Costs and Cost-Effectiveness of Artesunate Against Quinine Treatment Therapy for Severe Malaria in Children Under 14 Years in Zambia.

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Research

Abstract

Background

Malaria exerts a significant economic burden on health care providers and households. Also, the cost of inpatient care for a case of severe malaria further exerts a heavy financial burden on most countries with already limited recourses. Therefore, it is essential to provide policy makers with relevant economic evidence on economic benefits of health care control, preventive and curative strategies.

Methods

Cost-effectiveness analysis of severe malaria treatment was conducted from a healthcare provider perspective using a decision tree. Standard costing was performed for the identification, measurement and assessment phases, with data from Zambia annual quantification reports for anti-malaria commodities. The data was collected from Health Management information system, and meta-analysis. Average and incremental cost-effectiveness ratio were estimated. The uncertainties were assessed through probabilistic sensitivity analysis.

Results

Severe Malaria in Children has been shown to account for over 45% of the total monthly curative healthcare costs incurred by households compared to the mean per capita monthly income. The cost of treating severe malaria depleted 7.67% of the monthly average household income. In addition, the cost attributed to loss of income in taking care of a sick child is the highest contributor $10.5 of total cost followed by direct medical costs $7.75. According, to the cost effectiveness analysis the of Artesunate with quinine the ICER was $105 per death averted.

Conclusion

The use of Artesunate over Quinine in the treatment of severe malaria in children under 14years is a highly cost-effective strategy for the healthcare provider in Zambia.

Background

Malaria remains a major public health problem in Zambia, despite significant progress made in fighting the disease in the last decade. Malaria prevalence varies across all provinces and districts with 18 million people at risk, including the most vulnerable groups, such as pregnant women and children. The country's last two iterations of the National Malaria Strategic Plan (NMSP) aimed to reduce transmission through multiple strategies, including the distribution of long-lasting insecticide-treated mosquito nets (LLINs), increased indoor residual spaying (IRS), mass drug administration, improved case management using rapid diagnostic tests (RDTs)/Microscopic laboratory tests, and treatment with artemisinin-based combination therapy [1][2]. In the current NMSP (2017–2021), the Government of Zambia through the Ministry of Health and the National Malaria Elimination Program (NMEP) adopted an ambitious agenda to eliminate malaria through deployment of the above outlined interventions, inclusion of new tools and innovations and strengthening of routine surveillance at all levels. The efforts towards nationwide malaria elimination with regard to malaria case management, emphasizes the need to have diagnostic and curative services as close to homes as possible while utilizing community health workers as extensions for the health facility within the community. In the recent past the NMEP has provided an annual sustained supply of more than 15 million treatment courses of the recommended artemisinin combination therapies and over 20 million rapid diagnostic tests. This is in addition to ensuring availability of more than 5.5 million tablets for intermittent presumptive treatment for pregnant women. With an estimated 20.3% parasite prevalence, the NMEP has adopted therapeutic approaches such as mass drug administration (MDA) to accelerate the decline of parasite prevalence. On the other hand, case management coverage has greatly improved through strengthening of general health

