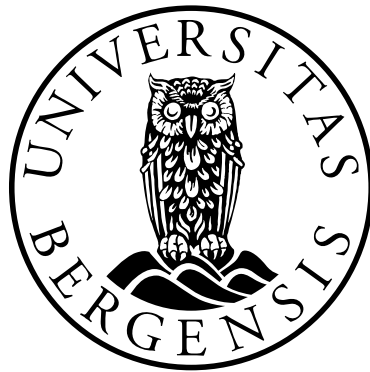# Pharmacoeconomics and Formulary Decision-Making in Tanzania

Generating Evidence for Antimalarial Drugs

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Abstract

Introduction: Increasing expenditure on pharmaceuticals has prompted many authorities, mostly in high-income countries, to deploy pharmacoeconomic analysis as a tool to guide formulary decision-making. However, the role of pharmacoeconomics in low-income countries is less well known, notwithstanding an extreme scarcity of healthcare resources. This study aims to assess the role of pharmacoeconomics in formulary decision-making and to generate economic evidence for anti-malarial drugs in Tanzania.

Methods: The thesis consists of four sub-studies, which were conducted using four different methodologies. Paper I is a systematic review study which describes the status of pharmacoeconomic analysis studies and their influence in formulary decision-making processes. Paper II is a qualitative case study about national formulary decision-making processes, the criteria used, and the underlying sources of evidence. Data was collected via in-depth interviews with key informants and document reviews and the analysis was done thematically. Paper III uses a Markov decision-model to compare the cost-effectiveness of dihydroartemisinin-piperaquine (DhP) and artemether-lumefantrine (AL) for the treatment of uncomplicated malaria in children, from the provider's perspective. Cost data was collected at a public district hospital located in an urban area. Paper IV uses a dynamic Markov decision-model to predict the budget impact on drugs and diagnostics when DhP is used as a first- or second-line drug to treat uncomplicated malaria in children. Probabilistic sensitivity analyses were used to test the robustness of model results.

Results: Our study identified twelve pharmacoeconomic analyses which met the eligibility criteria for inclusion in the systematic review. Half of these studies were relatively recent, conducted between 2007 and 2011. Nine of the twelve studies addressed infectious diseases, seven of which targeted three of the top four disease conditions in Tanzania, i.e. HIV/AIDS, malaria and diarrhoeal diseases. Only one of these studies was found to have informed the formulary decision-making process; there was no evidence to suggest the remaining studies had any influence on formulary decisions.

Decisions to authorize the listing of new drugs in the national formulary are made by committees of experts which often use discretionary judgement and anecdotal evidence, mostly about efficacy and safety, to guide decision-making processes. For diseases of national priority, such as malaria and HIV/AIDS, decisions are usually influenced by WHO recommendations. Limited understanding of the concept of pharmacoeconomic analysis among expert committee members is among the key impediments to its consistent application in national formulary decision-making.

The study also found that DhP is more cost-effective than AL when it is used as the first-line drug to treat uncomplicated malaria in children, with an incremental cost-effectiveness ratio (ICER) of US$ 12.40 per Disability Adjusted Life Year (DALY) averted. It further predicted that the current treatment policy for malaria, which uses DhP as the second-line drug (AL+DhP), will save about US$ 66,800 per year, while achieving a 3% (248,437) reduction in the number of malaria cases, compared to a reference policy of AL+quinine. However, if this policy is replaced with the one which uses DhP as the first-line drug (DhP+AL), it will consume an additional US$ 737,800 per year, while achieving a further 5% (364,517) reduction in the number of malaria cases in children.

Conclusions: Pharmacoeconomic analysis has a limited role in formulary decision-making in Tanzania. The current situation in the country, which is characterized by an increasing trend in pharmaceutical expenditure on the one hand and limited healthcare budgets on the other, warrants a more consistent application of pharmacoeconomic analysis to guide resource allocation decisions. This study has also generated new pharmacoeconomic evidence which may support the adoption of dihydroartemisinin-piperaquine as the first-line drug to treat uncomplicated malaria in children in Tanzania.

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List of original papers

This thesis is based on the following original research papers, which will be referred to as Papers I-IV as indicated below:

Paper I	**Mori AT** and Robberstad B: Pharmacoeconomics and its implication on priority-setting for essential medicines in Tanzania: a systematic review. *BMC Medical Informatics and Decision-Making* 2012, 12(1): 110
Paper II	**Mori AT**, Kaale EA, Ngalesoni F, Norheim OF, Robberstad B: The role of evidence in the decision-making process of selecting essential medicines in developing countries: The case of Tanzania. *PloS ONE*, 2014, 9(1): e84824
Paper III	**Mori AT**, Ngalesoni F, Norheim OF, Robberstad B: Cost-effectiveness of dihydroartemisinin-piperaquine compared with artemether-lumefantrine for treating uncomplicated malaria in children at a district hospital in Tanzania. *Malaria Journal* 2014, 13: 363
Paper IV	**Mori AT**, Norheim OF, Robberstad B: Budget impact analysis of using dihydroartemisinin-piperaquine to treat uncomplicated malaria in children in Tanzania. *PharmacoEconomics (under review)*

List of figures and tables

Knowledge is not power. Getting the right information and learning how to apply it to your life is power.

Powter S, 1994.

Scientific environment

This research is a product of collaboration between Muhimbili University of Health and Allied Sciences (MUHAS) and the University of Bergen (UiB). At MUHAS, the candidate was affiliated with the School of Pharmacy and at UiB with the Centre for International Health (CIH) within the Department of Global Public Health and Primary Care. At UiB, he was a member of the Research Group for Global Health Priorities. Fieldwork was conducted while at MUHAS and the remaining work at CIH.

Acknowledgements

My odyssey to PhD has been made possible by so many people whose help and support have contributed in many ways to the timely and successful completion of this thesis. The list is so long that I cannot mention each and every one, but I have been moved by some of them to whom I am indebted and they deserve a special mention.

When I was just starting to write this thesis, my main supervisor, Prof. Bjarne Robberstad, gave me a mind-awakening piece of advice, cautioning me not to be complacent in writing the synopsis. Even when I thought it was almost over, as many of us often do at this juncture, he still reminded me that I was not yet over the finishing line. This is the person I have worked with most closely, more perhaps than anybody else for almost four years. To him, maintaining the highest attainable standard of work from the beginning to the end is the cornerstone of achieving a distinguished academic career. I thank you for your mentorship, as a protégé I have learned so many things from you which have shaped my academic career and me as a person. I am sorry that I stormed into your office so many times without an appointment or invitation. Yes! Appointments do not work quickly enough for me. I will not forget that whenever I came to your office you always said *"karibu"* (welcome) and when I left you said *"karibu tena"* (welcome again).

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My wife Asnath and our beloved children Arabella and Christian, I am very proud of you for your mental strength which enabled you to withstand many days and nights of loneliness. I remember I started my journey in quest of a PhD when Arabella was just one week old. For any parent, this dilemma is not an easy one to resolve, but with strength from the almighty God, Asnath you helped me to make the right choice. You are a wonderful wife and mother of our children and for that glory be to God. At last, I am coming home, and I promise I will not leave you again, at least not for another PhD! My mother Evenerda and grandmother Eliaichi, brother and sister Goodluck and Grace, your prayers and blessing have worked wonders for me, thank you for everything and may God bless you.

Professor Eliangiringa Kaale, you are my colleague, friend, teacher and mentor in many ways. You have always been with me throughout this difficult journey, encouraging me and offering technical help when needed. You have been my role model and you always will be, both in life and in academia, thank you. My other friends and colleagues at CIH, MUHAS and Fantoft, I don't want to mention your names to avoid the guilt of forgetting anyone. Just know that you are awesome and great people, thank you all. For those whom I leave behind in Bergen still pursuing their studies, I wish you all the best and keep up the good work and momentum. Surely as the days pass by, know that you are moving closer and closer to that day when you will be writing the same thing as I do here.

1.   Introduction

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. World Health Organization, 2002 [1]

In 1978, the Alma Ata Declaration established the foundations for the provision of essential medicines as a key component of a primary health care for the attainment of an acceptable level of health for all by the year 2000 [2]. In 2000, through the Millennium Development Goal Target 8, the United Nations re-emphasized the importance of the provision of essential medicines: "In co-operation with pharmaceutical companies, provide access to affordable essential medicines in developing countries" [3]. In 2008, the World Health Organization, in its World Health Report entitled "Primary Health Care: Now More Than Ever" urged countries to revert to primary health care, which is focused on universal coverage, people-centred services, healthy public policies and good leadership [4]. However, nearly four decades since the Alma Ata, access to essential medicines remains elusive to many people in low-income countries.

Efforts to close the access gap in low-income countries are largely being hindered by rising healthcare costs, which are mainly driven by increasing demand for healthcare services and the high prices of essential medicines. Increasing pharmaceutical expenditure due to the high prices of new medicines is a worldwide challenge. This situation has prompted many authorities in high-income countries to include cost-effectiveness as a 'fourth hurdle' in addition to evidence of safety, quality and efficacy to inform formulary decisions [5]. The aim is to ensure that the added health benefits produced by a new drug are worth the extra costs imposed on the health system. The application of pharmacoeconomic analysis in middle-income countries has also been growing in recent years, albeit at a much slower pace [6-8]. The inefficient allocation of scarce financial resources to new drug therapies carries a huge opportunity cost which reduces access to other important health services with the potential to improve quality and longevity of life.

1.1. Research problem

Pharmacoeconomics plays a key role in promoting efficient use of scarce health resources for drug therapies in high-income countries, but very little is known about its application in decision-making processes in low-income countries. In fact the role of pharmacoeconomics in these countries has been debated in the literature. Babar and Scahil (2010) have questioned the usefulness and applicability of the 'complex' science of pharmacoeconomics in low-income countries [9, 10]. Other scholars have conceded that these countries have already been left behind, but they remain optimistic that pharmacoeconomics will eventually develop and assume a key role in resource allocation decisions for health [11-15]. These debates highlight an existing knowledge gap in the understanding of the contexts in which formulary decisions are made, and the processes and value of the information generated by pharmacoeconomic analyses for low-income countries.

Pharmacoeconomic evidence for malaria, which is one of the most important infectious diseases in Tanzania and other endemic countries, is scarce. Timely availability of such evidence is important considering that national malaria treatment guidelines are frequently changed in response to the emergence of drug-resistant strains. Recently, the WHO recommended the use of dihydroartemisinin-piperaquine (DhP) – a new artemisinin-based combination therapy for the treatment of uncomplicated malaria [16]. Tanzania has already adopted the use of DhP as the second-line drug in its malaria treatment guidelines and it has been listed in the National Essential Medicine List [17]. However, economic evaluation evidence is lacking for the question of whether DhP represents value for money and what will be the budget impact of such an important policy decision.

1.2. Organization of the thesis

This thesis is organized into eight sections. Section one provides a general introduction to the thesis by defining the concept of essential medicines, key milestones and the research problem. Section two provides background information about Tanzania, its health system, health financing, health expenditure, and the burden of disease including malaria. Section three is a literature review of health technology assessment, pharmacoeconomic analysis and malaria. Section four elaborates the study objectives and section five describes the methods used in the four sub-studies. In section six we present the most important results, which are then discussed in detail in section seven. Section eight contains the conclusions and recommendations for future research.

2.   Background

The United Republic of Tanzania is a union of Tanganyika and Zanzibar, which was formed on 26 April 1964 and it is located between longitudes 29^0 and 41^0 east of Greenwich and latitudes 1^0 and 12^0 south of the equator, in the East African region. It is the largest country in this region, with a population of about 45 million people and an area of 945,085 km^2, which includes 61,000 km^2 of inland waters. Zanzibar lies 40 km from the mainland coast and includes the islands of Unguja and Pemba. About 80% of Tanzanian people reside in rural areas. The annual population growth rate has been estimated to be 2.7%. With a GDP per capita of about US$ 540, Tanzania has been classified by the United Nations as one of the least developed countries on earth and is ranked 159th on the Human Development Index [18]. Its economy is largely driven by agriculture, which accounts for more than 40% of the GDP and has been estimated to grow at 7% annually [19].

Tanzania is administratively divided into 30 regions, of which 25 are located on the mainland (Tanganyika) and 5 are on Zanzibar (Figure 1). These regions are further sub-divided into 169 districts. The capital city is Dodoma, which is about 500 km from Dar es Salaam, the main business hub of the country. Tanzania is an ethnically diverse country, with more than 120 spoken local languages. Indigenous people account for 99% of the total population and the rest are mostly Asians, Europeans and Arabs. Despite the existence of diverse dialects, most people speak the national language, Kiswahili. English is the second official language of communication and the language of instruction in secondary schools and higher learning institutions. The literacy rates for adult men and women are 79% and 67%, respectively. Christianity and Islam are the major religious groups.

2.1   Health system

Tanzania's health system is administered by the Ministry of Health and Social Welfare (MoHSW) and the Prime Minister's Office Regional Administration and Local Government (PMORALG). The main responsibilities of the MoHSW include: formulation of health policies, mobilization and supply of resources, technical support, and monitoring of disease patterns and quality of health services. It also co-ordinates the functions of semi-autonomous institutions like the Tanzania Food and Drugs Authority (TFDA) and the Medical Stores Department (MSD), among others. The PMORALG is responsible for the implementation of health policies as well as monitoring the use of funds.

Within local councils, Council Health Management Teams (CHMT) develop Comprehensive Council Health Plans (CCHPs) in alignment with the National Package for Essential Health Interventions. The CCHPs contain all the priority health interventions that should be implemented within the district, including all sources of funds; i.e. government, donor funds and local sources. Once approved at the district level, the CCHP is reviewed by the Regional Health Management Team (RHMT) before submission to the MoHSW and PMORALG for final approval and disbursement of funds [20].

Figure 1: Map of Tanzania

The health system consists of public and private health facilities, which are organized in a pyramid-like structure, with tertiary hospitals at the apex and primary health facilities (health centres and dispensaries) at the base. Other levels include regional and district hospitals, which function as referral points for primary health facilities. There are approximately 6,150 health facilities, of which about 90% are dispensaries and three-quarters belong to the government [21]. About 90% of the population lives within a distance of 5 km from a primary health facility. A dispensary usually provides outpatient preventive and curative services, including normal deliveries to local communities. A health centre typically has a bed capacity of 20–30, and acts as a referral point for dispensaries and, like the dispensaries, provides limited inpatient and outpatient services.

2.1.1. Drug registration

The Tanzania Food and Drugs Authority (TFDA) is an executive agency under the Ministry of Health and Social Welfare, and was established in 2003, by the Tanzania Food, Drugs and Cosmetics Act No.1 of 2003. The head office of the TFDA is located in Dar es Salaam, but the agency has five zone offices which are located in other regions of the country. The main functions of the TFDA include evaluation and registration of food, drugs, herbal drugs, cosmetics, poisons and medical devices, including diagnostics. The agency evaluates safety, efficacy/effectiveness and quality of all pharmaceutical products under its portfolio prior to granting a market authorization licence. The agency is also responsible for the inspection and surveillance of clinical trial sites of drugs and post-marketing surveillance of products already circulating in the Tanzanian market. It also inspects industries to ensure they comply with Good Manufacturing Practices. Cost and cost-effectiveness evaluation are not part of drug registration requirements in Tanzania [22].

2.1.2. Selection of essential medicines

Tanzania launched its first national formulary, i.e. the National Essential Medicine List (NEML) in 1991, although it had begun to implement the concept of essential medicine as part of the primary health care package well before that period [23]. The current NEML was updated in 2013 and is used to guide the procurement and distribution of medicines across different levels of the country's healthcare system [17]. Any drug must be approved by the National Medicines and Therapeutic Committee in order to be listed as essential in the NEML. Despite many years of use, little has been written about the process and underlying criteria for the selection of essential medicines in Tanzania.

2.1.3. Drug distribution system

The Medical Stores Department (MSD) is a semi-autonomous, non-profit public entity which is responsible for the procurement, storage and distribution of medicines in public facilities. Budget allocations for each facility are deposited into their accounts, which are located at the MSD, and deductions are made in accordance with received medicine orders [24]. The country also has a comprehensive network of private pharmacies and drug shops from which health facilities can procure medicines that are not available from the MSD. As a consequence of resource scarcity, medicines are frequently out of stock in public facilities, forcing patients to buy from private premises which are regulated by the Pharmacy Council. Pharmacies are supervised by registered pharmacists and hence are allowed to stock prescription-only and over-the-counter medicines, but their distribution is limited to the main cities and towns, and about 60% are located in Dar es Salaam [25]. Drug shops are more concentrated in under-served areas, but they only stock a limited list of drugs, including antibiotics, and do not require supervision by pharmacists.

2.2. Health financing

The Tanzanian health system is financed from different sources, which also use different financing strategies. The public sector is financed through domestic and external sources of funds; the latter consists of general budget support, basket funds and direct programme support. User fees in public facilities were introduced in 1994 as a form of cost-sharing to complement government budgets, and require patients to pay at the service delivery points [26]. Vulnerable groups, including under-five children, pregnant women and the elderly are exempted from user fees. As a percentage of total health expenditure, donors contribute about 40% of the finances, followed by insurance or out-of-pocket expenditure at 34% and the remaining 26% is financed by the government [27].

The National Health Insurance Fund (NHIF) is a statutory health insurance scheme which was established by parliament in 1999. It is currently the largest health insurance scheme in the country and is compulsory for civil servants. The contribution is 6% of the employee's gross salary, which is shared equally between the employer and the employee. The Community Health Fund (CHF) is a voluntary scheme, established in 2001, targeting the informal sector [28]. Other social health insurance schemes include the Social Health Insurance Benefit (NHIB), which is administered by the National Social Security Fund (NSSF) and targets employees in the formal private sector. There are also some private health insurance schemes but their coverage remains very low. Overall insurance coverage is about 14% of the total population [29].

2.2.1. General health expenditure

Healthcare costs have been rising sharply in Tanzania, as in many other countries around the world. According to data from the National Health Accounts, which are routinely published by the MoHSW, between 2002 and 2010 the annual total health expenditure (THE) more than doubled, from US$ 734 to US$ 1,751 million. As a percentage of GDP, THE increased from 5% to 8% [27], and this has remained somewhat constant over the years. Allocation to the health sector in Tanzania is far less than the 15% target of the Abuja Declaration of 2001 by African Union countries [30].

2.2.2. Pharmaceutical expenditure

Pharmaceutical expenditure accounts for about 30% of total health expenditure and is one of the main drivers of increasing healthcare costs in Tanzania [31]. Between 2007 and 2012, the budget for pharmaceuticals grew from 45 to almost 80 billion Tsh (US$ 70 to 130 million) which reflects a five-fold increase in donor support (basket funds) and a decrease in government funds of one-third (Figure 2) [21]. Antiretroviral drugs, vaccines, artemisinin-based combination therapies (ACTs), anti-TBs, HIV-testing kits and malaria rapid diagnostic tests (mRDTs) are almost exclusively funded by global health initiatives. The budget for these commodities is about US$ 5 per capita per year [21]. Therefore, the introduction of new health technologies is a prime factor in the escalation of pharmaceutical expenditure in Tanzania, as it is in high-income countries.
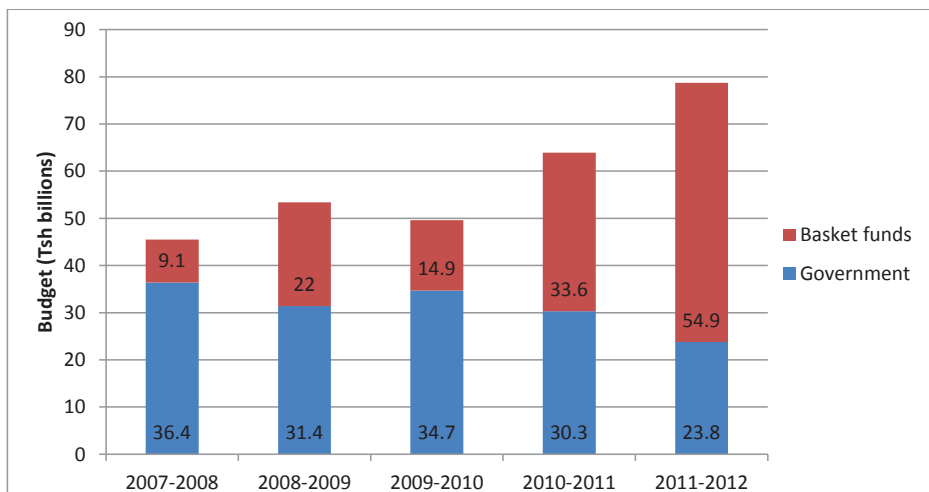
Figure 2: Budget for pharmaceuticals

Source: Health Sector Performance Profile Report, 2011 [21]

2.3. Burden of disease

2.3.1. General trend

The burden of disease within a population is typically measured by Disability Adjusted Life Years (DALYs), which quantify both premature mortality (Years of Life Lost i.e. YLL) and disability (Years Lived with Disability i.e. YLD) [32]. Currently the top four causes of DALYs in Tanzania are HIV/AIDS, malaria, lower respiratory infections and diarrhoeal diseases [33]. The burden of disease is largely dominated by infectious diseases, most of which predominantly affect children. Non-communicable diseases such as congenital anomalies, cardiovascular diseases and diabetes contribute relatively less to the burden of disease than injuries from road accidents, fire and interpersonal violence. From 1990 to 2010, YLLs from HIV/AIDS increased by 315% while that from diarrhoeal diseases and malaria decreased by 58% and 29%, respectively (Figure 3).

# YLLs in thousands (% of total)	Rank and disorder 1990	Rank and disorder 2010	# YLLs in thousands (% of total)	% change
4,260 (21.9%)	1 Malaria	1 HIV/AIDS	4,503 (20.6%)	315
3,034 (15.6%)	2 Lower respiratory infections	2 Malaria	3,068 (13.9%)	-29
2,218 (11.4%)	3 Diarrheal diseases	3 Lower respiratory infections	2,000 (9.2%)	-34
1,086 (5.6%)	4 HIV/AIDS	4 Diarrheal diseases	930 (4.3%)	-58
1,044 (5.4%)	5 Protein-energy malnutrition	5 Neonatal encephalopathy	851 (3.9%)	76
571 (2.9%)	6 Preterm birth complications	6 Preterm birth complications	812 (3.7%)	43
484 (2.5%)	7 Tuberculosis	7 Protein-energy malnutrition	676 (3.1%)	-35
469 (2.4%)	8 Neonatal encephalopathy	8 Neonatal sepsis	636 (2.9%)	64
432 (2.2%)	9 Syphilis	9 Syphilis	615 (2.8%)	42
408 (2.1%)	10 Neonatal sepsis	10 Road injury	512 (2.3%)	83
374 (1.9%)	11 Measles	11 Tuberculosis	501 (2.3%)	3
279 (1.4%)	12 Road injury	12 Maternal disorders	491 (2.3%)	92
255 (1.3%)	13 Maternal disorders	13 Congenital anomalies	252 (1.2%)	20
208 (1.1%)	14 Congenital anomalies	14 Fire	236 (1.1%)	33
183 (0.9%)	15 Meningitis	15 Interpersonal violence	216 (1.0%)	125
179 (0.9%)	16 Fire	16 Drowning	214 (1.0%)	65
146 (0.8%)	17 Stroke	17 Meningitis	215 (1.0%)	15
133 (0.7%)	18 Epilepsy	18 Epilepsy	209 (1.0%)	58
137 (0.7%)	19 Drowning	19 Stroke	203 (0.9%)	38
123 (0.6%)	20 Ischemic heart disease	20 Ischemic heart disease	175 (0.8%)	42
112 (0.6%)	21 Poisonings	21 Self-harm	157 (0.7%)	110
103 (0.5%)	22 Cirrhosis	22 Diabetes	145 (0.7%)	103
96 (0.5%)	23 Interpersonal violence	23 Cirrhosis	127 (0.6%)	25
75 (0.4%)	24 Self-harm	24 Poisonings	125 (0.6%)	6
71 (0.4%)	25 Diabetes	25 Typhoid fevers	146 (0.7%)	74
	26 Typhoid fevers	38 Measles		

Figure 3: Changes in the top causes of YLL in Tanzania between 1990 and 2010.

The red colour indicates infectious diseases; blue colour indicates non-communicable diseases and the green colour indicates injuries. Solid lines indicate that a cause has moved up in rank or remains unchanged. Dotted lines indicate that a cause has moved down in rank.

Source: Institute of Health Metrics and Evaluation, 2010 [33]

Health indicators show that the burden of disease in Tanzania is characterized by relatively high child and maternal mortality rates and a low life expectancy at birth of 52 years [34]. A major trend is that over the past two decades the under-five mortality rate has decreased steadily from 141 to 81 (per 1,000 live births) and the country is on course to achieve Millennium Development Goal 5 by the end of this year. The infant mortality rate has also decreased by almost half during the same period (Figure 4). Between 1994 and 2001, the maternal mortality rate was reduced by 60%, from 934 to 543 (per 100,000 live births) [35], and currently it stands at 454 per 100,000 live births [34].
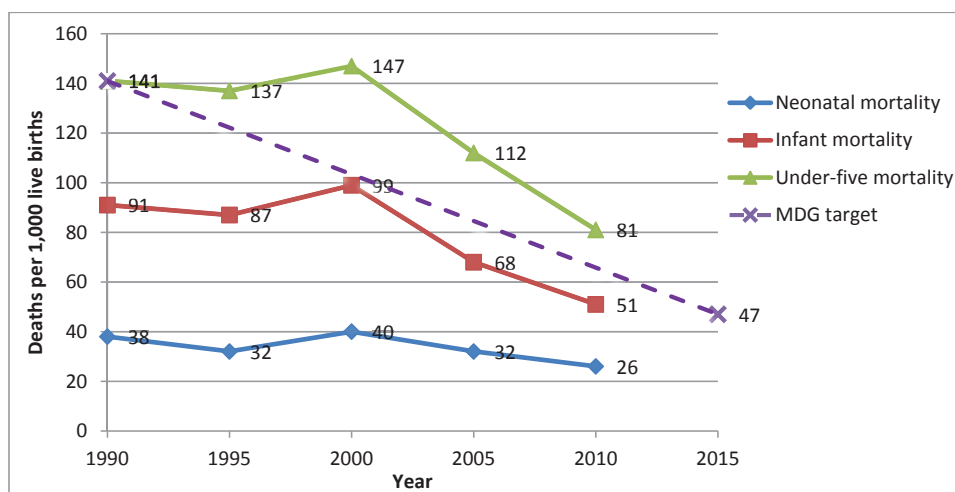
Figure 4: Trend in reduction of child mortalities

Source: Demographic and Health Surveys [34, 36-39]

2.3.2. The burden of malaria in Tanzania

Malaria is a major health challenge in Tanzania, where it is estimated to cause between 10 and 12 million cases and 60,000–80,000 deaths each year [40]. The burden of malaria is mostly concentrated among children under the age of five years, where it contributes about 33, 41 and 37% of outpatient visits, admissions and deaths, respectively. Malaria is also the major cause of admissions and deaths in older children and adults [41]. The National Malaria Control Programme (NMCP) is implementing various intervention strategies, including malaria case management, integrated vector control and behavioural change, in order to reach its target of reducing the burden of malaria by 80% by 2020 [40]. These strategies have been estimated to account for about 2% of the Gross Domestic Product, equivalent to 20% of the total health expenditure in Tanzania [27].

3. Literature review

3.1. Health Technology Assessment

Health Technology Assessment (HTA) is a dynamic and rapidly growing multidisciplinary field of health policy analysis that examines the short- and long-term consequences of adopting a health technology. It involves a systematic evaluation of the properties, effects and/or impact of new and existing health technologies, such as pharmaceuticals, devices and medical procedures, that are used in the provision of health care [42]. The objective of HTA is to provide health authorities and consumers with information that will enable them to understand the value and benefits of health technologies and assist in decision-making [43]. Within HTA systems, different evaluations are conducted for various purposes, but increasingly the emphasis has shifted onto generating economic evidence to inform resource allocation decisions [44]. Pharmaceutical expenditure is one of the main drivers of increasing healthcare costs; hence, HTA plays an important role in informing resource allocation decisions [45]. HTA systems across the world have advisory and sometimes mandatory roles in assessing and presenting evidence to the responsible authorities on the eligibility of new drugs to be included in reimbursement lists.

3.1.1. HTA systems in high-income countries

High-income countries are defined as having a Gross National Income (GNI) per capita above US$ 12,745 [46]. Pharmacoeconomic guidelines were developed and used formally for the first time in the assessment of pharmaceuticals for listing decisions in Australia in 1992. The Australian government, through the Pharmaceuticals Benefits Advisory Committee (PBAC), made it mandatory for pharmaceutical industries to submit pharmacoeconomic analysis evidence to support their applications for listing new drugs in the Pharmaceutical Benefit Scheme [47, 48]. This methodology has spread to most European and other high-income countries, which have now established their own specialized HTA institutions. Currently, the European Network of Health Technology Assessment (EUnetHTA) involves 32 countries and 63 partner institutions [49]. The International Network of Agencies for Health Technology Assessment (INAHTA) currently has 55 members from 32 countries [50]. More high-income countries, including those in the Asia-Pacific region such as South Korea, have also established HTA institutions to facilitate the evaluation of new health technologies [51].

3.1.2. HTA systems in low- and middle-income countries

Middle-income countries are those with GNI per capita between US$ 1,045 and 12,745. These countries are further classified as lower-middle-income and upper-middle-income based on GNI per capita of US$ 4,125 [46]. Some upper-middle-income countries such as Brazil, Turkey, Argentina, Taiwan, Thailand, Malaysia, Israel and others in Latin America and the Caribbean currently have HTA institutions which provide guidance on pricing and reimbursement decisions [8, 51, 52]. However, HTA systems in the majority of these countries are at different stages of development; hence, the application of assessment criteria varies. For example, Mexico, Taiwan and Brazil already have pharmacoeconomic guidelines for industries to use when they are preparing supporting documents for reimbursement and pricing submissions [8].

Specialized HTA institutions are non-existent in low- and lower-middle-income countries and, as a result, new health technologies are approved based on less rigorous approaches which are largely guided by expert opinions and less by scientific evidence. Decisions are usually driven by historical norms, donor funding and lobbying pressures [53]. Many of these countries have essential medicine policies, including National Essential Medicine Lists (NEML), which are largely used as cost-containment tools [54]. Selection and approval of new medicines to be included in treatment guidelines and NEML are usually made by committees of experts. The members of these committees and the methods and basis of their appointment are not usually made clear [55, 56].

HTA is a formal discipline which requires highly trained professionals and an appropriate infrastructure in order to function properly, many of which are not readily available in low-income countries [57]. In the absence of specialized HTA institutions, Mathew (2011) has proposed the use of KNOW ESSENTIALS as an alternative tool to guide decision-making involving resource allocation for health technologies. He argues that while the establishment of the HTA system remains as a long-term objective, currently alternative but robust tools are urgently required. The KNOW ESSENTIALS tool incorporates all the elements of the formal HTA system and can be applied in low-income countries [58]. However, considering that this tool is relatively new and that it has not been tested in actual decision-making processes, it is difficult to judge its suitability for these countries.

3.2. Pharmacoeconomics

We are living in a world of scarce health resources and unlimited healthcare needs. Within this context, economic evaluation may be used to inform decisions about which interventions should be approved for funding and which should be avoided. The overall aims of these methods are usually to increase efficiency in the use of scarce health resources in order to maximize population health. Pharmacoeconomics is a sub-branch of health economics solely dealing with pharmaceuticals; it includes any study which compares the costs (resources consumed) and consequences (health and welfare) of alternative drug therapies and treatment strategies. Nowadays, pharmacoeconomic analysis plays an important role in helping decision-makers in different jurisdictions across the globe to decide whether a drug should be listed in national or hospital formularies. It also helps the pharmaceutical industries to decide beforehand, which drugs to develop and how prices should be set in the market [59].

3.2.1. Methods of pharmacoeconomic evaluation

Pharmacoeconomic evaluation is considered to be a full economic evaluation when both costs and outcomes of two or more alternatives are compared. However, when only the cost or outcome parameters are considered, or when the evaluation only considers a single intervention, this is referred to as a partial economic evaluation [60]. The four main types of economic evaluation studies are shown in Table 1.

