and women from accessing reproductive health services, such as contraception (mainly for young girls) and safe abortion [69].

In the face of those socio-economic determinants of maternal mortality and disability, the UNFPA recommends addressing the social and cultural barriers to seeking and accessing healthcare faced by girls and women, as well as improving and expanding health systems and educating girls and women [69]. Effective, community-based strategies that are in line with some of the above recommendations and increase demand for healthcare include the use of women groups [70], community mobilization, and financial incentives or subsidies [71,72].

Maternal health interventions are interconnected, and their effect on maternal and newborn health is synergetic, and a continuum of care should be emphasized in organizing delivery systems [73]. For instance, Carvalho and colleagues reported that although family planning emerged as the most cost-effective intervention in reducing maternal mortality, it had reached a level where it could not continue to be effective if access to obstetric care remained low [73]. Another renowned example is the increased health facility deliveries, thanks to cash transfer in India, which was not sufficient to reduce maternal mortality [74,75].

Barriers to implementation of well-known effective and cost-effective maternal health interventions that are commonly cited include insufficient or poor distribution of financial, human, and material (such as medicines, supplies, and equipment) resources; problems of collecting health information, information sharing, and poor communication; inadequate pre-service and in-service training; and provider attitudes and beliefs [76]. All of these factors can be classified into two broad categories: lack of political will and system inefficiencies.

To conclude this section, maternal mortality is still unacceptably high in low- and middle-income countries, despite the available evidence of effective and cost-effective interventions that can improve the demand and quality of the provision of maternal healthcare. Efforts to improve maternal health should go beyond the health sector to address socioeconomic, legal, and security factors that are related to maternal mortality and morbidity.

1.3.1. Cost-effectiveness of ANC

Collecting evidence of the efficacy of ANC programmes is not an easy task because of many factors [77]:

i) the complexity of the intervention, which contains many multi-faceted interventions within it;
ii) two target populations – women and babies – have to be considered;
iii) a large population sample is needed to reach a conclusion; and
iv) ANC relies heavily on the overall healthcare system and socio-economic context.

Moreover, an attempt to establish evidence of the efficacy of ANC would require finding a control group [78] . This would not be ethically correct, as it implies, in most cases, the deprivation of services to a certain group in the population [79].

1.3.1.1. Cost of ANC

The studies of costs of ANC are still relatively rare in the literature, and the majority of those available were linked to trials, which present a variety of methods and perspectives. The results of those studies are also a varied from country to country. For example, in the WHO trial, the mean cost of ANC in 1998 for two models of ANC in Cuba varied between US dollars 885.4 (SD=1632) and US dollars 956 (SD=1294) for the new and standard model, respectively. In Thailand, it varied between US dollars 167 (SD=145) and US dollars 206 (SD=173) for the new and standard models, respectively.

That is by far higher than the mean cost of ANC in other countries, such as Argentina (US dollars US$31.1) in 1999, Tanzania (US dollars 11.6) in 1997/98, and between US dollars 2.2 and US dollars 6.4 for Uganda, Ghana, and Malawi in 1997 [80].

Within various countries, the observed differences are mainly related to the level of the provider (primary, secondary, and tertiary care) and the type of provider (public, private, mission-based health facilities)[80].

1.3.1.2. Effectiveness of ANC

The scope of ANC effectiveness is wide, with respect to the target population and the timing of health benefits. ANC directly benefits both the mother and the child, and indirectly benefits the whole family and community through educational messages. The benefits of ANC are also observed during pregnancy, the period around intrapartum, and after child birth.

There is evidence of associations between ANC utilization and better birth outcomes [81–83], and long-term child nutritional status and survival in low- and middle-income countries [81]. ANC attendance also was reported to be associated with better utilization of subsequent maternal health services, including childbirth, in health facilities [84].

Effectiveness of specific intervention with ANC package

If there is less doubt of ANC effectiveness as a package, despite absence of efficacy studies on the package as a whole, it is probably due to the established evidence of effectiveness of individual interventions within the ANC package. Below are the most cited basic recommendations:

- Iron, folate, or iron with folate supplementation reduces the risk of decreases of hemoglobin concentration, hence reducing the risk of anemia and the need for transfusion [78][85]. It is therefore recommended in settings where iron deficiency is common [78].
- Tetanus toxoid immunization during pregnancy was associated with a significant reduction in the incidence of neonatal tetanus and neonatal mortality [86].
- Hypertensive disorders during pregnancy constitute one of the leading causes of maternal and perinatal mortality [78]. ANC is designed to ensure timely detection and diagnosis, primary prevention and secondary prevention from progression, and treatment [78].

- Screening for infection and treatment during ANC, including urinary tract infections and sexually transmitted infections, such as syphilis, chlamydia, and HIV, reduces the risk of death [86] and long-term sequelae for both the woman and the child.
- Other interventions, like anthropometric measures, nutritional screening, and history of previous caesarean section or prolonged labour, are effective in the prediction of the risk of cephalopelvic disproportion, leading to obstructed labour and referral to competent health facilities [78].

- During ANC, there are interventions that aim to diagnose and treat other maternal diseses that are not caused by pregnancy but that can impact on it, and they are highly related to the prevalence patterns in the general population [78][86]. These diseses include malaria, HIV, and hepatitis.

1.3.1.3. Number of ANC visits and pregnancy outcomes

In the recent past, there has been a shift in the WHO recommendations on the optimum number of ANC visits during pregnancy, from four to eight visits. This was supported by research and it was mainly directed towards low- and middle-income countries, since the number of ANC visits in high-income countries have been higher than 8 for many years [87].

In the late 1990s and early 2000s, there was a consensus, mainly from WHO ANC trials, that ANC programmes with a reduced number of ANC visits were not associated with adverse health outcomes for both the mother and the baby compared to ANC programmes with higher numbers of ANC visits [88,89]. This finding has resulted in the release, in 2001, of the WHO recommendations for ANC which suggested four focused ANC visits for a normal pregnancy (pregnancy without complications).

A decade later, a Cochrane review, that included both high- and low-resource settings, followed by a secondary analysis of WHO ANC with a randomized controlled trial, have both found that there is an increased risk of perinatal death in ANC programmes with reduced a number of ANC visits [87,90]. Women in all settings were not satisfied with reduced ANC visits. In 2016, a new WHO recommendation was released which suggested that for every uncomplicated pregnancy, a minimum of eight ANC contacts should be scheduled [85]. This receommendaton came when many low-income countries were still struggling to successifuly implement the 4-visit model.

ANC and postpartum health for mothers and newborns

ANC is commonly known to be preparing the woman to deliver a healthy baby, and therefore its effectiveness is usually measured with direct pregnancy outcomes [82,91–94]. However, ANC effects can be observed during the postpartum period as well.

For example, Nosrat and colleagues have assessed the effect of prenatal mother's education on women's quality of life during the first year post-partum and concluded that women who received education during antenatal care had higher scores on physical, psychological, and environmental health compared to the control group [95].

There was a gradient reduction of infants with neonatal [81], infant [81], and child mortality [96], in relation to the extent of ANC utilization in low- and middle-income countries. Better ANC utilization was associated with an increased use of the subsequent maternal and newborn services in low- and middle-income countries, such as delivery in health facilities and postnatal check-ups [97], as well as the likelihood of immunizing the child [94]. ANC utilization also influences women's behaviours during the postpartum period, including a decrease in smoking during the postpartum period and improved breastfeeding practices [98].

1.3.1.4. Cost-effectiveness of ANC

Full economic evaluations of ANC are lacking in the literature, probably because of the difficulties in evaluating ANC effectiveness, as explained above. However, cost effectiveness studies for specific activities within ANC have been sufficiently published from different contexts. Below, I cite just a few.

Antenatal screening for syphilis using the point-of-care test was reported to be highly cost-effective in sub-Saharan African countries [99], as well as in 11 Asian countries and 20 Latin American countries [100]. Screening all pregnant women for pre-eclampsia and provide prophylaxes to those at risk is potentially cost-effective, although the recommendation is not unanimous among all the studies [93]. Treatment of pre-eclampsia with magnesium sulfate was also reported to be cost-effective for severe cases, while another article concluded that induction of labour for term pregnancies was more cost-effective than monitoring of pregnant women [93].

1.3.1.5. Effectiveness and cost-effectiveness of ultrasound examination during pregnancy

A diagnostic ultrasound is "a sophisticated electronic technology, which utilizes pulses of high-frequency sound to produce an image" [101]. While the ultrasound screening during pregnancy has been close to universal in high-income countries for many years, the use of the technology in low-resource settings is relatively new and still limited [102].

Ultrasound examination is performed at different time periods during pregnancy, and different health benefits are expected depending on the aim of the scan and when the examination is performed. Ultrasound investigation before 24 weeks of gestation (early ultrasound) was associated with fewer inductions of labour for post-term pregnancy, a reduction in perinatal mortality due to the detection of foetal abnormalities and subsequent pregnancy termination, and it enables earlier diagnosis of multiple pregnancies [103]. WHO recommends this intervention, citing the following reasons: estimating gestational age; improving detection of foetal anomalies and multiple pregnancies; reducing induction of labour for post-term pregnancy; and improving a woman's pregnancy experience [85].

Although there is a consensus on effectiveness of ultrasound scans in early pregnancy [103], the debate on late (third trimester) ultrasound screening is still going on. Some evidence supports the hypothesis that late ultrasound can enable detection of previously unknown abnormalities [104][105]. On the other side, a recent Cochrane review (2015) has concluded that ultrasound screening during late pregnancy for unselected populations has no beneficial effect on the mother or the baby [103][106].

Benefits of ultrasound are extended to women's positive experiences towards ANC as a service [103] and increase ANC attendance in low-income countries (as a recent study from Uganda has reported [107]).

Regarding the cost and cost-effectiveness of ultrasound, it was noticed that there are few good quality cost and cost-effectiveness studies of ultrasound examination during pregnancy [103]. The routine ultrasound examination that is performed during the second trimester is reported to be relatively cost-effective [103].

Other recent systematic reviews of cost and cost-effectiveness of routine ultrasound are almost two decades old [103][108]. Both of these reviews reported poor quality of primary cost studies for routine ultrasound screening.

The findings of the two reviews have also shown a high variation in the cost of the ultrasound scan across different studies. For example, the cost of routine ultrasound examination varied between £18 to £204 in one review [108]. These findings support the argument about the transferability problems of economic evaluation results from one context to another, mainly on the costing side, as discussed in earlier sections.

It was reported that the skills of ultrasound operators and the time they use to perform the examination has a significant effect on the relative cost-effectiveness of ultrasound investigations [103]. Ultrasound technology is evolving, and it is believed that those improvements will result in reductions of cost, mainly due to improvements in portability, affordability, and durability of ultrasound machines [102][109], as well as improved detection capacity.

To conclude this section, it appears that evidence of effectiveness of the ultrasound is becoming increasingly available, but the cost-effectiveness part of this evidence needs to be developed further. Context-specific cost and cost-effectiveness studies will be of value for decision makers, given that there are substantial variations in cost, effectiveness, and methods of reporting on routine ultrasound among different studies.

1.4. Maternal health in Rwanda

Rwanda's maternal mortality ratio is still among the highest in the world, despite the sharp reduction in maternal mortality ratio during the last two decades, (from 1071 in 2000 to 210 per 100,000 live births in 2014/2015). This decrease has put Rwanda on the list of nine countries that have achieved the Millennium Development Goals (MDG) target related to maternal health.

The main causes of maternal mortality in Rwanda were reported to be postpartum haemorrhage (22.7%), obstructed labour (12.3%), obstetric infections (10.3%), and eclampsia (9.4%) [110]. The factors of maternal deaths that were attributed to health system deficiency materialized by substandard care were 61% against 30% believed to be related to community [110]. Maternal mortality reduction was achieved thanks to health system reforms that have allowed easy scale-up and use of key effective interventions [47,111–113].

The trends of maternal and newborn health and mortality indicators from 2000 to 2014/2015 in Rwanda are presented in Table 1. Overall, there has been impressive and sustained progress in all indicators over the last 15 years. However, the majority of the women still attend fewer than the recommended number of ANC visits, fertility is still high (4.2), and one in three children under the age of five is stunted. Progress on some indicators, such as family planning prevalence and four ANC visits, appear to be slower than other indicators between the last two surveys. Furthermore, there are persistent disparities in maternal health indicators among women by educational level, wealth, and residence [114].

Another threat to maternal health is the high prevalence of unintended pregnancies: 114 per 1000 women aged 15–44, of which 22% end in induced abortion [115], despite the unfavourable legal framework that allows abortion only under three specific conditions [116]. It was estimated that 40% of the abortions end in complications that require treatment, but in Rwanda, one-third of those who needed treatment did not received it [117].

Table 1. Progress of key maternal, newborn and child health and mortality indicators

	2000	2005	2010	2014/15
Indicators of maternal health and mortality				
ANC attendance - 1 visit (%)	92	94	98	99
ANC attendance - 4 standard visits (%)	10	13	35	44
Deliveries assisted by skilled provider (%)	31	39	69	91
Contraceptive prevalence among married women (%)	7	17	52	53
Maternal mortality ratio (per 100.000 live births)	1071	750	487	210
Total fertility rate	5.8	6.1	4.6	4.2
Indicators of newborn and child health and mortality				
Percentage of children fully immunized	76	75	90	93
Percentage of stunted under 5 children	43	51	44	38
Neonatal mortality (per 1000 live births)	44	37	27	20
Infant mortality (per 1000 live births)	107	86	50	32
Under 5 mortality (per 1000 live births)	196	152	76	50

Sources: Demographic and health surveys 2000, 2005, 2010, 2014/2015 [118–121].