services and the provision of adequate diagnostics and medicines according to national guidelines. The national objective is to ensure that 100% of all suspected malaria cases in all districts receive parasitological (microscopy or RDT) analysis and all parasitological confirmed malaria cases receive prompt (within 24 hours), effective antimalarial treatment. Moreover, attaining Universal coverage by providing service for all, with early diagnosis and effective treatment is a key strategy in reducing morbidity and mortality. The total malaria commodity needed to meet client needs per year with a full pipeline of 6 months of stock is estimated at around $ 27,374,448 which possess financial challenges [3]. Despite a better understanding of pathophysiology and management of malaria, childhood mortality remains unacceptably high [4]. Thus, Over the past decade, there has been some progress in defining best practices for antimalarial treatment. The Artesunate versus Quinine in Severe Malaria in African Children Trial (AQUAMAT), conducted in 9 African countries and involving 5425 children, showed that Artesunate-treated children had a 22.5% (95% confidence interval, 8.1 to 36.9) lower relative risk of death than those receiving the time-honored quinine [5]. Therefore, In 2011 the World Health Organization (WHO) recommended parenteral Artesunate in preference to quinine as first-line treatment for people with severe malaria. Prior to this recommendation many countries, particularly in Africa, had begun to use artemether, an alternative artemisinin derivative. Nevertheless, Artesunate is recommended for treating adults and children that have severe malaria as studies have shown that it results in fewer deaths compared to treatment with quinine [6]. Notwithstanding, severe and fatal Plasmodium falciparum malaria continues to affect young children in sub-Sahara Africa representing approximately 90% of total global the cases, and one of the main cause of hospital admission and inpatient mortality [7]. Malaria exerts a significant economic burden on health care providers and households. Particularly The total annual costs for malaria interventions in Ghana, Tanzania and Kenya were estimated at US$ 37.8 million, US$ 131.9million and US$ 109 million respectively.in addition, out of pocket towards treatment ranged from US$5.98 to US$45.23 for families[8] .Also, the cost of inpatient care for a case of severe malaria has been estimated between US$ 12 and US$ 75 which further exerts a heavy financial burden on most countries with already limited recourses[9][10][11] . Most recently, many Governments of the sub-Saharan region adopted plans to aggressively eliminate malaria in the region and sustained efforts towards malaria elimination in most of the countries have been seen to produce desirable results and thus in the right direction to attaining the intended goal. Therefore, In the context of increasing attention towards improved malaria control in settings with budget constraints, competing health problems and weak health systems, it is essential to provide policy makers with relevant economic evidence of the economic benefits of health care control and prevention strategies.

Methods

This study was designed to compare the costs involved in Artesunate and Quinine treatment regimen for severe malaria in Children under 14 years . Products compared were injectable formulations, Quinin 300mg ampoule and Artesunate 60mg ampoule and also the costs relating to severe malaria treatment. To determine the efficacy parameter, literature searches were conducted to identify published clinical trials for each of these products in the treatment of severe malaria. Search strategies included the generic drug names combined with hazard ratios. Selected articles were restricted to human studies published in English.

The cost-effectiveness model was constructed as a Markov model using stochastic parameters, created in Microsoft excel, with cycles having 1 year time period. Beta distributions were used for treatment probabilities and utilities in view of the fact that it restricts values between 0.0 and 1.0. while Gamma distributions were used for cost variables because of data skewness [12]. considering cost effectiveness is primarily utilized for formulary and reimbursement decision making, the perspective of the analysis was that of a health payer, a managed-care organization as a healthcare provider. It's worth mentioning that individual variables for costs, utilities, and probabilities were stochastic and based on their respective distributions [3] [13] [14] [15]. Data collection was from 1st January to 31st October,2020 and analysis was conducted in November of the same year.

Model overview

We modelled the disease progression for severe malaria. Five main states of health were distinguished: (1) healthy or disease-free; (2) transition state of uncomplicated malaria; (3) severe malaria; (4) transition state of hospitalization; and (5) death from severe malaria Figure 1. Other model input data, included mortality rates, hazard ratio and possible transitions probabilities between health states. Thus, these were deterministic within the Markov cycles taking a form that healthy children can either remain healthy, die or acquire uncomplicated malaria which progresses to severe malaria. Children in severe malaria state get hospitalized and receive Artesunate or quinine. Children in severe malaria state either recover fully or die. Children who recover after treatment enter the state healthy

Utilities

Due to scarcity of quality of life estimations in children affected by severe malaria, we took an approach to apply the methodology described McCarthy et al to estimate the age-specific quality-of-life utility weights for the different health states. Also, using a self-administered visual analogue scale (VAS) based on the scale employed as part of the EQ-5D instrument as well as Published articles were used to identify utilities for severe malaria [16].

