



Review article

Systematic review of microeconomic analysis of pregnancy-associated malaria

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ARTICLE INFO

Keywords:

Malaria
Pregnancy
Economic evaluations
Cost-effectiveness
Costs
Systematic review
Public health
Infectious disease
Women's health
Evidence-based medicine
Economics

ABSTRACT

Introduction: Pregnancy-associated malaria (PAM) is a health problem with serious clinical, epidemiological and economic effects.

Purpose: To analyze the microeconomic evaluations of PAM reported in the world scientific literature.

Methods: Systematic review with 15 different search strategies in PubMed, ScienceDirect, Scielo, Google Scholar and Malaria in Pregnancy (MiP) Library. A search, selection and extraction protocol was applied, which guaranteed completeness and reproducibility in accordance with preferred reporting items for systematic reviews and meta-analysis guidelines. The methodological quality was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guide. The analysis were based on frequencies, costs and average and incremental cost-effectiveness ratios in 2018 US dollars adjusted for purchasing power parity.

Results: Twenty-two evaluations published between 1990 and 2018 were analyzed, of which 82% addressed cost-effectiveness in Africa. Twelve interventions were studied; of these, intermittent preventive treatment in pregnant women with sulfadoxine-pyrimethamine (IPTp-SP) was the most frequent strategy. The main outcomes were low birth weight, anaemia and DALYs avoided. The best average cost-effectiveness ratio was reported in IPTp-SP with a cost of US\$ 2 per DALY avoided, followed by the administration of IPTp-SP in pregnant women with HIV (US\$ 14.2).

Conclusions: The studies focus on Africa with a high heterogeneity in the interventions, outcomes, resources and populations studied. All the interventions were highly cost-effective, which demonstrates the importance of including prevention, care and control resources for PAM as a priority in health sector budgets. This is especially true considering the importance of its intervention for social progress and overcoming poverty in endemic areas.

1. Introduction

Malaria affects 40% of the world population. The World Health Organization (WHO) estimates 300–500 million people at risk, of which 109 live in America, with approximately one million deaths caused by paludism [1, 2]. Among the most vulnerable groups are pregnant women; in this group, the disease causes 15% of severe anaemia and 35% of low birth weight (LBW) [3, 4]. Pregnancy-associated malaria (PAM) affects the health of pregnant women, fetuses, newborns and children, causing anaemia, cerebral malaria, severe malaria, intrauterine growth retardation, premature birth, abortions, LBW, congenital malaria, higher risk of coinfections and malnutrition, and maternal, intrauterine, neonatal and infant mortality [4, 5, 6, 7, 8, 9].

With respect to the investigation, there are several meta-analysis available on the efficacy of different drugs to prevent PAM and LBW [10, 11, 12]; on intermittent preventive treatment in pregnant women (IPTp) and the use of mosquito nets with insecticides [13]; the burden of PAM and its effects on maternal and infant health [14] or about specific outcomes such as the risk of abortion and stillbirth [15]. A meta-analysis estimated that IPTp reduces the risk of severe PAM 38%, prophylaxis with chloroquine or IPTp decreases the risk of LBW by up to 43% and prophylaxis with antimalarials, IPTp or insecticide-treated mosquito nets (ITMs) reduces perinatal mortality 27% [16].

In addition, some experts have indicated that investigation on PAM should focus on four areas: *i*) vaccines and malaria in the first trimester of pregnancy, *ii*) prevention, control and combination of actions in

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Received 27 May 2020; Received in revised form 16 July 2020; Accepted 22 July 2020

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populations with different transmission risks, *iii*) increased coverage of existing interventions and *iv*) immunology, pathology, physiology, diagnosis, burden of disease and economic impact of PAM [17].

Consistent with the last recommendation, microeconomic health assessment studies involve technologies or interventions that not only are effective and safe but also present feasible costs for health systems, that is, they show an optimal relationship between the resources used and benefits obtained [18]. However, in case of PAM, this type of studies seems to be restricted to Africa, and there is marked heterogeneity of designs, interventions, costing types, evaluated outcomes, among other relevant items of the health economy that are dispersed in the scientific literature. In this order of ideas, cost-effectiveness studies are available for IPTp with sulfadoxine-pyrimethamine (SP), the use of ITMs [19, 20], the costs of diagnosis and management PAM [21] and direct and indirect treatment costs [22].

Although subject reviews [23] or systematic reviews [24] of malaria prevention have been published, they exclude partial economic evaluations associated with gestational malaria. In addition, because they are not circumscribed only in PAM, these reviews do not include all available economic studies in this field [21, 22] and did not perform a methodological evaluation of the studies included in the review, which inhibit the determination of internal and external validity of each economic evaluation analyzed.