1.4.1. ANC in Rwanda

Indicators of ANC attendance and practice have been improving over time in Rwanda. The percentage of mothers who attend at least one ANC visit has been sustained at more than 90% for almost two decades [118,119,121]. Attendance of at least four standard visits has also improved from 10% in 2000 to 44% in 2014/2015 [118][121], although this remains low.

The health systems reforms that were undertaken during the same period are believed to have played a paramount role in improvements on many health indicators [111], and maternal, newborn, and child health have probably benefited the most from those reforms.

However, there are persisting gaps that need to be addressed for the intervention to be optimally effective. Below, I describe the gaps that could be reported on by the demographic and health survey, bearing in mind that if other research methods were used, more could be documented.

The schedules of ANC visits prescribed in the current guideline are not fully respected: women register for the first ANC visit late, and in 2014/2015 only 56% of mothers made their first visit before the fourth month of pregnancy [121].
Some of the factors associated with delayed booking of the first ANC visit include: perceived distance to the health facility, having many other children already, and unwanted pregnancy [122].
There are also cultural factors that have not yet been documented, whereby pregnancy is primarily considered as a family secret that needs to be kept hidden for as long as possible – most of the time without any reasons, or sometimes for the purpose of preventing any harm from people who are not happy with the family achievement.

Moreover, only 44% of mothers attend four standard visits. Some of the factors associated with this situation include older age, being single, and having poor social support [123]. The poor quality of ANC consultations, including the negative attitude of service providers especially towards women who are very late in their pregnancy, and those who come for their first visit without their partners, are some of the factors behind delayed initiation of ANC or inability to complete the required visits [124].

Not all mothers who attend ANC visits get all the ANC components as per the guidelines: 16% of women report not having their blood pressure measured, 21% were not informed about signs of pregnancy complications, 42% reported not having their urine sample taken, and 18% were not protected against tetanus in 2014/2015 [121].

The differences in ANC components received among socio-demographic subgroups suggest that this might have something to do with either attitude and/or training of providers. For example, the percentage of mothers who received the urine test and those who were informed about signs of complications are higher among mothers from advantaged families with regards to education, place of residence, and wealth [121].

1.5. Knowledge gap and contribution of this thesis

In section 1.2.3, I have discussed the challenges to evidence availability and use in low-resource settings. I strongly believe that Rwanda shares many if not all of the challenges with its peers. Moreover, the relatively limited availability of evidence on effective and cost-effective interventions in comparison to evidence on the magnitude of the health problems is also a reality in Rwanda. Economic evaluations are particularly rare compared to other studies performed in Rwanda.

To illustrate this point, using the advanced search in PubMed, with "cost" OR "cost-effectiveness" OR "economic" AND "health" AND "Rwanda" as key words, without any other filter, I have found only five publications. Two are related to HIV, two are related to ANC (one being our costing study, and another about mentorship for ANC improvement), and the last is on the cost of abortion. When I searched for any health-related research on Rwanda using "health" AND "Rwanda", I found 209 results. The search was performed in September 2018.

Taking the example of malnutrition among children under 5 years of age, there is evidence on the magnitude of the problem from community health workers reports, health facilities information systems, and information from the surveys conducted every five years. It became a government priority to eradicate malnutrition, especially because Rwanda is believed to be food secure. However, so far, I have never come across any empirical study on what works in reducing malnutrition rates in Rwanda.

Another example is ANC in Rwanda, which, as highlighted in the previous section, has the potential to be improved. In the previous section, I have highlighted the gaps in healthcare during pregnancy in Rwanda, namely, late registration for the first ANC visit, inability to respect the scheduled visits, and components of ANC not being adequately provided. All those gaps imply that there are numerous options to bring positive change in ANC at both the demand and the supply sides of the intervention in Rwanda.

Furthermore, the new WHO recommendations for ANC (2016) suggested modifications and new activities that, if implemented, could make ANC more effective. For example, the recommendation indicates that i) increasing the number of visits or contacts from the current four to a minimum of eight could potentially reduce perinatal mortality; and ii) introducing ultrasound scans before week 24 could reduce preterm births, among others [85]. Some of the changes can be made by improving efficiency in the system, while others (such as increasing the number of visits from four to eight) would likely entail additional costs, whether it is borne by the provider (mainly the government) or by the households (users of the service), with the expectation of getting more health benefits or saving on future costs.

There is little evidence of the relative cost-effectiveness of ANC as a package that belongs to the wide maternal health interventions [66], mainly because of its complexity and interconnectedness with other maternal health interventions. Most of the studies on the effectiveness of ANC have looked at its effect on direct delivery outcomes both on mothers and newborns.

Yet it has been argued that some of the ANC interventions, such as education and counselling related to nutrition, hygiene, tobacco cessation, and others, aim to improve health outcomes even after delivery for both mothers and newborns. The literature on the cost of ANC is dominated by studies that vary in methods, perspectives, and results, and they can hardly be transferable from one context to another.

The majority of strategies that were reported to be cost-effective in low-income countries were also more costly than the comparators, which means that policymakers who would want to improve maternal health would also be willing to allocate more financial resources. On the other hand, it was also found that the link between investment in health and health outcomes is not always assured, mainly because the marginal increase of health budgets may be invested in expensive and less-productive interventions [125]. Governments are therefore urged to improve efficiency, reprioritize health expenditures, and initiate innovative financing mechanisms [126].

In Rwanda specifically, much is known on maternal mortality and utilization of maternal health services, but less is known on the relative effectiveness and cost-effectiveness of the interventions currently being implemented or not yet implemented to reduce maternal and perinatal mortality and morbidity. Postpartum health is also an area that is less known in Rwanda, yet it was reported that for every maternal death, there are 20 cases of acute or chronic morbidity [127]. Some of them leave long term sequelae [127], and very few women in low- and middle-income countries seek care after delivery [128]. Therefore, maternal mortality itself is not a good indicator, because the cases of death are rare [129].

This thesis has addressed some of the gaps highlighted above using a variety of methods. We have provided the estimation of the cost of ANC in Rwanda, which was previously unknown.

We have investigated the effectiveness of ANC utilization with HRQoL, a measure known to include the patients' or participants' perspective in the evaluation of health interventions [130] and combine the effect of many conditions into one measurement. This measurement was also chosen because it can capture health problems that are rarely fatal [131], and it is often used in health economic evaluations [51].

Furthermore, this thesis offers a timely contribution to policy discussions on the 2016 WHO ANC recommendations for Rwanda and low-resource settings, by combining evidence from various sources. One of the sources of evidence is expert elicitation, a method that can add value to policy discussions in low-income countries, especially when time and other resources cannot allow for the use of other research methods, or, when available, evidence is of less relevance to the context. Lastly, in this thesis, we conducted a systematic review of economic evaluations for obstetric ultrasound to synthetize several results from different contexts and to support informed decision making on this technology.

1.6. Aim and objectives

The general aim of this thesis was to contribute to the use of health economic evidence for informed health care decisions in low-resource settings, using antenatal care (ANC) policy in Rwanda as a case study.

1.6.1. Specific objectives

- To determine the association between antenatal care utilization and women's health-related quality of life after delivery, as well as other determinants of women's health-related quality of life (Paper I).
- To estimate the current cost of antenatal care services from the health care provider and household perspectives in Rwanda (Paper II).
- To estimate incremental cost and outcomes from the implementation of the 2016 WHO antenatal care recommendations for Rwanda (Paper III).
- To review the evidence base for cost and cost-effectiveness of routine ultrasound scan during pregnancy (Paper IV).

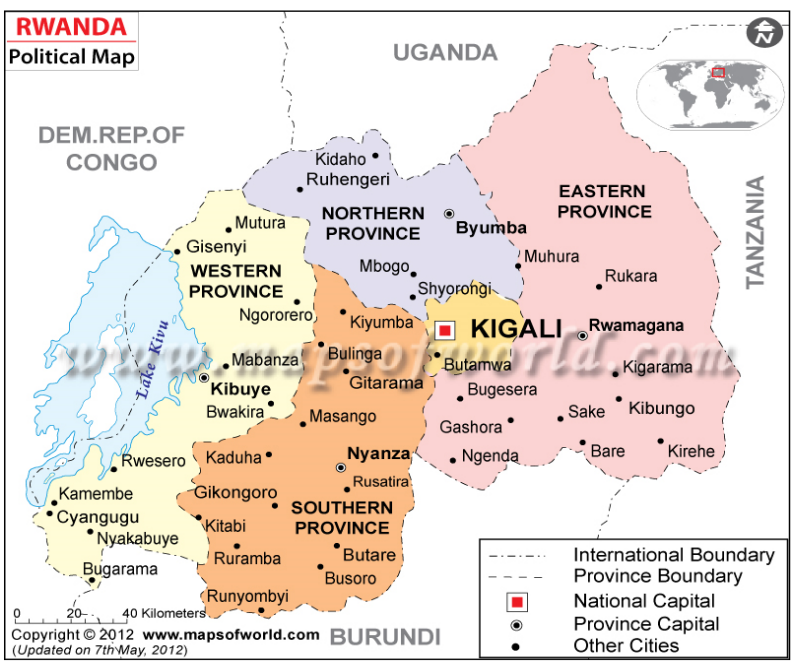
2. MATERIALS AND METHODS

2.1. Study setting

2.1.1. General country context

Rwanda is one of 54 countries on the African continent. It is located in the central-eastern region of the continent, bordering Uganda in the north, Tanzania in east, the Democratic Republic of Congo in the west, and Burundi in the south. Rwanda is most known for its recent tragic history, characterized by a genocide against the Tutsi that claimed close to 1 million lives, nearly 1/10 of its population in three months, and that resulted in the displacement of more than half of its population in the aftermath of the genocide [132].

The country's population was, in 2015, estimated at 11.3 million [133], mostly young, a demographic pattern which is not different from many other African countries. The total fertility rate is 4.2 children per woman at reproductive age [121]. Rwanda is one of the most populated countries with 467 inhabitants per square kilometre [133]. The life expectancy at birth was 64.6 years for males and 68.4 years for females [133].



Source: www.mapoftheworld.com

The main economic activity is agriculture, mostly for subsistence, practised by 65% of the active population [134]. The US $ 729 annual income per capita puts Rwanda on the list of the low-income countries. The Gini index was 0.448 in 2013/2014.

2.1.1.1. Healthcare organization and performance in Rwanda

The Rwandan health sector has not been spared the consequences of the genocide against the Tutsi of 1994. Many healthcare providers were killed, others become refugees, and others were involved in committing crimes and are still facing their sentences. Some of the infrastructures were destroyed, and equipment was stolen. In the aftermath, the country's main concern was putting the healthcare system back to work [113].

Currently, the healthcare system in Rwanda is organized in a pyramidal structure. At the peripheral level, healthcare is provided by community health workers, at 471 health posts, 499 health centres, and 36 district hospitals. At the intermediate level, there are four provincial hospitals (newly created), and at the national level, there are eight National Referral hospitals [135]. Public and mission-based health facilities are distributed across the country, while private health facilities are concentrated in cities. Nearly (96%) every administrative sector (25,000–30,000 inhabitants) has a health centre [136], and every district (350,000–450,000 inhabitants) has at least one district hospital and three ambulances, on average [135]. It takes nearly one hour (57 minutes) on average to walk to the nearest heath centre (31 and 61 minutes for rural and urban households, respectively [137]). However, the predominant mountainous landscape, which is source of the country's nickname of "the country of a thousand hills", can make the geographical accessibility a challenge even when distance is not too long.

Regarding ownership of health facilities, of the 1285 health facilities counted in 2016 in Rwanda, 20% of them were owned by the private sector [135]. They are usually authorized and supervised by the Ministry of Health.

In the last two decades, the Rwandan healthcare system has successfully implemented health system reforms which have improved the demand and supply of health care and generated impressive results that are not usually observed in countries of its income levels.

On the demand side, key reforms are:

1. Community health system: around 45,000 community health workers (CHW) recruited from the community and trained by the Ministry of Health are deployed in each village. 65% are female.

They provide basic promotive, preventive, and curative services, mainly in areas of maternal and child health, but also in malaria, HIV, nutrition, and pneumonia. In 2016, they diagnosed and treated 28% of malaria cases and accompanied 83% of women who gave birth in the public health facilities [135].

2. Community-based health insurance: this is a health insurance scheme that covers mainly people in informal sectors who represent the majority of the Rwandan population. It was introduced in 2006 and revised in 2010. Every family pays an annual premium for each member of the family according to their wealth status. The highest individual annual premium is $8.2 (0.5% of the population), the middle category – representing the majority of the population (83.5%) – pays $3.5 for every member, and for the lowest category (16% of the population), a premium of $2.3 is covered by the government. The subscription fluctuates every year between 75% and 95%. For instance, at the end of 2017 (June 2017), it was at 83.6% [136].

At the supply level:

1. Expansion of primary and secondary healthcare: in 10 years, the number of public health facilities have more than doubled, with the creation of health posts and provincial hospitals, and subsequent deployment of health workers in health facilities. For example, from 2008 to 2015, the number of medical doctors and nurses in public health facilities has increased from 550 and 6261 to 742 and 8751, respectively [138][133].

2. Performance-based health financing: introduced in 2006, this is a contractual system where the health facilities are paid on the condition of their performance on key agreed indicators related to the coverage or quality of care [113]. The largest percentage (approximatively 70%) is distributed among healthcare workers on top of their salary, and the remaining goes to the health facility. This mechanism has proven effective on key indicators including institutional deliveries and HIV [139].

3. Other health system strengthening initiative: this is the development of a monitoring system enabled by a well-functioning electronic information system [140].
   To monitor specifically maternal health indicators at the community level, the government of Rwanda and its partners have launched a phone application called “Rapidsms” or “mhealth” used by CHW to report to health facilities on maternal and child health indicators and give alerts in cases of emergency. The system was recently reported to have impacted on the use of maternal health services [141].