Costs

The Zambia annual quantification report for anti-malaria commodities 2017-2018 was used to determine monthly costs of each treatment. This document was selected because it integrates both product cost and any applicable freight cost from all suppliers of the commodities, is readily available, and avoids the ambiguity of various product discounts and additional costs without freight charges from average landing cost. Other costs were obtained from hospital local procurement documents and local wholesalers and published literature. Drug administration cost per dose of Artesunate and quinine included costs of a pair of examination gloves,2 needles,5mg syringe and ,2 needles ,5mg syringe,1000ml normal saline, IV infusion set respectively. Also, diagnostic costs were included in the model. Treatment costs for severe malaria were divided into pharmacological treatment, laboratory and nursing care. all cost conversions from Zambian kwacha to united states dollar was based on the exchange rate of October month end of the same year.

Cost-effectiveness analysis

The cost-effectiveness model was constructed as a Markov model using stochastic parameters. The Markov model, created in Microsoft excel, with cycles having of 1 year time period. Beta distributions were used for treatment probabilities and utilities in view of the fact that it restricts values between 0.0 and 1.0. while Gamma distributions were used for cost variables because of data skewness [12]. considering cost effectiveness is primarily utilized for formulary and reimbursement decision making, the perspective of the analysis was that of a health payer, a managed-care organization as a healthcare provider. In addition, populations were created and followed until death to estimate costs and QALYs time horizon of 14 years. Also, the model was employed to calculate the ICER for the case of a single cohort of 1,000 children aged between1-14 years who are healthy and are prone to the high prevalence of malaria. As cost-effectiveness analysis is generally applied for a single cohort, these complementary results permit comparison with published data.

Probabilistic sensitivity analysis

In any economic evaluation such as this there are a number of key variables that are subject to uncertainty. A probabilistic sensitivity analysis was in excel using Monte Carlo simulation to assess the effect of uncertainty surrounding the costs

and effectiveness estimates. Each variable was allocated a distribution fitting the range of all possible values with each simulation randomly generating and select the value for each variable from the specified distribution. Consequently, examining the effect of joint uncertainty in the variables of the model through cost-effectiveness plane and acceptability curve. The cost-effectiveness plane shows the incremental cost on the vertical axis and effectiveness on the horizontal axis for 1,000 simulation runs. Also, results showed the mean value and 95 % confidence intervals (CI) for total costs and QALYs. Sensitivity analysis allows exploration of the impact of change in one or more of these variables on the result robustness [18].

Results

The total costs of direct and non-direct medical costs of the two arms Artesunate and Quinine as well as the variables used in the model are as shown in **Table 1**.

Table 1: Costs and model values

	Model value	Mean	Standard error	Alpha	Beta	Distribution type	Formula	Source
Mortality								
Age <14 years	0.11	0.11						[17]
Severe Malaria	0.23	0.36						[38]
Transition probabilities								[14]
Drug costs								
Artesunate drug	7.8							
Other drugs	3.6							
Fluids	10.7							
Laboratory Tests	6.4							
Nursing Care	37.1							
Total drug Cost	65.6	66	9	53.777778	1	gamma		[19] [13] [20] [39]
Quinine drug	2.6							[19] [13] [21]
Other drugs	3.8							
Fluids	11.0							
Laboratory Tests	6.6							
Nursing Care	37.4							
Total drug cost	61.4	61	6	103.361111	1	gamma		
Cost hospitalization	65	65	19	11.7036011	6	gamma		[13] [22] [23]
Hazard ratio								
HR die Artesunate	0.78	64	0.01	-	-	normal		[24] [25]
HR disease Artesunate	0.64	64	0.01	-	-	normal		[24] [25]
HR hospitalization Artesunate	1.02	1	0.001	-	-	normal		[24] [25] [26]
Utility								
Utility healthy	0.98	0.98	0.07	3	0	beta		[16] [27]
Utility disease	0.80	0.80	0.05	50	13	beta		[16] [28]
Utility decrement	0.1	0.1	0.08	1	12	beta		[28]

hospitalization					
Discount Rate	5.0%	5.0%	-	-	-	-	-	[1]