Table 1: Main types of full economic evaluation

Type	Measurement of costs	Measurement of consequences
Cost-effectiveness analysis	Monetary units	Natural units such as mm Hg reduction in blood pressure, number of patients cured or life years added
Cost-utility analysis	Monetary units	This incorporates both the quantitative and qualitative dimensions of health such as Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs).
Cost-benefit analysis	Monetary units	Monetary units
Cost-minimization analysis	Monetary units	Commonly use natural units or generic measures such as DALYs and QALYs

Source: Drummond, 2005 [60]

3.2.2. Measuring cost-effectiveness

The results of pharmacoeconomic analyses are expressed by means of an incremental cost-effectiveness ratio, commonly abbreviated as ICER. The ICER is the ratio of change in costs between a new drug and its alternative (the existing standard treatment or do-nothing) to the change in their effectiveness. It reflects the costs of producing an additional unit of health outcome by employing a new drug.

$$\text{ICER ratio} = \frac{\text{Cost}_{New}-\text{Cost}_{Reference}}{E_{New}-E_{Reference}}$$

Where E represents effectiveness

From the equation above, it is clear that an ICER can assume a positive or negative value depending on the location of the new drug in the four quadrants of the cost-effectiveness plane shown in Figure 5. In principle, there are four possible scenarios, entailing four different decision rules based on the ICER ratio.
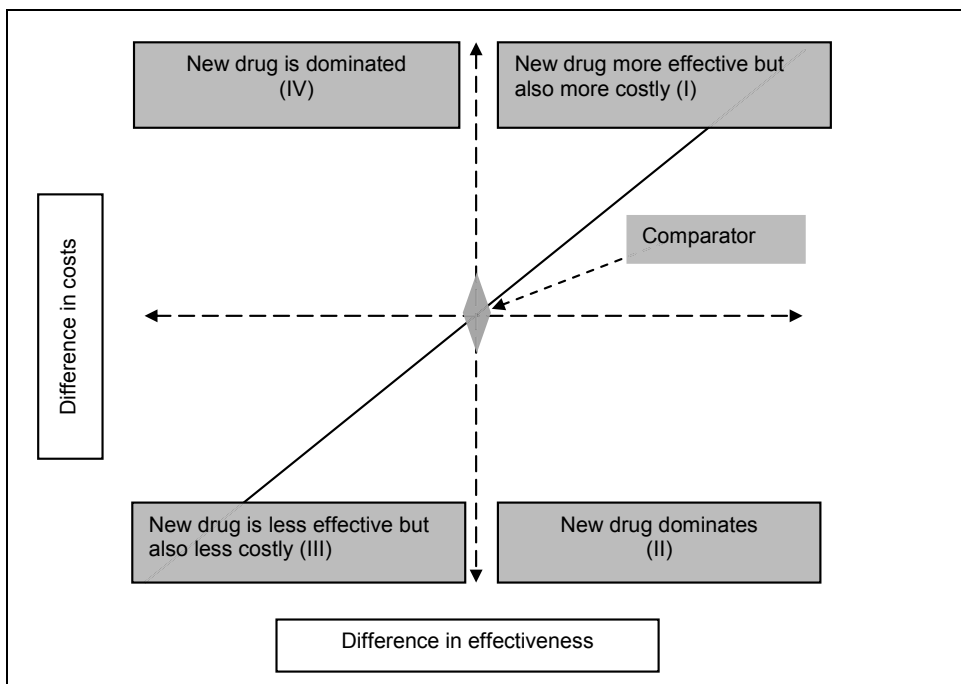
Figure 5: Cost-effectiveness plane

The inclined solid line represents the willingness-to-pay threshold (WTP), and when the ICER of a new drug is less than the WTP it is considered to be cost-effective

In quadrant I, the new drug is both more expensive and more effective than the comparator. In this case, the change in costs and effectiveness are both positive, which produces a positive ICER value. A majority of the innovative drugs that are released onto the markets fall under this category. Cost-effectiveness is assessed by comparing the calculated ICER to a threshold ICER known as the willingness-to-pay threshold (WTP), also called the cost-effectiveness threshold (CET). If the ICER is below the CET cut-off point then the new drug is considered to be cost-effective and vice versa. In this scenario, interventions with small ICERs are in most cases given high priority.

In quadrant II, the new drug produces more health benefits at a lower cost compared to the comparator. In this case the change in cost is negative while change in effectiveness is positive, hence producing a negative ICER. In this situation the new drug strongly dominates the comparator and it should be approved to treat the disease in question because it produces more health benefits with lower costs.

In quadrant III, the new drug is less effective and less costly than the comparator; hence, changes in costs and effectiveness are both negative, resulting in a positive ICER value. Although the ICER is positive, care must be taken in making decisions as it implies that the new drug is cost-saving but at the expense of forgone benefits. For this reason, the drug with the largest ICER should be given preference as it saves more money for each benefit forgone, and therefore the money can be spent elsewhere.

In quadrant IV, the new drug is more expensive but less effective than the comparator; hence, the change in cost is positive while the change in effectiveness is negative, resulting in a negative ICER. In this scenario, the new drug is considered to be strongly dominated by its comparator and it is rejected right away even without consideration of the CET because it produces fewer health benefits at higher costs.

3.2.3. Extended dominance

Extended dominance may occur in an economic evaluation involving more than two drugs where a linear combination of any two them that are mutually exclusive produces more health benefits at a lower cost than other drugs. In this scenario the excluded drug is said to be extendedly dominated by the linear combination of the two drugs [61]. In practical terms, this means that, during implementation, a certain proportion of the eligible population will receive one of the drugs while the rest receives the other. If one of the two drugs is inferior to the other this will raise ethical concerns in deciding which group of people should receive the more effective drug and which should receive the less effective one, which at times may also mean receiving no treatment at all [62].

3.2.4. Cost-effectiveness threshold

In health systems with fixed budgets, the cost-effectiveness threshold (CET) is a measure of the 'opportunity costs' in terms of health benefits forgone by committing scarce resources to a particular intervention which, as a consequence, cannot be used to fund other alternatives. It implies that, if the additional financial resources required to fund the new health technology come from external sources such as out-of-pocket (OOP) payments, then the CET represents consumption forgone elsewhere as a result of increased OOP expenditure [63]. Health systems usually operate under fixed budgets; hence in the literature, CET is commonly translated as a measure of a country's willingness-to-pay (WTP) for an additional unit of health benefits [64-66].

The WHO has recommended CET of 1 to 3 times the country's GDP per capita for low- and middle-income countries [67]. This threshold rests on the premise that 3-times per-capita GDP is a 'fair share' of a country's wealth entitlement for each member of a society. Another CET of US$ 150 per DALY averted has also been widely used for these countries [68]. According to Woods et al. (2015), these commonly used CETs represent an aspirational willingness-to-pay for health improvements rather than the opportunity costs of displaced health benefits due to additional costs imposed on the budget [63]. Therefore, using CET for the UK as a reference, they applied income elasticity of value of health to estimate CETs for other countries [69]. For low-income countries, a maximum CET value of 51% of GDP per capita was recommended [63]. Therefore, for a country like Tanzania which has a GDP per capita of US$ 540, the maximum CET will be US$ 275.

3.2.5. Pharmacoeconomics in low-income countries

In 1998, the WHO-CHOICE project was initiated in order to increase the use of economic evaluation evidence in healthcare decision-making in resource-poor settings [70]. The objective was to provide evidence for policy-makers about which interventions can produce the greatest health gains from the limited resources. Due to the lack of research focusing on this area, it is not known how, and to what extent, pharmacoeconomic analysis informs healthcare decisions in these countries. Several researchers have investigated the state of health economic evaluations in countries such as Zimbabwe, Nigeria, India, Vietnam and Ghana and discovered only a few, poor-quality studies [71-76]. Robberstad and Hemed (2010) did similar work in Tanzania and came up with the same findings [77]. It is also important to note that since 2002, when the WHO adopted the use of evidence-based procedures in selecting essential medicines, the use of the cost-effectiveness criterion has proved difficult to apply in developing countries [78].

3.3. Malaria

Malaria is a vector-borne disease which is transmitted between humans by several species of female mosquitoes belonging to the genus *Anopheles*. Malaria infection in humans can be caused by four species of *Plasmodium* parasites, namely: *P. falciparum, P. ovale*, *P. vivax* and *P. malariae*. Among the four species, *P. falciparum* is the main cause of malaria disease in sub-Saharan African countries, including Tanzania. *P. falciparum* is also the main parasite commonly responsible for causing severe malaria, which is the most serious form of the disease and which almost always leads to fatal outcomes without appropriate care. Malaria is ranked seventh among the major contributors to the global burden of disease and is an important barrier to socioeconomic development in low-income countries, especially in sub-Saharan Africa, where the disease is endemic [32]. In 2013, the estimated number of cases of malaria infections globally ranged between 123 and 243 million and deaths ranged from 367,000 to 755,000 [79]. The burden of malaria disease is concentrated in children under the age of five years residing in the WHO's Africa region (Figure 6), who account for nearly 80% of all malaria deaths [79]. Children under the age of five years and pregnant women are most vulnerable to malaria.
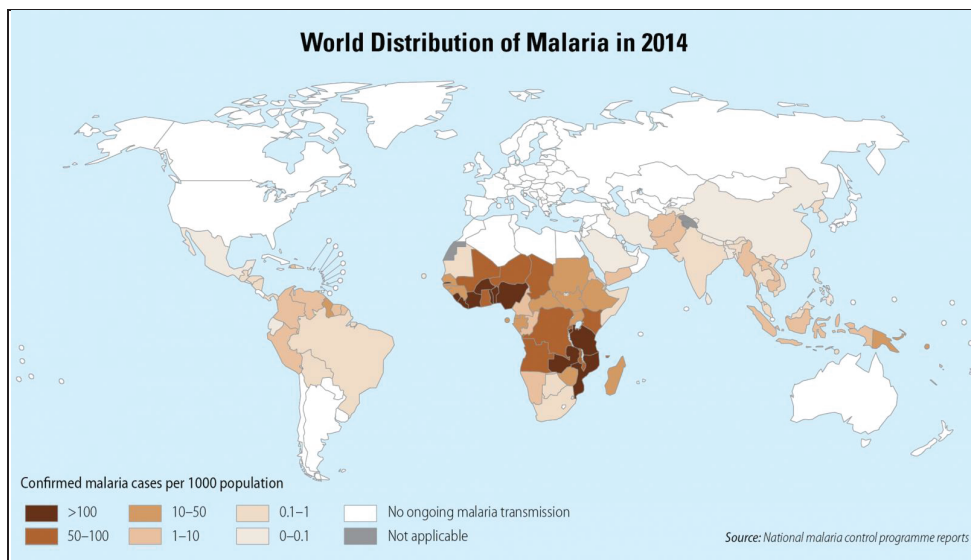
Figure 6: Global distribution of malaria

The map shows that malaria is endemic in sub-Saharan Africa and Tanzania is one of the countries with the highest burden of malaria. Countries in Asia, Latin America and the Middle East are also affected with malaria but to a lesser extent.

Source: World Malaria Report, 2014 [79]

3.3.1. Treatment policies for malaria

In the absence of effective drugs, uncomplicated malaria can rapidly progress to severe malaria, which is almost always fatal. Therefore, Tanzania has repeatedly changed its malaria treatment policies due to the emergence of *P. falciparum* strains resistant to previously effective drugs. Chloroquine was used as the first-line drug for the treatment of uncomplicated malaria but was replaced with sulphadoxine-pyrimethamine (SP) in 2000 [80]. By 2006, parasite resistance to SP was widespread and had reached unacceptable levels [81, 82], which triggered another policy change. SP was replaced by artemether-lumefantrine (AL), based on a WHO recommendation to use artemisinin-based combination therapies (ACT). Quinine also replaced amodiaquine as a second-line drug to treat uncomplicated malaria [83]. More recently, in 2014, dihydroartemisinin-piperaquine (DhP) replaced quinine as the second-line drug of choice to treat uncomplicated malaria [84]. DhP is a new ACT among the five that have been recommended by the WHO for the treatment of uncomplicated malaria in endemic countries [16].

3.3.2. Economic evaluation of anti-malarial drugs

Country-specific economic evaluation evidence for drug therapies in Tanzania is extremely scarce, but has been considered relatively good for anti-malaria drugs [77]. In 2000, Abdulla et al. conducted a study using a decision-tree model to compare costs, effects and cost-effectiveness of three drug options, namely: SP, amodiaquine and quinine, as alternatives to replace chloroquine as a first-line drug for the treatment of uncomplicated malaria. The findings of this study showed that SP was more cost-effective than the other drug options, with an ICER of US$ 32.85 per death averted [85].

Also in 2000, Gonzalez et al. conducted an economic evaluation study to analyze the cost-effectiveness of three chemoprophylactic strategies for the Intermittent Prevention Therapy of severe malaria in infants (IPTi). The interventions compared were deltaprim (a combination of pyrimethamine and dapsone) + iron, deltaprim alone and iron alone. The cost-effectiveness ratio of deltaprim + iron was US$ 9.7 per DALY averted and that of deltaprim alone was US$ 10.2 per DALY averted [86].

In 2006, Wiseman et al. conducted a study alongside an effectiveness trial to compare the cost-effectiveness of antimalarial drug combinations to replace SP as first-line drug for the treatment of uncomplicated malaria. Three drugs were compared against amodiaquine, namely: amodiaquine-SP, amodiaquine-artesunate (AQ-AS) and artemether-lumefantrine (AL), from the providers' and societal perspectives [87]. These were the drugs that were recommended at that time by the WHO to replace monotherapy antimalarials [88]. The

study showed that AL was equally as cost-effective as AQ-AS with a net saving of about US$ 22.4 per case averted [87].

In 2007, Njau et al. conducted a study to estimate the cost associated with a change in national malaria treatment policy from SP to AL. The study was conducted in one district; however, costs were extrapolated to estimated scale-up costs for national-level implementation. They included drug and non-drug costs and relied on the assumption of clinical diagnosis of malaria. The study found that the national implementation of ACT would require US$ 48.3 million, over a three-year period. This was equivalent to a 6-fold increase in the annual budget for the treatment of malaria [89].

In 2009, Hutton et al. conducted a study to evaluate the cost-effectiveness of Intermittent Prevention Therapy in infants using SP (SP-IPTi). The study was conducted from a societal perspective using efficacy trial data collected at Ifakara, Tanzania, and Manhica, Mozambique. SP-IPTi was cost-effective with an ICER of US$ 3.7 per DALY averted and US$ 1.57 per case averted in Tanzania, compared to placebo [90].

4. Rationale and objectives

4.1. Rationale

Low-income countries, including Tanzania, are facing an extreme scarcity of health resources to address the high burden of communicable and non-communicable diseases. Health policy-makers and politicians are all looking for new approaches capable of bridging the existing gap between the available resources and unmet healthcare needs. Pharmacoeconomic analysis is used to increase the efficiency of resource allocation to drug therapies in high-income countries. Although formulary decisions involving the adoption of new and more expensive drugs are constantly being made in Tanzania, it is not known how and to what extent pharmacoeconomic analysis has been used to guide such decisions. The use of pharmacoeconomics in Tanzania can contribute to maximizing the amount of health benefits generated from its scarce resources.

As part of its intensified efforts to fight malaria, Tanzania recently adopted the use of dihydroartemisinin-piperaquine (DhP) as the second-line drug for the treatment of uncomplicated malaria. However, this decision was not informed with economic evidence, which is still lacking for Tanzania. DhP is both more expensive and more effective than artemether-lumefantrine (AL), which is the recommended standard drug for the treatment of uncomplicated malaria in Tanzania; hence, it is not known whether the added benefits are worth the extra costs. It is equally important that policy-makers are as well informed about the budget impact (for the drugs and diagnostics) of such an important policy decision. Pharmacoeconomic analyses are therefore warranted to generate the required pharmacoeconomic evidence for DhP in Tanzania.

4.2. Broad objective

To assess the role of pharmacoeconomics in formulary decision-making and to generate economic evidence for anti-malaria drugs in Tanzania

4.2.1. Specific objectives

1. To determine the number of pharmacoeconomic analysis studies that have been conducted in Tanzania and their role in formulary decisions **(Paper I)**

2. To describe the process, criteria and underlying sources of evidence used in updating the National Essential Medicine List **(Paper II)**

3. To evaluate the cost-effectiveness of dihydroartemisinin-piperaquine as a first-line drug for the treatment of uncomplicated malaria in children (**Paper III)**

4. To determine the budget impact on drugs and diagnostics when dihydroartemisinin-piperaquine is used as a first- or second-line drug for the treatment of uncomplicated malaria in children **(Paper IV)**

4.2.2. Research questions

1. How many pharmacoeconomic studies have been conducted in Tanzania? To what extent did these studies inform formulary decisions?

2. How was the National Essential Medicine List updated? What criteria were used to guide the selection of medicines? What was the role of pharmacoeconomic analysis? What were the sources of evidence?

3. Is dihydroartemisinin-piperaquine more cost-effective than artemether-lumefantrine as a first-line drug to treat uncomplicated malaria in children?

4. What is the budget impact on drugs and diagnostics when dihydroartemisinin-piperaquine is used as a first- or second-line drug for the treatment of uncomplicated malaria in children?

5.   Methods

This section describes the methodologies used in the four sub-studies. First we provide summary descriptions, as shown in Table 2. Issues related to ethical clearance and permissions are discussed at the end of this section.

Table 2: Summary descriptions of methodologies used in this thesis

	Type	Approaches and sources of data
Paper I	Systematic review	Search of articles from databases and reference lists, followed by screening based on well-defined inclusion and exclusion criteria. Economic evidence from eligible articles was linked to specific policy documents to see whether they were used to inform specific formulary decisions.
Paper II	Qualitative case-study	Triangulation of data collected by in-depth interviews and document reviews. Data was analyzed thematically using qualitative data analysis software.
Paper III	Cost-effectiveness analysis	Primary cost data was collected at a district-level hospital in Tanzania. Secondary effectiveness data was obtained from review of articles from sub-Saharan Africa. The study used a Markov decision-model and analysis was done from a providers' perspective. The TreeAge Program was used to run Monte Carlo simulations with 10,000 iterations for a time horizon of four and a half years.
Paper IV	Budget-Impact Analysis	Only drug and diagnostic costs were included in the analysis. Reference prices were obtained from relevant sources. The study used a dynamic Markov decision-model and the analysis was done from a providers' perspective. An actual population of under-five children from recent census data was modelled in the TreeAge Program which was used to run Monte Carlo simulations with 10,000 iterations for a time horizon of one year.

5.1. Paper I

Mori AT and Robberstad B: Pharmacoeconomics and its implication on priority-setting for essential medicines in Tanzania: a systematic review. *BMC Medical Informatics and Decision-Making* 2012, 12 (1):110

5.1.1. Sources of data

In this systematic review we searched and critically appraised articles based on pre-defined eligibility criteria. Reporting of the study was guided by the PRISMA statement, which consists of a checklist and a flow diagram containing four stages involving identification, screening, eligibility and number of included studies [91]. The databases searched were PUBMED, CINAHL, EMBASE and COCHRANE. Other articles were identified through Google search and the scanning of reference lists. The following MeSH terms were used in various combinations: "economic evaluation", "cost-effectiveness analysis", "cost-benefit analysis" and "Tanzania". The search was limited to the English language and the last search was performed on 30 December 2011. Phase two involved a review of relevant policy documents, including national formularies, in order to verify whether the identified studies were used as a source of evidence to guide decision-making. The majority of these documents were available on the internet but the principle investigator was also in possession of hard copies of the National Essential Medicine Lists.

5.1.2. Study selection criteria

Inclusion criteria

1. Study design: Full economic evaluation studies comparing costs and outcomes
2. Study interventions: drug therapies or vaccines only, since these are the ones listed in the National Essential Medicine List
3. Study setting: Tanzania
4. Publication type: Original full articles or reports

Exclusion criteria

1. Economic evaluation studies of interventions other than drugs and vaccines, because they were beyond the study focus.
2. Partial economic evaluation analysis, since they provide insufficient information required for a cost-effectiveness assessment
3. Hypothetical interventions because they are not real intervention strategies.
4. Review articles, since they may contain information extracted from individual studies already included in the assessment.

5.2. Paper II

Mori AT, Kaale EA, Ngalesoni F, Norheim OF, Robberstad B: The role of evidence in the decision-making process of selecting essential medicines in developing countries: The case of Tanzania. *PloS ONE*, 2014: 9(1).

An understanding of formulary decision-making processes is an important prerequisite for designing interventions aimed at increasing the utilization of pharmacoeconomics in low-income countries. Qualitative case-study was an appropriate design which provides rich descriptions of the phenomenon under investigation and an understanding of the contexts in which policies and programmes will be implemented [92]. This method allowed our study participants to give detailed descriptions of the process of updating the National Essential Medicine List. While often regarded as a less reliable research method because results cannot be generalized, it remains one of the best approaches to studying decision-making processes. In recent years, calls for the integration of qualitative research into health technology assessment has gained a lot of momentum [93, 94].

5.2.1. Data collection methods

Qualitative data were collected via in-depth interviews and document reviews. Our participants represented a group of high-ranking officials at the MoHSW, pharmacists and specialists, mainly from referral hospitals. We contacted our participants by phone calls or when feasible we visited them at their workplaces. We explained the purpose of the study to them and upon agreement we arranged a date to conduct the interviews. Interviews with the first few participants were mainly focused on pre-testing the interview guide and after that we went on to interview our full list of participants. Conversations were held in English and recorded with a digital voice recorder with permission from interviewees and on average each took between 30 and 45 minutes.

In addition, we conducted reviews of important policy documents related to our inquiry in order to complement the interview data. We were already in possession of most of the relevant documents, which were used in paper I. We were not able to observe the decision-making processes in real-time when the expert committees were conducting their deliberations. Instead we reviewed the minutes, proceedings and other documents containing important information about the whole process.

5.2.2. Sampling and sample size

In qualitative studies sampling is in most cases purposive, meaning that investigators select participants based on their potential to provide rich information relevant to the study. In this sub-study, sampling was based on previous involvement with formulary processes, geographical, institutional, professional and speciality representations. A sufficient number of participants were selected from the Pharmaceutical Service Section (PSS) at the MoHSW in order to have a clear understanding of the process.

The sample size for qualitative studies is usually smaller than for quantitative research and not pre-determined. The actual sample size is governed by the level of data saturation during data collection in the field. This is the point at which more interviews do not return more new information, but instead participants largely repeat what has already been said. A sample may be estimated prior to data collection only for budgeting purposes. Some scholars have proposed that, for a homogeneous group of participants, a sample of about twelve is sufficient to achieve data saturation [95]. In this study, eighteen participants were interviewed to reach saturation level.

5.2.3. Thematic analysis

Thematic analysis is perhaps the most fundamental method utilized for analyzing qualitative data and it is focused on identifying the patterns and describing the themes which are embedded in the data [96]. Data preparation and transcription was guided by a standardized protocol adapted from McLellan et al. (2003) [97]. Audio data from the interviews was transcribed into text shortly after each interview section by the principle investigator while the conversations were still fresh in his memory. Transcripts were loaded into ATLAS.ti version 7 software and each was read and re-read several times to become familiarized with their contents. Quotations belonging to specific themes were linked to the data by using codes with names reflecting their contents. Some code names were defined *a priori* while we were developing the interview guide but others were discovered as the analysis progressed. Quotations were read with constant comparisons and the main descriptions and interpretations were summarized into memos. Information retrieved from the document review that complemented data from the in-depth interviews was incorporated in the relevant memos under the respective themes. Reporting followed the sequence of events as a primary organizing principle [98].

5.3. Paper III

Mori AT, Ngalesoni F, Norheim OF, Robberstad B: Cost-effectiveness of dihydroartemisinin-piperaquine compared with artemether-lumefantrine for treating uncomplicated malaria in children at a district hospital in Tanzania. *Malaria Journal* 2014, 13: 363

Dihydroartemisinin-piperaquine (DhP) is a new artemisinin-based combination therapy (ACT) which is highly recommended for the treatment of uncomplicated malaria in endemic countries. Recently, Tanzania adopted it as the second-line drug to treat uncomplicated malaria in its national malaria treatment guidelines and since then it has been listed in the National Essential Medicine List. This drug is both more expensive and more effective than artemether-lumefantrine (AL), which is the standard drug used to treat uncomplicated malaria. It is not known whether the additional benefits produced by DhP are worth the extra cost, which warrants a cost-effectiveness analysis.

5.3.1. Study setting

We conducted a costing study at Mwananyamala hospital in Dar es Salaam region. This area is largely urbanized; it is located on the shores of the Indian Ocean and includes the three districts of Ilala, Temeke and Kinondoni. Dar es Salaam has a population of about 4.5 million people and the prevalence of malaria in under-five children is 3.6% [99]. This is an area with low malaria transmission [100]. Mwananyamala is a public district hospital located in Kinondoni, with 400 beds and about 400,000 visits annually, and it acts as a referral hospital for primary health facilities in the district.

Cost data was collected from a providers' perspective for one financial year which began on 1 July 2011, running until 31 June 2012. We used the basic procedures usually employed in costing studies, which involves the identification, quantification and valuation of cost items. We first identified the primary cost centres that were directly involved with patient care and finally the overhead centres such as administration and transportation, which only play a supportive role for the primary centres. Costs were categorized as capital costs if they were incurred on items that last longer than a year and usually cost more than US$ 100. Capital items included furniture, equipment, vehicles and buildings. Recurrent costs are those incurred on items that are used up during the course of a year and involve salaries, supplies, utilities such as electricity and water bills, drugs and diagnostic tests. Overhead capital and recurrent costs were apportioned to the primary cost centres by the direct allocation method, which ignores interdepartmental interactions [101].

5.3.2. Drug costs

ACTs are procured using reference prices that have been set by the Global Funds and the manufacturers, which for AL is US$ 0.83 and DhP is US $ 0.93 per unit dose for an under-five child [102]. As for the other drugs used in the management of severe malaria and the associated co-morbidities, prices were obtained from the MSD Price Catalogue for 2012/2013. Prices of ACT were inflated by 10% and further by a factor of 1.43 to account for freight, insurance and programme costs [103].

5.3.3. Model structure

A Markov decision model was constructed with TreeAge Pro-2013 software. The model included four exclusive health states: "well", "uncomplicated malaria", "severe malaria" and "death" as an absorbing health state (Figure 7). Children aged 6 months enter the model in a "well" state and then transit to other health states based on the risks of malaria, access to treatment and the effectiveness of anti-malaria drugs. Children were tracked until they reached five years, when their vulnerability to malaria was assumed to have waned due to acquired immunity. Age-specific background mortality rates were adjusted downwards by 11% to account for deaths due to malaria [104].
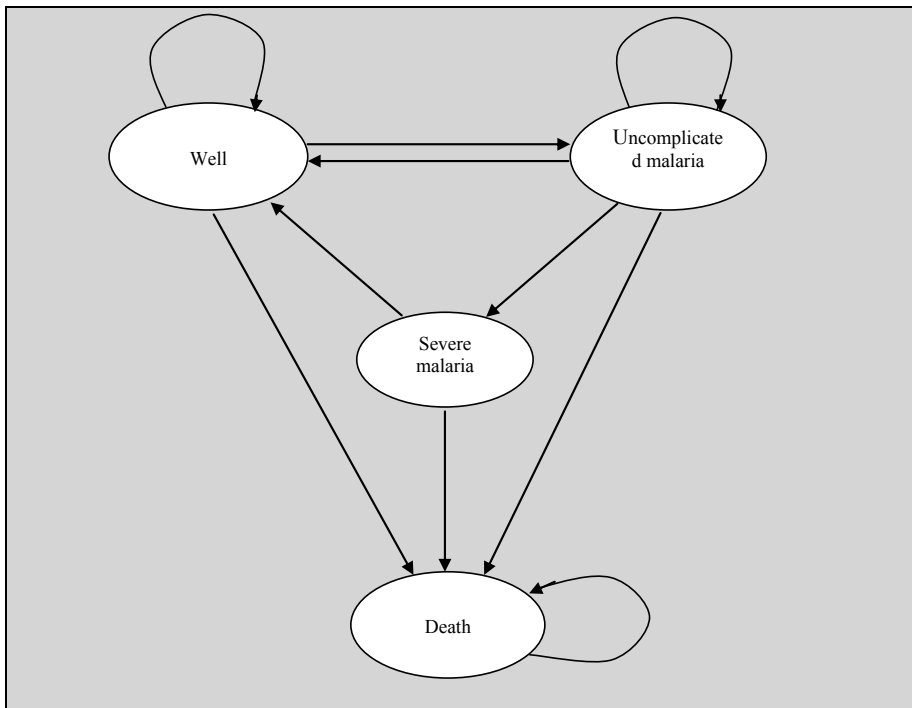
Figure 7: State transition diagram

The model was populated with clinical and epidemiological data from a review of literature from sub-Saharan Africa. Health outcomes were measured in DALYs, which combines years of life lost due to premature deaths and by living with a disability [32]. We used disability weights of 0.005 and 0.21 for uncomplicated and severe malaria, taken from the most recent Global Burden of Disease Study 2010 [32]. We omitted the moderate state because in clinical practice malaria is only classified as uncomplicated or severe. DALYs were not age-weighted; however, in the sensitivity analysis we tested the impact of age weighting on the cost-effectiveness results. A one-week cycle length was used, as this corresponds to the progression of malaria from one state to another.

5.3.4. Analysis

We performed a Probabilistic Sensitivity Analysis (PSA) based on Monte Carlo simulations with 10,000 iterations. PSA is a recommended method of analysis as it allows uncertainties surrounding all the parameters to be propagated in the model using probability distributions. Beta distributions were used for probability parameters in order to constrain them from 0-1 and gamma distributions to constrain cost data from 0 to positive infinity. For compliance rates, we used uniform distributions based on our literature review. Furthermore, deterministic sensitivity analyses were used to identify the most influential parameters and to test the robustness of the results to extreme variations. Uncertainties in the PSA results were presented using Cost-effectiveness Acceptability Curves and Tornado diagrams were used to represent many one-way sensitivity analyses.

5.3.5. Anti-malarial drug properties

Both AL and DhP belong to the group of artemisinin-based combination therapies (ACTs). A large head-to-head clinical trial in several countries in sub-Saharan Africa showed that DhP is slightly more efficacious than AL, i.e. with cure rates of 97.3% compared to 95.5% [105], and hence it is highly recommended as an alternative first-line drug for malaria [106, 107]. In addition, DhP has a simple once-a-day dosage regimen compared to the relatively complex twice-a-day dosage regimen of AL, which also needs to be administered with high-fat meals. The lesser frequency of taking DhP increases adherence to treatment, which was recently reported in Malawi at 88% compared to 79% for AL [108]. It is important to note that evidence on the head-to-head comparison of compliance rates for DhP and AL was not available when we were doing the analysis. Therefore we used a compliance rate of 38–65% for AL [109] and an assumed conservative estimate of 60–80% for DhP based on other ACTs with a similar dosage regimen [110, 111].

5.4. Paper IV

Mori AT, Norheim OF, Robberstad B: Budget impact analysis of using dihydroartemisinin-piperaquine to treat uncomplicated malaria in children in Tanzania. *PharmacoEconomics (under review)*

A cost-effective drug may consume a substantial budget when the disease it targets, such as malaria, affects a large number of people. In paper IV we conducted a budget impact analysis (BIA), which is being increasingly recommended as part of a comprehensive health technology assessment [112]. The most critical part of a BIA is the size of the population eligible to receive the new drug, and for low-income countries medicine utilization data are not always available. To overcome this challenge, a dynamic Markov model was developed and populated with care-seeking, clinical and epidemiological data in order to estimate the number of malaria cases in under-five children.

5.4.1. Intervention mix

Three policies, each consisting of the first- and second-line drug for the treatment of uncomplicated malaria, were considered. A regimen consisting of a three-day dosage of parenteral quinine followed by an oral dose of the first-line drug was employed as a standard treatment for severe malaria. The competing policy options were:

1. AL+quinine: This is our reference policy in which AL and quinine are used as first- and second-line drugs. This policy was used as the standard treatment for uncomplicated malaria in Tanzania from 2006 to 2014 [83].

2. AL+DhP: This policy option substitutes quinine with DhP as the second-line drug in the reference policy. This is the current treatment policy for uncomplicated malaria in Tanzania [17] and follows the WHO recommendations regarding treatment of uncomplicated malaria using ACTs [16].

3. DhP+AL: The composition of this policy resembles that of the current policy in Tanzania except that DhP is used as the first-line drug while AL is the second-line drug. This policy aims to exploit the benefits of DhP, which include relatively higher efficacy and compliance rates compared to AL.

5.4.2. The model structure

The budget impact model resembles the cost-effectiveness model we used in paper III. However, it was modified slightly in order to allow the entrance of new members through a birth-rate corresponding to that of the Tanzanian population. The model uses a cycle length of one week and follows a cohort of children under the age of five years for a one-year period. This means that, for each cycle, a certain proportion of children aged between 4 and 5 years will exit the cohort as they pass beyond the fifth year. To capture this in the model, we divided the number of children in this age interval from census data, by the 52 weeks of the year to estimate the exit rate. In order to simplify the model structure, the net entry rate was calculated as the difference between the birth and the exit rate. In addition, children leave the model through death, which can be caused by severe malaria or other causes. The simplified structure of the model is depicted in Figure 8.
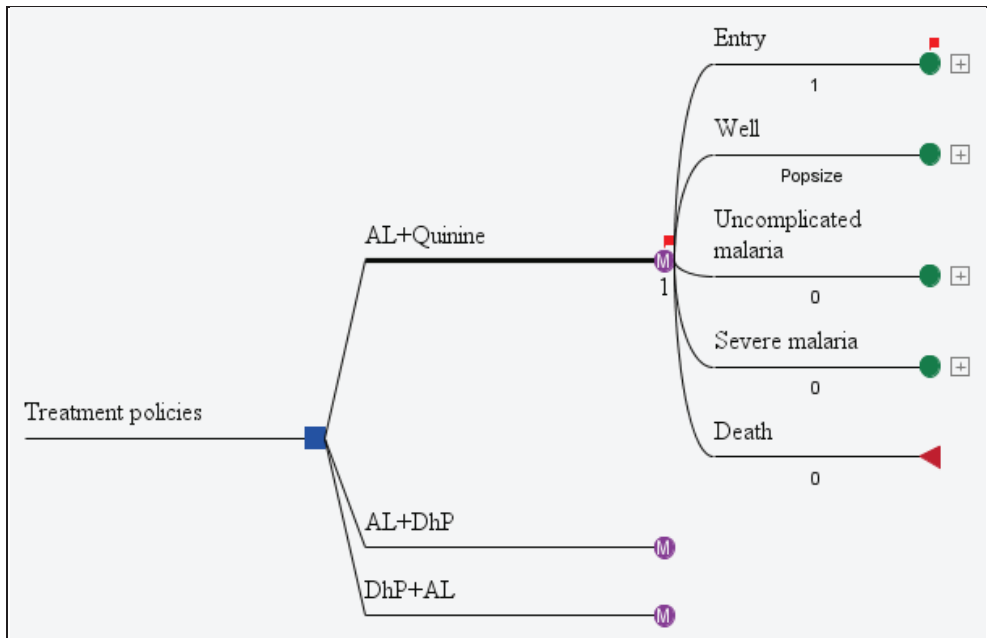
Figure 8: A dynamic Markov model

The three branches attached to the decision node represent the two alternative malaria treatment policies under consideration and the reference policy in the top branch. Popsize represents the size of the eligible population which begin in the "well" state.