4. The Rwandan health sector also benefits from the overall governance system from central levels to peripheral levels [135][142]. One example is the performance contracts in the public system, where every district mayor and every cabinet minister signs performance contracts with the President, which are evaluated at the end of the year, and the best performers are then recognized.

The aforementioned health system reforms have resulted in impressive performance on many indicators, including maternal and child health indicators [113]. One of the immediate results of the reforms is the increase in access to and utilization of health services and the reduction of out-of-pocket expenditures [143]. Life expectancy has doubled in just 20 years [111] from the lowest levels caused by the 1994 genocide. Child survival indicators have significantly improved between the year 2005 and 2010, the period when many reforms were initiated, and inequality in child survival has reduced considerably [144].

Nevertheless, the Rwandan Health system shares the challenges with most of the other low-income countries. Below, I list three major ones:

1. The major threat to the Rwandan Health system is overdependence on external funding, which poses a serious risk to the sustainability of effective programmes. For instance, the resource tracking report from 2016 showed that of the total 2013/2014 health sector expenditure, only 41% was from domestic resources, while another 52% came from only two partners: the United States of America and the Global Fund for HIV, TB and Malaria [145].
2. The increasing cost of healthcare that is not correlated with an increase in household income threatens the sustainability of the community health insurance programme.
3. Low capacities to respond to the increasing burden of non-communicable diseases (NCDs) and other types of specialized care. The focus on health system investments in recent decades was placed on primary healthcare and responses to traditional diseases. Now, we are observing the limited capacity of the healthcare system to deliver certain services at the secondary and tertiary levels, such as surgical services [146].

2.2. Primary data sources

Data used in this thesis were gathered from primary and secondary data collections. The primary data collections included a cross-sectional household survey that targeted women during the one-year postpartum period (Paper I) and health facility cost data collection (Paper II). Those data, together with secondary data, were used in the calculation of the incremental cost of ANC in relation to the new WHO ANC recommendations (Paper III). Effectiveness of the 2016 WHO ANC recommendations was estimated from primary data collected through expert elicitation (Paper III). Lastly, we conducted a systematic search of papers on cost and cost-effectiveness of routine ultrasound during pregnancy (Paper IV).

Primary data collections were conducted as part of the Maternal Health Research in Rwanda (MatHeR). This is a research project implemented by the School of Public Health of the University of Rwanda in collaboration with Umeå and Gothenburg Universities in Sweden. The main focus of this project is maternal health status and healthcare utilization, from pregnancy to delivery and during the postpartum period.

The MatHeR study was implemented by three investigators including myself and three other academic staff of the School of Public Health of the University of Rwanda, who were also PhD students in Sweden, with mentorship from supervisors from the same school and from the two aforementioned Swedish universities.

2.2.1. Household survey

2.2.1.1. Study area

A household survey was conducted in the city of Kigali and the northern province of Rwanda, two of five provinces of Rwanda. The city of Kigali has a population of 1,135,428 (in 2012), living in three districts, mostly with urban characteristics, although there are a few parts of the city considered to be semi-urban and rural. The northern province has eight districts and a population that was estimated at 1,729,927 (in 2012), living mostly in rural areas. The two provinces were selected to represent other provinces, because going to all provinces would be logistically demanding and would not add much value, since previous country-wide surveys, including the demographic and health surveys, have not reported major geographical differences in reproductive indicators, other than rural-urban patterns [119–121].

2.2.1.2. Study design, participant selection, and sampling process

The household survey used a cross-sectional study design. The study targeted women who gave birth between 1 and 13 months prior to the day of interview. The sample size was calculated based on the prevalence of hypotensive disorders during pregnancy in Africa [147], one of the outcomes that was to be investigated in the MatHeR study. The desired level of precision was set at 0.05, and the design effect of 1.5 was considered. 10% of the sample size was added to cater for the potential non-response, although it was known to be less than 4% in many surveys previously conducted in Rwanda. In total, 922 women were to be randomly recruited using a three-stage sampling process.

First, 48 villages (representing 1%) of the total number of villages of the two provinces (4791) were randomly selected using the Epi Info random function. The number of villages selected in each village was proportional to the total number of villages in that district. Twenty percent of the villages selected were from urban areas, so as to mirror the rural-urban pattern in the country. Second, the number of households selected in each of the 48 villages was determined considering the total number of households in each village. In the third stage, households with women who delivered within a period of 1 to 13 months previous to the survey were randomly chosen with the help of CHW, who keep records of recently delivered women. In case a village did not have the required number of women fulfilling the criteria, the remaining number was recruited from the closest village. All women agreed to participate.

2.2.1.3. Data collection procedure

Data collection was conducted in July–August 2014 by the School of Public Health of the University of Rwanda. A questionnaire comprising sections related to socio-economic situation, health status, and healthcare utilization during pregnancy, delivery, and the postpartum period was developed in English and translated into Kinyarwanda.

Data collection was conducted by 12 data collectors recruited from the School of Public Health database, on the condition of having a nursing or other health-related high school degree (12 years of schooling); and being a female with experience in data collection. They received a 3-day training course, including one day of piloting the survey in a village out with the sampled area. The training was conducted by four investigators (PhD students) led by one (Jean Paul Semasaka Sengoma) who had prior experience in conducting household surveys in the School of Public Health. Four local supervisors also occasionally offered support during training and field work.

Data collectors conducted face-to-face interviews, guided by the four main investigators. The latter were also in charge of working with CHW to select households, to ensure that all selected households are visited, and to check for completeness of the questionnaires. Data entry was performed in the SPSS template by four experienced data entry clerks selected in a pool of data clerks of the School of Public Health, with supervision by one data entry manager.

2.2.1.4. The survey questionnaire and variables of interest

The survey was intended to be used for the 4 PhD projects. The variables of interest for this thesis were related to ANC attendance, the HRQoL, and socioeconomic and demographic characteristics of the participants.

The main variables of ANC utilization used in Paper I include the number of ANC visits attended during the most recent pregnancy, the timing of the first visit, the time it takes to attend the ANC service (including travel time), the means of transport, and payment for transport to reach the ANC services.

The HRQoL information was collected with the EQ-5D-3L instrument, which has two main parts. The first is comprised of questions about five dimensions (mobility, self-care, pain or discomfort, usual activities, and anxiety or depression) and three options for each of the five dimensions (severe problems, moderate, or no problems). The second part, usually called the Visual Analogue Scale (VAS), presented on a scale from 0 to 100, and participants were asked to show how good or poor their health was on the day of interview by indicating a point on that scale. Zero represented the worst imaginable health state, while 100 represented the best imaginable health state.

The information on socioeconomic and demographic variables included the place of residence, educational level, age, social support, possession of assets in the household, marital status, number of children, and the age of the youngest child.

2.2.2. Health facility survey

The purpose of the health facility survey was to collect information on resources (including human resources, drugs, supplies, and space in the building) used to deliver routine ANC, as well as their quantity and value.

The survey was conducted in January 2015. Six health facilities were selected from the northern province, which is predominantly rural, and Kigali City, which has urban characteristics. The selection criteria were the geographical location (representation of the two provinces) and ownership of the facility (government, mission, or private).

With the exception of the private health facilities, the government-owned health facilities and those owned by missions (mainly because of the subsidies they receive from the government) follow the same guideline. It was therefore believed that six health facilities would give the information needed, and additional numbers will be added if significant variation between facilities is observed.

A data collection guide was developed in English based on the ANC guidelines that were followed in Rwanda at the time of interview. Rwandan guidelines were developed based on the 2001 WHO recommendation that suggested the schedule of four focused ANC visits during pregnancy [88].

The data collection guide was comprised of identification of the health facility, resource use during the each of the four ANC visits, and resources used by the overhead department.

2.2.2.1. Data collection procedure

Data collection was performed by the main investigator (myself). Each of the six health facilities was first contacted to secure an appointment. A meeting with the head of the health facility was organized to explain the objective of the study and the data collection procedures. I was subsequently introduced to the staff working in the ANC department for interview. The face-to-face interview aimed to understand the ANC procedures, as well as resources involved in delivering ANC, in each of the health facilities. The resources were expressed in different units depending on how they are used in practice. For example, if we were considering folic acid tablets, the unit was number of tablets per woman.

The staff responsible for ANC, then referred me to other departments such as the laboratory department to identify and quantify more resources used during ANC visits. After identification and quantification of recourses, information on their cost as well as overhead costs were collected from finance department.

To complete the information from the health facility survey, the following sources were consulted:

1. The National Health Information System (attendance figures)
2. The Medical Technology and Infrastructure Division of the Rwanda Biomedical Center (cost of building, and medical equipements)
3. Central medical store (cost of drugs)

2.2.3. Expert elicitation

The aim of expert elicitation was to gather opinions from specialists on potential maternal and perinatal mortality reductions that Rwanda can expect from the adoption of the 2016 WHO ANC recommendations, compared to the current practice. A questionnaire that could be self-filled or interviewer-administered was developed and comprised the following three sections:

1. A brief background of trends and current levels of maternal and perinatal mortality in Rwanda, the causes of maternal mortality in Rwanda, and causes of perinatal mortality in low-resource settings. The section also briefly presented the main changes suggested in the 2016 WHO ANC recommendations.
2. The second section asked specialists to estimate cause-specific and all cause maternal and perinatal mortality reduction that could be expected from the adoption of the 2016 WHO ANC recommendations.
3. The third section asked participants to suggest alternative changes to the current guidelines and their potential implications on maternal and perinatal mortality in Rwanda.

The first round of opinion collection was conducted in April 2017 in Kigali, Rwanda. It targeted obstetricians who had at least 5 years post-training experience practising in Rwanda. From a list of a total of 70 gynecologists and obstetricians obtained from one member of the association, 19 who fulfilled the criteria were identified and contacted through email, and the questionnaire was sent to them. One week later, a follow-up and a request for appointment through phone call/sms was done. Six specialists did not respond to the invitation, and three replied that they could make time for interview either for travel or time constraints. Two agreed to participate, but could not secure time during the three-week data collection period. Lastly, eight specialists responded to the questionnaire.

After initial analysis that revealed variations in responses, it was decided to give respondents an opportunity to re-evaluate their responses in comparison with the group responses, following some aspects of the Delphi technique.

A second opinion collection was organized in July–August 2017, targeting the same group of specialists. They were re-contacted and presented with anonymized group responses and a new questionnaire to fill out. Five of the specialists maintained their initial responses, two of them made modifications, and one did not respond. The non-response for the latter was considered as approval of the initial estimations. The results of the second round of data collection were then considered for the analysis.

2.2.4. Systematic review of cost and cost-effectiveness of routine ultrasound scan during pregnancy

A systematic search of scholarly publications on the cost and cost-effectiveness of routine obstetric ultrasound during pregnancy was conducted. It included research published between 1/1/1999 and 1/4/2018. The choice of the period was based on the assumption that the publications before that date had been covered in two previous systematic reviews that had an objective related to ours [103][108].

The search was conducted by the first author (myself) and was based on the search strategy outlined in the protocol agreed on by three co-authors. The search included primary and secondary economic evaluation studies (including cost, cost-effectiveness, cost utility, and cost consequence) and effectiveness studies that report on elements of cost, such as the quantity of resources used. The intervention was routine ultrasound examination, compared to no or selective ultrasound scans in a group of pregnant women without previously identified risks.

2.2.4.1. Search strategy

The search was conducted based on the following keywords that reflect the intervention, population, and research methods. Those terms included: cost*, cost-effectiveness, economic, economic evaluation, resource ultrasound, sonography, doppler, pregnant, pregnancy, antenatal, prenatal, obstetric, fetal, and perinatal. The search was conducted from three databases: PubMed, Scopus, and the Cochrane database. The detailed search strategy is contained in Appendix 1 of the Manuscript 4.

2.2.4.2. Selection process

The selection was done in 3 phases: the initial selection was concerned with limiting publications to those that are relevant to the topic; the second checked the appropriateness of the methods; and the third was the quality check. The first phase aimed at categorizing publications into four groups, namely:

A. Primary research studies that present a formal economic evaluation or the cost of routine ultrasound in pregnancy
B. Studies that present economic aspects of ultrasound, such the quantity or cost of some resources used, or partial costing studies, using either primary or secondary data (e.g. the cost reported in another paper)

C. Studies that can potentially fall into categories A or B, but for which categorization requires more information than what is provided in the title, abstract, and MeSH headings. For example, the title may include key words, but the abstract is not available, or lacking in sufficient detail.
D. Studies that have no relevance for the economic evaluation of routine ultrasound in pregnancy

Full text or abstracts that fell into category C because of lack of information to allow proper categorization were searched, read, and re-categorized by the two authors either in categories A, B, or D.

The second screening concerned publications that were considered in categories A or B. Publications were categorized into the following groups:

1. Formal economic evaluations of routine ultrasound in pregnancy, such us cost effectiveness, cost benefit, cost utility, or cost minimization analyses
2. Costing studies of routine ultrasound in pregnancy
3. Studies of the effectiveness of routine ultrasound in pregnancy that report on some resource implications
4. Reviews of the effectiveness, cost, or cost effectiveness of routine ultrasound in pregnancy (whether systematic or not)
5. Other studies that report relevant information but do not fall into 1, 2, 3, or 4, such as study protocols, clinical guidelines, commentaries, and letters.
6. Studies with no relevance to the economic evaluation of routine ultrasound in pregnancy

The third stage (quality check) considered papers that were categorized as A(1), A(2), B(1), B(2), and relevant studies in categories A(3), A(4), B(3), and B(4). A quality check was conducted on basis of the CHEERS guidelines for the quality assessment of economic evaluations [148].