Costs involved in each severe malaria episode for children under 14 years revealed on average about $10.5 was incurred by the caregivers due to productivity loss days of work. This represented approximately 26% of the mean per capita monthly income **Table 2**. While registration fee, consultation fee, drugs/surgical, diagnostic tests and transportation representing $0.75,$4.5,$2,$0.5 and $5.2 respectively.

Table 2: Household income expenditure

	VARIABLES	MINIMUM AVERAGE COST	MAXIMUM AVERAGE COST	AVERAGE COST(SD)	PERCENTAGE MEAN PER CAPITA MONTHLY INCOME %
Direct Medical Cost	Registration fee	0.15	4.25	0.75(0.65)	1.9
	Consultation fee	4.24	17.5	4.5 (4.1)	11.3
	Drugs/surgical	0.25		2.0(1.8)	5
	Diagnostic Tests (RDT/Laboratory)	0.5	2.5	0.5 (0.3)	1.3
Sub-Total				7.75	19.3
Direct Non-Medical Cost	Transportation	2.0	6.5	5.2(2.7)	13.0
Indirect Cost	Loss of Income			10.5(0.28)	26.25
Overall Cost				23.45	48.75

The incremental cost-effectiveness ratios were estimated as the total healthcare cost per death averted. Compared with the strategy of using Artesunate/ quinine has an ICER of $105 per death averted.

Table 3: Incremental cost effectiveness ratio

Treatment			Incremental		ICER
	Costs	QALY			
Artesunate	430	6.23	77	0.74	105
Quinine	352	5.49			

Scatter plot of 1000 samples of mean incremental costs plotted against mean incremental effectiveness generated for 1000 patients for Artesunate therapy versus Quinine therapy. The most of the points lie in the upper right-hand quadrant, indicating increased costs and increased effectiveness with a few points in the lower right-hand quadrant indicating cases being dominant in the stimulation **figure 2**.

According to **figure 3,** base-case acceptability curve for Artesunate therapy versus Quinine therapy generated from 1000 samples of mean incremental costs versus mean incremental effectiveness generated for 1000 patients treated with either Artesunate therapy or Quinine. The acceptability curve shows how likely it will be that Artesunate therapy is cost-effective for any particular willingness to-pay.

Discussion

The introduction of injectable Artesunate by governments requires effective communications on its effectiveness and benefits in the context of each country, for a clear definition of the projected national funding requirements and availability of financial sources. The cost of severe malaria treatment is high and households bear a greater portion of this cost due to a high level of indirect costs. To some households this may be catastrophic. There is need to buffer this with some sort of financial risk protection mechanisms and the health care system needs to be strengthened to function more effectively and decrease overall out of pocket payments to aid in alleviating economic burden of malaria.

Severe Malaria in Children has been shown to account for over 45% of the total monthly curative healthcare costs incurred by households compared to the mean per capita monthly income. On the other hand, the cost of treating severe malaria depleted 7.67% of the monthly average household income [36]. In addition, the cost attributed to loss of income in taking care of a sick child is the highest contributor $10.5 of total cost followed by direct medical costs $7.75 as shown in **Table 2**. Similar findings were reported by the central statistical office of Zambia in the 2015 living condition monitory survey showing the average amount spent on medication and/or consultation by person consulted. At national level, the average amount spent on consultation or medication was about $12.while, Rural/urban analysis indicated on average $8 and $19.5 respectively. Household spending on malaria can be classified into expenditure on prevention and expenditure on treatment. Individual or household direct cost of malaria treatment include direct payment of drugs, consultation, laboratory tests, transportation fees to and from the health facility, and the caregiver's productive time lost due to malaria.