5.4.3. Resource costs

In this study we included the cost of drugs and Rapid Diagnostic Tests only since our aim was to predict how the adoption of DhP as the first-line or second-line drug will impact on the total budget for medicines and diagnostics for malaria case management. This also took into account the fact that personnel costs were only collected at one facility; hence, the costs obtained could not be generalized to all the other facilities in the country. Unlike in the cost-effectiveness model, in the BIA costs were not discounted since the interest is to provide a nominal financial forecast for each point in time.

5.5. Ethical clearance

The study was given ethical clearance with certificate no. NIMR/HQ/R.8a/Vol.IX/1362 from the National Institute of Medical Research (NIMR), in Tanzania. Permission was also granted by the District Medical Officers of the respective districts where costing studies were undertaken. In addition, hospital administrations also approved the studies to be conducted at the various hospital facilities. Ethical clearance and letters of permission are attached as appendices at the end of this thesis. Participants for study II also provided verbal informed consent to be interviewed.

6. Results

6.1. Paper I

Mori AT and Robberstad B: Pharmacoeconomics and its implication on priority-setting for essential medicines in Tanzania: a systematic review. *BMC Medical Informatics and Decision-Making* 2012, 12(1): 110

6.1.1. Study selection

Out of the 396 articles we identified from various sources, 384 were excluded because they did not fulfill the inclusion criteria. Therefore, only 12 articles qualified for inclusion in the qualitative analysis, as shown in Figure 9.
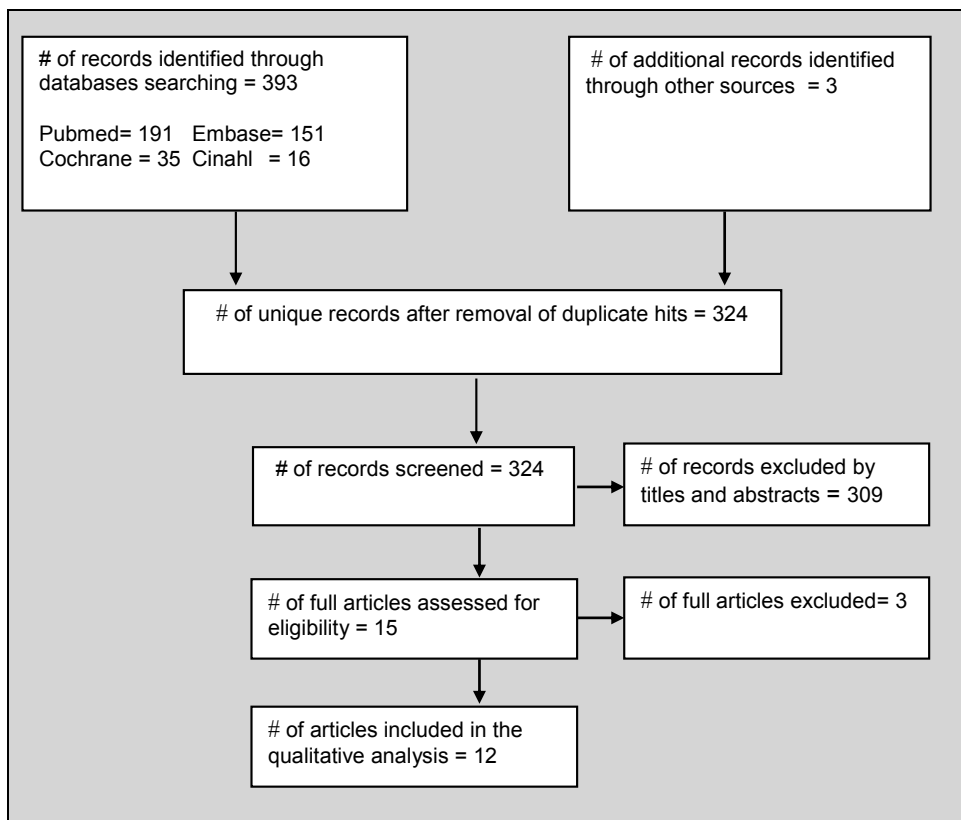
Figure 9: Flow of information in the systematic review

6.1.2. Status of pharmacoeconomics

Nine of the twelve studies which met the eligibility criteria for inclusion in the systematic review addressed infectious diseases. Six of these nine studies are relatively recent, conducted between 2007 and 2011. Seven of the nine studies analyzed drug therapies against three of the top four disease conditions in Tanzania, i.e. HIV/AIDS, malaria and diarrhoeal diseases (Table 3). Six of the twelve studies targeted high-risk groups, which include under-five children and pregnant women.

Table 3: Studies identified linked to the ranked conditions on the burden of disease

Authors	Year	Intervention		Rank of disorder (YLLs)
Guerriero et al.	2011	Tranexamic acid		1. HIV/AIDS
Robberstad et al.	2010	HAART/PMTCT		2. Malaria
Guerriero at al.	2010	Tranexamic acid		3. ARI
Hutton et al.	2009	SP		4. Diarrhoeal diseases
Shim et al.	2009	Anti-rabies vacc		5. Neonatal encephalopathy
Robberstad et al.	2007	CVD drugs		6. Preterm birth complications
Wiseman et al.	2006	AL		7. Protein-energy malnutrition
Robberstad et al.	2004	Zinc		8. Neonatal sepsis
Sweat et al.	2004	Nevirapine		9. Syphilis
Abdulla et al.	2000	SP		10. Road injury
Gonzalez et al.	2000	Iron		11. Tuberculosis
Murray et al.	1991	Anti-TB		12. Maternal disorders

HAART- Highly active antiretroviral drugs (Option B); PMTCT- Prevention of Mother to Child Transmission of HIV/AIDS, CVD- Cardiovascular diseases; AL- Artemether-lumefantrine; SP- Sulphadoxine-pyrimethamine; ARI- Acute respiratory tract infections. The red colour represents economic evaluation studies targeting infectious diseases and grey represents studies that targeted non-communicable diseases or accidents.

6.1.3. Influence of pharmacoeconomics in formulary decisions

Apart from the study by Abdulla et al. (2000), which informed the change of malaria treatment policy from chloroquine to SP, there was no evidence to suggest that other studies had influenced the listing of any drug in the NEML. Most of the studies were published after decisions had already been made (Table 4).

Table 4: Influence of economic evidence in formulary decisions

	Intervention	Main findings and their influence in formulary decisions
1	HAART for PMTCT	Highly cost-effective with an ICER of US$ 162 per DALY averted compared to single dose nevirapine. Adopted recently in Tanzania based on WHO recommendations..
2	AL for uncomplicated malaria	A cost-effective drug with an ICER of US$ 22.4 per death averted compared to amodiaquine. AL is the current first-line drug to treat uncomplicated malaria. The study was published after policy decisions had already been made.
3	SP for uncomplicated malaria	SP was very cost-effective compared to other alternative options. The study was commissioned to inform the policy-change decision from chloroquine to SP in 2000.
4	SP for IPTi of malaria	Very cost-effective with an ICER of US$ 1.6–12.2 per DALY averted. Recommended by the WHO in 2010, but not being implemented in Tanzania due to parasite resistance to SP.
5	Zinc as adjunct therapy to diarrhoea	Cost-effective when combined with Oral Rehydration Salt, with an ICER of US$ 73 per DALY averted. Listed on the NEML but a decision was made based on WHO recommendation.
6	Tranexamic acid injection for surgical bleeding and trauma	A cost-effective drug with ICERs of US$ 93 and 48 per life saved, for surgical and trauma patients, respectively. Currently not indicated to treat these conditions in Tanzania.
7	Short-course chemotherapy for TB	A cost-effective strategy with an ICER of US$ 1–4 per life year saved. This is the current strategy for the management of Tuberculosis but we did not find evidence about how this study influenced decision-making.
8	Iron+deltaprim for prophylaxis of anaemia and malaria	A cost-effective strategy with an ICER of US$ 8 per DALY averted. This intervention was not implemented.
9	Selected antihypertensive drugs	Diuretics, Aspirin+Diuretic and Aspirin+Diuretic+β-blocker are very cost-effective with ICERS of US$ 85, 143 and 317 per DALY averted. They are listed on the NEML but not for preventive cardiology.
10	Anti rabies vaccine	Very cost-effective with an ICER of US$ 27 per DALY averted. Listed on the NEML before the publication of the study.

HAART- Highly active antiretroviral drugs (Option B); PMTCT- Prevention of mother to child transmission of HIV/AIDS; IPT- Intermittent prevention therapy for infants

6.2.   Paper II

Mori AT, Kaale EA, Ngalesoni F, Norheim OF, Robberstad B: The role of evidence in the decision-making process of selecting essential medicines in developing countries: The case of Tanzania. *PloS ONE*, 2014: 9(1).

6.2.1. Updating of the National Essential Medicine List

The National Essential Medicine List (NEML) contains the list of medicines that are supposed to be made available at different levels of the healthcare system. Therefore, the list is used to guide the procurement and distribution of medicines. Figure 10 summarizes the key events in the process of updating the NEML.
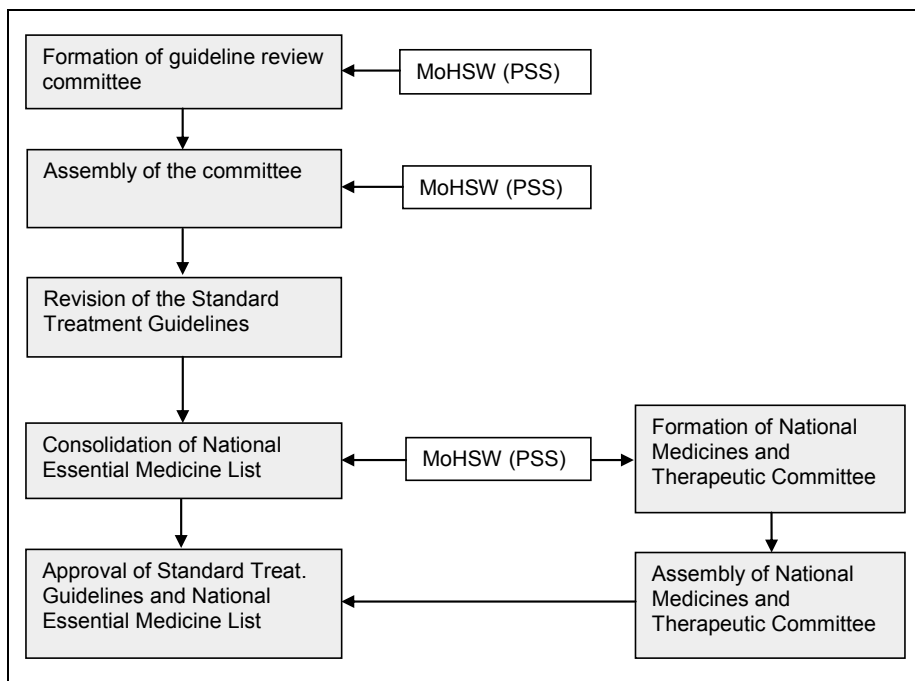
Figure 10: Key events in updating the NEML

PSS stands for Pharmaceutical Service Section, which coordinated the review process

6.2.2. Expert committees, criteria and use of evidence

Table 5 summarizes our findings about the composition of the expert committees, the criteria that were employed to guide the selection of medicines and sources of evidence. In addition, the study explored the use of cost-effectiveness criteria and the understanding of this concept among committee members.

Table 5: Summary of key findings for paper II

Theme	Description	Selected quotes
Composition of the committee of experts	The National Essential Medicine List (NEML) was updated by a multidisciplinary committee of experts who came from different institutions.	"First we had an internal meeting where we decided the kind of people to involve in the process; we wanted a mixture of people from the primary to the tertiary-level facilities, including people from various programmes."
Selection criteria for drugs	The committee was divided into groups and there was no uniformity in the application of drug selection criteria. Efficacy, safety, prices, availability, and compliance rates were used to varying degrees by different groups. WHO recommendations influenced decisions for diseases under vertical programmes. Drug representatives were also accused of influencing decisions.	"We were using an evidence-based approach that a recommended drug must have shown that clinically it was more potent and produced more benefits and there is research evidence for that." "We asked ourselves whether the medicines we were selecting were actually available in the market."
Cost-effectiveness criteria	A majority of the committee members acknowledged not having any knowledge about cost-effectiveness analysis. They said they have never attended any training on the subject but were enthusiastic about using it in future reviews. Those who claimed to be knowledgeable were unfortunately not able describe it.	"Economic evaluation was not used at all. I think that means there should have been some studies about economic evaluation of medicines in Tanzania, which I am not sure if there is. Honestly, we have not taken on board such a criterion in the medicine selection process."
Use of scientific evidence	A majority of clinicians said that they used feedback from their patients as a source of evidence for the effectiveness and safety of medicines. Some claimed to have used meta-analysis studies but without sufficient evidence to substantiate their claims.	"We asked the physicians if the evidence they were giving to support their recommendations was actually based on scientific research! Unfortunately no one said it was scientific evidence but observations from their clinical practice and feedback from their patients."
Approval process	Approval was given by the National Medicines and Therapeutic Committee (NMTC), which is also a multidisciplinary team, with 18 members.	"Is an evidence-based process used by the NMTC at the moment? I don't think so. Is the committee applying an evidence-based framework in decision-making? I don't think that's what is being done at the moment."

6.3. Paper III

Mori AT, Ngalesoni F, Norheim OF, Robberstad B: Cost-effectiveness of dihydroartemisinin-piperaquine compared with artemether-lumefantrine for treating uncomplicated malaria in children at a district hospital in Tanzania. *Malaria Journal* 2014, 13: 363

6.3.1. Treatment costs

The unit costs of treating a child with uncomplicated malaria at a district level hospital in urban Tanzania with AL and DhP was US$ 8.40 and 8.54, respectively. The hospitalization cost of treating severe malaria was US$ 83.84 per child.

6.3.2. Cost-effectiveness analysis

Table 6 shows the results of the base-case cost-effectiveness analysis, for which the model predicted that DhP was more cost-effective than AL, with an Incremental Cost-Effectiveness Ratio (ICER) of US$ 12.40 per DALY averted. In the base-case analysis we assumed that DhP has a compliance rate ranging between 60 and 80%, higher than that of AL, which ranges between 38 and 65%. Use of compliance rates of 88% for DhP, and 79% for AL from a recent study in Malawi did not change the results.

In the scenario analysis, we assumed that DhP has the same compliance rate as AL, which ranges between 38 and 65%. With this assumption the model predicted that AL was more cost-effective than DhP with an ICER of US$ 12.54 per DALY averted compared to US$ 101.52 per DALY averted for DhP.

Table 6: Base-case cost-effectiveness analysis

Strategy	Cost (US$)	DALYs	Δ cost	Δ DALYs	ICER
Do-nothing	0.00	17.60	0.00	0.00	0.00
AL	165.42	4.47	165.42	13.13	Extendedly dominated
DhP	166.22	4.22	0.80	0.25	12.40

Δ- Incremental change; DALY- Disability Adjusted Life Years; ICER- Incremental Cost-effectiveness Ratio. AL was extendedly dominated by a combination of DhP and do-nothing.

6.3.3. Cost-effectiveness scatter plot

Figure 11 shows an incremental cost-effectiveness scatter plot for the base-case analysis. At a willingness-to-pay threshold of US$ 150 per DALY averted, the model predicted that DhP was cost-effective in 97% of the simulations.
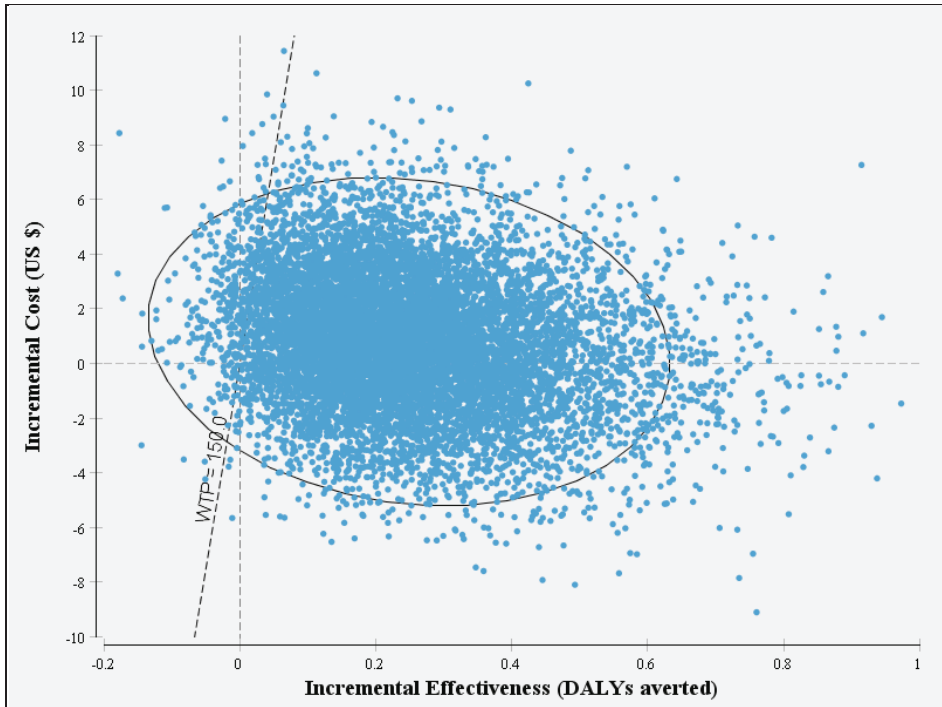
Figure 11: Cost-effectiveness scatter plot of DhP versus AL

The dots represent incremental cost-effectiveness pairs for DhP versus AL for 10,000 Monte Carlo simulations and the ellipse represents 95% confidence intervals. The inclined dotted line represents a willingness-to-pay (WTP) threshold of US$ 150 per DALY averted.

6.3.4. Cost-effectiveness acceptability curves

Figure 12 and Figure 13 show cost-effectiveness acceptability curves (CEAC) for base-case and scenario analyses. The base-case CEAC shows that at a willingness-to-pay (WTP) threshold of US$ 150 per DALY averted, DhP has a 97% probability of being cost-effective compared to AL. In the scenario analysis, we assumed that AL and DhP have equal compliance rates of 38–65% and DhP was still likely to be more cost-effective than AL with a probability of 51%. However, it should be noted that at a WTP threshold of less than US$ 90 per DALY averted, AL was more likely to be cost-effective than DhP.
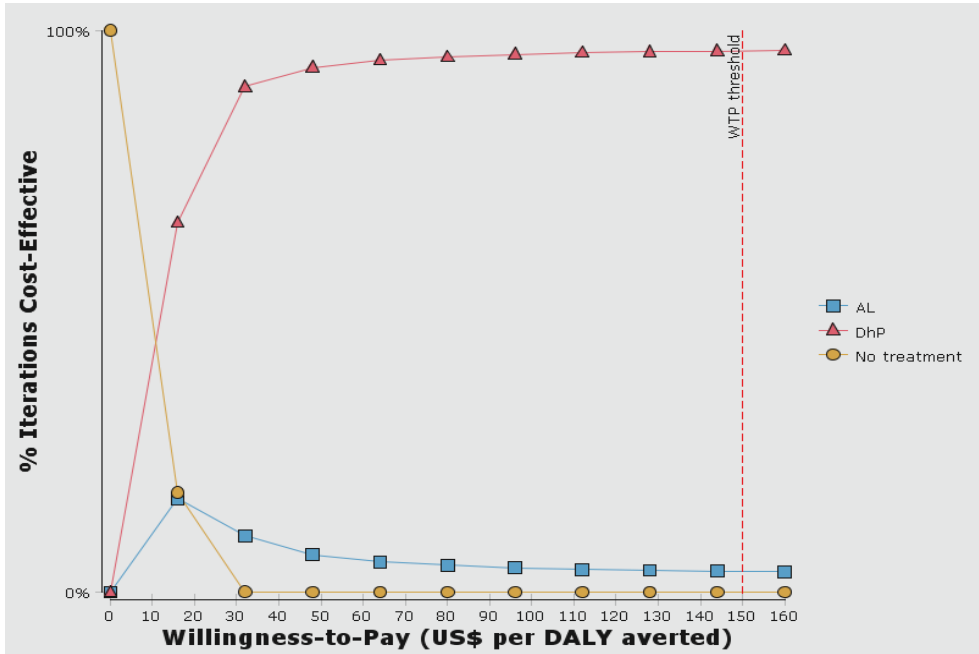
Figure 12: Cost-effectiveness acceptability curve for base-case analysis
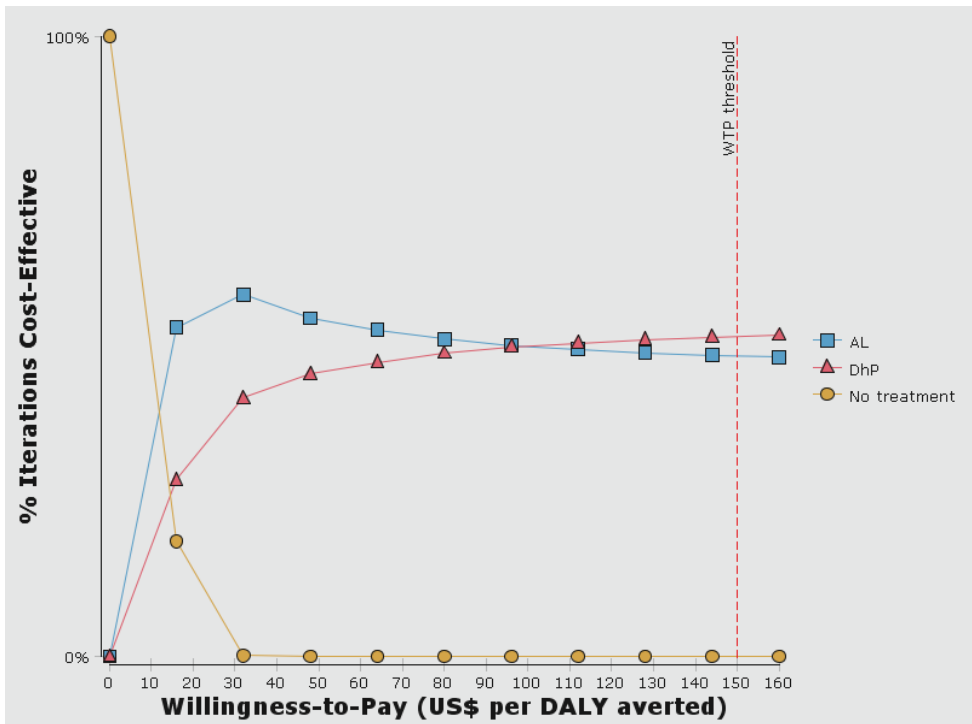
Figure 13: Cost-effctiveness acceptability curve for scenario analysis

6.3.5. Sensitivity analyses

One-way sensitivity analyses were conducted to explore the impact of uncertainties in the model parameters. These are presented in a Tornado diagram which ranks them in order of decreasing influence on the ICER (Figure 14). Given that AL was extendedly dominated in the base-case analysis, the diagram represents the comparison of DhP versus do-nothing. Plausible changes in the values of the various parameters cause ICER to vary between US$ 8 and 18 per DALY averted, which implies that the model was robust. Parameters describing the natural history of malaria were the most uncertain; hence, these are responsible for changes in ICER. The cost-effectiveness of DhP increases with increased probabilities of progression to severe malaria and case fatality rate of untreated severe malaria, and decreases with an increase in the probability of having self-limiting malaria in the do-nothing arm. An increase in the incidence of malaria increases the cost-effectiveness, which implies that DhP is very useful in high transmission areas.
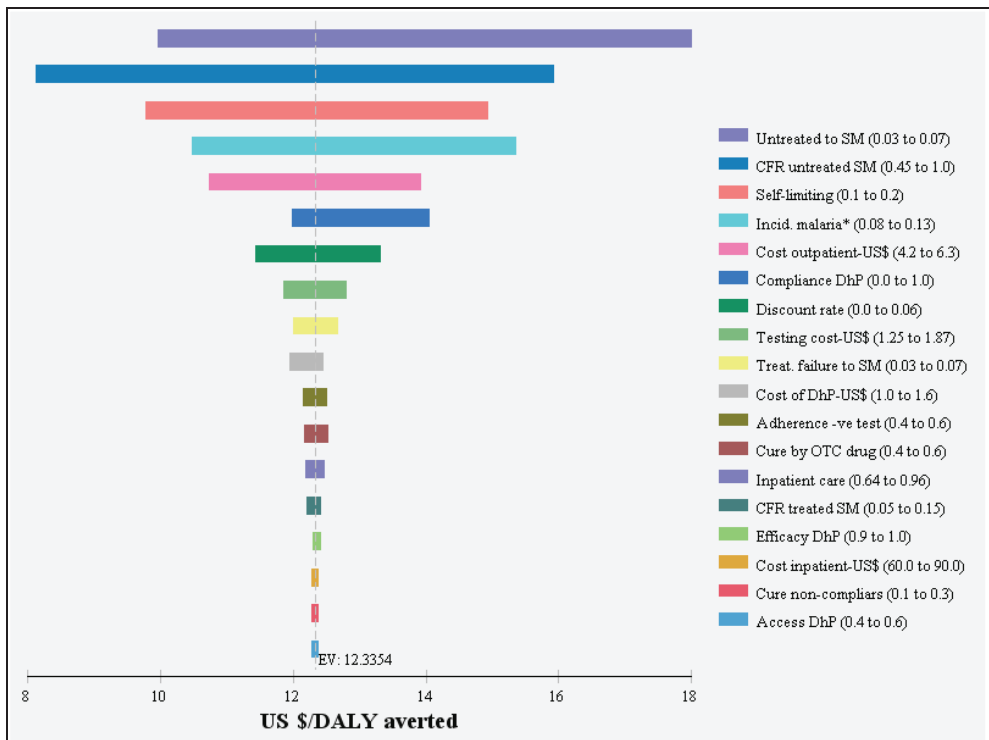
Figure 14: ICER tornado diagram of DhP versus "do-nothing"

Incid malaria * - incidence of malaria as a proportion of fever; SM - severe malaria. The horizontal bars in the Tornado diagram show ranges of the Expected Value (EV) of ICERs at the decision node based on variations in parameter values.

6.4. Paper IV

Mori AT, Norheim OF, Robberstad B: Budget impact analysis of using dihydroartemisinin-piperaquine to treat uncomplicated malaria in children in Tanzania. *PharmacoEconomics (under review)*

6.4.1. Model validation

The Budget Impact Analysis model was validated using a reference policy consisting of AL and quinine as first- and second-line drugs. The aim was to ensure that the modelled morbidity and mortality results replicate those reported in the literature. The predicted number of clinical cases of uncomplicated malaria was 7,510,727, equivalent to about two-thirds of all suspected clinical cases, which have been estimated to range from 10 to 12 million [40]. The model also predicted 173,600 clinical cases of severe malaria, which is approximately two-thirds of the 300,690 cases estimated in the WHO report of 2013 [113]. The total number of deaths is 134,028, which falls within the reported range of 123,100–186,700 [114]. As for malaria-attributable deaths, the model predicts 26,973 deaths, which is also within the reported range of 10,928–49,663 for Tanzania [115].

6.4.2. Budget impact

The model predicts that the current policy of AL+DhP will save about US$ 66,800, which is equivalent to a 0.3% reduction in budget per year, when compared with the reference policy of AL+quinine. If the current policy of AL+DhP is replaced with that of DhP+AL, it will consume an additional budget of about US$ 737,800, which is equivalent to a 3.5% increase in budget per year (Table 7). Note that the budget impact involves drugs and rapid diagnostic tests for malaria for children under the age of five years only.

Table 7: Budget impact of different treatment policies from a providers' perspective

Policy options	mRDT costs	Drug costs	Total cost	Incremental cost
AL+quinine	6,446,783	14,488,735	20,935,518	-
AL+DhP	6,420,571	14,448,147	20,868,718	-66,800 (0.3%)
DhP+AL	6,273,601	15,332,923	21,606,523	737,800 (3.5%)

Costs are in US dollars (US$), mRDT- Rapid Diagnostic Test for malaria

6.4.3. Impact on health outcomes

The model predicts that the treatment policy of AL+DhP has the potential to reduce all clinical cases of malaria by 248,437 (3.2%) compared to the reference policy of AL+quinine. This means that it reduces cases of uncomplicated malaria by 235,855 (3.1%) and severe malaria requiring hospitalization by 12,582 (7.2%). If the current policy of AL+DhP is replaced with that of DhP+AL, the overall clinical cases of malaria among children under the age of five years will be further reduced by 364,517 annually, equivalent to a 5% reduction. Specifically, this policy will reduce cases of uncomplicated malaria by a further 346,055 (4.8%) and severe malaria by 18,463 (11.5%) (Table 8).

Table 8: Impact of each treatment policy on the number of malaria cases

	Uncomplicated malaria	Incr. cases	Severe malaria	Incr. cases	All cases of malaria	Incr. cases
AL+quinine	7,510,727	-	173,599	-	7,684,326	-
AL+DhP	7,274,872	235,855 (3.1%)	161,016	12,582 (7.2%)	7,435,888	248,437 (3.2%)
DhP+AL	6,928,818	346,055 (4.8%)	142,554	18,463 (11.5%)	7,071,371	364,517 (4.9%)

The policy of AL+quinine is the comparator, and the incr. cases represent reductions in the number of cases from the preceding alternative policy in the list. This means that AL+DhP is compared with AL+quinine while DhP+AL is compared with AL+DhP.

6.4.4. One-way sensitivity analysis

The cost and compliance rates of AL and DhP were the most influential parameters on the budget impact results. The base-case analysis showed that AL+DhP was the only cost-saving treatment policy although it produces fewer health benefits than DhP+AL. However, a one-way sensitivity analysis showed that at a cost of about US$ 0.84 per child dose of DhP, the policy of DhP+AL becomes a cost-saving option, as shown in Figure 15. Considering that this cost was inflated by 20% to cover operational costs, it represents an ex-factory price of about US$ 0.7 per child dose of DhP. This means DhP+AL becomes the cheapest malaria treatment policy to implement while at the same time it achieves greater health benefits than the treatment policy consisting of AL+DhP.
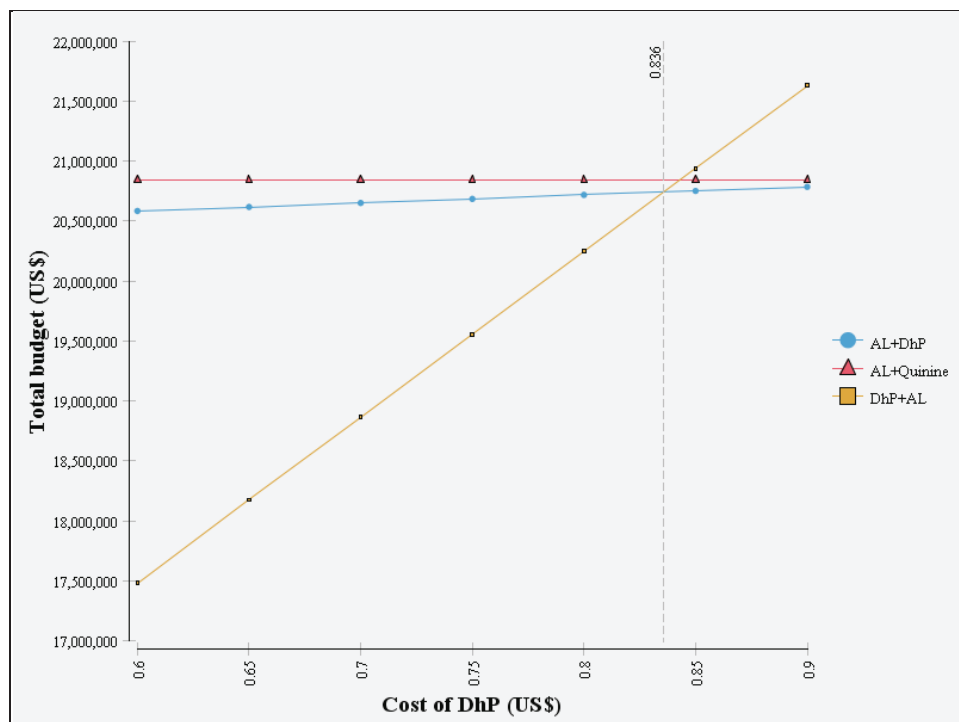
Figure 15: Changes in the total budget versus variations in the cost of DhP

The y-axis represents the total budget for drugs and Rapid Diagnostic Tests (mRDT) and the x-axis represents the cost of DhP, which consists of 20% operational costs. Reduction in the cost of DhP does not have a great influence on the budget for AL+DhP i.e. when it is used as a second-line drug because of a smaller number of children requiring the second-line drug.