2.3. Ethical consideration

The MatHeR study protocol for both the household and the health facility data collections was presented to and approved by the University of Rwanda, School of Public Health Internal Review Board (Ref: 010/UR/CMHS/SPH/2014). The household survey was also cleared by the National Institute of Statistics (Ref: 0425/2014/10/NISR), as required by the national rules for household surveys conducted at the national level. Participants were informed about their voluntary participation and their right to withdraw at any stage of the surveys. Before any interview, written informed consent was obtained from the participants.

The data collection of expert elicitation did not involve the collection of sensitive personal data. Advice was sought from the Internal Review Board of the College of Medicine and Health Sciences, and the decision was not to request a separate ethical approval.

The household survey included questions on sensitive personal information, such as intimate partner violence, personal health, income and expenditures, among others. Furthermore, it was anticipated that some participants would not be able to read and/or write properly. The survey planning, including recruitment and training of data collectors, considered those realities. For a data collector to be qualified, she had to be female, with training in nursing or other health-related training, and have experience in household data collection. They received a three-day training course, which included the introduction to the survey tool, simulation exercises to anticipate any situation that might arise, and a one-day pilot on one neighbourhood outside the sampled area. There was a provision of referral to the nearest health centre in anticipation of cases that might need medical assistance.

Each participant was given a choice between reading the consent form herself or having it read to her by the interviewer, and she signed with a pen or a thumbprint. Interviews were administered by the interviewer (data collector) in the local language, Kinyarwanda (i.e. reading the question for the participants, listening to answer, and marking accordingly), as it is usually the case in many household surveys in Rwanda. Interviews were conducted mostly in the participant's household, in a place chosen by her that guarantees her privacy.

Participant confidentiality rules written in the consent form were ensured through the use of identification codes and the separate storage of the questionnaire and identification sheet.

2.4. Data analysis

2.4.1. Cost of ANC – Current practice and 2016 WHO ANC recommendations

The cost of the current ANC practice in Rwanda was estimated through analysis of primary data, while the estimation of incremental cost from the 2016 WHO ANC recommendations was conducted through simulation of attendance and adaptation of the primary data according to changes suggested by the WHO.

2.4.1.1. Cost of current ANC practice for the health sector and for households (Paper II)

Provider side cost

The economic cost of providing ANC services was estimated in four stages (Table 2), which were reflected in the health facility survey instrument. Data analysis was done using a predominantly bottom-up approach. In some cases, a top-down approach was used, and in others, both approaches were used concurrently.

Table 2. Cost data collection process and sources of information

	Steps	**Source of information**
1	Understanding of the process of ANC service in each of the health facilities	Interviews with the staff responsible for ANC
2	Identification of resource used during the process	Interviews with staff in ANC and Laboratory departments
3	Measurement of quantification of resources used	Interviews with staff in ANC and Laboratory departments
4	Economic value of the resources used	Financial records, list of drug prices, procurement records (infrastructures)

Below, I describe how data collected for each of the categories of resources was used and anlyzed.

Cost of human resources

The time use by staff involved in ANC service provision (mainly in the ANC and Laboratory department) for one typical individual/couple coming for the first, second, third, or fourth visits was collected through interviews.
The time use for a typical day, week, and month was also collected from interviews. The person-hours for the staff that can be attributed to ANC were estimated. Finally, the qualification and monthly salaries of the staff involved in provision of ANC in the health facility were collected from the finance department and used to estimate the total cost of human resources for the facility in a year and the human resource cost for a typical visit at visit one, two, three and four.

Cost of drugs and supplies

The description and quantities of drugs and supplies, such as iron folic tablets, laboratory reagents, and tetanus vaccine, that are used in providing one typical ANC visit (at visit one, two, three, and four) were collected from the interviews with staff. The cost of those supplies was obtained from the price lists of medical products that are provided to each health facility by the district pharmacy on regulat basis. The prices reflect the cost of acquisition from the central medical store and a percentage management fee added by each of the two levels involved in the supply chain (district pharmacy and health centre). The cost of products that are subsidized by the government, such as the HIV test, for which the cost did not appear on the price list, were obtained from the central medical store. The total annual cost of drugs and supplies for each health facility was obtained by multiplying the cost of one ANC visit with the total number of women who attended the ANC in the health facility.

Cost of equipment

Equipment and the time for which it is used during one visit were identified through interviews. The cost at acquisition was obtained from the central division in charge of infrastructure and equipment, for public and mission-owned health facilities, and in financial records of the private clinic. The cost was annuitized using a three-year lifetime for electronic equipment, and a five-year lifetime for other equipment.

Cost of buildings

The space used for ANC consultations and waiting rooms was measured, in comparison to the total space of the health facility, to obtain a percentage of the space used for ANC-specific activities.

As opposed to the surveyed private health facility, which had the cost of the building in their records, the standard cost of the building for a typical health centre was obtained from the ministry's division in charge and annuitized using a 20-year lifetime. The percentage of the space used for ANC activities was applied to obtain the annual cost of the building attributable to ANC.

Overhead cost

The resources identified as overheads included the general supplies and utilities, cleaning tools and other equipment shared among different departments (such as the power generators), and administrative staff.

Those resources were measured, and their costs were collected from the finance departments of the health facilities. The allocation of overheads to ANC was done by applying the direct allocation method with the proportion of ANC staff-time as the allocation formula.

Household cost

The elements of household cost of attending ANC was collected through the household survey. The variables used here were:

- Time used to attend ANC: participants in the household survey reported the time it usually takes them to attend a typical ANC service, including the travel time to and from the health facility and the time it takes to receive the service.

- Cost of transport: this comprises the means of transport usually used by participants to reach the health facility and how much they pay for transport.

- Occupation for participants is categorized into three groups: paid employment, self-employed, and no employment. The percentages of each of the categories were applied to the numbers of annual attendance in each of the health facilities.

- Accompaniment to the health facility: the majority of the women reported being accompanied to their first visit (88.5%). During the subsequent visits, few reported being accompanied to the health facility: 6.9%, 3.8%, and 4.6% for the second, the third, and the fourth, respectively.

The section of the household questionnaire that was used to construct household cost variables was attached as additional file to paper II and can be fond at: https://doi.org/10.1186/s12913-018-3013-1.

The cost of time

The cost of time for a woman or couple attending ANC services was estimated by multiplying the proportion of time usually spent to attend ANC by the median monthly income for each of the three occupation categories (paid employment, self-employed, and no employment) from the 2016 National Labour Survey [134]. For the first visit, the cost of time was doubled to count for the time of the person who accompanied the women (usually the partner). Our household survey has revealed that 89% of women were accompanied at the first ANC visit.

The cost of transport

The cost of transport was estimated by multiplying the median cost of transport by the proportion of women who reported that they usually pay for transport (15%).

Estimation of the national cost of ANC

The national cost of ANC was estimated using the average provider cost together with the national attendance figures from the national information system. In 2015, a total of 373,678 women were recorded as new ANC registrations. The rate of attendance to the subsequent visits from our survey was applied to estimate the number of women who attended those visits.

Only public and mission-owned health facilities were considered in the calculation of total national cost of ANC. There were two reasons for this: first, there were large differences in the cost of ANC between public health facilities and the surveyed private clinic; second, the household survey showed that 95% of women who seek ANC receive it from public and mission-based health facilities.

2.4.1.2. Incremental cost of the 2016 WHO ANC recommendations for Rwanda

Incremental cost was estimated in three steps: first, ANC attendance for a hypothetical situation in which the 2016 WHO ANC recommendations are implemented in Rwanda was simulated; second, the assumptions of changes in cost of ANC were suggested, building on the cost study (Paper II) and the recommended activities from the WHO guideline. Lastly, the national cost of each of the eight suggested visits was estimated using the inputs from the two first steps.

Simulation of ANC attendance

A Monte Carlo simulation of normal distribution was performed to generate three probable attendance scenarios with different mean estimates. This was done because the 2016 WHO recommendations have not yet been implemented in Rwanda, true attendance is not known.

The three mean estimates were suggested based on our understanding that in the short and medium term, the average of ANC attendance is unlikely to be as high as the eight visits recommended by the WHO if Rwanda decides to implement the policy. We base that understanding on the factual elements in the literature on ANC attendance in low-income countries. ANC attendance in many low-income countries, including Rwanda, is lower than the visits recommended by national policies [87]. Some of these reasons include late registration for the first ANC visit [149–153] and other social determinants that are hard to eradicate in the short term.

The three mean estimates for the distribution of the attendance scenario were assumed as mean=5, mean=6, and mean=7, respectively, from the current mean=3.3 (from MatHeR survey).

A hypothetical cohort of 373,679 women representing the notational new registrations for ANC in 2015 was used in the simulation. We assumed the same standard deviation (0.8) as for the distribution observed in the household survey in 2014. The scenarios from the simulation exercise are presented as follows:

- Scenario 1: mean=5, minimum=1, maximum=8
- Scenario 1: mean=6, minimum=2, maximum=10
- Scenario 1: mean=7, minimum=3, maximum=11

These attendance scenarios were labelled as conservative scenario (mean visits=5), middle scenario (mean visits=6), and ambitious scenario (mean visits=7).

Assumptions about the cost of ANC visits

The starting point for making assumptions about cost of ANC visits was the cost estimates for the current ANC practice in Rwanda (Paper II). Adaptions from those figures were made to reflect the main changes suggested by the 2016 WHO ANC recommendations that are likely to impact on the cost of the service. Those changes were:

a) The increase in the number of ANC visits from the current four to eight visits for a normal, uncomplicated pregnancy. Four more visits were added with assumption that they would cost the same as a standard ANC consultation, cost=$6, equivalent to visits two and three in the current model (Paper II), unless additional tests are scheduled during the visit.

b) Early ultrasound, i.e., ultrasound scan before week 24 of gestation: this scan could come either during the first or second ANC visit according to the WHO-recommended schedule, depending on how early women register for their first ANC visit. In any case, the cost will be the same, and therefore we suggested counting it during the first ANC visit, with cost=$3 as estimated in the costing (Paper II).

c) Repetition of certain lab tests during the course of pregnancy, the tests that were only recommended during the first ANC visit. Those tests are the test of bacteriuria and the test for anaemia, that were estimated from the literature at $3 and $0.75, respectively [154][155]. Those tests were added to the cost of a standard ANC consultation during visit three and visit six to reflect the WHO-recommended schedules.

The cost of the eighth visit was assumed to be the same as the cost of the last (fourth) in the current model ($11).

2.4.2. ANC and health outcomes

2.4.2.1. ANC, HRQoL and socioeconomic and demographic determinants (Paper I)

Data used to analyse the the association between ANC utilization, socioeconomic, and demographic determinants with HRQoL was the household survey. Below, I describe how variables were constructed and how statistical analyses were performed.

Independent variable

The main independent variable was the adequate utilization of ANC. An index was constructed following the Kessner prototype [156] to describe whether ANC attendance was adequate. Two variables – the number of ANC visits attended and the timing of the first ANC visit – were used to costruct a binary indicator variable.

Those who attended at least four ANC visits, and when the first visit was booked in the first trimester, were categorized as belonging to the group of “Adequate ANC utilization”. Those who did not fulfil the criteria above belonged to “Inadequate ANC utilization”. Other independent variables used in Paper I were related to socioeconomic and demographic characteristics of the participants. These included:

- Residence: categorized into two groups (rural and urban) according to the village (lowest administrative entity) of residence.

- Age: participant's age was categorized in five-year intervals

- Educational level: based on answers to the question about highest educational level, four categories were constructed (some primary, primary level, lower secondary or vocational, upper secondary or higher education)

- Social support: an index of social support was constructed from the answers to seven questions related to the kind of social support received by the participant. A participant who reported receiving four or fewer kinds of support was categorized into the group of poor social support, while those with more than four kinds of social support were categorized into the group of good social support.

- Wealth: a wealth index was constructed using principal component analysis from the answers to question of assets possessed by the households (radio, television, iron, mattress, mobile phone, computer) and characteristics of the household (materials used to construct the wall, source of water, access to electricity, fuel used in cooking).

- Marital status: this was categorized into four groups, namely, married, cohabiting, unmarried/single, and separated, divorced, or widowed.

- Number of children: from 1 to more than 6 children.

Dependent variables

The dependent variable was Health-related Quality of Life (HRQoL), measured using the EQ-5D-3L questionnaire. Two HRQoL variables were extracted from the responses to the two parts of the EQ-5D instrument:

- A HRQoL score was constructed from the responses to the questions on the five dimensions of health-related quality of life. For every participant, a combination was constructed based on her response to the five questions (e.g., 1,3,1,2,1). Every combination has a corresponding value, often called weights, generally between 0 and 1, although sometimes negative values can be expected, as was the case in our study, collected in representative populations studies in different settings. Given the lack of such studies in a Rwandan setting, we have used the weights from a United Kingdom population.

- The possible responses on the Visual Analogue Scale were between 0 and 100. Those values were used as such in the analysis.

Statistical analysis

Descriptive statistical analysis was performed to present the distribution of participants by different socioeconomic and demographic characteristics. Prevalence of HRQoL levels in each of the five dimensions were calculated using frequencies.

Association between HRQoL (outcome variable) and Adequacy of ANC utilization and socioeconomic and demographic characteristics (predictors) was tested through bivariate and linear regression analyses. First, a bivariate analysis was performed using an independent t-test and one-way analysis of variance with a 0.05% significance level to assess the association of the outcome variable and individual predictors.

Second, two separate multivariable linear regression analyses were performed using a stepwise method, and two different presentations of outcome variable: in the first model, the HRQoL was presented as EQ-5D weight, whereas in the second, the EQ-VAS (visual analogue) was used.