In our study, the cost of Artesunate was $65.6 which was costly than the quinine arm, this result compares favorably to the mean costs from studies by Lubell et al. who recorded $66.5 for the Artesunate arm and 61.4 for the quinine arm respectively [29]. According to the 2015 living condition monitoring survey by the central statistics of Zambia, the mean per capita monthly household income as defined by the total household income divided by the number of persons in the household was $40. thus, treatment of malaria with possess a financial burden on families as it costs more than the estimated monthly total expenditure, hence the need for government to sustain the provision of free malaria treatment [30].On the other hand, our model-based analyses suggest that the health benefits associated with the use of Artesunate in children with severe malaria is cost-effective when compared with the use of quinine at commonly accepted willingness-to-pay thresholds derived from the gross domestic product per capita [17].As shown in **figure 3** treatment with Artesunate over quinine indicating increased costs and increased effectiveness as well as some cases showing dominance. Moreover, use of Artesunate could significantly have cost savings through avoided drug administration costs and nursing care to alleviate risk of cardiotoxicity, as intravenous quinine administration needs rate-controlled infusion over four hours, three times a day, accompanied by cardiac monitoring if possible. A study examining malaria deaths showed that one in four patients had received incorrect dosing. [31]. in addition, due to high mortality rate among children, the benefits of expanded use of Artesunate could be a right step in the right direction to reduce the malaria burden [32]. The cost of averting malaria-related deaths in Zambia by switching from quinine to Artesunate had a value of ICER US$ 105 per death averted which is in line with the world health organization cost effectiveness for malaria interventions **Table 3.**To add on, the results are similar to the incremental cost per death averted in children in sub-Saharan African, estimated on average to be US$123 [5] [25] [33]. This compares very favorably with other interventions, such as the use of insecticide-treated nets, with a cost per death averted of US$ 254 to US$ 3437[13], [34]. On the other hand, costs of the drug used in the analysis and the costs associated with nursing time, Laboratory diagnostic tests, and costs of consumables like examination gloves, syringes, needles cannulas and infusion sets/solutions, were in-cooperated into the

model. Other researchers also suggest that administrative cost and nursing care time are more on the quinine arm and would even favor Artesunate to be more cost effective [35]. Not only Artesunate is cost effective but injectable Artesunate is simpler to administer, and given once a day while the comparative drug requires multiple dosing and close monitoring for cardiotoxicity. To add on, Artesunate also reduces episodes of hypoglycemia during treatment by 45% hence a cost saving therapy [32]. Consequently, the use of Artesunate in the management of severe malaria in children is seen to have more monetary benefits.

Furthermore, the robustness of our results over a range of varying assumptions was tested in the sensitivity analysis, even with conservative estimates around the parameters used in the model for sensitivity analysis, the findings remain cost-effective across a range of estimates in the model on assumptions at the threshold of willingness to pay. This threshold has been used frequently in similar studies and the World Health Organization recognizing 3 times the gross domestic product per capita as an upper threshold [33]. This study also revealed the cost-effectiveness acceptability curve having the probability of Artesunate being cost-effective being approximately 12% without any additional investment. In addition, with a willingness-to-pay of $150 and $300, Artesunate therapy produces a probability around 70%, and above 95% respectively. Figure 3.

Limitation

Our assessment had considerable limitations that are expected in the construction of any decision model. Firstly, societal perspective of economic evaluation has a more comprehensive framework for analysis but we took a healthcare perspective because Malaria treatment is free of charge from all government hospitals. Also, our assumptions were that of a patient having only one episode of severe malaria during the one year cycle.

Owing to the fact that cost effectiveness models can be sensitive to time horizon of the analysis, and in most cases covering a life expectancy time horizon. In the case the incremental cost comparisons may be somewhat accurate, but the cumulated incremental benefits may be significantly underestimated.