6.4.5. Two-way sensitivity analysis

Compliance with treatment is the main determinant on the effectiveness of anti-malaria therapies. Research evidence has shown that the compliance rate for DhP is higher than that for AL due to its relatively simple once-a-day dosage regimen. In the base-case analysis, the compliance rate for DhP was varied between 70 and 90% while that of AL, which is administered twice a day with fat-rich meals, was varied from 60 to 80%. The influence of simultaneous variations in the compliance rates of these two drugs on the total budget for each malaria treatment policy under consideration was explored in a two-way sensitivity analysis (Figure 16).Each coloured region in the diagram represents the range of compliance rates at which each of the three malaria treatment policies has the minimum budget. Note that the diagram does not reflect the impact on health benefits.
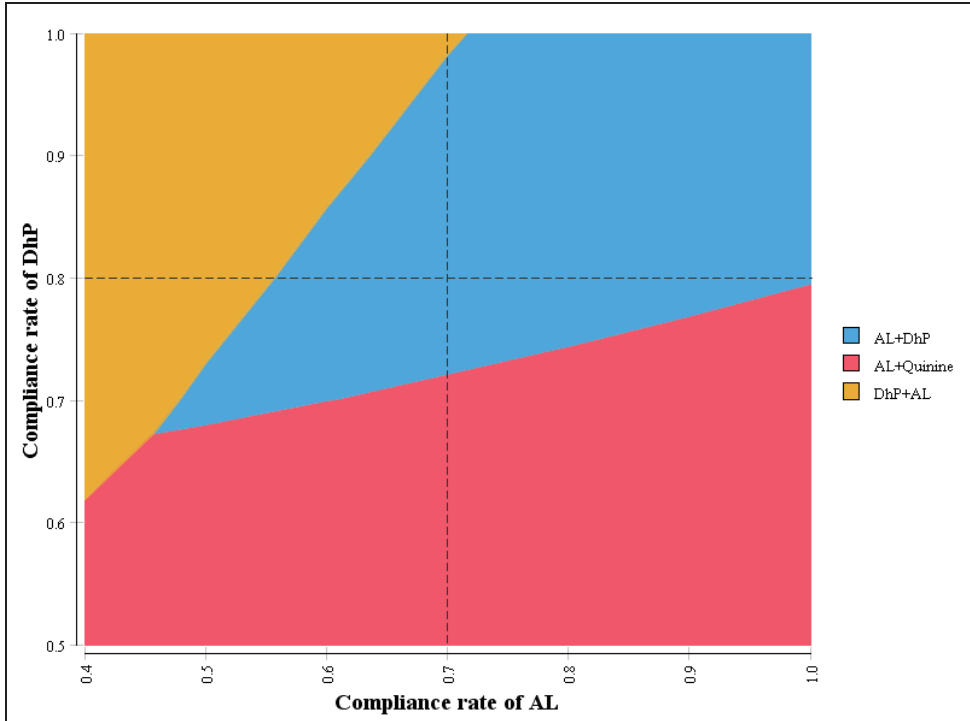
Figure 16: Influence of compliance rates on the budgets

Each coloured region represents different combinations of compliance rates for AL and DhP at which the respective treatment policy has a minimum budget. The intersection of the dotted lines represents the base-case analysis where AL+DhP was cost-saving.

7. Discussions

7.1. General discussion

In this chapter we discuss the main findings from all four papers, rather than categorizing them as we did in the two previous sections.

7.1.1. State of pharmacoeconomics in Tanzania

This study has revealed that only a few pharmacoeconomic analysis studies have been conducted in Tanzania. Robberstad and Hemed (2010) were able to identify only 23 health economic studies, which were published between 1980 and 2008 in Tanzania [77]. This finding is consistent with other low-income countries, in which several studies have shown that economic evaluation studies were also scarce [71-76]. The study also revealed an existing knowledge gap in the understanding of economic evaluation among decision-makers. This is not surprising, considering that the number of health economists in sub-Saharan Africa is extremely low [116]. Pharmacoeconomics is therefore a relatively new field in Tanzania, which partly explains the shortage of these studies [13]. Despite the existence of so few studies, it was encouraging to find that a majority of them were relatively new and addressed priority diseases in the country such as malaria and HIV/AIDS. This implies that there is a growing research interest in this important area.

7.1.2. Role of pharmacoeconomics in decision-making

It is widely accepted that economic evaluation is a key decision-making tool for medicine selection committees at micro, meso and macro levels [117-121]. However, this was not the case for Tanzania, where we identified only one economic evaluation study that had informed decision-making, leading to a change of malaria treatment policy from chloroquine to SP in 2000 [85]. We discovered that the majority of existing pharmacoeconomic studies were conducted long after formulary decisions had already been made. Decision-makers usually work within a very tight time schedule and are unlikely to wait long enough for economic evidence to present itself [122], especially when they do not understand or value such evidence. The poor availability and inconsistent use of pharmacoeconomic analysis evidence is an indication that it has a limited role in informing resource allocation decisions between competing drug therapies in Tanzania. More importantly, this reminds us that health policy decisions are inherently political in nature and hence may involve questions of power, as well as social and economic sustainability [123, 124].

It is estimated that between 20 and 40% of scarce health resources in low-income countries are wasted, and this has been identified as one of the key impediments towards achieving universal health coverage [125]. We argue that inconsistent use of pharmacoeconomic analysis could be a contributing factor in the inefficient use of scarce resources in low-income countries. It is important to note that not all the new drugs that are approved and promoted by drug companies possess the added clinical benefits they are claimed to have over the existing alternatives. In fact, some are more harmful due to the presence of side effects [126]. An independent drug bulletin, *La Revue Prescrire*, recently reported that less than 30% of new drugs approved in France were therapeutically better than the existing drugs [127]. This is a great concern for low-income countries, where drug regulatory frameworks are much weaker than those in high-income countries.

7.1.3. Economics of dihydroartemisinin-piperaquine

Our study has shown that dihydroartemisinin-piperaquine (DhP) is more cost-effective than artemether-lumefantrine (AL) with an ICER of US$ 12.40 per DALY averted, when it is used as a first-line drug to treat uncomplicated malaria in children. This ICER is relatively higher than the US$ 6.23 per DALY averted that was predicted for ACTs by the Committee on the Economics of Anti-malarial Drugs. This finding is consistent with what has been reported by two other separate studies [128, 129]. The study by Pfeil et al. (2014) showed that DhP was more cost-effective by saving US$ 0.96 and averting 0.03 DALYs compared to AL in moderate to high transmission settings in Africa [128].

This ICER is well below the CET commonly used for low-income countries such as 1 to 3 times the GDP per capita and the US$ 150 per DALY averted. It will also be far below the 51% of GDP per capita per DALY averted, i.e. US$ 275 for Tanzania, if the recent recommendation by Woods et al. (2015) was to be considered [63]. Resources to fund new drugs from a fixed budget are usually generated by displacing other health services. Therefore, as CET represents opportunity costs, it means that for every US$ 275 additional costs imposed on the Tanzanian health budget, an equivalent of 1 DALY is forgone as a consequence of displaced health services. However, a drug like DhP, which has an ICER of US$ 12.4 per DALY averted, will generate about 20 times more health benefits than have to be forgone. Therefore, the health benefits forgone as a consequence of replacing AL with DhP as the first-line drug are smaller than those that can be bought by the freed resources, which translates into an increased efficiency.

DhP is currently relatively more expensive than AL, which means its adoption as the first-line drug to treat uncomplicated malaria may have significant budget implications. Our model predicted that if DhP is used as the second-line drug (AL+DhP) as is recommended now in Tanzania, it will save about US$ 66,000 per year while reducing malaria cases by 248,437 (3%), compared to the reference policy of AL+quinine. However, if DhP is used as the first-line drug (DhP+AL), it will require an additional budget of about US$ 737,800 per year but may reduce the number of malaria cases in under-five children by a further 364,517 (5%). Pfeil et al. (2014), estimated a 9% reduction in a year when DhP was compared to AL [128], while Okel et al. (2014) found a 10−15% reduction over a duration of five years [129]. These studies assumed a higher access to treatment than in our study. Considering that our study did not take into account the longer post-treatment prophylactic effect of DhP, the estimated health benefits could be higher than those we found.

7.2. Methodological discussions

7.2.1. Qualitative methods

The strength of qualitative case studies lies in their ability to acquire knowledge from multiple sources such as interviews, document reviews, focus group discussions and direct observations [130]. However, due to time constraints, we could not participate in the meetings of the committees reviewing the National Essential Medicine List; hence, we lost the opportunity to gather data through direct observation. Similarly, focus group discussions were not feasible for the group of participants we had, owing to the nature of their work and positions in their institutions. We believe that data from direct observation and focus group discussions could have strengthened our study's findings.

In-depth interview was our main method of data collection but it has the weakness of introducing recall bias, especially if the phenomenon under investigation occurred a long time in the past [131, 132]. This was evident for some of our participants as they were not able to remember some important events that had occurred during the formulary review process. Analysis of qualitative data is also prone to interpretation bias by the person conducting the interviews and data transcription. In our case this was minimized, firstly by returning the transcripts to the interviewees so that they could cross-check and validate the transcripts. Secondly, we used a standardized transcription protocol which ensured that all the other investigators were thoroughly involved in all stages of the study.

7.2.2. Costing methods

In study II we used an ingredient costing approach which is sometimes called micro-costing. Unit costs were derived from the quantities and values of resources used [60], in our case to treat children suffering from malaria. However, costing a horizontal programme is a difficult undertaking in resource-poor settings because the availability and quality of data about resources used are often very poor due to the lack of reliable electronic data capture systems. Even when computerized systems are available, a shortage of human resources presents another challenge to the proper documentation of resource use. However, micro-costing improves the reliability and validity of cost estimates for hospitals where costs are not available or not properly documented [133-136].

We collected cost data from the perspective of healthcare providers rather than a broad societal perspective, which advocates the inclusion of all costs and benefits associated with the introduction of a new technology [137]. While we had hoped to use the societal perspective, in practice it was not feasible since the collection of societal costs is an expensive and time-consuming undertaking which was beyond our control. Our study was focused on generating evidence for health policy-makers; hence, the health providers' perspective was sufficient. The administration of AL, unlike DhP, requires fat-rich meals to increase its bioavailability [138, 139]; hence, it is associated with higher patient costs. Therefore, increased treatment costs in the AL arm would have favoured DhP in the cost-effectiveness analysis from the societal perspective.

We used a direct allocation method to distribute overhead costs across various departments. One weakness of this method is that it ignores the interaction between departments, as opposed to the step-down approach [60]. Use of the direct allocation method was inevitable in this study due to the lack of documents showing how overhead costs related to administration or how utilities were shared between hospital departments.

7.2.3. Decision-analytic modelling

Decision-analytical models are increasingly being employed when conducting economic evaluations of healthcare interventions to inform resource allocation decisions. As a consequence, a number of Good Practice Guidelines for Decision-Analytic Modelling have been published in the literature [60, 140-143]. While these guidelines have been useful in providing consistent advice and messages about some key aspects of modelling, they have on the other hand added conflicting and contradictory advice [144, 145]. Some of the areas of disagreement include: statement of the decision problem, justification of the modelling

approach used, model perspective, strategies to be included, cycle length and assessment of uncertainty [145]. We used the CHEERS statement, i.e. Consolidated Health Economic Evaluation Reporting Standards, which was published recently, in order to address the previous challenges and to create consistency in reporting [146]. For the Budget Impact Analysis, we used the most recent Good Practice Guidelines from the International Society for Pharmacoeconomics and Outcome Research (ISPOR), which guided the model construction, analysis and reporting of the results [112].

7.2.4. Handling uncertainty

Decision models are usually parameterized with data from numerous sources and hence the identification of relevant evidence for parameters is very important. However, the limited availability of high-quality data in low-income countries poses a major challenge. Evidence gaps are sometimes filled with expert opinions and assumptions, which may further create uncertainties for decision-makers [147]. Therefore, we used Probabilistic Sensitivity Analysis (PSA), which has assumed a predominant role in handling uncertainties in input parameters in decision modelling. In PSA, each parameter was assigned a relevant probability distribution and during the analysis they were varied simultaneously using Monte Carlo simulations [69, 148-152]. The choice of distribution for each parameter was based on recommendations from the literature [153]. The Monte Carlo simulations were run for 10,000 iterations in TreeAge program in order to ensure that we achieved stable estimates for the final mean values of the results [149].

In addition to PSA, we conducted a series of deterministic sensitivity analyses in order to evaluate the influence of variations in one or more parameters on the results. Tornado diagrams were used to present the results of many one-way sensitivity analyses in order to identify and rank the most influential parameters. These were complemented with two-way sensitivity analyses where two parameters were varied simultaneously. This was especially important for the compliance rates between the two drugs, which in real-world settings may vary simultaneously. In some cases we also performed threshold analyses to determine critical values for parameters that may change the conclusions of the study. Scenario analyses were also performed to test the implications of key assumptions, such as differences in compliance rates and drug costs.

7.2.5. Generalizability

As we have seen, pharmacoeconomic studies are scarce in Tanzania, and this is a common challenge for other low-income countries as well. In these countries, out-of-pocket purchases of essential medicines are rampant due to stock-outs in the public sector [154]. Access to essential medicines represents one of the largest family expenditures on health after food [155] and is also the largest recurrent government health expenditure after salaries. A majority of these countries have various forms of essential medicine policies to ensure the rational use of medicines at different levels of the health system [54]. Considering the lack of specialized HTA institutions with a capacity to perform systematic economic evaluations, we are confident that our findings regarding the role of pharmacoeconomics in formulary decisions are generalizable to other low-income countries.

For paper III we collected treatment costs at two district hospitals, but only data from the urban hospital was included. Unit costs from a rural hospital in the Southern Highlands, which were very much higher than in the urban hospital, were ignored because of discrepancies between the reported cases and the actual prevalence of malaria in the area. Malaria transmissions in rural areas are usually higher than in urban settings [156]. The unit costs of resources have been singled out as the main source of variability across different settings [157]. The ideal approach would be to collect data from a representative sample from across the country, but we were limited by our available resources and logistical challenges. To address this shortcoming, the economic evaluation results were subjected to plausible variations in the unit costs of resources as well as other parameters in the sensitivity analyses, and were found to be robust. Therefore, we believe that the results of our economic evaluation studies are generalizable to other settings with similar health systems, health-seeking behavior and malaria epidemiology.

8. Conclusions and recommendations

8.1. Conclusions

Firstly, this study has shown that pharmacoeconomic studies which are useful in informing formulary decision-making processes in Tanzania are extremely scarce. A majority of the studies that were identified were either narrow in scope or were conducted after formulary decisions had already been made; hence, they do not correspond to the practical resource allocation challenges facing policy-makers. Nonetheless, despite the lack of evidence to show their influence in formulary decision-making, it was encouraging to find that half of the studies were relatively recent, which shows an increasing research interest in this area. More importantly, most of the existing pharmacoeconomic analysis studies address three of the top four conditions in the burden of disease.

Secondly, the study has also shown that the recent selection of essential medicines to be listed in the National Essential Medicine List was largely influenced by experience and the discretionary judgement of experts in preference to scientific evidence. Pharmacoeconomic analysis, which is one of the key criteria recommended for medicine selection, is poorly understood by members of the medicine selection committees. In order to reduce the current burden of disease using the existing scarce resources, health authorities must adhere more to evidence-based processes in choosing cost-effective interventions. The failure to use evidence in formulary decision-making could be due to several reasons, but one hypothesis that remains to be tested is whether training experts in evidence-based decision-making processes will improve similar undertakings in the future.

Thirdly, this study has shown that dihydroartemisin-piperaquine (DhP) was more cost-effective than artemether-lumefantrine (AL) as the first-line drug against uncomplicated malaria in Tanzanian settings. It further showed that using dihydroartemisin-piperaquine as the second-line drug, as currently recommended in Tanzania, is slightly cost-saving, but the greatest health benefits will be obtained when it is used as the first-line drug, despite requiring an additional financial investment. These findings challenge the recent change in the malaria treatment guidelines in Tanzania in which DhP was recommended to be used as the second-line drug to treat uncomplicated malaria.

8.2. Recommendations

8.2.1. Policy recommendations

These policy recommendations focus on addressing the barriers to the use of economic evaluation in Tanzania and treatment policies for malaria.

Barriers to the use of economic evidence

For simplicity, barriers to the use of economic evaluation have been classified into three main groups, namely: institutional, cultural and educational, and political.

i. *Institutional barriers*

Tanzania does not have a specialized HTA system which can be put in the same category as NICE in the UK or the PBAC in Australia; however, it does have a National Medicines and Therapeutic Committee (NMTC). Evidence shows that, on several occasions, treatment guidelines for diseases such as malaria and HIV/AIDS which are under vertical programmes have been changed to adopt new technologies without the sufficient involvement of this committee. This committee should be restructured, strengthened and empowered if it is to effectively perform its role of technology assessment and its responsibilities need to be stipulated more clearly in the policies and guidelines.

In order for it to function more effectively, one possible approach could be to make the committee more independent, with members who have technical knowledge in areas related to health technology assessment such as epidemiology, biostatistics, health economics and pharmacology, as well as clinicians, pharmacists and policy analysts. These experts could be drawn from various institutions in the country, including universities, disease programmes, regulatory authorities and the MoHSW, as well as patients' representatives. The committee could receive support from experienced organizations such as Health Technology Assessment International (HTAi), which offers educational and internship scholarships as well as travel grants for individuals from low-income countries.

ii. *Cultural and educational barriers*

As we have seen, formulary decisions in Tanzania are predominantly made based on the clinical aspects of a drug, such as efficacy and safety, without considering economic evaluations or other relevant criteria. This can be partially explained by a lack of training in economic evaluation, which was not included in the training curriculum for physicians and other healthcare professionals for many years. However, this trend has changed in recent

years, and health economics is slowly being introduced in universities. For example, Muhimbili University of Health and Allied Sciences offers a health economics module as part of some of its Masters' programmes. Other training institutions must follow this example to ensure that health economics is incorporated into their curricula. The lack of local health economic competencies on the drug selection committees is one of the key barriers preventing consistent applications of such evidence in decision-making in Tanzania. Despite this, the evidence suggests that health actors at different levels in low-income countries recognize the importance of cost-effectiveness analysis as a criterion in informing resource allocation decisions [158-160].

iii.   Political barriers

The introduction of economic evaluation as a tool to increase efficiency in resource use is not viewed as a priority area during the development of policy and strategic plans. As a consequence, there is a lack of policies and legislation encouraging the systematic and consistent application of pharmacoeconomic analyses in resource allocation decisions. In addition, very little, if any, funding has been directed towards capacity-building in economic evaluation research in Tanzania. Health economics will remain dormant unless politicians and those in decision-making positions at the MoHSW embrace the concept and make the necessary changes in order to create and enable an HTA system to function. To start with, it could be made mandatory that key policy decisions involving changes in the guidelines for priority diseases such as malaria, HIV/AIDS, diarrhoea and vaccination programmes must be informed with economic evaluation evidence.

Treatment policies for malaria

Both clinical trials and economic evaluation studies have shown that dihydroartemisinin-piperaquine (DhP) is a better drug than artemether-lumefantrine (AL) to treat uncomplicated malaria. DhP is more efficacious, has higher compliance rates and, more importantly, it has a longer post-treatment prophylactic effect which can protect individuals from a recurrence of malaria. In light of this evidence, policy-makers in Tanzania should reconsider their decision to use it as the second- rather than first-line drug.

The use of multiple artemisinin-based combination therapies such as DhP and AL as first-line drugs to treat clinical episodes of uncomplicated malaria is also a viable option and has been recommended in the literature. Evidence shows that, at a population level, this strategy minimizes the total clinical episodes of malaria, reduces treatment failures and slows down the emergence and spread of drug resistance [161, 162].

8.2.2. Research recommendations

- This study only looked at national-level formulary decision-making processes. Therefore, more research is needed to understand the attitudes of decision-makers towards the use of economic evaluation in resource allocation decisions at other levels of the healthcare system.

- Future research should focus on the public health insurance system, particularly the formulation of reimbursement lists, the criteria employed to guide decisions and the role of economic evaluation in decision-making.

- More research is also needed in Tanzania to understand the extent to which evidence-based priority setting decision-making is practiced and what evidence counts more than others among decision-makers.

- Economic evidence is extremely scarce for priority diseases such as HIV/AIDS, diarrhoea, pneumonia and non-communicable diseases such as cardiovascular diseases and diabetes. Therefore, more research should focus on these diseases to address the scarcity of economic evidence.

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RESEARCH ARTICLE   **Open Access**

Pharmacoeconomics and its implication on priority-setting for essential medicines in Tanzania: a systematic review

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Abstract

Background: Due to escalating treatment costs, pharmacoeconomic analysis has been assigned a key role in the quest for increased efficiency in resource allocation for drug therapies in high-income countries. The extent to which pharmacoeconomic analysis is employed in the same role in low-income countries is less well established. This systematic review identifies and briefly describes pharmacoeconomic studies which have been conducted in Tanzania and further assesses their influence in the selection of essential medicines.

Methods: Pubmed, Embase, Cinahl and Cochrane databases were searched using "economic evaluation", "cost-effectiveness analysis", "cost-benefit analysis" AND "Tanzania" as search terms. We also scanned reference lists and searched in Google to identify other relevant articles. Only articles reporting full economic evaluations about drug therapies and vaccines conducted in Tanzania were included. The national essential medicine list and other relevant policy documents related to the identified articles were screened for information regarding the use of economic evaluation as a criterion for medicine selection.

Results: Twelve pharmacoeconomic studies which met our inclusion criteria were identified. Seven studies were on HIV/AIDS, malaria and diarrhoea, the three highest ranked diseases on the disease burden in Tanzania. Six studies were on preventive and treatment interventions targeting pregnant women and children under the age of five years. The national essential medicine list and the other identified policy documents do not state the use of economic evaluation as one of the criteria which has influenced the listing of the drugs.

Conclusion: Country specific pharmacoeconomic analyses are too scarce and inconsistently used to have had a significant influence on the selection of essential medicines in Tanzania. More studies are required to fill the existing gap and to explore whether decision-makers have the ability to interpret and utilise pharmacoeconomic evidence. Relevant health authorities in Tanzania should also consider how to apply pharmacoeconomic analyses more consistently in the future priority-setting decisions for selection of essential medicines.

Keywords: Tanzania, Essential medicines, Pharmacoeconomics, Cost-effectiveness, Priority-setting, National essential medicine list, Decision-making, Disease burden, Low-income countries

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Background

Pharmacoeconomic analysis is the comparison of costs and consequences of alternative drug therapies so as to maximize therapeutic outcomes when resources are limited. Use of pharmacoeconomics is important in priority-setting between drug therapies since budgets are finite and there is great variance in value for money for products in the market. Some products are more costly but add little or no extra benefits when compared to the existing drug therapies. In other situations new and more expensive drugs represent large potential health improvements. Pharmacoeconomic evidence can help decision-makers judge whether the therapeutic benefits produced by a new drug are worth the extra costs [1].

In high-income countries pharmacoeconomic analysis is widely used to guide priority-setting decisions for pharmaceuticals [2]. National Institute of Clinical Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technology in Health (CADTH) are examples of institutions which have been established for pharmacoeconomic evaluation of new pharmaceutical products and technologies [3,4]. Pharmacoeconomic evaluation has also gained acceptance at hospital level in formulary decision-making in these countries [5]. By contrast, in low-income countries applied economic evaluation studies are not only scarce, but their usefulness on essential medicine selection has also been debated in the literature [6,7].

Essential medicines are those which address priority healthcare needs of the populations. Since its inception, the concept of essential medicines aims to increase availability and accessibility of medicines in low-income countries [8]. The strategy was consolidated in the Alma Ata conference where access to essential medicines was listed as one of the key component of the primary healthcare package [9]. Increase in access to high quality essential medicines is today viewed as the most important global strategy to reduce the burden of diseases [10]. This strategy is of particular importance for low-income countries which carry a disproportionately large share of the disease burden [11], but yet are accounted for as little as one per cent of the total global pharmaceutical expenditures [12].

Tanzania had its first national essential medicine list in 1991, while the current edition of 2007 is the third in the series. The national essential medicine list is considered to be in line with the WHO recommendations under the Tanzania conditions [13]. WHO proposed the use of evidence-based approach in the selection process of essential medicines, with cost-effectiveness comparisons being one of the key criteria [14]. Little country specific cost-effectiveness evidence is available for Tanzania [15], which raises questions on whether, how

and to what extent such evidence is actually used to guide priority-setting decisions. Therefore this systematic review aims to identify and briefly describe pharmacoeconomic studies which have been conducted in Tanzania and assess their influence on the priority-setting process for selection of essential medicines.

Methods

We used the PRISMA checklist which is suited for reporting systematic review of randomized trials but also recommended for other systematic review studies [16]. Some modifications were done to adopt the checklist to report economic evaluation studies.

Information sources

Pubmed and Cinahl databases were searched for all years, limiting the search to English language using the combinations of the following search terms: "economic evaluations", "cost-effectiveness analysis", "cost-benefit analysis" AND "Tanzania". Cochrane library was searched using the key word "Tanzania" in its NHS economic evaluation databases, and using "cost-effectiveness analysis" AND "Tanzania" in its Cochrane Control Register of Controlled Trials Database. Embase was searched from 1980 to 2011(week 51) limiting the search to English language and "Human". "Economic evaluations" AND "Tanzania", "cost-effectiveness analysis" AND "Tanzania" and "cost-benefit analysis" AND "Tanzania" were used as search terms. Last search of these databases was 30th December 2011. Other articles were identified by scanning reference lists and searching by Google search engine using the above mentioned search terms.

The Tanzanian national essential medicine list and other relevant policy documents related to the identified articles were also screened for information related to the use of economic evaluation evidences as a criterion for the selection of the recommended medicines. Also we aimed to determine whether the medicines listed in these policy documents were similar to those recommended by the authors of the articles we had identified.

Study selection criteria and rationales
Inclusion criteria

1. Study design: economic evaluation since the aim was to compare costs and outcomes of alternative interventions competing for the same resources
2. Study interventions: drug therapies or vaccines only since these are the ones listed on treatment guidelines and national essential medicine list
3. Study setting: Tanzania
4. Publication type: Original full articles or reports

Exclusion criteria

1. Economic evaluation studies of the methods used to distribute the drugs or vaccines to the patients since this was not our study focus
2. Studies presenting only costs or only effectiveness results since they provide insufficient information required for cost-effectiveness assessment
3. Hypothetical interventions since they do not represent actual intervention strategies
4. Review articles since they contain information extracted from individual studies already included

Each article was initially screened based on its title and the abstract to see whether it met our inclusion and exclusion criteria. Articles which passed the screening stage were subjected to full text assessment for eligibility. Eligible articles were selected for the qualitative analysis.

Data extraction procedure
Necessary information such as names of the authors, publication year, the target intervention, study perspectives and the recommended drug therapies and their cost-effectiveness ratios were extracted from each of the twelve articles. Ranking of the disease burden was extracted from the Tanzania national package of the essential health interventions. Generic names of the recommended drugs and vaccines and the rationales behind them, were extracted from the national essential medicine list and other relevant policy documents.

Results
Study selection
396 articles were retrieved from various databases and other sources in which 72 were excluded because they were duplicate hits. The remaining 324 unique articles were screened by titles and abstracts after which 309 articles were excluded. Three articles out of the remaining 15 were excluded because one was a brief communication [17], the second was about a hypothetical malaria vaccine [18], and the third was a review study [19]. Therefore only 12 full articles qualified for the qualitative analysis [20-31] (Figure 1).

Burden of diseases versus availability of pharmacoeconomic studies
Tanzania has a list of twelve priority disease conditions referred to as a national package of essential health interventions, on which to prioritize the allocation of its scarce resources for health. This list rank disease conditions according to their burden of disease and is dominated by infectious diseases – HIV/AIDS, malaria and diarrhoeal diseases are at the top. Ranking of the disease

Figure 1 Flow of information through the different phases of the systematic review.
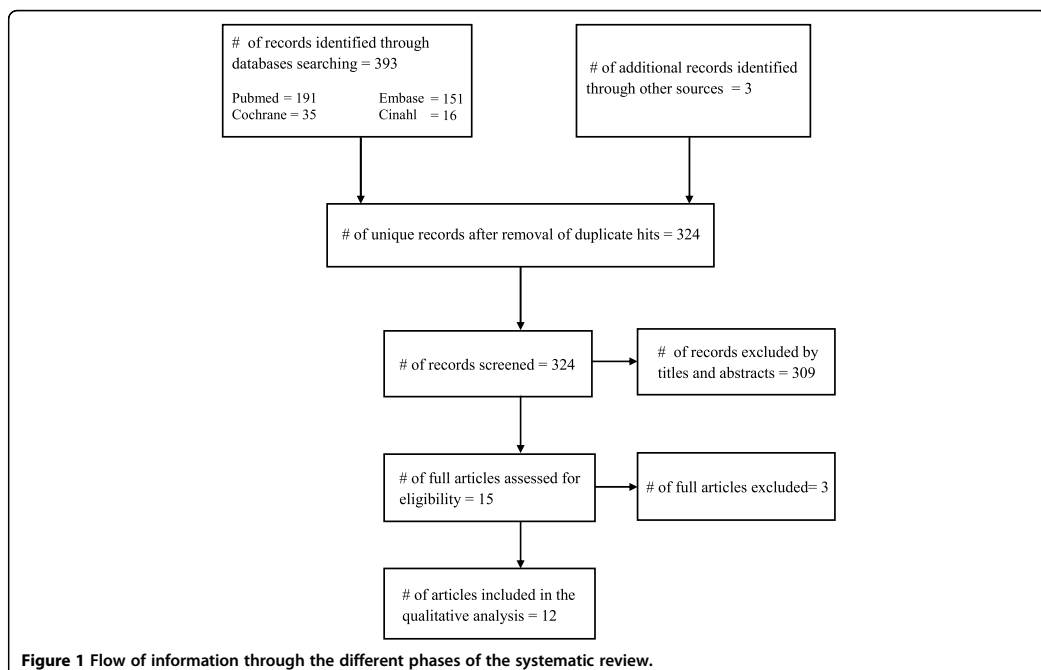
conditions is fairly consistent with the number of pharmacoeconomic studies we have identified. Nine out of the twelve pharmacoeconomic analysis studies addresses the four highest ranked disease conditions (Table 1) It is disappointing to note that only one pharmacoeconomic study addresses non-communicable diseases, and none are available for acute respiratory tract infections, diabetes, cancers, and nutritional deficiencies.