In both models, all the predictors (Adequacy of ANC utilization and socioeconomic and demographic characteristics) were entered, with the exception of one predictor variable, "number of children", because of its high proportion of missing values (31.4%) that could lead to model bias.

Only variables that were statistically significant at p=0.05 remained after a stepwise elimination process in the model.

Collinearity among predictor variables was tested using a variance inflation factor, after which none of the variables was found to be above the ceiling of 10.

The recommended method of estimation of standard error when many subjects achieve the upper bound, as it was the case for our EQ-5D data, the ordinary least square with heteroskedasticity-consistent (robust) standard errors [157] was used in regression analysis.

Statistical analyses were performed using Stata software version 13 (Stata: release 13-statistical software. StataCorp, College Station, TX).

2.4.2.2. Incremental health outcomes of the 2016 WHO ANC recommendations

Incremental health benefits were estimated in terms of years of life saved (LYS) from maternal and perinatal deaths averted. The intervention was the implementation of the 2016 WHO ANC recommendations in Rwanda, and the comparator was current practice. LYS were computed for a hypothetical one-year birth cohort from maternal and perinatal mortality reduction estimated through expert elicitation.

The transition from percentages of maternal and perinatal mortality reduction to LYS was done in two stages. First, we translated mortality into death counts using the data on age-specific maternal mortality deaths and perinatal deaths from the most recent (2014/2015) demographic and health survey (DHS) [121]. Second, the LYS were calculated using the information from the first stage and the life expectancy for females (used in calculation of LYS from maternal mortality reduction) and for both sexes (used in calculation of LYS from perinatal mortality reduction), as reported by the recent general census in Rwanda (2012) [121].

Two outcome scenarios were then constructed and labelled as "optimistic scenario" (higher rates of mortality reduction) and "pessimistic scenario" (lower rates of mortality reduction).

2.4.3. Cost-effectiveness of the 2016 WHO ANC recommendations

Six cost effectiveness ratios for each combination of the three attendance scenarios (conservative, middle, and ambitious) and two outcome scenarios (pessimistic and optimistic) of the 2016 WHO ANC recommendations were computed using current ANC practice in Rwanda as the comparator. The incremental cost effectiveness ratios were expressed as cost per LYS.

In addition to those scenarios, we have calculated the incremental cost of ANC for a scenario in which the current policy is maintained, but coverage increases, so that all women have exactly four ANC visits.

The cost-effectiveness threshold (CET) used was based on the Rwandan GDP per capita as recommended by the WHO for countries such as Rwanda with no official CET [158]. The WHO advised that an intervention is very cost-effective when it can avert a Disability Adjusted Life Year (DALY) at a cost less than an average GDP per capita, and it is considered cost-effective if it can avert a DALY at a cost not exceeding three times the country's GDP per capita [159]. The World Bank statistics showed that the GDP per capita for Rwanda in 2015 was USD 697 [160].

3. RESULTS

3.1. Socio-economic and demographic characteristics, HRQoL and ANC utilization of participants

3.1.1. Socio-economic and demographic characteristics of participants

Socioeconomic and demographic characteristics and ANC attendance of the recently delivered women who participated in the household survey are presented in Table 3. Sixty-one percent of participants had not attended ANC adequately during their last pregnancy. That is, they either registered late (after the first trimester) or they had fewer than four ANC visits.

A majority of the participants (69%) were 30 years of age or younger, 77% were living in rural areas, and 75% were educated at most at a primary level. Fifty-three percent of participants were officially married, 32% were cohabiting with their partners, 2.5% were separated, divorced, or widows, while 13% were single. Sixty-six percent of participants had three children or fewer, and 65% had good social support.

3.1.2. HRQoL for women during the postpartum period

Prevalence of problems in each of the EQ5D domains among participants are presented in Figure 4. The most prevalent problems reported are anxiety or depression and pain or discomfort. Seventeen percent and 3% of participants reported some problems and severe problems of anxiety or depression, respectively. Fifteen percent and 1% of participants reported some problems and severe problems of pain or discomfort, respectively. Five percent of participants reported some problems of mobility.

The median HRQoL score was 1.00 using EQ-5D and 70 using VAS.

Table 3. Distribution of women by socio-economic and demographic categories (N=922)

Variables	N	%	[95% CI]
ANC adequacy			
Inadequate ANC	563	61.5	58.3 - 64.6
Adequate ANC	352	38.5	35.4 - 41.6
Residence			
Rural	706	76.7	73.8 - 79.3
Urban	215	23.3	20.7 - 26.2
Age groups			
15-20	95	10.3	8.5 - 12.5
21-25	267	29	26.2 - 32.0
26-30	271	29.5	26.6 - 32.5
31-35	173	18.8	16.4 - 21.5
36-40	85	9.2	7.5 - 11.3
>40	29	3.1	2.2 - 4.5
Education level			
Primary but not complete	417	50.2	46.8 - 53.6
Primary level	202	24.3	21.5 - 27.3
Lower secondary or Vocational	112	13.5	11.3 - 15.9
Upper secondary or Higher education	100	12	9.9 - 14.4
Marital status			
Married	482	52.4	49.1 - 55.6
Cohabitant	292	31.7	28.8 - 34.8
Separated/Divorced/Widow	23	2.5	1.6 - 3.7
Not married/Single	123	13.4	11.3 - 15.7
Social support categories			
Poor social support	315	34.6	31.5 - 37.7
Good social support	596	65.4	62.3 - 68.4
Number of children			
1 child	41	6.5	4.8 - 8.7
2 children	227	35.9	32.3 - 39.8
3 children	148	23.4	20.3 - 26.9
4 to 5 children	138	21.8	18.8 - 25.3
>=6 children	77	12.2	9.8 - 15.0
Wealth quintiles			
Lowest	168	20.3	17.7 - 23.2
Second	167	20.2	17.6 - 23.1
Middle	192	23.3	20.5 - 26.3
Fourth	150	18.2	15.7 - 20.9
Highest	148	17.9	15.4 - 20.7

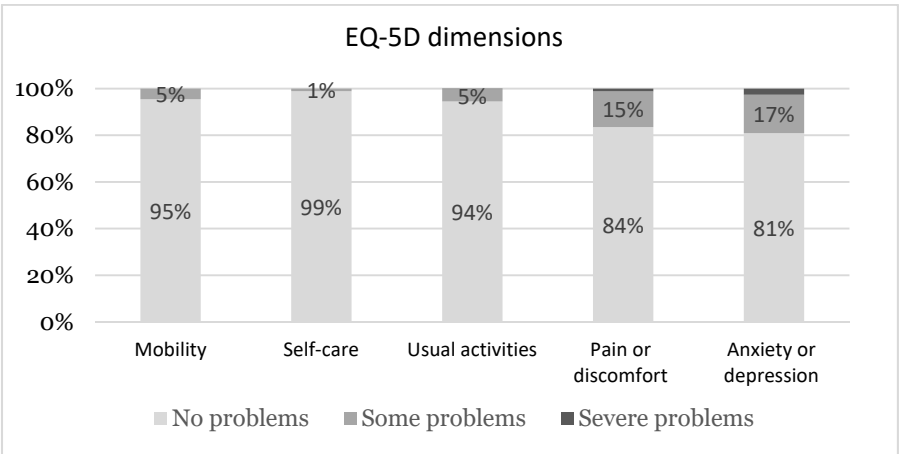


Figure 3. Prevalence of the dimensions of quality of life (N=922)

3.2. Cost of ANC–Current practice and 2016 WHO ANC recommendations

3.2.1. Cost of ANC for the healthcare system and for the households – current practice (Paper II)

3.2.1.1. Description of health facilities surveyed

The costing study collected information from six health facilities that are presented in table 4. Two of the six health facilities were from the city of Kigali, while the four remaining were from the northern province. Three health facilities are owned by the government, two are faith-mission-owned, while one health facility was private. Annual ANC attendance in 2015 ranged between 2833 and 20,022.

Table 4. Description of selected health facilities

Name of facility	Province	Type of facility	Ownership	Number of women attending first ANC visit (2015)	Estimated annual number of ANC visits
Hopital Croix du Sud	Kigali	Polyclinic, tertiary care	Private	5 985	20 022
Muhoza Health Centre	North	Primary health care	Public	3 454	11 555
Masaka Health Centre	Kigali	Primary health care	Faith-based	1 550	5 185
Nemba Health Centre	North	Primary health care	Faith-based	1 184	3 961
Kinigi Health Centre	North	Primary health care	Public	1 004	3 359
Rutare Health Centre	North	Primary health care	Public	847	2 833

3.2.1.2. Cost of ANC for the health sector and households

The cost of ANC for the health sector and households is presented in Table 5. On average, for a woman who attends four ANC visits, the cost was estimated at $44. The cost of each of the ANC visits was estimated at $21, $6, $6, and $11 for the first, the second, and the fourth visit, respectively.

The total national cost was estimated at $13.9 million, of which 9% is from the household side (1% for the transport and 8% for the opportunity cost of time).

The cost category that represents the biggest share of the cost was drugs and consumables (54% for the private clinic and 73% for the public and mission-based health facilities).

Table 5. Societal cost of ANC

	Annual total cost (USD)					
Private health facility	**1st visit**	**2nd visit**	**3rd visit**	**4th visit**	**Sum (4 visits)**	**%**
Personnel	108 393	79 254	70 897	24 757	283 302	34%
Drugs and consumables	301 336	60 352	54 531	42 150	458 369	54%
Equipment	2 396	1 752	1 567	547	6 262	1%
Cost of building	969	709	634	221	2 533	0%
Overheads	26 614	19 459	17 407	6 079	69 559	8%
Transport (households)	1 408	1 373	1 228	643	4 653	1%
Time cost (households)	7 485	4 138	3 595	1 899	17 117	2%
Total cost (1 facility)	**448 601**	**167 037**	**149 859**	**76 296**	**841 794**	**100%**
Annual number of visits*	5 985	5 835	5 220	2 734	19 773	
Cost per visit	**75**	**29**	**29**	**28**	**160**	
Public and faith-based health facilities	**1st visit**	**2nd visit**	**3rd visit**	**4th visit**	**Sum (4 visits)**	**%**
Personnel	18 868	7 358	6 582	5 516	38 324	13%
Drugs and consumables	131 700	30 188	27 005	28 871	217 764	73%
Equipment	1 037	404	362	303	2 107	1%
Cost of building	969	709	634	221	2 533	1%
Overheads	5 833	2 275	2 035	1 705	11 848	4%
Transport (households)	1 892	1 046	908	480	4 326	1%
Time cost (households)	10 054	5 559	4 828	2 551	22 992	8%
Total cost (5 facilities)	**170 353**	**47 538**	**42 354**	**39 648**	**299 893**	**100%**
Mean total cost per facility	34 071	9 508	8 471	7 930	59 979	
Annual number of visits*	8 039	7 837	7 011	3 672	26 559	
Cost per visit	**21**	**6**	**6**	**11**	**44**	
National ANC utilization	373 678	364 299	325 885	170 696	1 234 557	
Estimated total national cost	**7 918 560**	**2 209 701**	**1 968 732**	**1 842 977**	**13,939,970**	

Notes to Table 5. * The number of 1st visits refer to the year 2015

3.2.2. Incremental cost from the WHO ANC recommendations

Figure 2 presents the three scenarios from the Monte Carlo simulation of ANC attendance in a hypothetical situation where the 2016 WHO recommendations are implemented in Rwanda.

In a conservative scenario (blue colour on the graph), the mean number of visits is five, with a minimum of one visit, and a maximum of eight. In the middle scenario (green colour), the mean number of visits is six, the minimum is two, and the maximum is ten. Lastly, in the ambitious scenario (orange colour), the mean number is seven, the minimum is three, and the maximum is eleven.

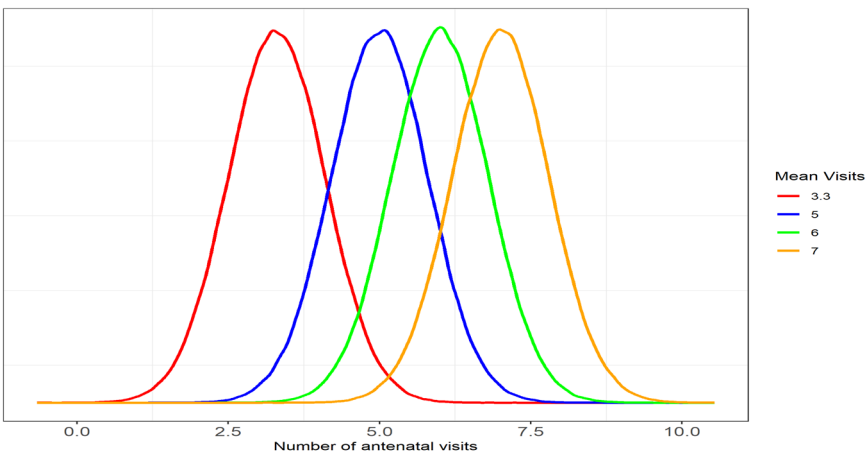


Figure 4. Simulation of ANC attendance

The incremental cost of the 2016 WHO ANC recommendations compared to current practice in Rwanda is illustrated in Figure 3 for the three attendance scenarios. The cost of current practice is $13.9 million. The incremental cost ranges between $5.8 million and $11 million in the conservative and ambitious ANC attendance scenarios, respectively. Besides the three simulated scenarios, the incremental cost of a hypothetical situation where ANC policy does not change, but the attendance to the four ANC visits becomes 100%, would cost $2.5 million.