Conclusion

Injectable Artesunate is the WHO-recommended treatment for severe malaria in children and adults. Thus, Countries that have not yet made a clear recommendation of injectable Artesunate as a first-line treatment, should also work with WHO to align its guidance to global WHO recommendations. https://www.severemalaria.org/resources/injectable-artesunate-assessment-report

The Artesunate therapy is highly cost effective and anticipated to significantly reduce the current mortality caused by severe malaria in Zambia. Unfortunately, to date, not all malaria-endemic countries have adopted and implemented the WHO recommendations. There is an urgent need to speed up the adoption and implementation of this new policy. Recommendations for effective interventions have been proposed. the synergic effect of preventive and curative interventions coupled with Financial support from governments and malaria funding organizations is a key component in achieving this goal.

Abbreviations

DHIS District Health Information System

ICEAR Incremental cost effectiveness ratio

IRS Indoor Residual Spraying

LLINs Long Lasting Insecticide Nets

MACEPA Malaria Control and Elimination Partnership in Africa

MOH Ministry of Health

NMEP National Malaria Elimination Program

PMI President's Malaria Initiative

RDTs Rapid Diagnostic Tests

USAID United States Agency for International Development

WHO World Health Organization

Declarations

This study received ethical approval from in China from the institutional review board of China Pharmaceutical University (Nanjing, China). While in Zambia from the National Health Research Authority(NHRA), Ministry of health public health and research unit and relevant authorities at the ministry of health.

Consent for publication

Not Applicable

Availability of data and materials

The data set used/analyzed are available from the corresponding author on request

Competing Interests

The authors declare that they have no competing interest

Finding

There is no funding for this study

Authors Contribution

MM and WX contributed to the conceptualization of the study. The design by MM, JLM and DWW. Data collection by MM and JLM.MM and JLM analyzed and interpreted the data.MM and XZY wrote the first draft of the manuscript. XZY, DWW and WX revised the article for important intellectual content. All authors read and approved the final manuscript

Acknowledgments

We would like to express our special thanks to the Zambian Ministry of Health, Monitoring and Evaluation unit for giving us access to the district health information system and the hospital staff from varies hospitals, health centers, and clinics working in the records/registry department

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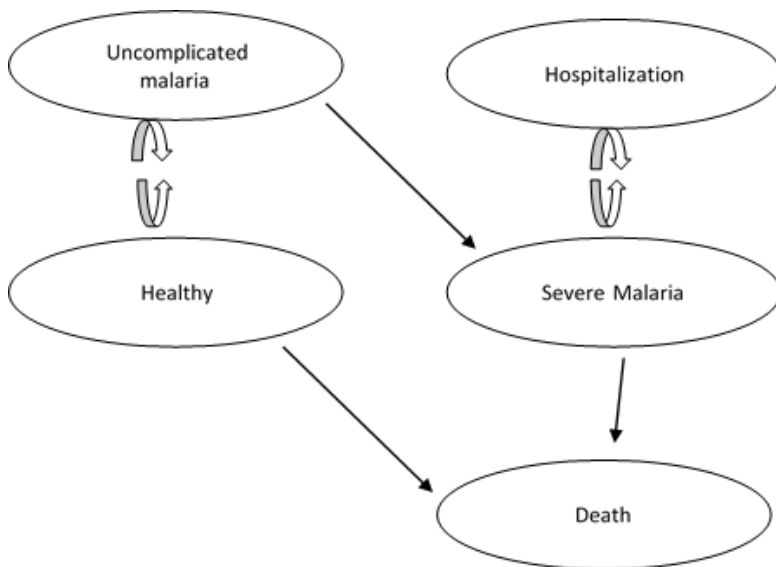
Figures