The purpose of this research was to analyze the economic evaluations of PAM carried out at the global level through a systematic review. The advantages of this type of research include drawing conclusions with a greater extrapolation framework, more precise estimates and a higher level of evidence, allowing for the orientation of subsequent health or investigative actions [25] or public policies based on the evidence, which maximize the efficient in the use of health resources.

2. Materials and methods

2.1. Type of study

Systematic review of the literature.

2.2. Question PICO-RT: population intervention comparator outcome (Outcome) resources and time (Time frame of the economic evaluation)

Population: Pregnant women with malaria or at risk of infection. PAM includes gestational malaria, placental malaria or the presence of *Plasmodium* in placental tissue, and congenital malaria that affects the product of pregnancy in the uterus or up to 30 days of age, ruling out the fact that it was acquired by anopheline bite or blood transfusion.

Intervention: Pharmacological alternatives with chloroquine (CQ), mefloquine (MQ), IPTp with SP and ITMs.

Comparator: Pharmacological measures other than intervention, with or without educational messages.

Outcome: LBW, anaemia, clinical malaria, years of life lost (YLL) and disability-adjusted life years (DALYs) avoided.

Resources: The costing items included in the partial and full economic evaluations.

Time frame: At least one semester of pregnancy.

2.3. Research protocol according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guide

Identification: Nine search strategies were used combining the MeSH (Medical Subject Headings) terms 'malaria', 'paludism' and 'Plasmodium' with the Boolean 'AND &' 'pregnancy', 'placenta' and 'gestation' in PubMed, ScienceDirect, Scielo and Google Scholar. They were complemented by a search in the Malaria in Pregnancy (MiP) Library using the terms 'economic evaluation', 'costs', 'cost-minimisation', 'cost-effectiveness', 'cost-utility' and 'cost-benefit'. All searches were conducted in English, Spanish and Portuguese.

Screening: The selection of studies was conducted independently and in duplicate by the two authors. After eliminating the duplicate articles in Zotero, screening was performed with three criteria; first, studies that were original thus filtering the secondary studies as reviews, books, editorials and meta-analysis; second, research in which the population was pregnant women with malaria thus filtering other issues as malaria in children, in general population or in patients of health care institutions different to pregnant, this second criterion also allowed to exclude other populations as coinfections with Human immunodeficiency virus (HIV), helminths and other; and third, manuscripts that did not include economic outcomes such as clinical cases, observational studies, clinical trials. The search was conducted without restrictions by year of publication; the time delimitation was made based on the oldest publication and the last application of the search and selection protocol that was made in October 2018 (with update on March 2019 without new economic evaluations that fulfill the protocol).

The search strategies included are shown in Table 1.

In the databases, only the title, abstract or keywords filter was applied; no other filters were applied (for example, type of publication, humans, etc.), since they decreased the exhaustiveness and sensitivity of the search. Besides, these filters are different in each database, which would affect reproducibility to the extent that some criteria such as "human studies" could be filtered automatically in PubMed but in the other sources it would have to be done manually, using reading of the title-abstract. For this reason, it was decided to apply selection criteria manually in the references manager, where a common source was configured for the titles obtained in all the strategies.

Eligibility: In this phase, a full text reading was performed to apply two exclusion criteria; first, research that was not carried out in humans thus filtering preclinical studies in animals, *in vitro* models or models whose unit of analysis was cell cultures, and modeling studies; second, articles which were not available, the latter corresponds to articles removed from the databases or without the full text, and for which no response was obtained to the message sent to the authors.

Review of studies: Studies that met the above criteria were characterised based on the following variables: title, authors, year of publication, country, type of economic evaluation, alternatives analyzed, outcomes included, costs, primary and secondary result (such as costs or average and incremental ratios of cost-effectiveness) and conclusion.

2.4. Reproducibility and methodological quality assessment

The reproducibility of the search and selection was guaranteed, as was the extraction of the study variables, through the independent application by the two researchers; in the event of disagreement *a priori*, it was determined that these would be resolved by consensus between the two researchers. Kappa index for qualitative data and intraclass correlation coefficient for the quantitative variables, was calculate in the selection of manuscripts, and data extraction.

The methodological quality was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guide [26].

2.5. Data analysis

The qualitative synthesis was based on frequencies and was performed for the DALYs avoided with different interventions. For cost comparison, deflation was made to 2018 international dollars, and they were then unified with the Parity of Purchasing Power (PPP) conversion factor of the World Bank's International Comparison Program's database, which accounts for the monetary units a country would need to acquire the same units with US dollars on the national market. In the cost-effectiveness studies, the analysis were based on WHO recommendations that define an alternative as highly cost-effective for incremental ratios less than a gross domestic product (GDP) per capita and cost-effective for values less than three times the GDP per capita [27].