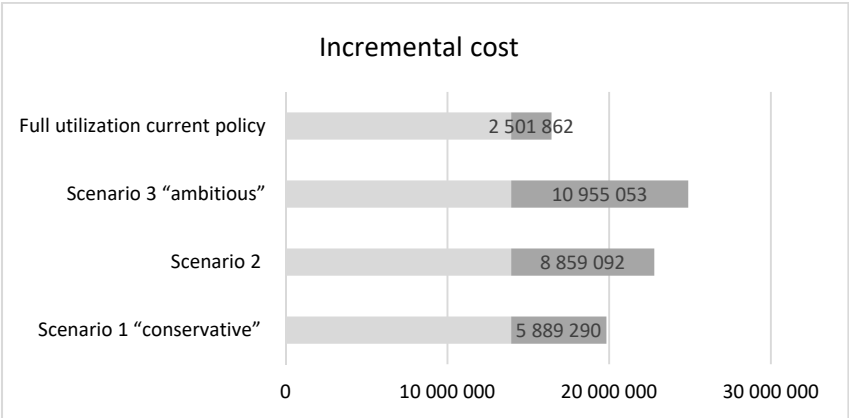


Figure 5. Incremental costs

3.3. ANC and Health Outcomes

3.3.1. Adequacy of ANC attendance by HRQoL and socioeconomic and demographic characteristics

Table 6 presents the final results of two linear regression models that were performed to test the association between Adequacy of ANC attendance, socioeconomic and demographic variables (as predictors on one side), and HRQoL measured with EQ-5D in the first model and EQ-VAS in the second model (as the outcome measure on the other side).

Adequate ANC utilization was associated with better HRQoL. The association was statistically significant (3.5 points higher in quality of life for women with adequate ANC utilization) using EQ-VAS, but not using EQ-5D.

Two other variables were significantly associated with HRQoL in two regression models, namely, social support and wealth levels. The group that had received good social support had 0.062 points higher in HRQoL in Model 1 (EQ-5D) and 9.2 points higher in HRQoL in Model 2 (EQ-VAS) compared to the poor social support group. Belonging to the highest wealth category was associated with better HRQoL using EQ-5D (0.013 points) and EQ-VAS (9.2 points) compared to lowest wealth category, but the association was not consistent across wealth categories. Other variables that were significantly associated with HRQoL in either of the models are educational level, marital status, and residence.

Table 6. Association between health-related quality of life and ANC utilization: Regression analysis using the EQ-5D and EQ-VAS

	Model 1 (EQ-5D as the outcome)			Model 2 (EQ-VAS as the outcome)		
	Coef.	**P**	**[95% C. I.]**	**Coef.**	**P**	**[95% C. I.]**
Social support (ref=Poor social support)						
Good social support	0.062	0	0.033; 0.091	9.222	0	6.264; 12.180
Wealth quintiles (ref=Lowest)						
Second	0.024	0.287	-0.020; 0.069	4.124	0.081	-0.516; 8.766
Middle	0.047	0.016	0.009; 0.086	5.807	0.005	1.781; 9.834
Fourth	0.005	0.813	-0.038; 0.049	4.399	0.063	-0.239; 9.038
Highest	0.059	0.013	0.012; 0.107	9.2	0	4.615; 13.785
Place of residence (ref=Rural)						
Urban	-0.04	0.008	-0.077; -0.011			
Educational level (ref=Some primary)						
Primary completed				-4.26	0.012	-7.583; -0.936
Lower secondary or vocational				-0.266	0.895	-4.216; 3.684
Upper secondary or university				2.205	0.292	-1.901; 6.312
Marital status (ref=Married)						
Cohabitant				-4.164	0.006	-7.150; -1.178
Separated				-5.757	0.263	-15.848 ; 4.334
Unmarried/Single				-7.585	0.001	-12.069; -3.101
ANC utilization (ref=Inadequate ANC attendance)						
Adequate ANC				3.551	0.008	0.924; 6.179

Notes: Using robust standard errors

3.3.2. Incremental health outcomes from the 2016 WHO recommendations

Table 7 presents the LYS from potential maternal and perinatal mortality reduction as a result of implementation of the 2016 WHO ANC recommendations. In 2014/2015, perinatal deaths were estimated at 239, while maternal deaths were estimated at 34 [121]. Estimates from the expert elicitation suggested that perinatal mortality would reduce by a percentage between 22.5% and 55%, while maternal mortality reduction would range between 7% and 52.5%. LYS saved from perinatal mortality reduction would range between 3442 and 8413, while LYS from maternal mortality would range between 77 and 576.

Table 7. Incremental health benefits

Mortality measure	Mortality (DHS 2014/2015*)	Deaths (DHS 2014/2015*)	Mortality reduction			Life-years saved
			Scenarios	% Change	Avoided deaths	
Perinatal mortality	29 per 1000 pregnancies	239	Pessimistic	-22.50%	54	3 442
			Optimistic	-55%	131	8 413
Maternal mortality	210 per 100,000 live births	34	Pessimistic	-7%	2	77
			Optimistic	-52.50%	18	576

*DHS 2014/2015: Demographic and Health Survey 2014/2015 [121].

3.4. Incremental cost-effectiveness

Incremental cost-effectiveness of the 2016 WHO ANC recommendations for Rwanda for the three ANC attendance scenarios and two outcome scenarios, together with the GDP-based CET, are presented in Figure 5. Out of six possible scenarios, four are below the threshold and hence are cost-effective. If the optimistic outcome estimates are considered, the intervention is cost-effective for all three attendance scenarios. The two scenarios that are not cost-effective are at the intersection of middle- or high-attendance scenarios and the pessimistic outcome estimations.

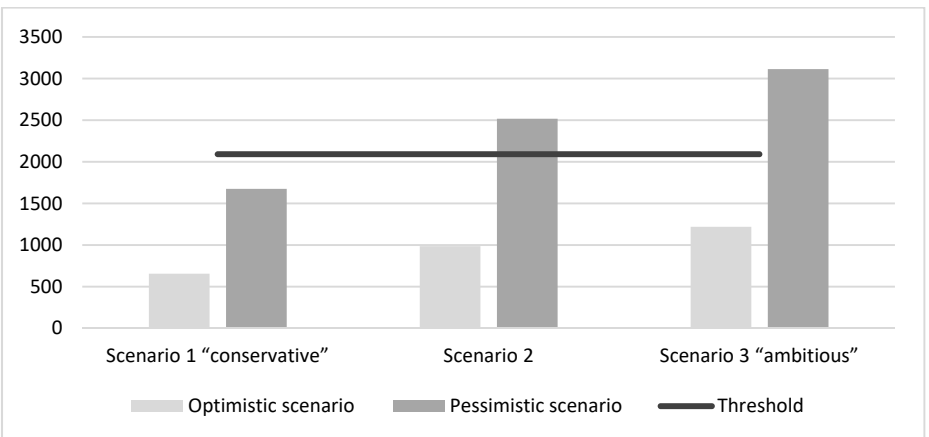


Figure 6. Incremental cost-effectiveness of the 2016 WHO ANC recommendations for Rwanda

3.5. Results of the systematic review of cost and cost-effectiveness of ultrasound during pregnancy

Six hundred and six studies were retrieved from the databases. With the endnote duplicate search function, one hundred were automatically identified as duplicates.

The first screening identified 79 more duplicates and 335 papers that were not relevant for the review objectives. The second screening considered 52 papers, of which 39 were eliminated either because the research question did not match the aim of this review or the methods used were not appropriate for economic studies.

Five out of the remaining 13 were systematic reviews. Two of the reviews that collected data for a period up to the year 1998 were eliminated. The remaining 3 reviews were read, and relevant papers that were not included in this review were extracted. The quality assessment was conducted for 12 papers, out of which three were eliminated because they did not fulfil minimum quality requirements. Data was extracted from the nine remaining papers (Figure 6).

The majority (seven out of nine) of the studies that reached the final stage are model-based economic evaluations, one is a costing study of routine ultrasound, and the last is a prospective study. All the studies were conducted in high- and middle-income countries (Unites States of America, United Kingdom, Italy, Canada, and South Africa).

Routine ultrasound scan during pregnancy was reported to be cost-effective in screening for vasa praevia (Cipriano, 2010), detection of fetal malformation (Vanara 2014), and assessment of cervical length (Miller 2013). It was also cost-saving from averted births of fetuses with anomalies (Vintzileos 2000). Routine community based ultrasound screening was associated with reduction of referrals to higher levels in South Africa (Geerts 2004).

Model-based economic evaluation shared a common methodological limitation, namely, weak methods of retrieving cost and outcome data used as model parameters. For instance, some authors mentioned that cost information was collected from their own estimations without further explanation (Vanara 2004, Vintzileos 2000, Cipriano 2010). In other instances, effectiveness information was said to have been retrieved from the literature, but no search strategy was described (Miller 2013, Cipriano et al 2010, Vanara 2004, Vintzileos 2000).

The majority of the papers that were eliminated at the second stage were evaluating ultrasound screening for Downs Syndrome. Because the objective of Downs Syndrome Screening differs from the objectives of routine ultrasound screening, the Downs Syndrome studies were not retained, because in many cases, they were looking at cost and outcomes of procedures that follow routine ultrasound screening.

The cost estimates were not comparable. For instance, in the South African study [161], the cost per scan was GBP 1,996, while in the Liverpool study [162], the cost varied between GBP 14 and GBP 16, depending on the purpose of the scan. One of the reasons for this is differences in methods and scope of the scan.

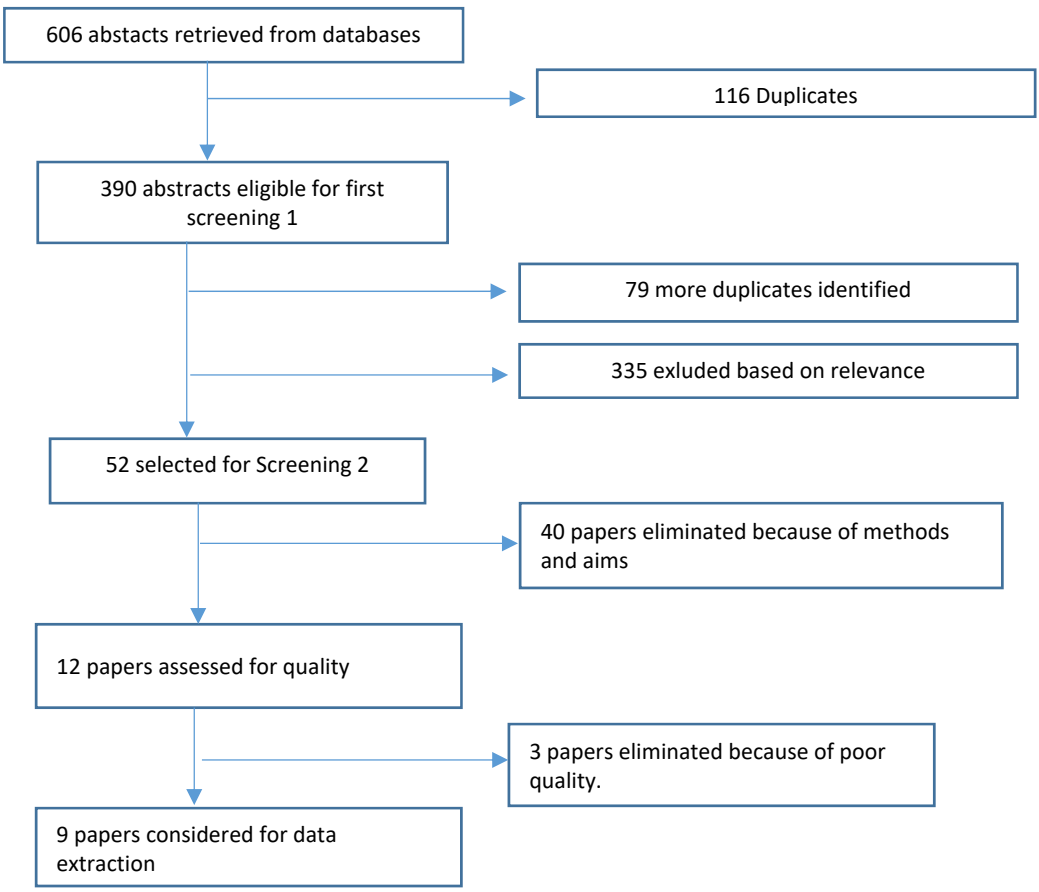


Figure 7. Screening process of papers

4. DISCUSSION

Decision making is one of everyday tasks of policymakers in healthcare in any setting, whether explicitly or implicitly, and whether evidence-informed or not. The typical decisions include: introducing new technologies or replacement technologies, treatment or intervention, deciding to add or remove an intervention from the list of reimbursable interventions by public insurances etc. Decision makers in healthcare, especially those that aspire to move their countries towards universal health coverage, need to take rational resource allocation decisions. Health economic evidence is the appropriate tool to enable them to achieve that aim in an explicit and transparent way [51]. The type of evidence that economic evaluation provide to support such decisions is the comparative analysis of cost and health outcomes for alternative treatments and interventions [51].

The production and use of scientific evidence, particularly economic evaluations, for healthcare decisions is still limited in low-resource settings. There are opportunities of producing more evidence in general and economic evidence in particular, hence making decisions more evidence-informed, particularly in low-resource settings, where many lives can still be saved or improved.

In this thesis, using the case of ANC policy in Rwanda, I present the results of economic evaluation from primary data collections, an expert elicitation, and the literature, which I believe are relevant to Rwanda and other low-income countries, both in content and in methods.

In the first objective, the cost of ANC for the household and the health sector is presented; the second objective investigated the HRQoL among women during the postpartum period and its association with ANC utilization; the third provides the analysis of incremental cost and health outcomes for the 2016 WHO ANC recommendations for Rwanda; and the last objective presents the results of the systematic review of cost and cost-effectiveness of ultrasound during pregnancy.