Figure 1
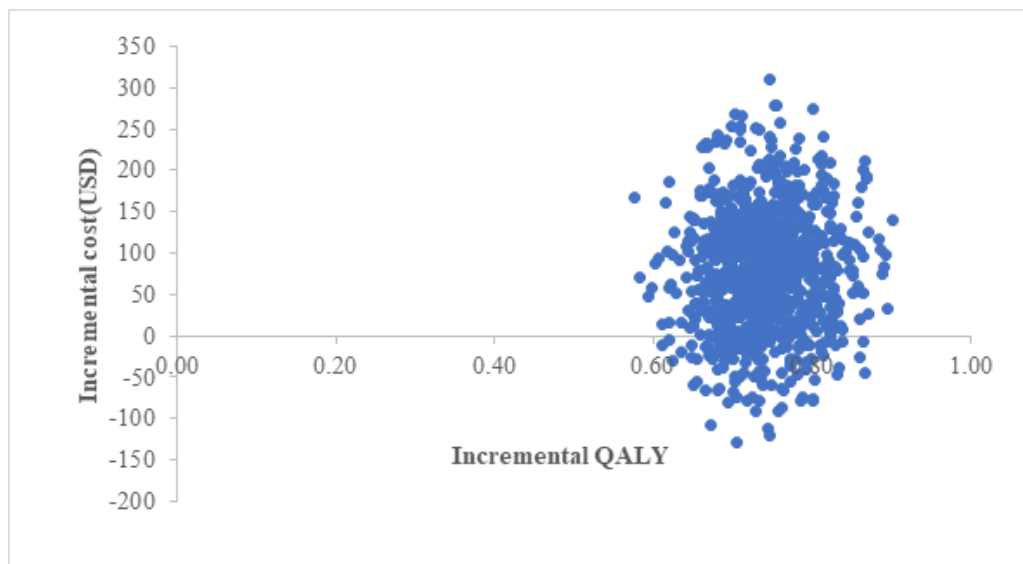
Structure of the model

Figure 2
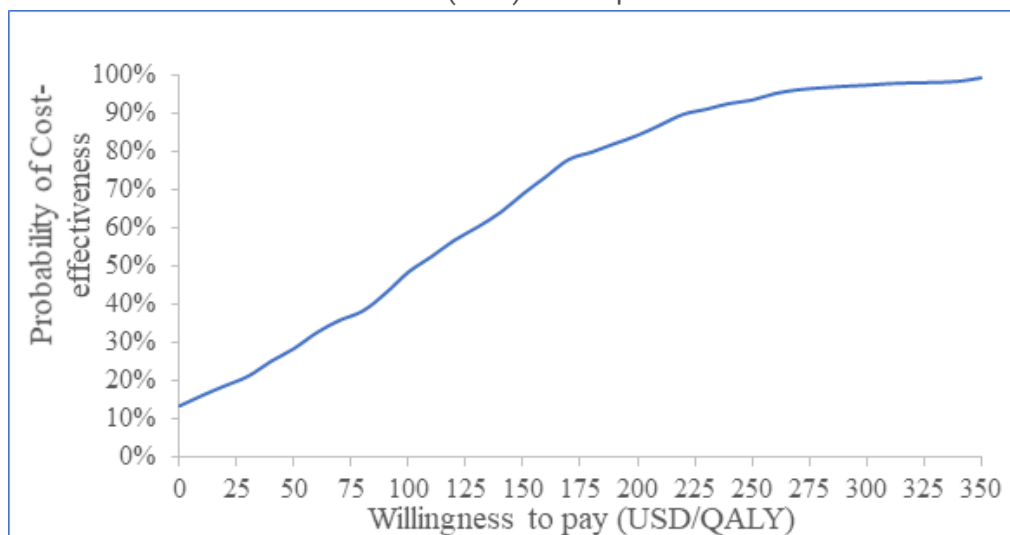
Incremental Cost-effectiveness ratio(ICER) Scatterplot

Figure 3

Cost-effectiveness acceptability curve