Table 1. Syntax used in each database.

Database	Syntax
PubMed	1. (Malaria [Title/Abstract]) AND pregnancy [Title/Abstract]
	2. (Malaria [Title/Abstract]) AND placenta [Title/Abstract]
	3. (Malaria [Title/Abstract]) AND gestation [Title/Abstract]
	4. (Paludism [Title/Abstract]) AND pregnancy [Title/Abstract]
	5. (Paludism [Title/Abstract]) AND placenta [Title/Abstract]
	6. (Paludism [Title/Abstract]) AND gestation [Title/Abstract]
	7. (<i>Plasmodium</i> [Title/Abstract]) AND pregnancy [Title/Abstract]
	8. (<i>Plasmodium</i> [Title/Abstract]) AND placenta [Title/Abstract]
	9. (<i>Plasmodium</i> [Title/Abstract]) AND gestation [Title/Abstract]
Science Direct	10. Title, abstract, keywords: malaria pregnancy
	11. Title, abstract, keywords: malaria placenta
	12. Title, abstract, keywords: malaria gestation
	13. Title, abstract, keywords: paludism pregnancy
	14. Title, abstract, keywords: paludism placenta
	15. Title, abstract, keywords: paludism gestation
	16. Title, abstract, keywords: <i>Plasmodium</i> pregnancy
	17. Title, abstract, keywords: <i>Plasmodium</i> placenta
	18. Title, abstract, keywords: <i>Plasmodium</i> gestation
Scielo	19. (ti:(ab:(malaria pregnancy))))
	20. (ti:(ab:(malaria placenta))))
	21. (ti:(ab:(malaria gestation))))
	22. (ti:(ab:(paludism pregnancy))))
	23. (ti:(ab:(paludism placenta))))
	24. (ti:(ab:(paludism gestation))))
	25. (ti:(ab:(<i>Plasmodium</i> pregnancy))))
	26. (ti:(ab:(<i>Plasmodium</i> placenta))))
	27. (ti:(ab:(<i>Plasmodium</i> gestation))))
Google Scholar	28. allintitle: malaria pregnancy
	29. allintitle: malaria placenta
	30. allintitle: malaria gestation
	31. allintitle: paludism pregnancy
	32. allintitle: paludism placenta
	33. allintitle: paludism gestation
	34. allintitle: <i>Plasmodium</i> pregnancy
	35. allintitle: <i>Plasmodium</i> placenta
	36. allintitle: <i>Plasmodium</i> gestation
MiP Library	37. Search (current: economic evaluation AND Bibliographic reference: RECORDTYPE)
	38. Search (current: cost AND Bibliographic reference: RECORDTYPE)
	39. Search (current: cost-minimisation AND Bibliographic reference: RECORDTYPE)
	40. Search (current: cost-effectiveness AND Bibliographic reference: RECORDTYPE)
	41. Search (current: cost-utility AND Bibliographic reference: RECORDTYPE)
	42. Search (current: cost-benefit AND Bibliographic reference: RECORDTYPE)

Note: These same searches that appear in English, were applied in Spanish and Portuguese.

3. Results

In total, 368,411 studies were identified and 3,724 abstracts were screened, of which 1,128 were eligible, and only 22 studies were included (Figure 1). The intraclass correlation coefficient between the two researchers was 1.0 for the number of studies analyzed at each stage of the search and selection process; for each one of the extracted variables, a kappa index of 1.0 was found for the qualitative variables and the intraclass correlation coefficient was also 1.0 for the quantitative variables.

The methodological quality was excellent because they fulfilled >70% of the CHEERS guide criteria, with the exception of Goodman's study [28], which met 67% of them. The least specified criteria were: not choice a decision model [30], not explain assumptions for the model and the analytical method [28, 30], not specify the evaluation's time frame [19, 28, 33], not present uncertainty or sensitivity analysis [21, 28, 29,

30, 41, 45], and not describe the cost and incremental effectiveness [28, 29, 30, 31, 32, 37, 41] (Figure 2).

Publications between 1990 and 2018 were found: 91% were from Africa, one from Brazil and one from Colombia; 80% corresponded to cost-effectiveness studies and 20% to cost studies; the most frequently measured outcome was LBW (65%), followed by DALYs (55%), maternal anaemia (41%) and maternal malaria (29%). The efficacy data were extracted from clinical trials and meta-analysis; 78% of the cost-effectiveness studies evaluated IPTp-SP compared with other drugs or at different doses, and 72% included the health care provider's perspective (Table 2).