Table 1 Disease burden rank, pharmacoeconomic evidences and their main findings, implications and current listing status

Rank	Disease	Tanzanian pharmacoeconomic evidence	Main findings, implications and current listing status
1	HIV/AIDS	HAART for PMTCT [21]	Highly cost-effective intervention with ICER of US$ 162 per DALY averted when compared to sd-NVP, however it is 40% more costly but 5 times more effective
			(Listing status: HAART *is one of the two options recommended by WHO but not the one being implemented in Tanzania, an area for future research*)
		Sd-NVP for PMTCT [24]	(Listing status: Use of Sd-NVP *is the old policy which was also based on WHO's recommendations but currently being phased out in Tanzania*)
2	Malaria	ALu for non-severe malaria [26]	A cost-effective drug which saves US$ 22.4 per case averted when compared to amodiaquine. (Listing status: ALu *is one of the few artemisinin-based combination therapies recommended by WHO and is the current drug of choice in Tanzania*)
		SP for non-severe malaria [25]	(Listing status: *Use of SP was replaced by ALu since 2007 due to parasite resistance but still listed as essential medicine for IPTp*)
		SP for IPTi [27]	A cost-effective intervention with ICER of US$ 1.6-12.2 per DALY* averted. SP-IPTi reduces episodes of clinical malaria and anaemia by 30 and 21 percent in areas of moderate to high malaria transmissions, in the first year of life [32].
			(Listing status: *SP-IPTi is a new intervention strategy recommended by WHO since 2010 but not yet adopted in Tanzania*)
3	Diarrhoeal diseases	Zinc as adjunct therapy [23]	A highly cost-effective intervention when combined with ORS with ICER of US$ 73 per DALY averted
			(Listing status: *Listed on essential medicine list since 2007, based on WHO's recommendations*)
4	Injury/ Trauma	Tranexamic acid Inj for surgical bleeding and trauma patients [20,29]	A highly cost-effective intervention with ICER of US$ 93 and US$ 48 per life saved for surgical and trauma patients*. TXA reduces number of transfusions by one-third and volume of blood per transfusion by one unit in elective surgery [33]. TXA reduces risks of death by 21% if administered within 3 hrs after injury [34].
			(Listing status: Tranexamic acid Inj. *was listed recently on WHO's list of essential medicine but not yet listed in Tanzania*)
5	ARI	None	None
6	TB	Short-course chemotherapy [31]	A highly cost-effective option with ICER of US$ 1–4 per LY saved. Short-course chemotherapy increases cure rate by 25% compared to the long regimens.
			(Listing status: *Listed; Introduced and adopted in Tanzania in mid 1980's*)
7	Prenatal conditions	None	None
8	Maternal deficiencies	None	None
9	Nutritional deficiencies	Iron+ Deltaprim to prevent anaemia and malaria in infants [28]	Considered to be a cost-effective intervention, support the evidence shown by SP-IPTi in reduction of both anaemia and malaria
			(Listing status: Deltaprin (dapsone +pryrimethamine) *is not listed as essential medicine in Tanzania*
10	CVD and Diabetes	Preventive cardiology [22]	Diuretics, Aspirin+Diuretic and Aspirin+Diuretic+β-blocker are very cost-effective with ICERS of US$ 85, 143 and 317 per DALYS averted.
			(Listing status: *new evidence but these drugs were already listed as essential medicines before the publication of the study*)
11	Neoplasms	None	None
12	Immunisable diseases	Anti-Rabies vaccine [30]	A very cost-effective intervention with ICER of US$ of 27 and 32 per DALY* averted from provider and societal perspectives.
			(Listing status: *New evidence, but the vaccine was already listed as essential medicine before the publication of the study*)

* Compared to do nothing, ALu-artemether-lumefantrine, SP- sulphadoxine-pyrimethamine, Sd-Single dose, HAART-Highly active antiretroviral drugs, ORS-Oral rehydration salt, ARI-acute respiratory tract infections, CVD-cardiovascular diseases.

Discussion

The World Health Report has classified interventions with cost-effectiveness ratios of less than the country's per capita GDP as highly cost-effective and those which are 1–3 times the per capita GDP as cost-effective [35]. Most of the interventions we have identified in this study have cost-effectiveness ratios which are well below the Tanzania's estimated GDP per capita of US$ 550 [36], hence they can be considered as highly cost-effective. On the other hand, Tanzania has a per capita expenditure on health of about US$ 14 per year [37], which is below the US$ 40 recommended by WHO to finance essential health interventions [38]. This means its ability to implement and scale-up even what can be considered as a highly cost-effective intervention is limited.

Our literature review shows that only a few pharmacoeconomic studies have been conducted in Tanzania. Nine out of the twelve studies were on drug therapies and vaccine against infectious diseases which are responsible for more than two-third of the disease burden in sub-Saharan Africa [39]. Nine studies were published within the last ten years, of which six are less than five years old indicating an increasing focus on this research area (Table 2). Antimalarial and antiretroviral drugs were the most researched drugs, which mean that to some extent researchers have responded to the importance of the two diseases for the burden of diseases in Tanzania (Table 1). Half of the identified studies were on interventions targeting pregnant women and children under the age of five years, reflecting concerns for the high mortality rates for these vulnerable groups in Tanzania.

Table 2 Study characteristics

Authors	Year	Target Interventions
Guerriero et al. [20]	2011	Injury (Bleeding Trauma Patients)
Robberstad et al. [21]	2010	HIV/AIDS (Prevention of Mother-to-Child Transmissions)
Guerriero et al. [29]	2010	Surgical Bleeding
Hutton et al. [27]	2009	Malaria (Intermittent Prevention Therapy in Infants)
Shim et al. [30]	2009	Rabies vaccination
Robberstad et al. [22]	2007	Cardiovascular diseases
Wiseman et al. [26]	2006	Case management of non-severe malaria
Robberstad et al. [23]	2004	Diarrhoeal diseases
Sweat et al. [24]	2004	HIV/AIDS (Prevention of Mother-to-Child Transmissions)
Abdulla et al. [25]	2000	Case management of non-severe malaria
Gonzalez et al. [28]	2000	Malaria (Intermittent Prevention Therapy in Infants)
Murray et al. [31]	1991	Tuberculosis

HIV/AIDS

HIV/AIDS is the number one priority health problem in Tanzania, and affects the most productive age group ranging from 15–59 years, hence impairing the country's economic growth [40]. About 20 per cent of the mortalities for admitted patients above five years of age recorded in Tanzania each year are due to HIV/AIDS and Tuberculosis [41]. Our study found two pharmacoeconomic studies on prevention of mother-to-child transmission (PMTCT) and none on case management of HIV/AIDS.

PMTCT programs are in transition in Tanzania, responding to the current recommendations consisting of two prophylactic options provided by the WHO. Option A consists of zidovudine (AZT) which is initiated on week 14 of pregnancy, followed with single dose nevirapine (sd-NVP) plus lamivudine (3TC) at the onset of labour until delivery. AZT and 3TC are then continued for 7 days postpartum. Option B is composed of triple ARV drugs which are also initiated on week 14 of pregnancy until one week after cessation of breastfeeding [42]. The task of choosing which option to implement rests on individual countries and should be based on the feasibility, acceptability, safety and costs [42]. This is a practical example where pharmacoeconomic analysis should be used to guide medicine selection.

Tanzania has opted to implement option A [43], however, without being guided by cost-effectiveness comparison evidence for option A and B. An economic evaluation study by Robberstad et al. at Haydom Lutheran Hospital in Northern Tanzania showed that option B was highly cost-effective in the Tanzanian settings with incremental cost-effectiveness ratio of US$ 162 per DALY averted. This regimen was however 40 per cent more expensive than sd-NVP but 5 times more effective [21]. Since option A at the time of the study was not being implemented at the study site, they did not make cost-effectiveness comparisons of option A and B relative to sd-NVP. Drug costs for option B relative to option A which were approximately up to five times in 2009, have been reduced significantly down to two times by the end of 2011 [44]. WHO has recently released a new PMTCT update advising countries to adopt the use of option B plus, where a pregnant woman is placed on option B for life regardless of CD4 cell count or clinical staging [45].

Malaria

Malaria is second after HIV/AIDS on the disease burden in Tanzania. On average about 46 per cent of all in-patient and out-patient cases registered in the healthcare facilities each year are due to malaria [41]. Malaria is the leading cause of morbidity and mortality among children under the age of five years [40,41]. Malaria during

pregnancy is also associated with low birth weight [46], which is recognized as the single greatest risk factor for neonatal and infant mortalities in sub-Saharan countries [47]. A recent study showed that the burden of malaria among adults has been highly underestimated. According to the findings of this study, malaria is also the major cause of deaths among adult populations [48].

Our review found four pharmacoeconomic studies on malaria, two of them being on malaria case management. Tanzania has changed its national malaria treatment policy twice over the past ten years due to drug resistance to formerly effective antimalarials. These policy changes involved replacement of chloroquine (CQ) with sulphadoxine-pyrimethamine (SP), which was subsequently replaced by artemether-lumefantrine (ALu) [49,50]. Both SP and ALu were at the time the most cost-effective antimalarials compared to alternatives which were available [25,26]. Our review of treatment guidelines and other relevant policy documents showed inconsistent use of pharmacoeconomic evaluations during malaria treatment policy change. As a result the decision to change to ALu unlike that of changing to SP has been criticized for largely being based on the efficacy rather than cost-effectiveness comparisons [51].

The other two studies were on presumptive treatment of malaria using SP in infants (SP-IPTi) and Deltaprim (a combination of pyrimethamine and dapsone) plus Iron in infants and pregnant women. Studies from African settings have shown that SP-IPTi could reduce episodes of clinical malaria, anaemia and rates of hospitalization in infants by 30, 21 and 38 per cent respectively [32]. As a result SP-IPTi has been adopted by WHO since 2010 as a new malaria intervention strategy targeting infants residing in areas with moderate to high malaria transmissions, but with low resistance to SP [52]. SP-IPTi was demonstrated to be highly cost-effective in Tanzania with incremental cost-effectiveness ratios of US\$ 1.57 (0.8-4.0) and US \$ 3.7 (1.6-12.2) per malaria episode and DALY averted, respectively [27]. Even though Global Fund and other donors have made financial resources available to support the implementation of this intervention [53], SP-IPTi has not yet been adopted in Tanzania. Studies from the Northern and Southern areas of the country have reported low protective efficacy results from the use of this intervention [54,55].

Diarrhoeal diseases

Diarrhoea is ranked third on the disease burden in Tanzania and is considered the second main cause of deaths among children under the age of five years worldwide after malaria [56]. Oral rehydration salts (ORS) reduce the duration of diarrhoea episode and replaces the lost water and electrolytes hence preventing the occurrence of dehydration. When Zinc is given as an adjunct therapy for 10–14 days, it has been proved to reduce the duration of acute diarrhoea by 25 per cent and treatment failure or death due to persistent diarrhoea by 42 per cent. It also prevents episodes of subsequent infections for up to three months [57,58]. In 2004, WHO and UNICEF recommended that countries adopt the use of Zinc and low osmolarity oral rehydration salts (lo-ORS) in their revised guidelines for treatment of diarrhoea [59]. Zinc was included in WHO model list of essential medicines in 2005 based on the evidence of cost, efficacy, safety and cost-effectiveness in the management of diarrhoea [60].

We found one pharmacoeconomic study by Robberstad et al. on Zinc as adjunct therapy which reported it to be cost-effective in Tanzania [23]. Tanzania adopted the new diarrhoea treatment guidelines which incorporated the use of Zinc in July 2007 [61] followed by its listing in the national essential medicine list the same year [13]. Our review of documents revealed that a task force committee which was composed of representatives from the government, WHO, UNICEF, and non-governmental organization was formed to advocate for adoption of Zinc [61]. However there is no evidence of whether economic evaluation was among the criteria on which the local decision was based apart from the WHO/UNICEF recommendation.

Injuries

Injuries/trauma and emergencies is ranked fourth on the disease burden in Tanzania [62]. Victims of injuries/trauma often require blood transfusions to replace the massive amount of blood lost. Other recipients of blood transfusion include pregnant women, patients coming from surgery and those with anaemia. Pregnant women in African settings who need blood transfusions during or after delivery often suffer preventable deaths due to shortages of blood supplies [63]. Even though blood transfusion is considered a lifesaving intervention, it also exposes its recipients to blood-borne viral infections such as HIV/AIDS and Hepatitis B. In Tanzania the average HIV/AIDS prevalence among blood donors has been estimated to be 9 per cent [41]. Shortages of blood supply for transfusions and risks of disease transmissions make alternative options not requiring blood transfusions more attractive.

We found two pharmacoeconomic studies on Tranexamic acid (TXA) – an antifibrinolytic drug which reduces post-operative blood loss and transfusion requirements to injury victims [64]. TXA can reduce the risks of death due to bleeding by 21 percent if administered within three hours after injury [34]. For elective surgery, TXA reduces the requirement of blood transfusion by one-third and the volume per transfusion by one unit [33]. The incremental cost-effectiveness of

administering TXA to bleeding trauma patients in Tanzania was 48 US$ per LY gained [20], while the incremental cost-effectiveness for surgical bleeding was US $ 93 per life saved [29]. Despite being reported to be very cost-effective in Tanzania, TXA injection is not on the national essential medicine list, but has recently been added to the WHO's model list of essential medicines [65].

Tuberculosis

TB is ranked sixth on the disease burden in Tanzania in spite of being recognized as having one of the most successful national TB programs in the world, with a treatment success rate of 88 per cent [37]. We found one relatively old economic evaluation study by Murray et al. which compared the cost-effectiveness of short-course versus long-course anti-TB chemotherapies. The study showed that short-course chemotherapy was less costly per death averted and per LY saved when compared to the long, 12-months chemotherapy for both hospital and ambulatory care [31]. The short-course strategy was found to be very cost-effective with incremental cost-effectiveness ratio of 1–4 US$ per life year saved. In areas with an organized healthcare system the short-course regimen increased the cure rate by a quarter when compared to the standard therapy [31]. Short-course chemotherapy was already introduced in Tanzania before the publication of the study conducted by Murray et al. However, our review of documents showed that the decision to adopt the use of short-course chemotherapy was grounded on evidence of better treatment outcomes at less costs shown by the short-course regimen in Tanzania [66].

Cardiovascular diseases

Cardiovascular diseases are ranked tenth on disease burden and are the leading causes of mortality in elderly in Tanzania [40]. We found one pharmacoeconomic study by Robberstad et al. who explored the cost-effectiveness of 14 drug therapy combinations given to patients with cardiovascular diseases. They found incremental cost-effectiveness ratios ranging from 86 US$ to about 4,600 US$ per DALY saved, hydrochlorothiazide – a diuretic drug, being the most cost-effective option [22]. Review of the national essential medicine lists shows that many of the drug therapies they studied were already on the list but again without cost-effectiveness evidences for their selection.

Rabies

About 5 people out of 100,000 die of rabies in Tanzania each year [67]. Deaths due to rabies, mostly from dog bites, can be prevented through post-exposure prophylaxis with anti-rabies vaccines. We found one pharmacoeconomic study by Shim et al., on anti-rabies vaccine for post-exposure prophylaxis which reported an incremental cost-effectiveness ratio of US$ 32 and US$ 27 per QALY gained, from societal and provider perspectives respectively [30]. This intervention is highly cost-effective and if scaled-up can avert 5,000 QALYs lost each year [30]. Anti-rabies vaccine has been on the national essential medicine list since 2007 [13], therefore the cost-effectiveness evidence provided by the study published by Shim et al. is too recent to have had influenced the decision to include the vaccine on the national essential medicine list.

Use of pharmacoeconomic data from other settings

With only a few pharmacoeconomic analysis studies available for decision-makers in Tanzania, one is tempted to deploy economic evidences from studies conducted elsewhere. Cost-effectiveness studies are context specific and generalizations must always be done with great caution [68]. For example, healthcare costs depend on factors such as the structure and functioning of the healthcare systems, availability of healthcare resources and pricing mechanisms, which can vary from one setting to another. Effectiveness of drug therapies on the other hand depends on their utilization and performance in the real life conditions. Utilization of a drug depends on its acceptability and perceived side effects among the users. Therefore, before cost-effectiveness results from one setting can be applied to inform decision making in other settings, the relevance of such context specific factors should be evaluated by considering the impact of the differences on the results and conclusions. In well designed and well reported studies, such assessments can be accommodated with sensitivity and scenario analyses. We have seen that pharmacoeconomic studies conducted locally are scarce; therefore we argue that decision-makers in Tanzania sometimes can make use of pharmacoeconomic data available from similar African countries. However when the differences in context specific factors are large, or when the sensitivity of the results are insufficiently explored, such generalizations should not be made.

Limitations of the study

The findings of this study are only based on information retrieved through systematic review of articles and relevant policy documents, and hence must be interpreted with care. We did not conduct any interviews to supplement the information we extracted from the policy documents which are neither readily nor consistently available in Tanzania due to logistic challenges. We therefore believe that our search may have not been exhaustive, and so there might be other policy documents containing relevant information related to this study which we did not manage to access.

Conclusions

There are only a few pharmacoeconomic studies which have been conducted in Tanzania and which are useful to guide selection of essential medicines. The majority of these studies are narrow in scope hence do not correspond to drug selection challenges decision-makers are always confronted with in priority-setting decisions. We found little evidence suggesting that the existing pharmacoeconomic studies had impact on the selection and hence listing of drugs in the national essential medicine list. While we encourage more studies on pharmacoeconomic analysis to fill the existing gap, we also emphasise the importance to assess whether decision-makers in the drug selection committees have the ability to interpret and utilise cost-effectiveness evidence when assessing pharmaceuticals for inclusion in the treatment guidelines and essential medicine list. We also encourage Tanzanian health authorities to consider how health economic evidence should be applied more consistently in priority-setting decisions for selection of essential medicines.

Authors' contributions
ATM and BR both conceived and designed the study. ATM carried out the reviews, data extraction and prepared the draft of the manuscript. BR supervised the review process and contributed on the manuscript writing. Both authors read and approved the final manuscript.

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II

The Role of Evidence in the Decision-Making Process of Selecting Essential Medicines in Developing Countries: The Case of Tanzania

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Abstract

Background: Insufficient access to essential medicines is a major health challenge in developing countries. Despite the importance of Standard Treatment Guidelines and National Essential Medicine Lists in facilitating access to medicines, little is known about how they are updated. This study aims to describe the process of updating the Standard Treatment Guidelines and National Essential Medicine List in Tanzania and further examines the criteria and the underlying evidence used in decision-making.

Methods: This is a qualitative study in which data were collected by in-depth interviews and document reviews. Interviews were conducted with 18 key informants who were involved in updating the Standard Treatment Guidelines and National Essential Medicine List. We used a thematic content approach to analyse the data.

Findings: The Standard Treatment Guidelines and National Essential Medicine List was updated by committees of experts who were recruited mostly from referral hospitals and the Ministry of Health and Social Welfare. Efficacy, safety, availability and affordability were the most frequently utilised criteria in decision-making, although these were largely based on experience rather than evidence. In addition, recommendations from international guidelines and medicine promotions also influenced decision-making. Cost-effectiveness, despite being an important criterion for formulary decisions, was not utilised.

Conclusions: Recent decisions about the selection of essential medicines in Tanzania were made by committees of experts who largely used experience and discretionary judgement, leaving evidence with only a limited role in decision-making process. There may be several reasons for the current limited use of evidence in decision-making, but one hypothesis that remains to be explored is whether training experts in evidence-based decision-making would lead to a better and more explicit use of evidence.

Introduction

Insufficient access to essential medicines is a major health challenge in developing countries; among poor populations more than half have been estimated to lack regular access to medicines [1]. Shortages of essential medicines are common in publicly-financed facilities, which constitute a major part of the health systems in most developing countries [2,3], and which are especially important for poor families seeking affordable services [4]. Commonly mentioned problems are insufficient public spending on pharmaceuticals, the high cost of medicines and challenges in the supply chains [3,4]. Efforts to improve access to essential medicines have been revitalised by the Millennium Development Goals [5] and a renewed global focus on Primary Health Care [6].

The essential medicines programme entails stocking a limited range of efficacious, safe and cost-effective medicines that are sufficient to meet the priority health needs of the people [7]. For many countries, essential medicines are those recommended in their treatment guidelines [8]. Consistent and appropriate use of adequately developed treatment guidelines and formularies improve the availability and use of medicines [8,9,10], and their effective implementation not only increases efficiency in resource use but also improves access and the overall quality of care [11,12,13].

The Essential Medicines Programme in Tanzania: Historical Perspective

Tanzania, one of the pioneers of the essential medicines programme, produced its first list of essential medicines in the early 1970s [14,15]. The programme was later adopted by the WHO, and in 1977 the first WHO modal list of essential drugs was produced [16]. In 1978, the provision of essential medicines was declared to be one of the key elements of Primary Health Care through the Alma Ata Declaration [17]. In 1990, Tanzania produced a national health policy document for the first time, adopting the Primary Health Care approach as its cornerstone strategy [18]. A year later, the country launched its first Standard Treatment Guidelines and National Essential Medicine List (STG/NEML) [19], which has subsequently been revised three times. The STG contains recommendations about appropriate healthcare decisions for common disease conditions in Tanzania and the NEML specifies the type of medicines and level of healthcare facility for which they should be made available. The NEML is also used to guide the procurement and supply of medicines in the public sector [11].

Tanzanian Healthcare System

Tanzania is categorised as a low-income country with a per capita expenditure on health of about 41 US$ per year [20]. The healthcare system has a pyramid structure, with tertiary facilities at the apex and primary facilities at the base; in between these lie the regional and district facilities. The Government owns about three-quarters of all healthcare facilities, while the rest are private, with some belonging to faith-based organizations [21]. As in other sub-Saharan African countries, the burden of disease is dominated by infectious diseases [22] and about 60 per cent of medicines listed as essential have been estimated to be available in district and primary facilities [23]. Indicators show that the Tanzanian health system is facing large challenges, including a relatively low life expectancy and relatively high infant, child and maternal mortality rates (Table 1).

Essential Medicine Selection in Developing Countries

Most developed countries have health technology assessment (HTA) systems, such as the National Institute of Clinical Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technology in Health (CADTH), which issue formulary recommendations for reimbursement decisions. Cost-effectiveness evaluation is a mandatory criterion employed to inform decision-making [26,27]. By contrast, essential medicines in developing countries, including Tanzania, are selected by expert committees that supposedly use the WHO's guidelines, which recommend selection to be based on evidence of efficacy, safety, cost and cost-effectiveness [28]. However, the extent to which the evidence-based approach has been implemented in developing countries is not well documented. Therefore this study aims to describe the process of updating the Standard Treatment Guidelines and National Essential Medicine List in Tanzania and further examines the criteria and underlying evidence used in decision-making.

Methods

Ethics Statement

The study was approved by the Ethical Review Committee of the Tanzania National Institute of Medical Research. The study was conducted during a period when there was a medical doctors' strike in the country and therefore we anticipated challenges in obtaining written consents. This concern was communicated to the ethics committee and authorisation was granted to use verbal consent. After self-introduction, the purpose of the study was explained to each informant and confidentiality was assured. All the informants were nevertheless, cautiously, asked for written consent before commencing the interviews, but they opted to give verbal consent. Each informant was assigned a code number which was entered on a consent form and signed to document that verbal consent had been given. Furthermore, the interviews were recorded with permission from the informants and the digital voice recorder and the transcripts were kept confidential.

The Study Design

This qualitative study utilises a descriptive case study design, which is an empirical inquiry that investigates a phenomenon within its real-life context [29]. This design is useful when studying complex and context-dependent undertakings, such as the selection of essential medicines [30]. The descriptive design was chosen in order to provide information-rich explanations of the decision-making processes [29,31]. The study adheres to the consolidated criteria for reporting qualitative research (COREQ) [32].

The Research Team

The research team consisted of two doctoral students, a senior researcher and two professors. ATM's background is in pharmacy, health policy analysis and management. FN's background is in medicine (MD) and health economics. EAK is a senior researcher (PhD) and has outstanding experience with the ATLAS.ti® data analysis software. OFN and BR are professors with extensive experience of national guidelines and drug reimbursement advisory committees in Norway.

Sampling and Sample Size

We used purposive sampling methods to select 18 information-rich informants from the list of experts who participated in the revision of the STG/NEML and two who did not participate, but who were perceived to possess important information for the study. We obtained this list, which contained the names, professions, specialisations, institutions and phone and email contacts, from the Ministry of Health and Social Welfare (MoHSW). Some informants were contacted through phone calls while others were visited at their work places. All the selected informants agreed to participate in the study. Several other informants were also involved in the study through informal interviews which were conducted in order to broaden our understanding of the inquiry.

Table 1. Selected demographic and health indicators for Tanzania.

Indicator	Data	Source
Population	44.9 million	Census, 2012 [24]
Life expectancy at birth	52	TDHS*, 2010
Fertility rates	5.4	TDHS, 2010
Infant mortality rate	51/1,000	TDHS, 2010
Under five mortality rate	81/1,000	TDHS, 2010
Maternal mortality rate	454/100,000	TDHS, 2010 [25]

*TDHS: Tanzania Demographic Health Survey.
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Descriptions of Study Participants

In selecting the informants, we chose those who had experience of participating in the previous revision process, but we also wanted to have good professional, institutional and speciality representations. Therefore our informants were pharmacists and clinicians with different specialisations from referral, municipal and specialised hospitals. Others were programme and section officers from the MoHSW (Figure 1). The final two informants were from the Food and Drugs Regulation Authority (TFDA). Eight of the 20 key informants were females working in hospitals, the MoHSW and the TFDA. Some of the participants, particularly the pharmacists, knew the interviewer in person.

Data Collection Methods

In-depth interviews and document reviews were the main methods of data collection and were carried out between June and December 2012, while the revision of the STG/NEML was still ongoing.

In-depth interviews. In-depth interviews were conducted face to face with key informants, in English, using a pre-tested, semi-structured interview guide. All formal interviews were conducted in the offices of our informants and nobody else was present during the conversations. Interviews were digitally recorded and each lasted for 30–45 minutes. The 18 formal interviews, including one repeat interview, with the STG/NEML review group and the two additional in-depth interviews with informants from the TFDA were sufficient for data saturation. In addition, some informal interviews were conducted without the interview guide.

Document reviews. Several documents containing information related to the implementation of the essential medicines programme in Tanzania were reviewed to supplement the interview data. This included the STG/NEML of 2007 and 2012, the national drug policy, minutes and proceedings of the review meetings, published reports and research articles. We reviewed the malaria and HIV/AIDS treatment guidelines in order to determine whether they are consistent with international guidelines. The research team was already in possession of some of these documents, which were used for a systematic review study about the use of pharmacoeconomics as a criterion of medicine selection in Tanzania [33].

Interview Guide

The interview guide contained questions and probes as described below. The flow varied from one participant to another depending on how the discussions unfolded. It was piloted with four participants and, because no major changes were introduced in the guide, we decided to include these interviews in the analysis.

The process of medicine selection. Informants were asked to describe how the review process was conducted and probed about how they became involved, how and by whom they were contacted and their personal views about the process. Those from the MoHSW who initiated and co-ordinated the process were in addition probed about how they selected the participants, the rationale for doing the review, composition of the committees etc.

Criteria for medicine selection. Informants were asked about how they selected the medicines, the selection criteria, how strictly the criteria were followed and to rank the criteria based on their importance/strengths. For each criterion they mentioned, they were probed to give the type and source of evidence and how they evaluated such evidence.

Use of economic evaluation evidence. Informants were asked whether they used economic analysis as a criterion if they had not mentioned it before, and how and to what extent economic evaluation was used (probed to give examples). They were further probed about challenges that hinder the use of economic evaluation and enabling factors for its use. Lastly they were asked if they had received any training in health economics.

Data Management and Analysis

Verbatim data were transcribed into text using a standardised transcription protocol [34]. Transcripts were loaded into AT-LAS.ti 7 Qualitative Data Analysis Software and analysed using a thematic content approach [35]. Each transcript was read carefully to identify relevant segments of text, which were then coded. Similar or related codes were organised into categories. Quotations attached to the codes were read with constant comparisons and the main descriptions were summarised in memos. Data from the interviews and document reviews were triangulated in memos. Finally, categories were organised under their respective pre-defined themes.
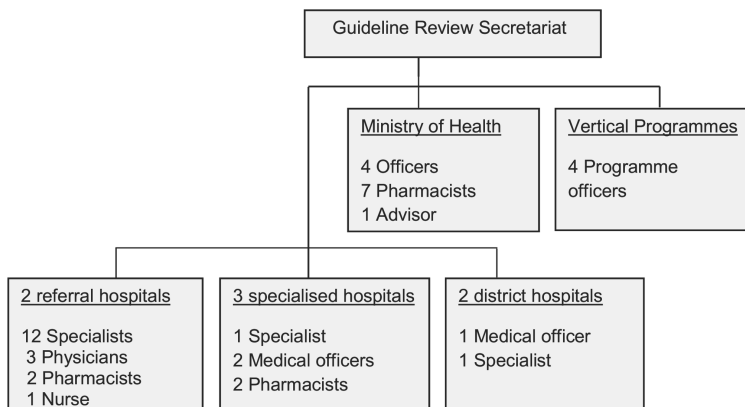

Figure 1. Summary of the key milestones during the revision process.
doi:10.1371/journal.pone.0084824.g001

Description of the Coding Tree

The coding tree consisted of three branches (themes); process, criteria and evidence. Under process there were two categories; the STG/NEML review and the approval process. Under criteria we did not have categories but only the codes for each criterion. Evidence was categorised as being drawn from experience and scientific study or from official documents. Code names reflected the content of each text segment.

Data Validity

Five measures were taken to ensure that the data obtained were valid and trustworthy. Firstly, informants were contacted informally to create a platform for self-introduction, to explain the purpose of the research and assure confidentiality. Secondly, informants were purposively selected to maximise representation of a wide range of perspectives on the subject. Thirdly, interviews were recorded and then transcribed shortly after each interview session to preserve the originality of the data. Fourthly, transcripts were shared with the informants for cross-checking and validation, after which ten of the 18 informants provided feedback, most of them without any changes and a few with minor editing. Fifthly, triangulation of data was performed to enrich and supplement the information collected by interviews and document reviews.

Results

This section provides results about the STG/NEML revision process, the criteria applied and the extent to which evidence was utilised during decision-making. To illustrate the findings, supporting verbatim quotes from the informants are provided. Informants are only identified by their institutions in order to avoid any breach of confidentiality.

Description of the Revision Process

The process of updating the STG/NEML was initiated in early 2012 by the Ministry of Health and Social Welfare (MoHSW). The process was co-ordinated by the Pharmaceutical Service Section (PSS) on behalf of the National Medicines and Therapeutic Committee (NMTC). The sequence of events is shown in Figure 2. An official from the MoHSW gave the following rationale for the revision.

The review was caused by two important things: first the number of diseases had increased and the required medicines to manage such diseases were not in the STG/NEML. Also it has been a long time since the existing STG/NEML was revised and there have been some new developments and changes in how certain diseases are managed in clinical practice. Basically, the WHO recommends revision after every 2–3 years. (Participant from the MoHSW)

To begin the review process, the PSS convened an internal meeting to establish a committee of experts, known as 'a guideline review secretariat' to revise the STG first; this was important because only those medicines recommended in the STG are listed in the NEML. One official explained:

First we had an internal meeting where we decided the kind of people to involve in the process; we wanted a mixture of people from primary to tertiary-level facilities, including people from various programmes. Therefore we consulted people from the malaria and HIV/AIDS control programmes who had the experience of reviewing their treatment

guidelines and they gave us guidance about who we should involve in the review process. (Participant from the MoHSW)

The STG/NEML document has two parts; the STG part contains 25 chapters covering common diseases in Tanzania, their clinical signs and symptoms, how they should be diagnosed and the recommended treatments or supportive care. The NEML part contains the list of all medicines that are recommended in the STG. It uses generic names and the medicines are arranged according to their pharmacological groups. The NEML also specifies the dosage form, its strength and the level of healthcare facilities where each medicine should be made available.

The guideline review secretariat. The guideline review secretariat was composed of a multidisciplinary team of experts (Figure 1) who were mostly selected and invited by the MoHSW. Nearly two-thirds of the experts came from referral hospitals, specialised hospitals and the MoHSW, and these were mainly physicians and specialists. Half of them were female. Through document review we found that only three had been involved in the previous review of the STG/NEML. Two informants said they had received training on evidence-informed decision-making. One of these said:

When I was pursuing my masters at […] we were at times being taught by people from foreign universities such as […] so they emphasised the use of evidence, particularly from meta-analyses in decision-making. (Participant from Hospital)

The revision of the Standard Treatment Guidelines. At its first meeting, the secretariat discussed the approach to update the STG. A consensus was reached to split into groups according to medical specialities to simplify and speed up the revision process. Each group was tasked with revising a specific section of the guidelines pertaining to its speciality. One informant said:

We started the review process by going through the old STG first; looking at what was missing, what to add and even what should be removed completely. We went through each disease condition one after another but not as a single panel. We were divided into specialities, people dealing with cancer looked at cancers, cardiology the same etc. (Participant from Hospital)

The revision process varied between groups; some groups organised discussion meetings and disseminated their recommendations around their respective departments for comment, while in other groups the task was a take-home assignment for group members. The majority of informants said that the organisation, participation and time allocated to the task were not satisfactory.

In my opinion the process is not perfect. First of all the time for review is very constrained, in such a way that you cannot have effective and detailed discussions on the management of patients and other important issues. (Participant from Hospital)
The process was so disorganised, I remember I presented the work of another person who was not there […]. I can say the whole organisation was not good. (Participant from Hospital)

During the second meeting, group leaders presented the proposed recommendations to the secretariat so that other members could provide comments. Thereafter, these group works were compiled into a first draft of the STG. The PSS then extracted all the recommended medicines from this guideline to
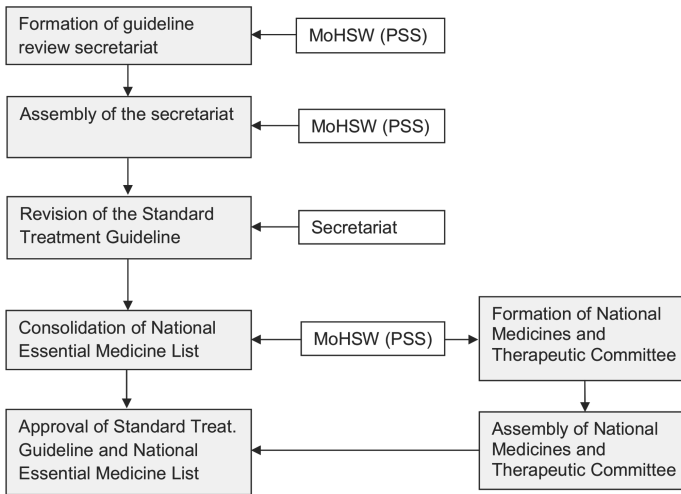
Figure 2. Composition and institutional representation of the guideline review Secretariat.
doi:10.1371/journal.pone.0084824.g002

formulate the NEML. The draft of the STG/NEML was disseminated to different experts before it was submitted to the National Medicines and Therapeutic Committee (NMTC) for approval. One informant said:

The draft of the STG/NEML was sent to the panel of reviewers for comment. Most of our reviewers come from major hospitals; we believe they have experience in research and publications. Then, after receiving their comments, we addressed them before we sent the document to the National Therapeutic Committee for approval. (Participant from the MoHSW)

Criteria used for Medicine Selection and the Underlying Evidence

The criteria employed and level of evidence varied between the groups updating different sections of the STG; some groups considered only one criterion while others used several. These criteria, together with their supporting evidence and other factors that influenced decision-making, are described below.