The methods that were used (expert elicitation, EQ-5D-3L, simulation of cost, estimation of incremental cost-effectiveness, systematic review of economic evaluation) are not new in the literature; however, these are uncommonly used in Rwanda, and they were certainly new to me. They all have advantages of providing the much needed but lacking type of evidence for informed health policy decisions, i.e. evidence on specific interventions and their impacts on the population's health and well-being in many places [7], particularly in low-resource settings.

Another advantage of these methods is that applying them in research is not as expensive and technically demanding as big cross-sectional surveys or interventions studies, such as RCTs. Therefore, it could be easier to use them more often in low-income countries.

Below, I discuss the key findings and their meaning for ANC policy in Rwanda. Later, I will present my reflections on the methods.

4.1. The cost of current (2015) ANC practice in Rwanda

The national cost of the current ANC practice in Rwanda was estimated at $13.9 million, and $44 per person who attends four ANC visits. The ANC cost in Rwanda is comparable to other low-income countries such as Uganda, Ghana, and Malawi [80], but not to middle- and higher-income countries, such as Cuba and Thailand [88], or high income countries, such as the United Kingdom [163], where the cost is much higher. The variation in unit prices of resources are different according to the country's income levels, which is likely to be a major contributing factor. Countries' ANC policies also vary in terms of the number of visits and activities provided in the package. Cost is therefore one typical example of the difficulties encountered in the transferability of economic evidence from one setting to another. For example, a salary of a midwife in Sweden cannot be compared to a salary of a midwife with the same qualifications in Rwanda. But the amount of resources, such as the time it takes to do one consultation, can be transferable.

The cost of ANC from the household perspective in Rwanda as estimated in this thesis reflects the cost of transport and opportunity cost of time. Their relative share of the total societal costs appear rather small (1% and 8% for transport and time, respectively); however, it is significant for a population where 60% spend less than $1.9 per day [160]. Furthermore, the cost of transport was incurred by only 15% of pregnant women, while the remaining 85% have to walk the distances to receive ANC – on average 1 hour [137] in a hilly landscape. The cost of time was low because of the low value of their time (based on median national income). This study has revealed that on average, a woman spends four and half hours walking to the health facility, receiving the ANC service, and walking back home.

4.2. What would be the incremental cost if Rwanda implements the 2016 WHO ANC recommendations?

The findings of this thesis show that it would cost between $5.8 million and $10.9 million for the conservative and ambitious attendance scenarios, respectively. How the level of women's attendance would react to the change of policy was presented as the main driver of the incremental cost, i.e. if more women attend, more resources would be used, and the cost would increase. Although the 2016 WHO recommendations suggest that every woman with a low risk pregnancy attend at least eight visits or contacts during pregnancy, it was assumed that adherence to the eight-visit schedule would be a gradual process, i.e. for a short time, the attendance would not be at the recommended level. The incremental costs presented in this thesis are based on the three attendance scenarios (mean visits = 5, 6, and 7), up from the 2015 attendance (mean=3.3).

Both the providers and households would be affected by the policy change. On the provider side, the change entails increased frequency of ANC visits, which is translated into more staff time, increased frequency of laboratory tests, and introduction of ultrasound examination during the first visit. On the household side, the cost of transport and cost of time will increase because women would be asked to attend more ANC visits than they do in the current practice.

The estimated additional resources are significant in relation to government financial means. They represent between 3% and 5% of the government allocation to the health sector during the fiscal year 2017/2018 ($216.5) [164], while the annual rate of increase from 2016/2017 to 2017/2018 was only 0.5% (from $ 216.5 to $ 217.6) [164,165]. This suggests that adopting the 2016 WHO recommendations for ANC would likely imply replacing some of the currently financed programmes in favour of the new policy, especially because the government is the main service provider in the Rwandan health sector.

4.3. ANC effectiveness in Rwanda

ANC has a potential of reducing maternal morbidity and mortality through timely detection and management of pregnancy-related and other unrelated but threatening illness among pregnant women, through identification of women with increased risk of complications during delivery, and through referral to an adequate delivery facility [78]. The effect of ANC should theoretically be greater in low-resource settings where morbidity and mortality are still high [78].

4.3.1. ANC and women's HRQoL during the postpartum period

Some pregnancy and delivery complications that can be prevented or can have their impact reduced by ANC have long-term consequences that affect the mother's physical and mental health [166]. In this thesis, HRQoL measurements were collected in a cross-sectional study in Rwanda using EQ-5D-3L, a tool that can summarize physical and mental health conditions in one measurement. Our assumption was that women who do not adequately attend ANC have lower levels of HRQoL during the postpartum period because of they are more likely to bear a heavier burden of the pregnancy as well as have delivery complications. The ANC utilization was associated with improved HRQoL using the Visual Analogue Scale (VAS), but the association was not found when HRQoL is measured with EQ-5D. One possible explanation is the limited answer options in the EQ-5D-3L format (severe, some problems, no problems). For example, a participant with a minor physical problem that does not alter her normal function could find "some problems" to be overstatement, and would therefore choose "no problem".

Our findings were supported by a study by Semasaka and colleagues that reported (using the same cross-sectional survey) poor self-reported health status among women who faced pregnancy and delivery complications during the early postpartum period, and that the self-reported health status levels improved as the distance from childbirth increased [167]. Based on the above information, the exclusion of mothers who were in less than a month-period after delivery at the time of interview, during our household survey, due to other outcomes that were targeted, could have resulted in exclusion of mothers with lower self-reported HRQoL.

Lastly, looking at the indicators of maternal, newborn, and child health in Rwanda (Table 1), there is high chance that nearly every woman comes in contact with healthcare providers at least once, during the period from pregnancy to delivery, and postpartum. This means that even women who have a health condition that would affect her HRQoL have a high chance of having the attention of the provider and getting back to a better HRQoL.

4.3.2. What would the incremental health outcomes be if Rwanda implements the 2016 WHO recommendations for ANC?

The information collected through expert elicitation suggests that it was estimated that the implementation of 2016 WHO ANC recommendations would save between 77 and 575 life years and between 3442 and 8414 life years from reduction of maternal and perinatal mortality, respectively. This finding echoes the evidence that suggests that the perinatal mortality reduction is the key outcome of the increased number of ANC visits during pregnancy [85][90]. Perinatal and maternal mortality reduction is one possibility of outcome measurement for ANC expansion. Other measurements include maternal and newborn morbidity and pregnancy outcomes such as birth weight and preterm birth [78].

4.3.3. Evidence on cost-effectiveness of ultrasound screening during pregnancy

For Rwanda and other low-resource countries with similar health system organizations, the introduction of early (before week 24) routine ultrasound during pregnancy is one of the major decisions of the 2016 WHO ANC recommendations in comparison with the current practice. This is because of cost implications as well as implications for the healthcare system. Currently in Rwanda, an obstetric ultrasound is commonly provided on a selective basis to pregnant women after other clinical examinations, and it involves transfer to the next level of healthcare, i.e. to district hospitals, where ultrasound is erated by physicians. At the health centre level, where the majority of women receive ANC service, there is no ultrasound equipment, and providers of ANC services (nurses or midwives) are not trained to use ultrasound. The adoption of the recommendation would imply task-shifting of ultrasound examination to nurses and/or midwives at the health centre level. Availability of equipment in the health centres and related maintenance capacity is to be guaranteed.

Cost and cost-effectiveness studies of ultrasound screening during pregnancy are still scarce, particularly primary studies. All the studies that were analysed were performed in high- and middle-income countries. The majority of available studies are model-based with significant methodological weaknesses. Data on cost and cost-effectiveness that were extracted were not comparable, mainly because of the large differences in scope, methods, and in the conclusions. There is a need to conduct more primary research on cost and cost-effectiveness of antenatal ultrasound scan, and to improve the methods of conducting and reporting modelling studies.

The results of this review do not provide a good evidence base for decision makers in countries similar to Rwanda, when considering adopting the WHO recommendations, as was expected. The available results are from high- and middle-income settings, yet it has been argued that the effectiveness of obstetric ultrasound can vary between two distinct contexts, depending, among other reasons, on the accuracy in diagnosis [168]. Our expectation before conducting this review was to find studies that reported the cost and cost-effectiveness of routine ultrasound from low-resource contexts. We were particularly interested in studies that used health outcomes that were the basis for the WHO to issue the recommendation, namely, early detection of fetal anomalies and multiple pregnancy and reduction of induced labour for post-term pregnancy as measures of evaluation of obstetric ultrasound effectiveness [85]. On the cost side, if there are no studies from low-income settings, the minimum would be to find studies that report the costs in a way that shows detailed resource use (amount of resources and their cost) in order to have an idea of adapting the cost in other contexts.

It is not uncommon that systematic reviews of cost-effectiveness studies reach this kind of conclusion. Numerous guidelines have been published (such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement). However, few journals make it a requirement to follow any specific guidelines, unlike RCTs, for example, where the Consolidated Standards of Reporting Trials (CONSORT) statement is well established.

However, there are ongoing efforts to collect evidence for costs and effectiveness of obstetric ultrasound in low-income settings, including the trial that started a few years ago [169] and another being conducted by the Preterm Birth Initiative in Rwanda. Those efforts would be a considerable input to the decision making as regards obstetric ultrasound.

4.4. Is it worth it for Rwanda to implement the 2016 WHO ANC recommendations?

The 2016 WHO ANC recommendation will likely be effective for Rwanda. They present the potential to reduce maternal and perinatal mortality. The implementation was estimated to also be cost-effective, as in four out of six scenarios presented, incremental cost per life year saved is below the GDP based threshold. Therefore, it would be advisable for Rwanda to implement the recommendation. However, significant financial resources will need to be deployed. The estimated incremental cost would range between USD $6 and USD $11 million, representing between 3% and 5% of the total health sector budget of 2017/2018.

Cost-effectiveness thresholds based on GDP per capita have been applied in the literature since their first introduction in the early 2000s [159][170], as few, mainly high-income, countries have explicitly established their CET. However, recently, they came under criticism. The common criticisms is that they are too high, which allow for less cost-effective interventions to be recommended [170][171]. Alternative methods of estimating CET for countries that did not set their own CET that were suggested include the bookshelves methods [172] and CET based on opportunity costs estimation [171]. Using the idea suggested by the latter method, it has been concluded that for countries for which the analysis was conducted (Malawi, Cambodia, El Salvador, and Kazakhstan), CET varied between 1% and 59% of the national GDPs [171].

A strength of the bookshelves methods is that it allows comparative analysis of cost-effectiveness of new interventions versus those that are already implemented and adjust to changes in health budgets [172]. However, doing so requires extensive documentation of the cost-effectiveness of currently implemented interventions in order to be able to compare with the new interventions, which is a challenge in many low-resource settings.

In line with the bookshelves idea, it would be interesting to compare the cost-effectiveness ratio of the intervention at hand (new ANC policy) with others that are currently implemented in Rwanda. If the cost-effectiveness ratio of the ANC policy change was lower than the least cost-effective policy among currently implemented interventions, it would be recommended for implementation [172]. However, as said before, there are not enough publications of economic evaluation on Rwanda, and that exercise would take time. I just compared cost-effectiveness ratios for the 2016 WHO recommendations for ANC and the human papilloma virus (HPV) accompanied by screening for cervical cancer (currently implemented in Rwanda), using the results for Uganda. The results show that the cost effectiveness ratio for HPV vaccine varied between $ 1000 and $ 5610 in one strategy and $ 1370 and $ 5450 in the second strategy. Alike to our results, out of six possible scenatios, four were cost effective while 2 are beyond the threshold. In conclusion, the recommendation remains the same, with the emphasis that if the country can afford the cervical cancer prevention strategy, it could also be able to implement the 2016 WHO recommendations for ANC.

The implementation of the 2016 WHO ANC recommendation could be done in a phased approach, given the resources required and limited fiscal space. The implementation should consider that, as discussed above, pregnant women already walk long distances and spend considerable amounts of their time, as do their partners (mainly during the first visit) to get the service according to the current policy.

Yet, the WHO recommendations suggest having five visits from week 30 to the time of childbirth [85]. This would be too demanding for pregnant women and can be a barrier to the use of the services.

4.5. Reflections on methods

The strengths of this thesis lie in the methods used and their relevance to the research questions. On the other hand, there are methodological limitations that need to be noted. In section below, I reflect on the methods used in this thesis and their implications on the interpretation of the results.

4.5.1. Costing of ANC in the provider side

The micro-costing approach used in Paper I is often referred to as one of the more precise methods for estimating cost of a programme or intervention [173,174]. It is preferable to macro-costing or other methods such as fee schedules because it better captures actual resource use. In this study, the identification of resources used to provide ANC was done through interviews with staff, asking what activities they usually perform and what resources are involved. This can hide some interruptions due, for example, to stock-outs of drugs or supplies. In that sense, the cost might be overestimated. On the other hand, inability to do an exhaustive census of all resources implies underestimating costs. Here, I consider the costs, such as cost of in-service training or supportive supervision from higher levels, that can directly or indirectly benefit ANC, which were not identified.

The gold standard would be to collect data through observation of ANC provision for a representative sample of women over a period of time that can allow capturing all variations in provision of care [51]. However, the additional cost of data collection needs to be balanced against the value of increased accuracy. In conclusion, it is not easy to collect 100% of the costs, hence we cannot claim to have covered everything, however, I believe an important proportion of the resources used in ANC in Rwanda were carefully identified, measured, and costed.

4.5.2. Estimating household cost

Measuring productivity losses in health economic evaluation is a challenging process and is sometimes excluded from analysis and reporting [175], despite the recommendation to account for all societal costs and benefits [51][175].