Efficacy and safety. A majority of informants said that they used an evidence-based approach in updating the STG/NEML. Efficacy and safety were the most cited criteria to have been used by different informants from the guideline review groups. Two informants said:

We were using an evidence-based approach that a recommended drug must have shown that clinically it was more potent and produced more benefits and there is research evidence for that. (Participant from Hospital)
At the time of the review […] was a hot cake, people were trying to assess whether it was safe for patients. In general the concern was how it fares in the field as compared to […]; there were some discussions and we reached a consensus as you saw in the guidelines. (Participant from Hospital)

Regarding the use of evidence, all informants acknowledged that evidence summaries for these criteria were not generated to inform decision-making, but claimed that such evidence was known to them through clinical experience. Two informants said:

Clinical experience was crucial, because you want to produce a practical guideline. Therefore frankly speaking, a lot of evidence came from my daily practice and this was not scientific evidence but simply my experience. (Participant from Hospital)
Doctors were the ones who were recommending medicines for the Standard Treatment Guidelines to manage diseases through their clinical practice. Our belief was that as long as the medicine is being used in the hospital then automatically there was clinical evidence for that medicine to be selected. (Participant from MoHSW)

The two informants who mentioned being trained in evidence-informed decision-making said that their recommendations were supported by research evidence from clinical trials and meta-analyses. However, during the interviews, as well as saying they did not develop evidence summaries, they were also not able to give sufficient explanation about how they searched and appraised the evidence. Some informants, particularly the pharmacists, recognised the lack of evidence in the decision-making process. One member of the secretariat expressed the following concern:

We asked the physicians if the evidence they were giving to support their recommendations was actually based on scientific research! Unfortunately no one said it was scientific evidence. They all said the evidence was observation from their clinical practice and feedback from their patients. (Participant from Hospital)

In some situations the interviewer challenged the informants with scientific evidence supporting the use of some medicines for a condition other than the one they had recommended. Surprisingly, some informants disagreed with such evidence, which was another indication of how difficult it was for scientific evidence to

find its way onto the decision-making table compared with that from clinical experience. One such example is Tranexamic Acid (TXA) injection, a drug which reduces the risk of death in bleeding trauma patients [36]. In the STG it is recommended for prevention of mucosal bleeding. One informant said:

I have never heard of any clinical trials done on tranexamic acid injection. I do not agree or believe in that research, it is not correct. Tranexamic acid is not a treatment, it is prevention and it is contraindicated in massive injuries. How can it help when someone has massive bleeding? (Participant from Hospital)

Availability. All informants said that it is very important that the medicines they select are available on the Tanzanian market so that patients can access them even when they are not available at public healthcare facilities. They said that the existing policy requires all medicines in the STG/NEML to be written with generic names rather than brand names because generics are readily available, relatively cheap and affordable.

We asked ourselves whether the medicines we were selecting were actually available in the market. The main question was: if a certain medicine in the list was prescribed will it be available in the Tanzanian market? We thought it would not make sense to have medicines in the STG/NEML which were not readily available in the country. (Participant from Hospital)

Informants from the Tanzania Food and Drugs Authority (TFDA) said that the availability of medicines depends on whether they are registered in Tanzania or not. They said that in order for any medicine to be allowed to enter the Tanzanian market it has to go through a rigorous registration process in which its quality, efficacy and safety are thoroughly checked. They said that the TFDA registers all medicines that meet a minimum level of prescribed standards and it is from this pool that essential medicines are selected. One official explained:

Drug registration actually involves many processes. In summary, the applicant, usually the manufacturer of the drug, must provide detailed information about the active pharmaceutical ingredient, the finished product and good manufacturing process which demonstrates the quality, safety and efficacy of the drug product. (Participant from the TFDA)

None of the informants mentioned having used the list of registered medicines from the TFDA. Instead they said they knew the available medicines through their practice. Through the interviews we learned that healthcare workers in Tanzania frequently receive drug information from representatives from pharmaceutical companies. One informant said:

We communicate a lot with our colleagues working with pharmaceutical companies, so they tell us if there are new drugs as first lines for certain diseases with better clinical outcomes. (Participant from Hospital)

Affordability. A majority of informants said that affordability was an important criterion in medicine selection because economically Tanzania is very poor. Despite this concession, some informants said that there were disagreements between the doctors and pharmacists about the limit on the number of medicines to be added to the STG/NEML and whether expensive

medicines should also be selected. Some doctors wanted the STG to have a variety of medicines from different therapeutic classes for each disease, some of which were considered expensive. Pharmacists, as the custodians of medicines, often opposed them because they were concerned about budget implications. There was no consensus about these disputes and the final ruling awaited the approval meeting of the National Medicines and Therapeutic Committee. One informant said:

There were disagreements between me and the doctors, I told them essential medicine means to have a limited number of affordable medicines but they said "No! We are the ones who are in the field treating patients". Therefore there is a need for people to be educated about the meaning of essential medicines. (Participant from Hospital)

Informants said that they also took into account the total cost of treatment rather than the unit prices of individual medicines, especially for chronic diseases. One informant said:

In some cases we looked at costs for a full course of treatment rather than unit prices. A month's cost of a 50 Tanzanian shilling (Tshs) tablet taken three times a day is 4,500 Tshs compared to 3,000 Tshs for a once-a-day sustained-release tablet which costs 100 Tshs. You see, this is cheaper and increases compliance with treatment. (Participant from Hospital)

Regarding the evidence for medicine prices, the majority said they knew the prices of most medicines through experience but some said they used price lists from the Medical Stores Department and drug representatives from private medicine suppliers. One informant said:

So if two drugs were equally efficacious but one is cheaper then we selected the cheaper one so long as it has acceptable quality. We used the price list from the Medical Stores Department to compare the costs of the drugs. (Participant from Hospital)

Cost-effectiveness. The understanding of cost-effectiveness analysis was poor among the majority of informants. Some confused it with cost comparisons and others were completely unaware of the concept. Those who said they were aware of it said that cost-effectiveness was not used as a criterion for medicine selection. They went on to say that economic evaluation studies are scarce in the country, and even if they were available they could not use them because they lack expertise.

Two informants said the following:

Economic evaluation was not used at all. I think that means there should have been some studies about economic evaluation of medicines in Tanzania, which I am not sure if there is. Honestly, we have not taken on board such a criterion in the medicine selection process. (Participant from the MoHSW)
Well, that one I cannot say much about since it is not part of our expertise. I don't remember in our group talking anything about economic evaluation of medicines, maybe in other groups but not the one I was with. (Participant from Hospital)

Only one informant said he had received training about the use of economic evidence. Amongst the others, besides saying this was

not an area in which they had expertise, one went further to comment that:

> Perhaps in the future, use of economic evaluation should be emphasised and the team involved in the review should be given lectures on pharmacoeconomics so that they can have knowledge about other criteria for inclusion of medicines in the Standard Treatment Guidelines besides clinical reasons. (Participant from Hospital)

Other Factors that Influenced Decision-making

International recommendations. Informants said that Tanzania has vertical programmes for HIV/AIDS, malaria, tuberculosis and leprosy. These programmes have their own guidelines, which are updated based on global recommendations. These recommendations were adopted in the STG. In addition, some informants said that they copied their recommendations from textbooks and guidelines from countries such as the USA, South Africa, Ghana and Lesotho. Regarding the use of international guidelines, one informant said:

> With malaria we follow the global recommendations, for example in 2010, the WHO malaria treatment guidelines were revised and artesunate injection was recommended for severe malaria. So it is the same with other ACTs, vaccines and some other medicines. (Participant from MoHSW)

Promotion of medicines by the pharmaceutical industry. Some informants accused medicine promotion for influencing prescription practices. They were concerned that the medicines recommended for addition in the STG were there because of these types of influence. Two informants said:

> The second and most important point is that selection was the direct influence of medical representatives [...]. They come here and talk to the doctors and they give them some free samples, what they get in return we do not know. With time doctors get used to these medicines and then they force their inclusion in the hospital formularies and later into the STG/NEML. (Participant from Hospital)
>
> Lobbying by medical representatives is a problem. This hospital has a policy that medical representatives should make presentations in the meetings but sometimes they do not do that, they follow us into our offices to convince us to prescribe their products. They give gifts and some other things. Honestly, this is a common practice. (Participant from Hospital)

To elaborate more on this practice, one informant said she used her experience and sometimes gathered evidence from journals. When she was asked to give the name of the journal, she said:

> Oooh! my Goodness I cannot remember the journal, but I can link you with those individuals at [...] pharmaceutical companies and they can give you that information. (Participant from Hospital)

In the informal interviews, drug representatives acknowledged that they persuade healthcare workers to procure and prescribe their products, and they do this by giving them free medicine samples and gifts such as stationery, refrigerators and televisions.

The Approval of the STG/NEML

The National Medicines and Therapeutic Committee (NMTC) is responsible for the approval of treatment guidelines and formularies in Tanzania and the PSS acts as the secretariat for this committee. The newly formed committee is multidisciplinary and consists of 18 members (Figure 3), with the Chief Medical Officer and the Assistant Director of PSS as the chairperson and secretary, respectively.

Process. The updated draft of the STG/NEML was submitted to the NMTC by the secretariat for approval in September 2012; about 130 new medicines were proposed to be added and five to be deleted. This draft was submitted without a summary of the changes and or the rationales behind them. Therefore the approval process proceeded first with the explanations given by the secretariat about the changes made in each chapter, followed by brief discussions. An excerpt from one of the document reads:

> The committee was taken through the reviewed STG and NEML, chapter by chapter. In each chapter presentations, the major changes which were made, in comparison to the STG/NEML edition of 2007, were explained to the panel. The NMTC members discussed and made recommendations.

Criteria used in the approval process and use of evidence. There was no specific set of criteria used by the NMTC to approve each of the proposed changes. However, through document reviews, we found that the proposal to add clindamycin injection for the management of malaria in pregnancy was rejected because of safety and affordability concerns. The committee also ordered the secretariat to shorten the NEML, citing budget limitations as the only factor. This shows that to a certain extent some criteria were considered but again were not supported by evidence. One informant who participated in the approval process said:

> Is an evidence-based process used by the National Medicines and Therapeutic Committee at the moment? I don't think so. Is the committee applying an evidence-based framework in decision-making processes? I don't think that's what is being done at the moment. (Participant from the MoHSW)

The fourth edition of the STG/NEML was released in July 2013, and contained nearly all the medicines that were initially proposed for addition. In contrast to the previous editions, the new STG/NEML contains, as appendices, application forms for addition, deletion and change of dosage form, strength and indication of the listed medicines. The guiding criteria include efficacy, safety, cost-effectiveness, cost comparison and budgetary impact. These criteria must be supported by relevant evidence, such as the results of clinical trials conducted in Tanzania. An excerpt from the application form reads:

> Reasons why the proposed drug is preferred to drugs already in the NEML (Please attach not more than five supporting pieces of evidence with respect to efficacy, safety, cost, cost-effectiveness, others). State briefly the results of clinical trials conducted in Tanzania [...]. If no official trials, state personal experience and/or submit documentary proof.
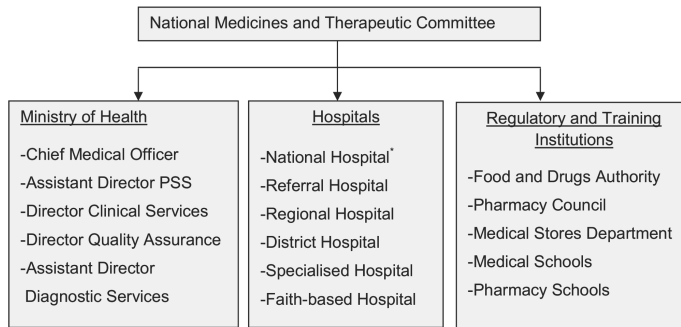
Figure 3. Composition of the National Medicines and Therapeutic Committee. *Three representatives.
doi:10.1371/journal.pone.0084824.g003

Discussion

The most important finding derived from this study is that essential medicines in Tanzania were largely selected through an experience-based process, in contrast to the evidence-based approach that was recommended by the WHO Expert Committee on Selection and Use of Essential Medicines in 2002 [13]. The use of an evidence-based approach has been documented as difficult to apply in developing countries [37], and this is consistent with our findings. The WHO Expert Committee usually publishes evidence supporting its decisions [38], hence decision-makers in developing countries can gauge the applicability of such evidence in their own context during medicine selection. We found that this opportunity was very rarely utilised in the case of Tanzania.

The review involved experts who were selected mostly from referral hospitals and the Ministry of Health and Social Welfare in a process that can be described as implicit and not sufficiently consultative. Participation by a wide array of stakeholders is important to ensure that the needs existing across all levels of the healthcare system are reflected in the STG/NEML. The effectiveness of guidelines is often compromised by the development process, and those guidelines that are imposed by higher levels have a high probability of being under-utilised or even rejected by healthcare workers [39].

We found that efficacy, safety, availability and affordability were the most commonly cited criteria employed in medicine selection. These criteria are to a large extent consistent with those recommended by the WHO [7]. Medicines to manage diseases such as malaria, HIV/AIDS, TB and leprosy, which are managed under vertical programmes, were adopted from international guidelines that usually employ the best available evidence. In addition, medical sales representatives were also considered to be influential in medicine selection as they are viewed as the main source of drug information for prescribers. Experience from East Africa shows that medicine promotion is widespread and poorly regulated and several studies have reported concerns about the influence of these sales representatives in medicine selection [40,41,42,43].

The criterion of cost-effectiveness was not used despite being one of the most important criteria employed by medicine management committees in developed countries to inform formulary decisions [45,46,47,48]. This finding is not surprising, considering the limited role of pharmacoeconomics in developing countries [49]. Several studies have cited the low availability of pharmacoeconomic studies in Tanzania [33,42,50] as the main

barrier, but this study found that a lack of training could also be an important limitation. Studies have shown that, without training, decision-makers cannot understand, translate or apply economic evidence even when it is made available to them [47,48].

Experience rather than scientific evidence played a major role in the decision-making processes. In the few cases where scientific evidence was claimed to have been used, there was neither a systematic search nor an appraisal of the evidence and evidence summaries were not generated to aid decision-making. Even for criteria such as availability and affordability, which are relatively easy to apply compared to efficacy and safety, evidence also mainly came from experience and not official sources such as the TFDA, Medical Stores Department or the International Drug Price Indicator Guide. This could be explained by the inexperience of the experts involved in the review process in using an evidence-based approach, the lack of guidelines on how to do the review and time constraints. Commitment to the use of research evidence and the availability of adequate infrastructures, tools and expertise are essential to facilitate evidence-informed decision-making [44].

Strengths and Limitations

This study employed a qualitative approach, which is suitable for phenomena of which prior knowledge or understanding is limited [51,52]. The method enabled participants to give detailed accounts of what they did, observed and experienced during the revision process, hence limiting the influence of any pre-conceived ideas held by the investigators. However, in-depth interviews have a tendency to introduce recall bias due to incorrect memorisation or failure to remember important aspects of the phenomenon under investigation [29], which was evident in our study. Recall bias was minimised because the study was conducted while the revision of the guidelines was still ongoing, albeit in the final stages.

The expertise of the principle investigator in essential medicine and the functioning of the medicine selection committees in Tanzania was instrumental in conducting this study. The potential influence of his prior experience on the interpretation and discussion of the findings was minimised through observing a well-accepted protocol for qualitative studies, and by involving co-authors in the analysis of the data, as well as in other phases of the study.

The committees were faced with many challenges in performing the reviews. Firstly, it appears that they were not given any training or guidelines about how to update the STG/NEML; secondly, the majority were performing a review for the first time;

thirdly, they were not given sufficient time or other resources to carry out the review and, lastly, even the organisers were constrained by limited capacity and resources to carry out a smooth review process. Therefore we believe that all those who were involved performed the review of the STG/NEML to the best of their ability. This paper has thus identified areas that can be improved in future reviews.

Conclusions

Recent decisions about the selection of essential medicines in Tanzania were made by committees of experts, who largely use experience and discretionary judgement, leaving evidence with only a limited role in decision-making processes. This practice increases the risk of adopting ineffective and costly interventions that may not be worth implementing. Because of this, the health authorities in Tanzania should take the necessary measures to ensure that limited health resources are allocated to proven interventions with the greatest potential to reduce the burden of disease and meet other public health goals. This can be achieved through the systematic application of relevant evidence-based criteria in priority-setting decisions between competing interventions. There may be several reasons for the current limited use of evidence in the decision-making process, but one hypothesis that remains to be explored is whether training experts in evidence-based decision-making would lead to a better and more explicit use of evidence.

Acknowledgments

Author Contributions

Analyzed the data: ATM EAK OFN BR. Wrote the paper: ATM EAK FN OFN BR. Coded the data: ATM. Conceived and designed the study: ATM EAK FN OFN BR. Collected the Data: ATM.

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III

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Cost-effectiveness of dihydroartemisinin-piperaquine compared with artemether-lumefantrine for treating uncomplicated malaria in children at a district hospital in Tanzania

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Abstract

Background: Dihydroartemisinin-piperaquine (DhP) is highly recommended for the treatment of uncomplicated malaria. This study aims to compare the costs, health benefits and cost-effectiveness of DhP and artemether-lumefantrine (AL) alongside "do-nothing" as a baseline comparator in order to consider the appropriateness of DhP as a first-line anti-malarial drug for children in Tanzania.

Methods: A cost-effectiveness analysis was performed using a Markov decision model, from a provider's perspective. The study used cost data from Tanzania and secondary effectiveness data from a review of articles from sub-Saharan Africa. Probabilistic sensitivity analysis was used to incorporate uncertainties in the model parameters. In addition, sensitivity analyses were used to test plausible variations of key parameters and the key assumptions were tested in scenario analyses.

Results: The model predicts that DhP is more cost-effective than AL, with an incremental cost-effectiveness ratio (ICER) of US$ 12.40 per DALY averted. This result relies on the assumption that compliance to treatment with DhP is higher than that with AL due to its relatively simple once-a-day dosage regimen. When compliance was assumed to be identical for the two drugs, AL was more cost-effective than DhP with an ICER of US$ 12.54 per DALY averted. DhP is, however, slightly more likely to be cost-effective compared to a willingness-to-pay threshold of US$ 150 per DALY averted.

Conclusion: Dihydroartemisinin-piperaquine is a very cost-effective anti-malarial drug. The findings support its use as an alternative first-line drug for treatment of uncomplicated malaria in children in Tanzania and other sub-Saharan African countries with similar healthcare infrastructures and epidemiology of malaria.

Keywords: Tanzania, Dihydroartemisinin-piperaquine, Artemether-lumefantrine, Malaria, Cost-effectiveness, Markov model, Disability adjusted life years

Background

Malaria is an infectious disease which disproportionately affects pregnant women and children under the age of five years, and the disease is a major health problem in sub-Saharan Africa. In 2012, an estimated 627,000 deaths occurred due to malaria globally, mostly in African children under the age of five years [1]. Malaria accounts for 3.3% (82,685,000) of all Disability Adjusted Life Years (DALYs) and is ranked seventh among the top leading causes of DALYs globally [2]. Over the years, countries in sub-Saharan Africa have repeatedly changed their treatment policies in response to parasite resistance to monotherapy anti-malarials [3]. Recently, more expensive artemisinin-based combination therapy (ACT) has been recommended and have become increasingly common as first-line regimens against *Plasmodium falciparum* malaria [1,3].

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The World Health Organization (WHO) recommends several artemisinin-based combinations for the treatment of uncomplicated malaria, including artesunate-sulphadoxine-pyrimethamine (ASSP), artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ), artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DhP) [4]. The newest ACT on this list is DhP, which has been proved to be more effective [5,6], but is unfortunately also more expensive than AL, which is currently the most commonly used ACT in sub-Saharan Africa. Despite being more expensive, DhP has been recommended as a first-line or second-line alternative treatment for uncomplicated malaria [7-13].

In 2007, Tanzania changed its malaria treatment guidelines and adopted the use of AL as the first-line treatment for uncomplicated *P. falciparum* malaria to replace SP [14]. In 2013, the standard treatment guidelines were updated and DhP was officially adopted as the second-line drug for uncomplicated malaria [15]. AL has been shown to be a highly cost-effective first-line drug for the treatment of uncomplicated malaria [16,17], but the cost-effectiveness evidence for DhP compared to AL is very limited [18].

Several countries in sub-Saharan Africa have officially adopted the use of DhP for the treatment of uncomplicated malaria [19,20], and many others in the region are also contemplating this change. New drugs are typically more expensive than the existing alternatives: hence good trial results alone should not guarantee their inclusion in treatment guidelines as the additional health benefits may not be worth the extra costs. Pharmacoeconomic analyses are increasingly being used to generate evidence for decision-making in developing countries [21]. Therefore, this study aims to compare the costs, health benefits and cost-effectiveness of DhP and AL alongside "do-nothing" as a baseline comparator in order to consider the appropriateness of DhP as a first-line anti-malarial drug for children in Tanzania.

Methods

Decision model

Cost-effectiveness was analysed using a Markov decision model with four mutually exclusive health states: "well", "uncomplicated malaria", "severe malaria" and "death" (Figure 1). Newborn children are assumed to be protected from malaria through breastfeeding, and enter the model when they are six months old in a "well" state. In the model, they are tracked until they are five years old, after which they are assumed to have gained sufficient clinical immunity against malaria [22,23]. During this time, children move between the health states in one-week cycles depending on risk factors, access to and effectiveness of anti-malarial treatments.
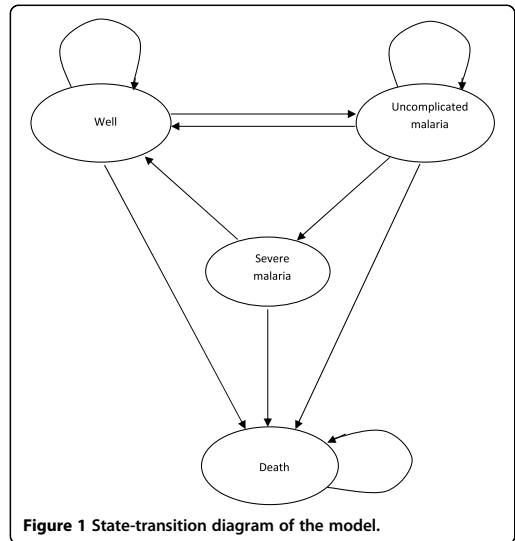

Figure 1 State-transition diagram of the model.

The model assumes that children first develop uncomplicated malaria, from which they may recover and return to the "well" state, or they may progress to "severe malaria", which requires hospitalization. "Death" is an absorbing health state, which may occur spontaneously (i.e. background mortality) or as an outcome of severe malaria. In each cycle the model captures and accumulates costs and utilities related to the patient's health state. Probabilistic Sensitivity Analyses (PSA) were based on a Monte Carlo simulation with 10,000 iterations using TreeAge Pro© 2014 software.

Collection of cost data

Cost data from a provider's perspective was collected at Mwananyamala Hospital in Dar- es Salaam region, from August to November 2012. This is an urban, district-level public hospital with about 400 beds and 400,000 visits per year. Costs were collected for the treatment of both uncomplicated and severe malaria in order to capture the additional costs for patients who develop severe malaria after unsuccessful treatment with the first-line drugs. A district hospital was chosen because it is the lowest level at which severe malaria can be managed effectively within the Tanzanian healthcare system. Costs represent the expenditures incurred during the financial year that ended on June 30th 2012 and were collected using an ingredient approach [24]. Costs were collected in the local currency and converted to US dollars (US$ 1 = 1,578 Tanzanian shillings) [25].

Four service centres were identified; namely the general outpatient department, general paediatric ward, pharmacy and the laboratory. Support departments, which included

general administration and transportation, were categorized as overheads. Costs for resources which last longer than a year were categorized as capital costs and included furniture, equipment and motor vehicles. Recurrent costs were those incurred on resources that are purchased regularly and used up in the course of a year, and include salaries rental charges, utilities and supplies [26].

Cost data were recorded in a pre-tested questionnaire which was designed to capture all the necessary data, including the types and quantities of items, their sources, prices and allocation base. Functioning capital items were identified, counted and valued using their assumed replacement market prices. The price catalogue from the Medical Stores Department (MSD) was used to value medical items and supplies [27]. Capital costs were annuitized at a discount rate of 12% as recommended by the Bank of Tanzania [25] and their useful life years were adopted from the WHO-CHOICE Project [28].

Staff members were identified and interviewed in order to discover their monthly earnings, including gross salary and other standard remunerations. Salary scales and remunerations were cross-checked and validated by the hospital secretary. Personnel costs attributable to malaria were calculated by multiplying total staff monthly earnings by the percentage of their time devoted to malaria. For the buildings, floor spaces were measured and valued as per the square metre rental charges recommended by the National Housing Corporation.

The Global Fund's maximum manufacturer prices for ACTs that are financed through the Affordable Medicines Facility-malaria (AMFm) was used to estimate the mean cost of a course of treatment with AL and DhP [29]. For AL the "6×2" tablet pack specified for children weighing 15–24 kg was used [13] and the "3×1" tablet pack for children weighing 13–24 kg was used for DhP [30]. These prices were inflated by 10% to account for freight and insurance costs [31] and further by a domestic margin factor of 1.43 to represent local opportunity costs [32]. Prices of all the other drugs used in the management of malaria were taken from the MSD's Price Catalogue.

Each service department was allocated a portion of the overhead costs proportional to its percentage contribution to the total allocation base by using the direct-allocation method [24]. For example, cleaning costs were allocated based on floor space. Allocation was difficult for some expenditure, such as electricity, medical supplies, stationery, which were paid for centrally but for which usage was not specified by the departments. Therefore, some of the overhead costs were equally distributed between the departments while others were allocated using an estimated weighted-allocation factor based on interviews with hospital

management. For more details about personnel costs and rental charges, see Additional file 1.

The hospital has Health Management and Information System (HMIS) tools to keep records of all the attendances and diagnoses made during each year. However, because of poor recording, the attendances of malaria patients in the pharmacy or the laboratory could not be tracked. Therefore, the unit costs for the treatment of uncomplicated and severe malaria were calculated by dividing the total costs attributable to malaria for the service centres by the respective number of outpatients (7,076 cases) and hospitalized patients (1,263 cases) recorded in the HMIS tools during the year.

Choice of health outcomes

Disability Adjusted Life Years (DALYs), which combines years of life lost due to premature death (YLL) and years of life lived with disabilities (YLD), was used as a measure of health outcomes [2]. Disability weights of 0.005 and 0.21 for mild and severe acute episodes of infectious diseases from the recent Global Burden of Disease study were applied for uncomplicated and severe malaria, respectively [33]. DALYs averted were calculated using standard methods [34] as a difference of DALYs lost with and without the intervention, based on a life expectancy of 57 years at age 5 for Tanzania [35]. Base case DALYs were discounted at 3%, without age-weighting. Results for age-weighted and undiscounted DALYs were reported in the scenario analysis.

Interventions compared

The study compares DhP (the potential new standard of care) and AL (the existing standard of care) alongside "do nothing" as a baseline comparator. Both drugs are administered for three consecutive days, but AL should be given twice a day with high-fat meals [36] while DhP is given once a day without the requirement for fatty meals [37]. Because of its relatively simple dosage regimen, it is likely that compliance with and hence the effectiveness of DhP will be higher than that of AL in clinical settings. DhP also offers a longer patient protection from re-infection with malaria because piperaquine has a significantly longer elimination half-life of 3–4 weeks compared to the 4–6 days of lumefantrine [38]. The impact of high compliance with DhP is included in the base-case scenario of our model, while that of longer protection is not.

Measurement of effectiveness

Patient compliance to treatment in routine clinical practice plays a key role in the effectiveness of anti-malarial therapies. Thus the effectiveness of each drug, E_{ff}, was

calculated by combining efficacy and compliance rates using the equation below:

$$E_{ff} = E_o C + E_{nc}(1 - C)$$

Where E_o is the efficacy, C is the compliance rate and E_{nc} is the proportion of non-compliers for whom treatment is effective, assumed to be 10–30%, which has been employed in several other cost-effectiveness studies for ACT [39-41]. Efficacy data were extracted from a large, head-to-head, randomized clinical trial which was conducted among 6–59-month-old children in seven African countries with different malaria endemicities: Uganda, Zambia, Mozambique, Rwanda, Nigeria, Gabon and Burkina Faso. The study used the 28-day PCR-corrected cure rate of 97.3% for DhP and 95.5% for AL, from the intention-to-treat analysis [13].

Evidence on compliance to ACT is very limited and diverse [42,43]; however, it has been reported that compliance to AL by "verified timely completion" ranges from 38 to 65% [43]. DhP is a new drug and evidence on its compliance is currently lacking. Since the potential benefit of its once-a-day dosage regimen consisting of only a few tablets is an improved compliance, a range of 60 to 80% was assumed in the base case analysis. This is a conservative assumption, considering that a compliance of 67–87% and 87.2–92.5% have been reported for co-blistered and fixed-dose ASAQ, among children in Tanzania and Madagascar, respectively [44,45]. ASAQ has a once-a-day dosing schedule similar to that of DhP. An assumed compliance similar to that of AL was explored in a scenario analysis.

Transition probabilities
Children enter the model in a "well" state, and can develop febrile episodes based on the estimated age-specific incidence rates shown in Table 1. All febrile children were assumed to be taken to the hospital for diagnosis, and 10.5% of the episodes were attributed to malaria [46]. Between 40 and 60% of children with uncomplicated malaria were assumed to have access to first-line drugs and the probability of cure depends on efficacy and compliance with treatment. Efficacies of AL and DhP were 95.5% and 97.3%, [13] and the base line compliance rates ranged between 38–65% for AL [43] and 60–80% for DhP. The remaining children were assumed to be treated with over-the-counter non-ACT anti-malarials, with effectiveness ranging from 40 to 60% [47,48].

In the "do-nothing" arm, between 3–7% of uncomplicated malaria cases progress to severe malaria [40], which has been estimated to have a case fatality rate ranging from 45 to 80% [51]. Between 10 to 20% of the uncomplicated malaria cases were assumed to recover spontaneously without treatment. In the DhP and AL arms, about 3–7% of the uncomplicated malaria cases progress to severe malaria in the event of treatment failure [41], of whom between 72–88% were assumed to have prompt access to inpatient care [53], which reduces case-fatality rate to 10.9% [52]. Besides malaria, children can also die of other causes at any state in the model based on adjusted age-specific probabilities of death taken from the Tanzanian Life Table [35].

Sensitivity and specificity of the test
Bayesian method was used to incorporate the sensitivity and specificity parameters of the microscopic test in the model, which have been estimated to be 71.3% (95% CI: 68.8–73.9) and 92.8% (95% CI: 91.3–94.3), respectively [56]. Rate of adherence by clinicians to negative test results was estimated to range from 40 to 60% [56].

Model simplifications
The model is a simplification of a complex disease with complex treatment-seeking behaviour and management practices. It is based on the following simplifying assumptions:

- A child cannot move directly from a "well" to "severe malaria" state, but severe malaria is always a progression from uncomplicated malaria.
- Uncomplicated malaria is not fatal, hence a child cannot move from "uncomplicated malaria" to the "death" state, except for deaths caused by other reasons (i.e. background mortality).
- In the event of treatment failure, patients with uncomplicated malaria will repeatedly use the same first-line drug, which we assumed will still be effective.

Uncertainty and sensitivity analyses
Uncertainties in parameters were included in the model by using probability distributions (Table 1). Maximum and minimum values for each parameter were taken from the literature and when these were not available, the mean values were varied by +/− 20% and efficacy data by +/− 2.5%. The gamma distribution was used to constrain costs on the [0,+∞] interval and the beta distribution to fix the probabilities on the [0,1] interval. Gamma and beta distributions were calculated using the method of moments [57]. Uncertainty in the PSA results is presented using a cost-effectiveness acceptability curve (CEAC). Sensitivity and scenario analyses were also performed to assess the influence of variations in the key parameters.

Table 1 Parameters used in the economic model and their distributions

Parameters	Estimates	Distributions	Sources
Age-specific probabilities of death			
Probability of dying between 0 and 1 year	0.0684 ± 20%	Beta	[35]
Probability of dying between 1 and 5 years	0.0424 ± 20%	Beta	[35]
Malaria-attributed deaths in under fives	11%	Point estimate	[49]
Weekly incidences of fever episodes per child			
Less than 12 months	0.106 ± 20%	Beta	[50]
Age 12–23 months	0.144 ± 20%	Beta	[50]
Age 24–35 months	0.105 ± 20%	Beta	[50]
Age 36–47 months	0.087 ± 20%	Beta	[50]
Age 48–59 months	0.06 ± 20%	Beta	[50]
Case fatality rates and other probabilities			
Untreated severe malaria	60 (45–80%)	Beta	[51]
Treated severe malaria	10.9%	Beta	[52]
Early treatment failure leads to severe malaria	5 (3–7%)	Beta	[41]
Untreated malaria becomes severe	5 (3–7%)	Beta	[40]
Spontaneous recovery from uncomplicated malaria	15 (10–20%)	Beta	Assumed
% of febrile episodes attributed to malaria	10.5 ± 20%	Beta	[46]
% of severe cases with access to inpatient care	80 ± 20%	Beta	[53]
% of uncomplicated cases with access to AL	50 (40–60%)	Beta	Primary data
Costs of treating malaria, by severity (US$/case)			
Uncomplicated malaria	6.81 ± 20%	Gamma	Primary data
Severe malaria	76.46 ± 20%	Gamma	Primary data
Drug costs (US$ per dose)			
DhP: 40 mg Dh, 320 mg P ("3×1" pack)	1.46 ± 20%	Gamma	[29]
AL: 20 mg A, 120 mg L ("6×2" pack)	1.31 ± 20%	Gamma	[29]
Quinine Injection, 300 mg/ml (2 ml ampoule)	2.15 ± 20%	Gamma	[27]
Diazepam Injection, 5 mg/ml (2 ml ampoule)	0.23 ± 20%	Gamma	[27]
Diclofenac Injection 25 mg/ml (3 ml ampoule)	0.20 ± 20%	Gamma	[27]
Dextrose 5% (500 ml bottle)	4.75 ± 20%	Gamma	[27]
Ferrous Sulphate + Folic acid, 200 + 0.25 mg	0.30 ± 20%	Gamma	[27]
Paracetamol Syrup 120 mg/5 ml	0.26 ± 20%	Gamma	[27]
Efficacy and compliance rates (%)			
Efficacy of DhP	97.3 ± 2.5%	Beta	[13]
Efficacy of AL	95.5 ± 2.5%	Beta	[13]
Effectiveness of non-ACT anti-malarials	50 (40-60%)	Beta	[47,48]
Compliance with AL	51 (38–65%)	Uniform	[43]
Compliance with DhP[a]	70 (60–80%)	Uniform	Assumed
Compliance with DhP[b]	51 (38–65%)	Uniform	Assumed
Non-compliers with ACTs who are cured	20 (10–30%)	Beta	[39-41]
Other parameters			
Disability weight for uncomplicated malaria	0.005 (0.033–0.081)	Beta	[33]
Disability weight for severe malaria	0.21 (0.139–0.298)	Beta	[33]
Discount rate	3%	Point estimate	[54]
Decision threshold (US$ per DALY averted)	150	Point estimate	[55]

Table 1 Parameters used in the economic model and their distributions *(Continued)*

Life expectancy at age 5 years	57	Point estimate	[35]
Sensitivity of Microscopy	71.3 (68.8–73.9%)	Beta	[56]
Specificity of Microscopy	92.8 (91.3–94.3%)	Beta	[56]

[a]Used in the base case analysis, [b]Used in the scenario analysis.

Cost-effectiveness threshold

An intervention that produces more health benefits at a lower cost than the comparator is considered to be "strongly dominant" and cost-effective. If it is more costly but also more effective, it is considered cost-effective only when its incremental cost-effectiveness ratio (ICER) is less than the willingness-to-pay threshold. "Extended dominance" occurs when the ICER of an intervention is higher than that of the next most effective option [58]. A willingness-to-pay threshold of US$ 150 per DALY averted, which has been recommended as a cut-off point for low- and middle-income countries was applied [55].

Ethics statement

This study was approved by the Ethical Review Committee of the Tanzania National Institute of Medical Research with clearance certificate no: NIMR/HQ/R.8a/Vol.IX/1362. The District Medical Officer in charge of Kinondoni and the management at Mwananyamala Hospital also gave permission to conduct the costing study. The interviewed health workers each provided written informed consent to participate in the study.

Results

Unit costs of treatment

Table 2 presents the estimated unit costs of treating cases of uncomplicated and severe malaria with the associated co-morbidities at an urban district-level hospital in Tanzania. For uncomplicated malaria, the cost per episode was US$ 8.40 with AL and US$ 8.54 with DhP. For severe malaria, the hospitalization cost per episode was estimated to be US$ 83.86.

Table 2 Unit costs (US$) for outpatient and inpatient care

Out-patient care for uncomplicated malaria

Cost category	Items	Service centres			Cost	Unit costs	
		Outpatient	Pharmacy	Laboratory	Total	AL	DhP
Recurrent	Antimalaria drugs	-	-	-	-	1.31	1.46
	Other drugs					0.26	0.26
	Personnel	22,988	7,748	6,066	36,802	5.20	5.20
	Rental of buildings	1,131	538	1,647	3,316	0.47	0.47
	Utilities	1,533	1,368	1,539	4,440	0.63	0.63
	Supplies	700	699	1,558	2,957	0.42	0.42
Capital	Equipment	31	89	108	228	0.03	0.03
	Motor vehicles	70	25	25	121	0.02	0.02
	Furniture	162	109	69	340	0.05	0.05
Total unit costs						8.40	8.54

Inpatient care for severe malaria

Cost category	Items	Paediatric ward	Pharmacy	Laboratory	Total	Unit costs
Recurrent	Drugs	-	-	-	-	7.40
	Personnel	75,895	1,202	845	77,942	61.71
	Rental of buildings	8,012	717	305	9,034	7.15
	Utilities	3,780	494	285	4,559	3.61
	Supplies	2,265	162	288	2,715	2.15
Capital	Equipment	442	21	20	482	0.38
	Motor vehicles	457	3	5	465	0.37
	Furniture	1,319	39	13	1,371	1.09
Total unit costs						83.86

Cost-effectiveness analysis

Table 3 presents the base-case analysis, for which the model predicts that DhP is more cost-effective than AL, with an ICER of US$ 12.40 per DALY averted. AL was eliminated in the base-case analysis because it was extendedly dominated by DhP, therefore, the base-case ICER value represents the comparison of DhP to a do nothing strategy. In the scenario assuming a lower compliance, similar to that of AL, ranging from 38–65%, AL was more cost-effective than DhP with an ICER of US$ 12.54 per DALY averted versus US$ 101.52 per DALY averted.

Incremental cost-effectiveness scatter plot

Figure 2 shows the base-case ICE scatter plot of DhP versus AL. The model predicts that DhP is cost-effective in 97% of the simulations and dominated by AL in 2% of the simulations, at a willingness-to-pay threshold of US$ 150 per DALY averted. With a compliance of 38–65%, DhP was cost-effective in 51% of the simulations and dominated by AL in 37% of the simulations.

Cost-effectiveness acceptability curve

Figure 3 shows the cost-effectiveness acceptability curves (CEAC) for the base-case and scenario analyses of DhP compared to AL. For the base-case, the probability of DhP being cost-effective was 97% at the willingness-to-pay threshold of US$ 150 per DALY averted. In the scenario analysis where we assumed the compliance with DhP to be 38–65%, the probability of DhP being cost-effective was 51% compared to 49% for AL at the same willingness-to-pay threshold of US$ 150 per DALY averted

Characterizing uncertainty

One-way sensitivity analyses were conducted to assess the influence of plausible variations of key parameters on cost-effectiveness of DhP versus AL. The result shows that the cost-effectiveness of DhP relies on the assumption that it has a higher compliance rate than AL, for which the evidence is weak. This is illustrated in Figure 4, which shows that when the compliance with DhP is assumed to be less than 50% it produces fewer health benefits at higher costs than AL (strongly dominated) and at between 50 and 56% it is less cost-effective than AL. When compliance exceeds a threshold of 57%, DhP becomes the cost-effective strategy by extended

dominance. Above 85%, DhP produces more health benefits at a lower cost than AL (strong dominance). Note that the compliance rate for AL was held constant at 51%.

Figure 5 shows a tornado diagram which ranks the parameters in the order of their decreasing influence on the base-line ICER value. In the diagram, DhP was compared to "do-nothing" because AL was eliminated in the analysis due to extended dominance. Uncertainties in parameters describing the natural history of malaria were the most influential on the ICER value. This includes the probability of progression to severe malaria (Untreated to SM), case fatality rate for severe malaria (CFR untreated SM) and the probability of "self-limiting" uncomplicated malaria. The cost-effectiveness of DhP increases with an increase in the values of the first two parameters but decreases with an increase in the probability of self-limiting malaria. The cost-effectiveness of DhP also increases with an increase in the incidence rates of malaria, making it a good choice in high-transmission areas.

Two-way sensitivity analysis

The existing evidence for compliance with AL is very diverse. We therefore performed a two-way sensitivity analysis (Figure 6), to determine various combinations of compliance rates at which the two drugs were cost-effective, at a willingness-to-pay threshold of US$ 150 per DALY averted. This shows that even when compliance is perfect for both drugs, DhP remains slightly more cost-effective than AL.

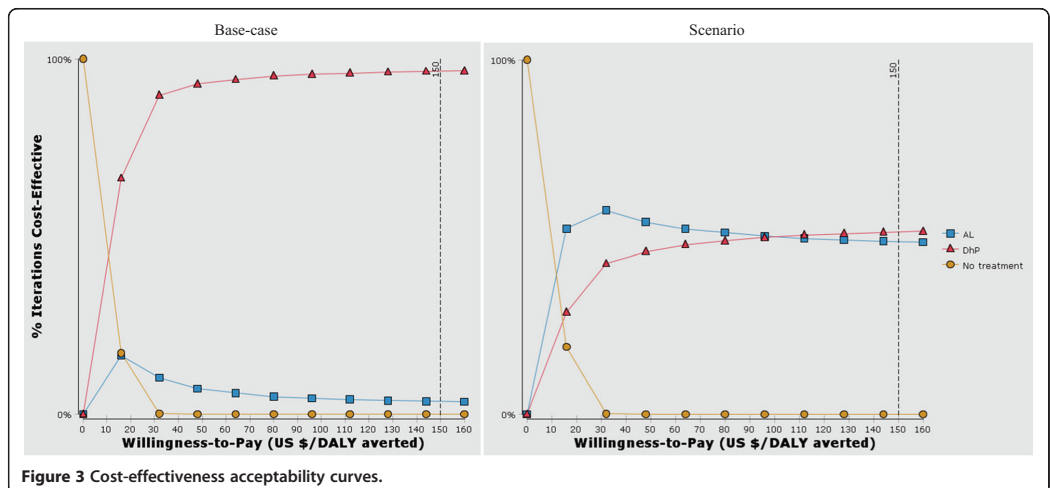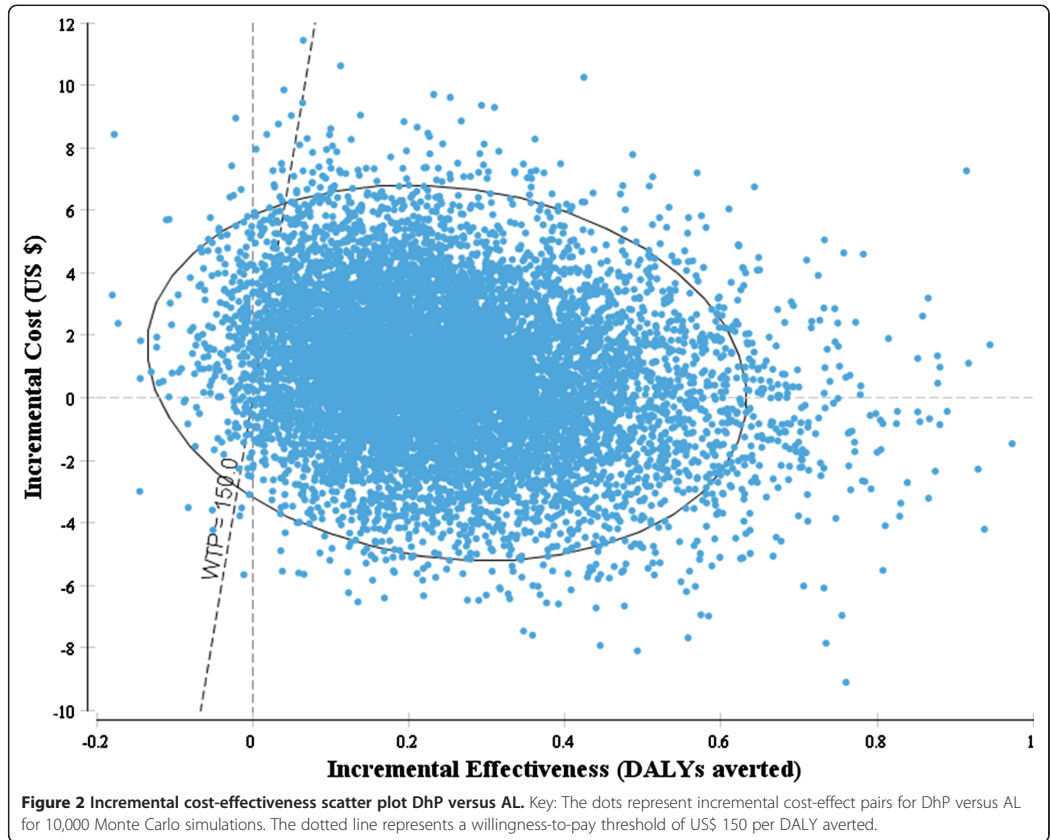### Impact of age-weighting and discounting

In the base-case analysis, DALYs were calculated without age-weighting and with a discount rate of 3%. When DALYs were not discounted, the ICER value of DhP compared to "do-nothing" in the deterministic analysis decreased from US$ 12.33 to 10.80 per DALY averted. Age-weighting assigns different values to time lived at different ages and when it was applied the ICER increased from US$ 12.33 to 18.00 per DALY averted. None of these choices of method had any influence on the conclusions.

Discussion

This study has shown that DhP is a cost-effective anti-malarial drug with an incremental cost-effectiveness

Table 3 Base-case cost-effectiveness analysis

Strategy	Cost (US$)	DALYs	Incremental cost	Incremental DALYs averted	ICER
No treatment	0.00	17.60	0.00	0.00	0.00
AL	165.42	4.47	165.42	13.13	Extendedly dominated
DhP	166.22	4.22	0.80	0.25	12.40

Figure 2 Incremental cost-effectiveness scatter plot DhP versus AL. Key: The dots represent incremental cost-effect pairs for DhP versus AL for 10,000 Monte Carlo simulations. The dotted line represents a willingness-to-pay threshold of US$ 150 per DALY averted.

Figure 3 Cost-effectiveness acceptability curves.

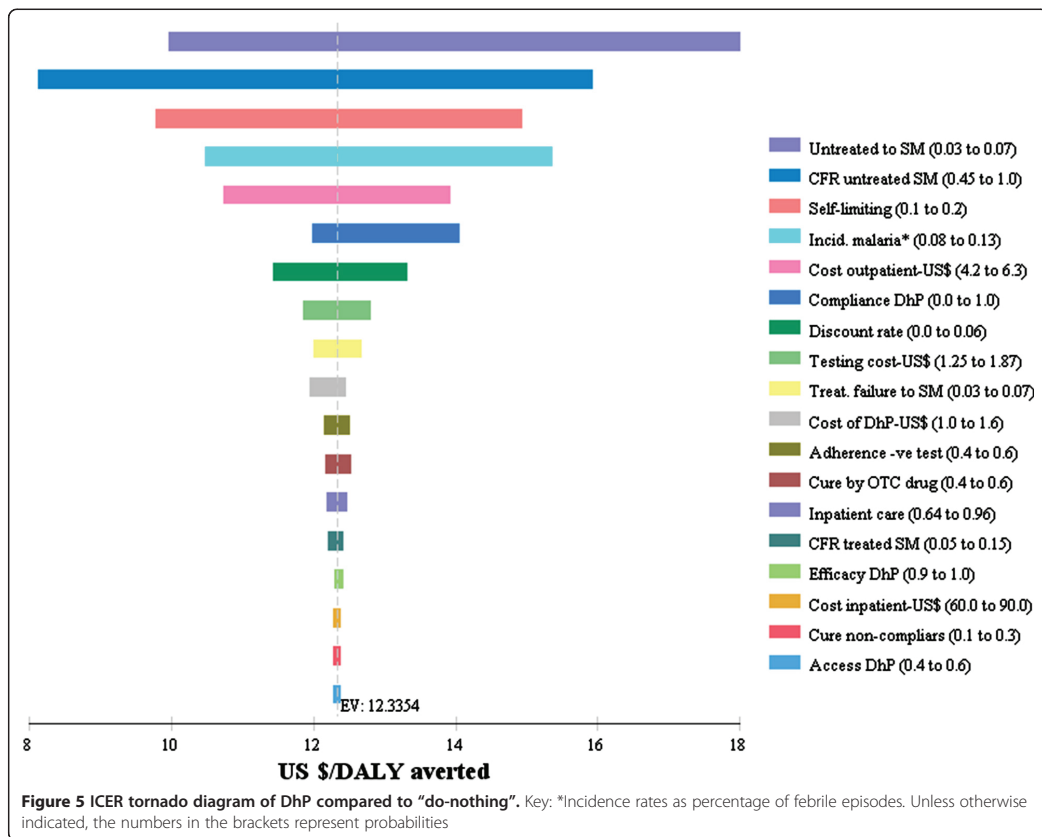**Figure 4 Sensitivity of ICER to variations in the compliance rates for DhP.**
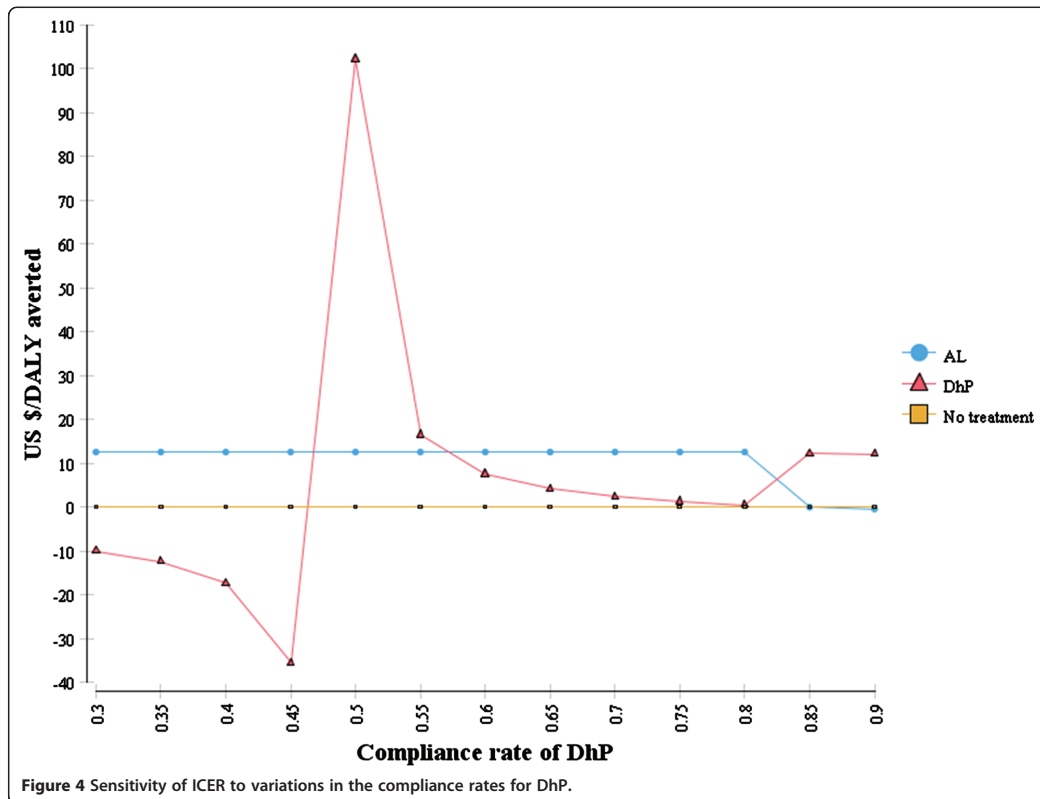
ratio of US$ 12.40 per DALY averted compared to AL. This finding is higher than the US$ 6.23 per DALY averted that was predicted by the Committee on the Economics of Anti-malarial Drugs, which compared ACT with "do-nothing", from the provider's perspective [40]. The ICER is well below all common rules of thumb for cost-effectiveness, including the GDP per capita for each DALY averted recommended by the WHO [59] and the US$ 150 per DALY averted suggested for low- and middle-income countries [55]. Therefore, adequate and timely provision of DhP can be considered a highly cost-effective treatment for uncomplicated malaria.

DhP is currently more expensive than AL and hence any decision to adopt it nationwide as a first-line drug will have significant budget implications. However, DhP has two major advantages over AL that make it an attractive weapon in the fight against malaria. Firstly, it has a relatively simple once-a-day, three-day dosage regimen and a bioavailability that does not require fat-rich meals [37]. This is likely to increase adherence to treatment, which will minimize wastage and improve therapeutic outcomes. Secondly, DhP has a long elimination half-life, which may give it a prolonged post-treatment prophylactic effect that would help to reduce future costs from recurrent infections [18].

In the base-case analysis, DhP was a dominant strategy based on the assumption that it has a compliance rate higher than that of AL; unfortunately, this has not been documented in clinical practice. Since the two drugs have similar safety profiles [13], and taking into account the complex dosage regimen and the pill burden of AL, it is unlikely that the compliance rate for DhP will be lower than that of AL. In addition, the prolonged post-treatment prophylactic effect of DhP, which we did not consider in the analysis, would increase its cost-effectiveness. A recent study has shown that DhP was strongly dominant over AL with a probability of 90%, by modelling the differences in post-treatment prophylactic effect of the two drugs [18].

DhP has received regulatory approval from the European Medicines Agency (EMA) and can now be procured with donor funds [60], at an affordable maximum price of less than US$ 1 per dose [29]. Sigma-Tau, the manufacturer of DhP (Eurartesim®), in collaboration with

Figure 5 ICER tornado diagram of DhP compared to "do-nothing". Key: *Incidence rates as percentage of febrile episodes. Unless otherwise indicated, the numbers in the brackets represent probabilities

Medicine for Malaria Venture, are also developing a new water-dispersible formulation for children under the age of five years [61]. With generic competition, the price of DhP is likely to decrease even further over the coming years.

Even though DhP is a very promising long-acting anti-malarial drug, concerns have been raised about its residual drug levels as a potential risk for the emergence of resistance, especially in high transmission areas [62,63]. A reliable surveillance system is therefore needed to monitor its therapeutic efficacy [13]. Several studies have also shown that the administered dosage and the resulting plasma concentrations are the most important predictors of treatment failures in children treated with DhP [64,65]. Thus, malaria experts have suggested increasing the minimum dosage of piperaquine recommended by the WHO from 48 to 59 mg/kg in order to achieve desirable plasma concentrations [64].

Presumptive treatments and non-adherence to negative test results is another common challenge facing the deployment of expensive drugs like DhP in endemic countries. Studies in Tanzania have shown that malaria is highly over diagnosed and non-adherence to negative test results may be as high as 53% [56]. The WHO's malaria report of 2011 showed that perfect compliance with negative test results would save US$ 68 million by eliminating the unnecessary use of ACT in the public sector in Africa [66].

Limitations
The study used the two-week self-reported prevalence of fever from a national survey to estimate the weekly incidence rates of febrile episodes in children [50]. This approach can overestimate or underestimate the actual incidence rates given the seasonal variation of fever episodes and when counting is not precise due to the overlapping of fevers during the two-week period. This is, however, a preferred approach in the absence of systematically collected data about the annual incidence rates of febrile episodes [66].

Figure 6 Two-way sensitivity analysis of compliance rates for DhP and AL.
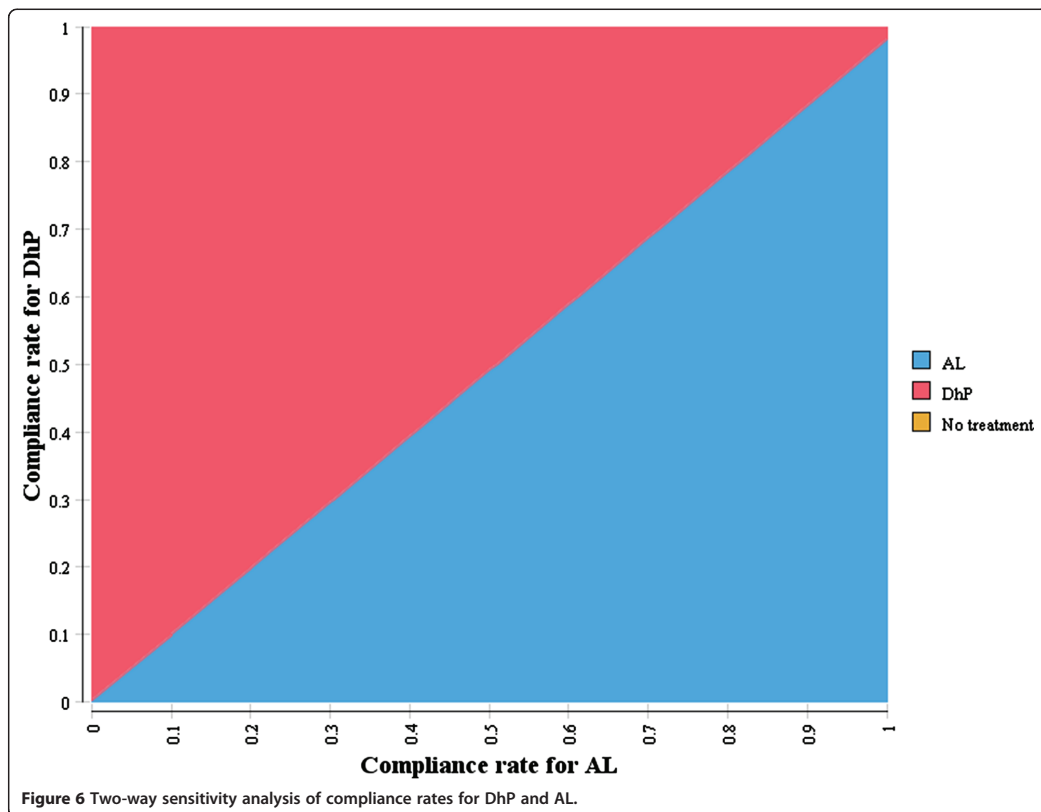
Pragmatic costing studies are difficult to undertake in low-income countries because resource use and attendances at specific departments are not always properly documented. Therefore, we did not include costs for consumables, such as cannulas, syringes, cotton wool and infusion sets. It was also very challenging to allocate overhead costs to service departments, and this forced us to use weighted factors. It was also difficult to adequately calculate unit costs for laboratory and pharmacy services because attendances at these units were not properly recorded. Therefore, the estimated unit costs may have underestimated the actual treatment costs for uncomplicated and severe malaria.

The study was conducted from a provider's perspective without including a more comprehensive societal perspective. Unlike DhP, the use of AL is associated with greater costs due to the requirement for fat-rich meals to optimize its bioavailability. A societal perspective may, therefore, increase treatment costs relatively more for AL, thus favouring DhP in the cost-effectiveness analysis.

The study was focused on health losses due to malaria only, therefore, DALYs lost from the associated co-morbidities of severe malaria such as anemia, convulsions and long-term neurological injury were not included in the model. Their inclusion would have favoured DhP in the cost-effectiveness analysis, because it is relatively more effective than AL due to its high efficacy and compliance rates.

Generalizability

The study used AL, which is the current first-line anti-malarial drug against uncomplicated malaria in many malaria-endemic countries, as a comparator. The drug prices also include freight and insurance charges as well as local administrative costs, which to a large extent accommodate uncertainties in supplier prices. Given that the results were robust to plausible variations in all the key parameters, they are likely to be relatively generalizable to other settings with similar healthcare infrastructures and malaria epidemiology.

Conclusion

DhP is a very cost-effective anti-malarial drug. The findings support its use as an alternative first-line drug for treating uncomplicated malaria in children in Tanzania and other sub-Saharan African countries with similar healthcare infrastructures and malaria epidemiology. A number of countries in malaria-endemic areas are currently considering the adoption of DhP in their malaria treatment guidelines. Therefore, policy-makers in these countries should employ this evidence in order to make informed decisions about allocating their limited resources to competing healthcare interventions.

Additional file

> **Additional file 1: Personnel costs and rental charges.**

Abbreviations

ACT: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AMFm: Affordability medicines facility-malaria; DALY: Disability adjusted life years; DhP: Dihydroartemisinin-piperaquine; MSD: Medical stores department.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ATM, FN, OFN and BR conceived the study. ATM collected the data and performed the analysis. ATM and BR prepared and designed the economic model. ATM and FN prepared and revised the first draft of the manuscript. BR and OFN supervised data collection and analysis and contributed to the manuscript writing. All authors read and approved the final manuscript.

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IV

Budget impact analysis of using dihydroartemisinin-piperaquine to treat uncomplicated malaria in children in Tanzania

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Abstract

Background: Dihydroartemisinin-piperaquine (DhP) is a very cost-effective anti-malarial drug. This study aims to predict the budget impact of using DhP as a first- or second-line drug to treat uncomplicated malaria in children in Tanzania.

Methods: A dynamic Markov decision model based on clinical and epidemiological data was developed to estimate annual cases of malaria in under-five children. The model was then used to predict the budget impact, from the providers' perspective, of adopting two different treatment policy options containing DhP as a first- or second-line drug. A probabilistic sensitivity analysis was performed for a period of one year.

Results: The model predicts that the recently adopted treatment policy for malaria, in which DhP is used as a second-line drug (AL+DhP), will save about 66,800 US$ per year, while achieving a 3% reduction in the number of malaria cases, compared to the previous policy of AL+quinine. However, a treatment policy in which DhP is used as a first-line drug (DhP+AL), will consume an additional 671,000 US$ per year, while achieving an 8% reduction in the number of malaria cases, compared to AL+quinine. Therefore, if AL+DhP is replaced by DhP+AL, it will consume an additional 737,800 US$ per year, while achieving a 5% reduction in the number of malaria cases in children.

Conclusion: The use of DhP as a second-line drug (AL+DhP) to treat uncomplicated malaria in children is slightly cost-saving. However, a policy in which DhP is used as a first-line drug (DhP+AL) is somewhat more expensive but with more health benefits.

Key points for decision-makers

- Understanding the financial burden that will be imposed by a new health technology on the health system is important for planning and budgeting

- Dihydroartemisinin-piperaquine is relatively more expensive than artemether-lumefantrine, but has a greater potential to reduce the burden of *P. falciparum* malaria when used as a first-line drug to treat uncomplicated malaria

1. Introduction

Malaria is an infectious disease, usually of short duration, which caused between 124–283 million cases and 367,000–755,000 deaths globally in 2013 [1]. In Tanzania, malaria is responsible for about one-tenth of all outpatient fevers in children [2]. Most malaria infections in sub-Saharan Africa are caused by *Plasmodium falciparum,* and without adequate treatment the disease can rapidly progress to life-threatening severe malaria. There is a lot of controversy surrounding the precise burden of malaria in African countries. In 2010, malaria deaths in Tanzania among children aged less than five years were estimated to range between 10,928 and 49,663 [3]. In 2013, WHO estimates showed that there were about 14.6 million cases of suspected malaria in the country, which places Tanzania among the countries with the highest burden of malaria in the sub-Saharan African region [1].

Tanzania has repeatedly changed its malaria treatment guidelines in response to *Plasmodium falciparum* resistance to anti-malarial drugs. In 2001, chloroquine was replaced with sulphadoxine-pyrimethamine (SP) as the first-line drug for case management of uncomplicated malaria. In 2007, SP was replaced by artemether-lumefantrine (AL), while quinine was recommended as a second-line drug (AL+quinine) [4]. In 2014, quinine was replaced with dihydroartemisinin-piperaquine (DhP) as the second-line drug (AL+DhP) [5]. AL and DhP are two out of the five artemisinin-based combination therapies (ACTs) recommended by the WHO to treat uncomplicated malaria [6] .

Recent research evidence indicates that DhP may be a better first-line drug to treat uncomplicated malaria than AL, because it is more effective [7], and offers a prolonged post-treatment prophylaxis, which reduces the risk of recurrent malaria infections [8, 9]. In addition, DhP has a simple once-a-day dosage regimen which enhances adherence to treatment [10]. Economic evaluation studies have also indicated that DhP is more cost-effective than AL and hence it represents better value for money when used as a first-line drug to treat uncomplicated malaria [8, 11, 12]. Mori *et al* (2014), showed that DhP was more cost-effective than AL from a providers' perspective with an incremental cost-effectiveness ratio of US$ 12.40 per DALY averted in a Tanzanian setting [12].

While consideration of cost-effectiveness as a criterion is important, affordability and feasibility are also of relevance. Budget impact analysis (BIA) is increasingly being recognized as a crucial part of a comprehensive health technology assessment. BIA estimates the financial consequences of adopting a new drug within a specific healthcare setting to guide formulary-listing decisions [13]. This study aims to predict the budget impact of adopting DhP as a first- or second-line drug in Tanzania compared to a previous policy composed of AL and quinine (AL+quinine), respectively.