The challenge becomes even more complex when it comes to valuing cost of time for patients or health service users in societies with high percentages of informal workers, characterized by disparities and undocumented income levels. The attempt to attach value to the time used to attend ANC (four and half hours on average) was done using the median incomes (both in cash and in kind) for self-employed and employed workers from the 2016 National Labour Force Survey in Rwanda [134].

However, the labour survey report acknowledges the challenges of underreporting in measuring income, which might have resulted in underestimation of median income [134]. In settings where there are higher employment rates and good documentation, the use of mean wage might give better estimates. Furthermore, in our costing study, we did not value the time for women who identified themselves as non-workers and students (representing 11.5%). Some other authors, such as Henderson and colleagues [162], prefer to estimate cost of time for non-workers using mean wage for a typical low-skilled job in their setting (in this case, they used a wage for a cleaner).

4.5.3. Measuring ANC cost and effectiveness (HRQoL) from observational studies

The measurements of cost and HRQoL were collected through observational studies (household and health facility cross-sectional studies). Observational studies are limited by the fact that the associations between exposure and outcome variables from such studies, as is the case for ANC utilization and HRQoL among postpartum women, do not imply causation [176]. There are criteria (Bradford Hill criteria) that have to be considered in order to strengthen the causation argument [176]. Those criteria include: "consistency, plausibility, dose-response, temporality, strength of relationship, reversibility, no other convincing explanation such as confounding" [176]. The last criterion was fulfilled through controlling for confounders in multivariable linear regression analysis. Although there are not many studies that assessed association between ANC and HRQoL, the argument in favour of plausibility and consistency criteria can be based on the study by Bahrami and colleagues, who reported an association between receiving prenatal education (counselling) and overall health and QoL. Other criteria, like temporality and reversibility, could not be assessed.

However, the design of a study itself is not the guaranty of validity in assessing effectiveness of an intervention. Indeed, a well-designed and implemented observational study can give better estimates than a poor quality trial [51].

Furthermore, observational studies are hailed by the fact that what they report reflects the real world as opposed to trials that impose protocol restrictions, but, on the other hand, that lack randomization [51].

The main limitation that observational studies are faced with when evaluating effectiveness of an intervention is the risk of selection bias, that threatens the validity of estimates [51]. Participants in our survey have been randomly selected through a rigorous three-stage process, so that selection bias is not a problem.

Finally, the reliability problem that is of a concern regardless of a study design was addressed by using a validated and widely known and used tool, EQ-5D-3L. The tool was translated into Kinyarwanda by a professional translator and was first tested together with the entire questionnaire in a one-day pilot exercise conducted before rolling out the study. The absence of tariffs validated in Rwanda has led to use of tariffs of the United Kingdoms' population. The measurements used to assess HRQoL among postpartum women can therefore considered as good, though not at the level of a good quality RCT, and as leading to appropriate conclusions.

To the best of our knowledge, the EQ-5D-3L has not been used in Rwanda before this study, and no official validation process has been conducted. We have used two methods of assessing the reliability of the HRQoL estimates using our data set. First the relation between the estimates of the two parts of the tool (EQ-5D and EQ-VAS) was tested by calculating the mean VAS score for participants who had maximum EQ-5D score (1), i.e., those who reported 1 in all the five dimensions against those who had less than 1 EQ-5D score. The results showed that mean EQ-VAS score was 73.3 for participants who had EQ-5D score of 1, against 59.1 for the remaining participants. This shows consistency in HRQoL estimates using both methods, despite different scales. Secondary, we have performed Pearson correlation between EQ-5D and EQ-VAS with another variable "self-reported health status today", that was on a scale 1 to 5 (1 =very good health, and 5 = very bad health). The results show that there is a significant negative correlation between EQ-5D estimates and the self-reported health (-0.2749 and -0.4318 for EQ-5D and EQ-VAS respectively). These results suggest that there is a consistency in reports of participants about their health status using different methods and tools.

ANC is an umbrella of interventions provided during pregnancy with the aim of ensuring good health during and after pregnancy for both the mother and the newborn [177]. In this thesis, the HRQoL measured with EQ-5D (Paper I) is one of many alternative measurements of ANC effectiveness, such as pregnancy outcomes, maternal mortality, etc.

This kind of measurement is appropriate in measuring long-term consequences of pregnancy and delivery complications, for some of which, good quality ANC can help to fully prevent or reduce their consequences.

For instance, pre-eclampsia or eclampsia, and pre-existing conditions such as malaria or anaemia, can be detected during ANC and attended to, while for other conditions, such as postpartum haemorrhage, that occur during delivery or after, the role of ANC is minimal [178].

On the other hand, acute obstetric complications that do not leave long term sequelae or maternal mortality that happened before the survey have certainly been missed in this outcome estimation. The average time from delivery to the time of interview among participants was 7 months.

Yet, as said before, women who were affected by pregnancy and delivery complications reported that their self-reported health status become batter as time passed after childbirth [167].

4.5.4. Assessing ANC effectiveness through expert elicitation

Technical judgements by experts is known to often be subject to cognitive heuristics and biases [179]. However, when used well, expert elicitation can provide estimates needed for policy decisions when evidence from other, stronger methods is lacking [179]. In our case, we have taken measures to improve the reliability of the estimates. Those measures include recruiting specialists that have at least five years of experience in Rwanda, are assumed to have knowledge of the burden and risk factors and can have a prognostic view on how people would attend ANC visits in the suggested schedule if recommendations are implemented. We provided, on the written questionnaire that was shared with respondents beforehand, the baseline evidence, on levels of maternal and perinatal mortality and their causes in Rwanda and sub-Saharan Africa, to help them to reflect before providing estimates. We have also used one of the Delphi techniques, which consists of giving the participants a chance to re-evaluate their own responses in relation to the group responses in an attempt to reach consensus [180].

Expert elicitation presents a potential for supporting healthcare decision making in LIC, mainly in situations where there is no available evidence from stronger methods. Its advantages include the short time used and few technical and financial resources involved in data collection and analysis, as well as possibility to make use of available expertise, given the understanding of the context by local experts.

4.5.5. Other methodological considerations

The extent to which the current ANC guidelines are followed was not explored in this thesis. If there are activities that are missed for reasons such as shortages of supplies, it may limit the observed effectiveness of the intervention. Although not yet sufficiently documented, there are already some reports of poor quality of ANC in Rwanda in terms of ANC activities implemented in practice [121] or attitudes of providers [124].

In the costing survey (Paper II), the selected private health facility is not representative of the remaining private clinics, because private health facilities in Rwanda vary in size and scope [135].

The same limitation could be suspected in public and mission-based health facilities, but to a lesser extent, because the two categories follow the same national guidelines, share the source of funding (mainly government and their own revenues), and they are all under the oversight of the local administration, and partly the Ministry of Health.

The estimation of incremental cost and health outcomes of the 2016 WHO recommendations (Paper III) necessarily involved a number of assumptions which may or may not entirely reflect the reality if Rwanda were to implement the recommendations. Moreover, our analysis assumed that the ANC delivery model would be the same as it is currently, with ANC visits happening in the primary health facilities by nurses or midwives. However, as the WHO suggests in the recommendations [85], Rwanda could implement the same recommendation in many other ways that can lower the cost. For example, based on the recent media report, during the discussion of models of implementing the 2016 WHO ANC recommendations in Rwanda, one of the options was to have some of the visits at a lower level of care (health post) that could potentially reduce the cost at the household side (transport and time).

Furthermore, there might be economies of scale as a result of efficiency maximization of the current resources, such as infrastructures serving more persons, or economies of scope if, for example, the health facilities use the ultrasound machines for other consultations.

5. CONCLUSION AND RECOMMENDATIONS

5.1. Conclusion

In this thesis, we have demonstrated the importance of evidence in informed decision making in healthcare. Evidence on effective and cost-effective intervention is less frequently used in healthcare decision making compared to evidence related to the spread and magnitude of diseases. Particularly in many low-resource settings, healthcare decision makers do not follow a systematic and consistent evidence use process, with pre-set criteria and appropriate institutional arrangements. There are many reasons for this, including low research capacities, political influences, and limited availability of context-relevant evidence.

ANC policy in Rwanda was used as a case to contribute to evidence-informed decision-making using health economic evaluation methods. Those methods are the measurement of ANC effectiveness with a population-based, cross-sectional survey (HRQoL) and expert elicitation (life-years saved); the measurement of ANC cost through primary costing study; and cost effectiveness analysis of a policy change combining estimates of incremental effectiveness and cost with future projections of changes in service use; and a systematic review of the health economic evidence for routine ultrasound in pregnancy.

Using the above methods, a number of conclusions that can inform ANC policy in Rwanda can be drawn. First, adequate ANC utilization is associated with better HRQoL among women during the postpartum period. Second, HRQoL is associated with other social determinants that reflect social and income inequalities, namely, social support, wealth levels, educational level, and marital status. Third, high quality studies on cost and cost-effectiveness of routine ultrasound during pregnancy are scarce, and the evidence contained in those is of limited use to decision makers, particularly in low-resource settings. Lastly, the 2016 WHO ANC recommendations are potentially cost-effective for Rwanda, but with significant budget consequences.

Health economic evidence should be used more in healthcare decision making, particularly in low-resource settings. Health economic methods that are less technically and financially demanding and use available resources and knowledge, such as expert elicitation and systematic reviews, should be particularly promoted in low-resource settings.

Using EQ-5D-3L instrument in a cross-sectional survey has worked well, as shown by correlations between EQ-5D-3L results and with variables of self-reported health. The use of the tool and other similar instruments could be used more to measure effectiveness of health interventions in Rwanda.

5.2. Recommendations

Evidence use in decisions regarding healthcare policies should be further promoted in low-resource settings. There should be a balanced use of all relevant types of evidence, including evidence on distribution of health conditions and their severity and evidence on effectiveness and cost-effectiveness of interventions.

Health economic evidence in decision making in low-resource settings should be particularly promoted, because it is currently among the least used types of evidence, yet there is a potential to gain QALYs, given the persistent, avoidable mortality and mortality, if there were to be a more efficient use of resources. Measures of burden of diseases such as QALYs, DALYs, LYS, and others, should be used more in research and decision making.

Low-income countries, particularly those that still have a high burden of maternal and perinatal mortality, should consider implementing the 2016 WHO ANC recommendations. In Rwanda particularly, the implementation of the recommendations will have significant cost implications. Therefore, a phased approach to implementation could be envisaged as an option.

The change of ANC policy in Rwanda (adoption of the 2016 WHO ANC recommendations) should give due consideration to the convenience of the service to the users, particularly geographical accessibility to the service and the time it takes to receive the service. An appropriate delivery model that would make it easier for women to attend ANC visits and contacts would also increase the chances of respecting the eight-visit schedule.

Decision makers in health sectors in low-income countries should be mindful about the relevance to their specific context when interpreting evidence produced in other settings, in relation to their specific context, because there is a portion of evidence which is not transferable.

Low-income countries should strengthen their research capacities to be able to generate the necessary evidence from within, including synthetizing and interpreting evidence generated elsewhere for more evidence-informed policy.

Academic institutions in low-resource settings should focus more on conducting research that is relevant to local policy, using affordable research methods and making use of available data.

6. EPILOGUE

It was not in my ambitions to do a PhD in health economics at the beginning of my professional life. The need for PhD studies emerged in 2013 when I was close to the end of the masters studies in Epidemiology at the University of Rwanda. Initially, my expectation from my masters studies was to understand public health indicators and their measurements in order to be able to do my job better (at the time I was the Planning Officer at the Ministry of Health of Rwanda). But, towards the end of the program, when I was attending classes in a module that had 4 courses including "introduction to health economics," and "health policy and cooperation," I changed my reasoning. I started feeling connected to health economics, not only because I was feeling at ease because of my educational background, but also because in the end I realized that it was very much related to my everyday work in the Ministry of Health. My main job was to facilitate the prioritization process of the health sector budget, a process that would end in an annual action plan and budget for the health sector. The "introduction to health economics course" opened my eyes as I leant about "cost-effectiveness analysis," but it was just an introduction. It only allowed me to realize how such economic analyses can help to make the prioritization easier, more objective, and ultimately lead to efficient use of scarce resources. It also allowed me to realize that I need to know more about the methods.

I didn't hesitate when an opportunity to do a PhD in health economics came my way. Maternal health was given to me as a health discipline to apply economic analysis. Knowing how important it was and still is for Rwanda I owned it.

In shaping this thesis and during the writing process, I kept reflecting on how prioritization of health sector resources can be optimized by more use of health economic evidence in Rwanda and low-income countries in general. Over time, the role of a health economist in decision making was becoming clearer to me. I am convinced that for countries such as Rwanda, there will be more demand for health economic evidence in the near future, especially because there is an increase in health care demand and cost, and a downward trend of international development assistance for health.

Although my main aim was to learn the health economic methods, conducting research and writing about antenatal care in Rwanda has never appeared as "just an exercise" for me. Maternal health is a real public health concern for Rwanda. Maternal mortality is still high (210/100.000 livebirths) and antenatal care is one of the strategies that, if optimized, can help the country continue its path to reducing maternal mortality and morbidity, and ultimately achieving its ambitious targets.

The publication of the 2016 World Health Organization's Antenatal Care Recommendations in the middle of my research has added flavor to an already exciting discussion. The PhD studies have changed the way I considered international guidelines; I learnt how to critically analyze them with an economist's eye and interpret them in the perspective of my context - Rwanda.

I discussed my findings in the perspective of a researcher, which is one of my duties as an academic staff member of the University of Rwanda, a position that I've occupied since the early stages of this project (November 2014).

7. ACKNOWLEDGEMENT

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