2. Methods

3.1. Analytical framework

The budget impact analysis was conducted using a dynamic Markov cohort model with four mutually exclusive health states: "well", "uncomplicated malaria", "severe malaria" and "death" as an absorbing health state. The model is a modified version of the one used to evaluate the cost-effectiveness of AL and DhP when used as first-line drugs in Tanzania [12]. While the original model was closed, this is an open model, with new members entering the cohort to reflect growth in population size (Fig 1). The cohort begins in a "well" state and

then transit to other states in one-week cycles based on risk factors for malaria, access to healthcare and cure rates of anti-malarial drugs.

The analysis was performed from the providers' perspective for a duration of one year, assuming a steady state of implementation of the new policy. A Probabilistic Sensitivity Analysis (PSA) was conducted using Monte-Carlo simulations to assess the robustness of the model considering the uncertainty associated with the input parameters. The analysis was run using TreeAge Pro 2015 software. The study adheres to the BIA guidelines from the International Society for Pharmacoeconomics and Outcome Research (ISPOR) task force, with minor modifications to suit the model design [13].

3.1. Intervention mix

Two competing treatment policies to treat uncomplicated malaria, each consisting of AL and DhP as first- or second-line drugs, were evaluated against a reference policy of AL+quinine. A regimen consisting of a three-day dosage of parenteral quinine, which is followed by an oral dose of the first-line drug, was employed as a standard treatment for severe malaria in all policies. The treatment policies involved are:

1. AL+quinine: This is a reference policy in which AL and quinine are first- and second-line drugs, respectively. This policy was launched in 2006 [4] and followed until it was replaced recently by AL+DhP [5].

2. AL+DhP: This policy option substitutes quinine with DhP as the second-line drug in the reference policy and is consistent with a recent policy change in the country [5]. This treatment policy is also consistent with WHO recommendations regarding the treatment of uncomplicated malaria [6].

3. **DhP+AL**: This policy option substitutes AL with DhP as the first-line drug in the reference policy, and at the same time changes AL to the second-line drug. This

policy would exploit the benefits of DhP, which include relatively higher efficacy and compliance rates. It is also consistent with WHO recommendations regarding the treatment of uncomplicated malaria [6].

3.1. Patient population

The study was conducted in a sub-population of 7,273,832 children under the age of five years in Tanzania [14]. Children are most vulnerable to malaria and account for more than two-thirds of all malaria deaths [1]. Estimates of the size of the eligible population was based on a two-week prevalence of fevers of about 20% [15], of which about 10.5% have been attributed to malaria infections [2]. Cohort growth is based on an adjusted weekly birth rate of 8,466 [14, 16] and an under-five mortality rate of 81 per 1,000 live births [17]. The latter all-cause mortality rate was adjusted downward by 11% to represent deaths due to causes other than malaria [18]. Progression to severe malaria and survival rates in each arm depend on the effectiveness of the first- and second-line drugs, which are influenced by differences in compliance rates.

3.1. Characteristics of anti-malarial drugs

A large head-to-head, multi-center randomized clinical trial indicated that DhP has a cure rate of 97.3% versus 95.5% for AL, based on an intention-to-treat analysis. The administration of drugs in this trial was directly observed and children stayed at the facilities long enough to check for any vomiting, which implies perfect adherence to treatment [19]. DhP is administered once a day while AL should be taken twice a day together with fat-rich meals, both for three consecutive days. Compliance rates for AL and DhP range from 60–80% and 70–90%, respectively [10, 20].

Quinine has been used as a second-line drug for the management of uncomplicated malaria in endemic countries for many years, mostly due to the lack of an appropriate alternative drug. The major limitations of quinine are its long, three-times-a-day dosage regimen, which extends to seven days, and cinchonism side-effects. In a nested clinical trial, quinine showed cure rates ranging from 88–98% in a head-to-head comparison with AL and DhP, when it was used as a second-line drug to treat recurrent malaria infection in children in Uganda [21]. An assumed compliance rate varying from 40–60% was used in this study, based on a clinical trial and one other economic study [22, 23].

Patient compliance to treatment is a primary determinant of therapeutic outcomes. Poor compliance to anti-malarial drugs increases the chances of treatment failure and, more importantly, drug resistance. However, in economic modeling studies it is commonly assumed that between 10 and 20% of non-compliers to multi-dosage treatments with anti-malarial drugs such as the ones considered in this study will spontaneously recover [24, 25]. Therefore, in order to predict cure rates, we combined efficacy rates from trial settings and adherence rates observed in routine clinical practice using the formula below:

$$Cure\ rate\ = E_0 C + E_{nc}(1 - C)$$

where E_0 is efficacy, C is compliance rate and E_{nc} is the proportion of non-compliers for whom treatment remains effective.

3.1. Care-seeking for diagnosis and treatment of malaria

Care-seeking behavior for the treatment of malaria is very complex and is influenced by many factors, such as: perceived severity of the disease, proximity to the facility, availability of medicine and the ability to pay for health services [26, 27]. In this study, caregivers are modeled to seek care for their febrile children from three main sources: the public sector, which also includes non-profit faith-based facilities; the private sector, which is composed of

accredited drug shops and pharmacies; and informal sources. A recent national HIV/AIDS and Malaria Indicator Survey reported that between 77 and 81% of caregivers sought care from formal health facilities [15]. Between 50 and 70% of these formal facilities are composed of public facilities and the remainder include private-sector pharmacies and drug shops, which are scattered all over the country [28].

Diagnosis with the rapid diagnostic test (RDT) was recently scaled up in public facilities countrywide to reduce the over-diagnosis and over-treatment of malaria [29]. Therefore, it was assumed that 50–70% of all febrile children in the public facilities are treated based on RDT test results [30] and the rest based on presumptive diagnosis. Non-adherence by health workers to an RDT negative test was estimated to vary from 7–20% [31, 32]. Test results were based on Bayesian calculations, with a prior positive test probability of 10.5%, and sensitivity and specificity of RDT of 95.4% (94.2–96.6) and 95.9% (94.8–97.0), respectively [33]. The sensitivity and specificity of presumptive diagnosis were set at 30% (20–40) and 90% (80–100), respectively [34].

It is assumed that all positive cases in the public facilities are prescribed the recommended first-line drug, with an availability of 40–80% [35]. Between 40 and 60% of those patients who are missing the recommended drug will be able to access it from private-sector drug shops and pharmacies [36]. The rest may purchase non-recommended drugs, with cure rates assumed to be in the range of 10–60% [37]. If a child still has uncomplicated malaria after the initial treatment, we assume the caregiver will choose to return to the public facility, where the second-line drug will be prescribed. The availability of second-line drugs was assumed to be 80–100% for quinine because it is relatively cheap and 40–60% for ACTs. For simplification, we assumed that the second-line ACT will be restricted in the public sector and when it is out of stock, we assumed patients will be given the first-line drug.

Private-sector drug shops and pharmacies are an important first point of care for patients with suspected malaria infections in Tanzania. However, diagnostic tests are usually unavailable; hence treatments are based on symptoms alone. A majority of these premises stock ACTs, following the implementation of the Affordable Medicines Facility-malaria (AMFm) program [38]. Considering that the major incentive of these premises is to maximize sales, we assume that between 60 and 80% of febrile children receive anti-malarials [39], of which between 40 and 60% are recommended first-line drugs [40]. To capture the complexity of care-seeking, we assumed that half of the patients who fail treatments will choose to shift to the public health facilities and the rest will remain in the private sector.

In Tanzania, only formal healthcare facilities, including the private-sector accredited drug shops and pharmacies, are authorized to stock anti-malarial drugs. Therefore, all treatments sought from informal sources, such as markets, local shops and traditional healers, are considered to be ineffective. However, we assumed that 10–20% of these cases recover spontaneously [12]. Those who continue to suffer from uncomplicated malaria will shift to the public healthcare facilities for further treatment.

We assume that 3–7% of untreated uncomplicated malaria cases, or those who experience treatment failure, progress to severe malaria [25, 41]. Data about care-seeking behavior for the treatment of severe malaria are scarce, and the existing information in the literature may be too old to represent the current situation in Tanzania [42, 43]. Therefore, we assume that 80–100% of severe cases of malaria have access to adequate inpatient care, which reduces the case-fatality rate to 10.9% [44]. The mortality rate for untreated severe malaria has been estimated to range between 45 and 80% [45].

3.1. Resource use and costs

A costing study which was conducted at an urban district-level hospital exists and this has been reported elsewhere [12]. However, due to its lack of representative cost data for personnel and other items, the current BIA study focuses on expenditures incurred on drugs and RDTs. For uncomplicated malaria, the drugs included are the recommended first- and second-line anti-malarials. SP is no longer recommended for this purpose, but it was assumed to be available in the private-sector premises [25]. Antipyretics such as paracetamol were omitted because they are relatively cheap and hence unlikely to have significant budgetary implications. For severe malaria, the cost of a standard regimen consisting of parenteral quinine, diclofenac, diazepam, folates and a first-line ACT was included [5].

The Global Fund's reference prices negotiated with the manufacturers of ACTs for under-five children [46] were used, as shown in Table 1. For SP, a price of US$ 0.32 (0.25–0.38) from the International Drug Price Guide was used [47]. These prices were inflated by 20% to account for program costs. Prices of other drugs were taken from the Price Catalogue of the Medical Stores Department [48]. An exchange rate of 1,670 Tanzanian shillings to 1 US$ was used [49]. Prices of RDTs have decreased recently due to price competition; hence a unit price of US$ 0.45 (0.36–0.55) was used [29].

3.1. Uncertainty

Probability distributions were employed to incorporate uncertainties in the parameters used in the model (Table 1). Beta distributions were used for probability parameters to limit their possible values to the interval 0–1, while costs were constrained between 0 to positive infinity by gamma distributions. Triangular distributions were used to describe estimated population size and birth rates while uniform distributions were used to represent compliance rates to different drug regimens. Overall uncertainty in the parameters was propagated in the

model by running a Probabilistic Sensitivity Analysis based on a Monte Carlo simulation with 10,000 iterations. One-way and two-way sensitivity analyses were used to test how variations in key parameters may potentially influence the results.

3.   Results

3.1.   Model validation

The model was validated using the reference policy (AL+quinine) to determine whether the predicted clinical results from the simulations correspond with the figures reported in the literature. The predicted number of uncomplicated malaria cases was 7,510,727, which is about two-thirds of all suspected cases, ranging between 10 and 12 million [29]. The predicted number of severe malaria cases was 173,600, which is about two-thirds of the 300,690 that was estimated in the WHO report of 2013 [51]. The predicted total number of under-five deaths was 134,028, which is within the range of 123,100–186,700 [52]. The predicted number of malaria-attributable deaths was 26,973, which is within the reported range of 10,928–49,663 for under-five children in Tanzania [3].

3.2.   Budget impact analysis

The model predicts that the treatment policy of AL+DhP will save about 66,800 US$ (0.3%), while that of DhP+AL will consume an additional 671,000 US$ (3.0%), per year, compared to AL+quinine. This implies that replacing AL+DhP with DhP+AL will consume an additional 737,800 US$ (3.5%) per year, as a budget for drugs and RDTs (Table 2). It is interesting to note that DhP+AL has the highest drug costs but the lowest costs for RDT compared to other policies. The reason for this difference in cost is that the higher effectiveness rate of DhP as a first-line drug reduces episodes of malaria and hence the requirement for RDT tests.

3.3. Impact on health outcomes

Table 3 shows the estimated change in overall annual health outcomes, as recommended by the new guidelines for reporting BIA analysis, for the two malaria treatment policies. The model predicts that the policy of AL+DhP has the potential to reduce the number of malaria cases by 248,437 (3%) compared to the reference policy of AL+quinine. However, the policy of DhP+AL, which is more expensive, has the potential to reduce the number of malaria cases by 612,955 (8%) compared to the reference policy of AL+quinine. This implies that if the policy of AL+DhP is replaced by DhP+AL, the number of malaria cases will be reduced by 364,517, which is equivalent to a 5% reduction.

3.4. Sensitivity analyses

The policy of AL+quinine has already been replaced with that of AL+DhP, and since it is probably not very attractive to revert to quinine-based therapy, policy-makers will be more interested in a comparison of DhP+AL versus AL+DhP. This is presented in the Tornado diagram shown in Fig 2, which expresses the potential influence of uncertain parameters on budget impact. Four parameters, representing the cost and the compliance rates for DhP and AL, were identified to be the most influential.

Considering that the cost of DhP is the most influential parameter, it was important to show how variation in the cost of DhP causes changes in the actual budget, as indicated in Fig 3. At a cost of 0.84 US$ per dose of DhP, the policy of DhP+AL is the cheapest option and requires a total budget of about 20.7 million US$ annually. It should be noted that this cost includes 20% program costs; hence, the actual acquisition cost is 0.67 US$ per dose. That is to say, Tanzania should buy DhP for children at a negotiated maximum price with the manufacturers not exceeding 0.70 US$ to avoid any increase in budget.

The tornado diagram also shows that variations in compliance rates have an important impact on budget. We therefore further explored the impact of varying compliance rates in a two-way sensitivity analysis (Fig 4). The policy of AL+DhP was found to represent the smallest budget (blue region) in the base-case analysis at compliance rates of 70–90% and 60–80%, for DhP and AL, respectively. However, as indicated by the orange region, the policy of DhP+AL becomes the cheapest alternative choice when the compliance rate is relatively lower for AL than for DhP.

4.   Discussion

Malaria is an infectious disease which consumes a substantial portion of the limited health budgets of sub-Saharan African countries. It is the leading cause of morbidity and mortality among outpatient visits and inpatient admissions in Tanzania. It has been estimated that malaria accounts for about 2% of the Gross Domestic Product, which is equivalent to about 20% of the total health expenditure in Tanzania [53]. This is the first study in Tanzania to estimate the budget impact of introducing DhP to treat uncomplicated malaria in under-five children either as a first- or second-line drug.

A majority of countries in sub-Saharan Africa are using AL as a first-line drug and quinine as second-line drug against uncomplicated malaria. Even though ACTs are the preferred choice for the treatment of uncomplicated *P. falciparum* malaria [6], it is understandable that some countries persist with the use of quinine as a second-line drug due to lack of alternative ACTs. Therefore, the emergence of DhP as a very promising ACT has changed the treatment dynamics of malaria in many countries in recent years. A number of countries have already adopted DhP as a second-line drug instead of quinine and many others are considering doing the same. Mainland Tanzania is one of the countries that recently replaced quinine with DhP as a second-line drug to treat uncomplicated malaria [5].

This study found that the use of DhP as a second-line drug (AL+DhP) to treat uncomplicated malaria in children is slightly cost-saving, i.e. US$ 66,800 per year from the providers' perspective. This represents a reduction in the number of malaria cases of about 3% compared to the previous policy of AL+quinine. The model also predicts that when DhP is used as the first-line drug (DhP+AL), it imposes additional costs on the health system, i.e. US$ 737,800 per year, while reducing the number of malaria cases by another 5% compared to AL+DhP. Pfeil et al. (2014) found that the use of DhP as a first-line drug in moderate-to-high transmission areas will avert 12% of malaria cases in children [11]. More recently, Okell et al. (2014) estimated a reduction of 10–15% in high-transmission areas [8]. Our study shows a smaller reduction in malaria cases because we did not consider the longer prophylactic effect of DhP, which reduces the recurrence of malaria [8, 9].

This study has a number of limitations and hence its results must be interpreted with care, and more importantly it should never be used as the sole basis for initiating policy change in Tanzania. Firstly, policy change is a very complex and expensive undertaking [54]. In 2000 it cost the Tanzanian government about 0.8 million US$ to implement the new malaria treatment policy, representing about 4% of total malaria expenditure and 1% of total public expenditure on health [55]. Another study estimated the costs of this policy change to be equivalent to 0.02 US$ per person [54].

Secondly, care-seeking behavior for diagnosis and treatment of malaria is very complex in sub-Saharan Africa and data may not always be readily available. In the model, a number of structural and parameter assumptions were made in an attempt to replicate how patients move from one type of facility to another in actual practice when seeking care. It is nearly impossible to model this with sufficient accuracy. The model assumptions portray caregivers seeking care from the informal and formal health facilities in a very orderly manner, which

rarely happens in reality. Even the diagnosis and treatment practices in public facilities vary from one location to another.

Thirdly, the study assumes that the majority of patients visiting public facilities are diagnosed with RDTs and all positive cases are prescribed with the recommended first-line drug, with a mean availability of 60%. While we believe that these are reasonable base-case assumptions, several studies have shown that quality of care in public facilities varies greatly and that diagnostic tests and drugs often completely run out of stock for prolonged periods of time [56, 57]. The availability of a second-line drug was assumed to be restricted in the public facilities, which may still not be the case. Dispensing practice in private drug shops and pharmacies is more complex than the way it is modeled here; hence, the estimated health benefits of the two malaria policies may deviate from the model predictions.

Fourthly, unlike other studies, this study ignored the potential prolonged post-treatment prophylactic effect of DhP compared to that of AL [8, 9], which is a conservative assumption. However, the study took into account their different compliance rates in the calculation of health benefits. A recent study has shown that the compliance rate for DhP is higher than that for dispersible AL in children in Malawi [10]. The higher compliance rate for DhP is largely due to its relatively simple once-a-day dosage regimen, compared to the twice-a-day dosage regimen of AL. Therefore, by ignoring the prolonged post-treatment prophylaxis, this study may have underestimated the actual health benefits of DhP.

Finally, but equally importantly, rational social planners are concerned not only about reducing healthcare costs, but also about broader considerations when distributing scarce healthcare resources, including considerations of efficient and equitable health care.

5.   Conclusion

In accordance with the present model's predictions, the use of DhP as a second-line drug (AL+DhP) to treat uncomplicated malaria in children in Tanzania is slightly cost-saving. However, the use of DhP as a first-line drug (DhP+AL) will consume an extra 737,800 US$ per year which represents a 3.5% increase in budget for drug and Rapid Diagnostic Tests compared to AL+DhP. Nevertheless, the use of relatively more expensive drugs such as DhP as first-line anti-malaria drugs, without proper diagnosis, should be approached with caution. Otherwise, the opportunity cost of presumptive treatment outweighs the benefits, due to over-diagnosis and overtreatment of patients without clinical malaria.

Ethical standards

The manuscript does not contain clinical studies or patient data.

Author contributions

ATM, OFN and BR conceived the study. ATM retrieved the data and performed the analysis. ATM and BR prepared and designed the economic model. ATM prepared the first draft of the manuscript. BR and OFN supervised data analysis and contributed to the manuscript writing. All authors read and approved the final manuscript.

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Table 1: Parameters used in the model and their distributions

Parameters	Estimates	Distributions	Sources
Cohort size of under-five population in millions	7,273,832±20%	Normal	[14]
Adjusted weekly birth rate	8,466±20%	Normal	[14, 16]
Under-five mortality rate per 1,000 live births	81 (72–90%)	Beta	[17]
Malaria-attributed deaths in under fives	11%	Point estimate	[18]
Two-week incidences of fever episodes per child	0.20±20%	Beta	[15]
% of febrile episodes attributed to malaria	10.5±20%	Beta	[2]
Case fatality rate of untreated severe malaria	60 (45–80%)	Beta	[45]
Case fatality rate of treated severe malaria	10.9%	Beta	[50]
Early treatment failure leads to severe malaria	5 (3–7%)	Beta	[41]
Untreated malaria becomes severe	5 (3–7%)	Beta	[25]
Probability of care-seeking in formal facilities	79 (77–81%)	Beta	[15]
% of formal facilities belonging to public sector	60 (50–70%)	Beta	[28]
% of severe cases with access to inpatient care	90 (80–100%)	Beta	[42]
Access to first-line drugs in public facilities	60 (40–80%)	Beta	[35]
Access to second-line drugs in public facilities	50 (40–60%)	Beta	assumption
% of children given antimalarials in private facilities	70 (60-80%)	Beta	[39]
% of antimalarials that are ACT in private shops [a]	50 (40–60%)	Beta	[36, 40]
Efficacy of DhP	97.3 (94.9–99.7%)	Beta	[19]
Efficacy of AL	95.5 (93.1–97.9%)	Beta	[19]
Efficacy of quinine	93.0 (88.0–98.0%)	Beta	[21]
Compliance with AL	60–80%	Uniform	[10, 20]
Compliance with DhP	70–90%	Uniform	[10, 20]
Compliance with quinine	40–60%	Uniform	[22, 23]
Non-compliers with treatments who recover	20 (10–30%)	Beta	[24, 25]
Sensitivity of RDT	95 (94.2–96.6%)	Beta	[33]
Specificity of RDT	96 (94.8–97.0%)	Beta	[33]
Sensitivity of clinical diagnosis	30 (20–40%)	Beta	[34]
Specificity of clinical diagnosis	90 (80–100%)	Beta	[34]
Adherence to a negative RDT result	10.5 (7.0–14.0%)	Beta	[31, 32]
Drugs and diagnostic costs (US$ per dose/test)			
DhP: 40mg Dh, 320mg P ("3x1" pack)	0.77 (0.56–0.93)	Gamma	[46]
AL: 20mg A, 120mg L ("6x2" pack)	0.67 (0.54–0.84)	Gamma	[46]

Quinine, 300mg/tablet	0.59 (0.47–0.70)	Gamma	[47]
SP: 500mg S, 25mg P ("3x1" pack)	0.32 (0.25–0.38)	Gamma	
Quinine Injection, 300mg/ml (2ml ampoule)	2.40 (1.92–2.87)	Gamma	[48]
Diazepam Injection, 5mg/ml (2ml ampoule)	0.23 (0.18–0.27)	Gamma	[48]
Diclofenac Injection 25mg/ml (3ml ampoule)	0.29 (0.23–0.35)	Gamma	[48]
Dextrose 5% (500ml bottle)	3.95 (3.16–4.74)	Gamma	[48]
Ferrous Sulphate+Folic acid, 200+0.25mg	0.26 (0.21–0.31)	Gamma	[48]
Cost of malaria Rapid Diagnostic Test (mRDT)	0.45 (0.36–0.55)	Gamma	[29]

[a] As a proportion of dispensed anti-malarial drugs

Table 2: Annual incremental cost from a providers' perspective (US$)

Policy options	RDT costs	Drug costs	Total cost	Incr. cost [a]	Incr. cost [b]
AL+quinine	6,446,783	14,488,735	20,935,518	Reference	
AL+DhP	6,420,571	14,448,147	20,868,718	-66,800 (-0.3%)	Reference
DhP+AL	6,273,601	15,332,923	21,606,523	671,006 (3.0%)	737,805(3.5%)

[a] Both AL+DhP and DhP+AL are compared to AL+quinine

[b] DhP+AL is compared to AL+DhP

Table 3: Impact on the number of malaria cases for under-five children

	Uncomplicated malaria	Severe malaria	All cases	Reduction in number of malaria cases
AL+quinine	7,510,727	173,599	7,684,326	Reference
AL+DhP	7,274,872	161,016	7,435,888	-248,437 (3.2%)
DhP+AL	6,928,818	142,554	7,071,371	-612,955 (8.0%)

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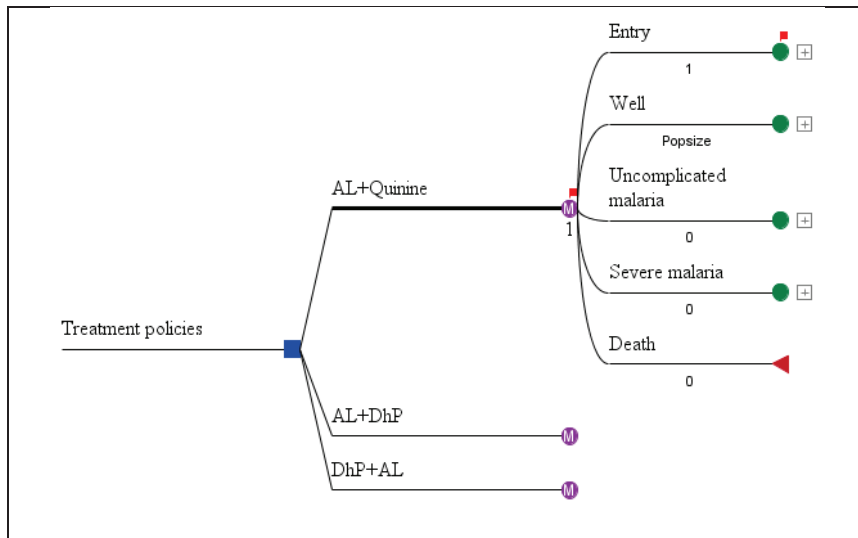
Figures

Fig. 1 A dynamic Markov decision model

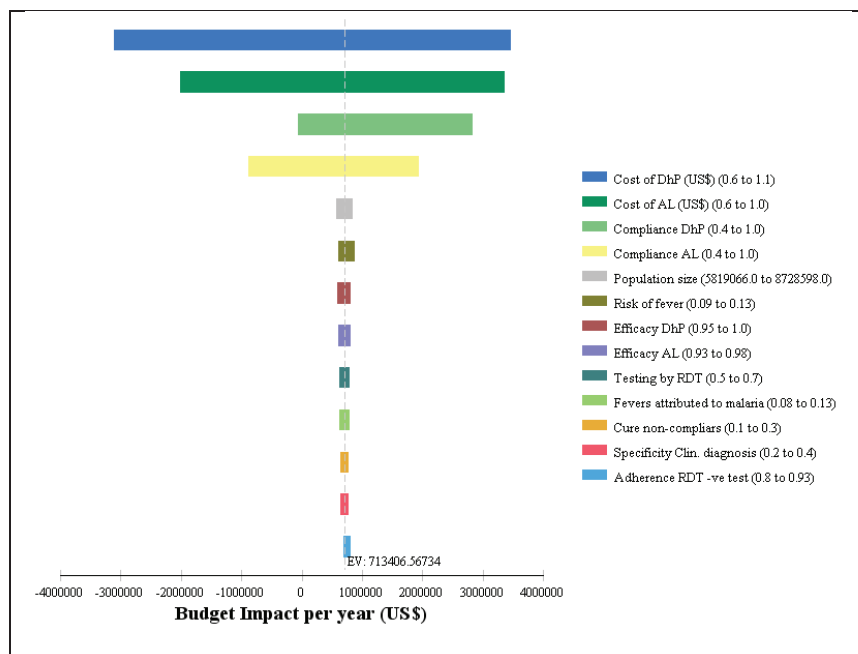[a] Popsize - the population size of children under considerations

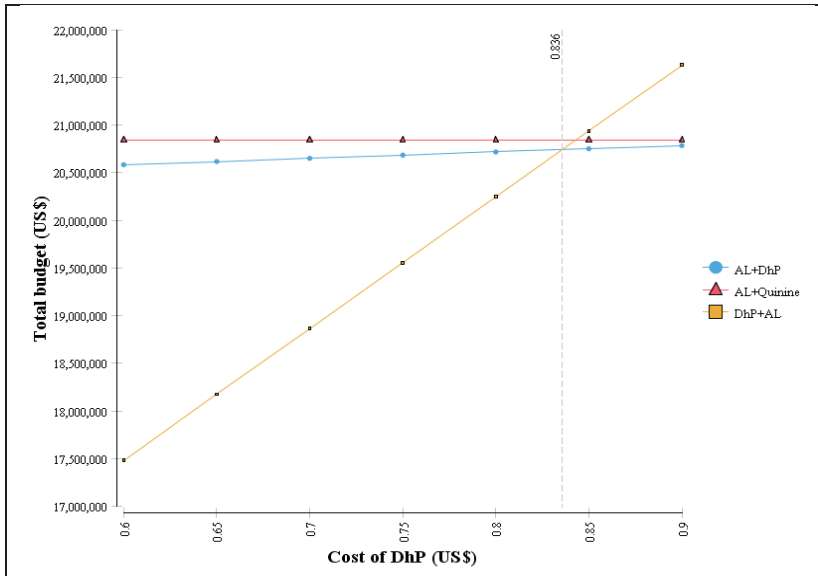**Fig. 2** Incremental Tornado diagram of DhP+AL versus AL+DhP

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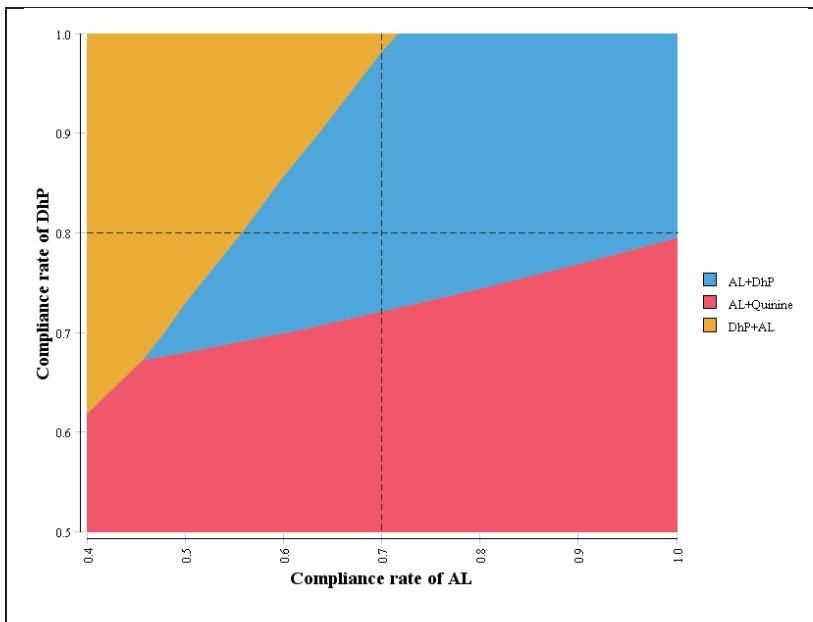**Fig. 3** Change in total budget versus variation in the cost of DhP

Fig. 4 Variations in the compliance rates for AL and DhP and how they affect annual budgets

[a] The dotted lines indicate mean compliance rates for DhP and AL

Appendices

THE UNITED REPUBLIC OF
TANZANIA

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P.O. Box 9083
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Fax: 255 22 2110986

23rd July 2012

Amani Thomas Mori
Muhimbili University of Health and Allied Sciences
Faculty of Pharmacy
P O Box 65013
DAR ES SALAAM

CLEARANCE CERTIFICATE FOR CONDUCTING
MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Evidence –based essential medicine selection: Generating pharmacoeconomic and coverage data for decision-making in Tanzania, (Mori A T *et al),* has been granted ethics clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:
1. Progress report is submitted to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health & Social Welfare and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Approval is for one year: 23rd July 2012 to 22nd July 2013.

Name: Dr Mwelecele N Malecela

Signature

**CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE**

Name: Dr Donan Mmbando

Signature

**ACTING CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL
WELFARE**

CC: RMO
        DMO

KINONDONI MUNICIPAL COUNCIL

ALL CORRESPONDENCES SHOULD BE DIRECTED TO THE MUNICIPAL DIRECTOR

Tel: 2171022

In reply please quote:

Ref. No. FD/K/14/79

MUNICIPAL MEDICAL OFFICER OF
HEALTH,
KINONDONI MUNICIPAL COUNCIL
P.O. BOX 61665,
DAR ES SALAAM

Date: 19/7/ 2012

② Mwananyamala Hosp — ~~~~~ 31/7/2012

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3 1 JUL 2012
RECEIVED

HEALTH FACILITY I/C
① **SINZA HOSP**
KINONDONI MUNICIPAL.

RE: PERMIT TO COLLECT DATA

MR . AMANI THOMAS MORO

The Office of Municipal Medical Officer of Health has allowed the above named
Student from **MUHAS SCHOOL OF PAHAMACY . Taking PhD Program in Health
Economics at the University of Bergen , Norway.** to conduct research work at your
facility .
The aim is to collect data on the estimate average inpatient and outpatient costs for
Malaria treatment in rural and urban settings in Tanzania and your facility was selected
for this exercise.
Please provide them with all necessary information and help.

Your Cooperation is highly appreciated.

F.MGANA
(Training Coordinator)
Kinondoni Municipal Council

Dr. Casto to
assist.

31/7/2012

Copy: To above mentioned Candidates.

Received
23/07/2012

JAMHURI YA MUUNGANO WA TANZANIA
OFISI YA WAZIRI MKUU
TAWALA ZA MIKOA NA SERIKALI ZA MITAA

HALMASHAURI YA WILAYA YA IRINGA

<u>**Kumb Na.DMO/IR/R/VOL I/40**</u>   <u>**02,OCTOBA,2012**</u>

Mganga Mfawidhii,
Hospitali ya Tosamaganga,
S.L.P 11,
Iringa.

    YAH: **KUMTAMBULISHA KWENU NDUGU AMANI THOMAS MORI KUTOKA MUHAS.**

Husika na kichwa cha habari hapo juu

 Tunamtambulisha mtajwa hapo juu kutoka MUHAS ili aweze kuja kukusanya takwimu zinazohusiana na Malaria. Mpokeeni na kumpatia ushirikiano.

Asante kwa ushirikiano.

Dr. I. Mlowe
Maganga Mkuu (W)
Iringa