Overall, 44% of the studies included primigravidas or women who were pregnant for the second time [28, 31, 32, 33, 34, 35, 36, 42] and 39% did not specify the number of pregnancies [19, 20, 29, 30, 38, 39, 41]; one study conducted an economic evaluation of women who had multiple pregnancies [37] and two included women with HIV [40, 43].

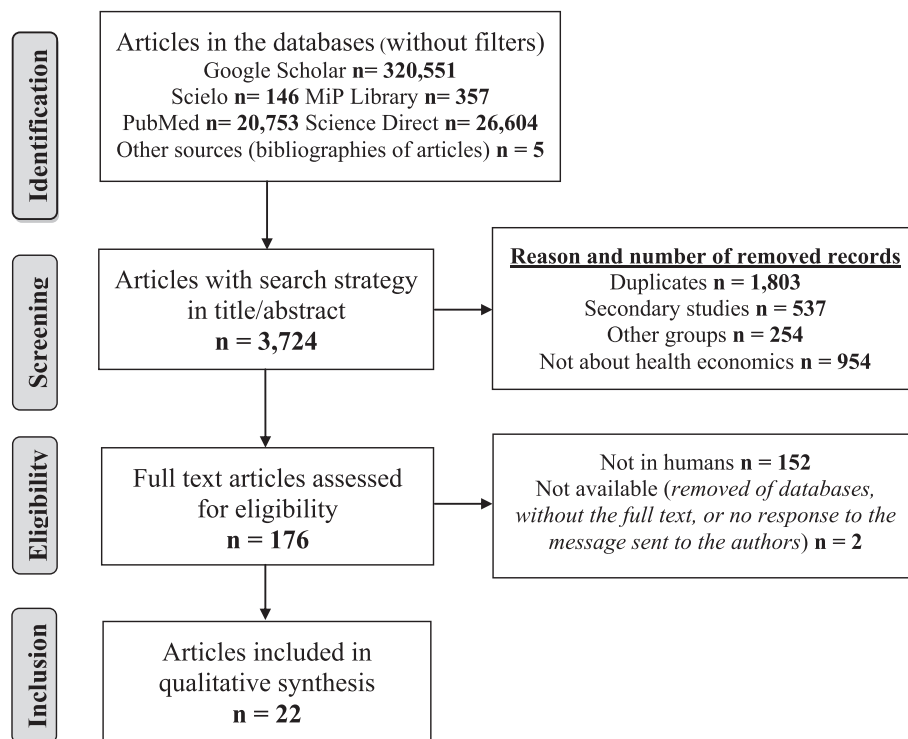


Figure 1. Flow gram of search and selection of studies.

Almost all interventions were performed during the second and third trimesters of pregnancy and those that evaluated LBW and infant death continued follow-up until one month after delivery.

The items most frequently included in costing were medications, the salaries of health personnel, training for workers and the costs of prenatal programmes based on institutional rates, scientific literature or consultation with experts. Expenses for the patient or her family included travel, loss of productivity and costs associated with the disease or its prevention, collected through patient surveys.

The cost studies reported that for each episode of malaria, 24.3% corresponds to direct costs (mainly drugs) and 75.7% to indirect costs, such as for travel time, waiting time and downtime [21]. In Brazil [22], the direct costs for pregnant women under ambulatory care were 35%, whereas for hospitalisation they were 15%. In Colombia, the direct costs of care for hospitalised women [45] represented 38%. Additionally, the costs of distributing ITM during prenatal care in Kenya corresponded to US \$ 3.81 [44].

The comprehensive economic evaluations showed that IPTp-SP was more cost-effective than IPTp-CQ in YLL and LBW prevention [34]. In Malawi, IPTp-SP was more cost-effective than IPTp-CQ, and its combination with SP helped in preventing LBW-associated neonatal death [32]. Another study in Malawi indicated that the IPTp-CQ was not cost-effective for cases of PAM which were avoided [29]. Subsequently, different forms of administration of the drug were evaluated in the same country, and it was determined that delivery to pregnant women with an educational message was found to be more cost-effective [30]. In Nigeria, IPTp-SP distributed via the community was cost-effective, and it was related to increases in newborn head circumference and lower probabilities of fetal death [41]. In the Democratic Republic of the Congo, the use of rapid tests for the diagnosis of PAM was more cost-effective [38].

Case management of PAM presented a cost of US\$ 6.2 for each DALY avoided, whereas the cost of IPTp-SP ranged from US\$ 0.5 to 16.9 and the distribution of ITMs was between US\$ 1.5 and 15.1. Avoiding a DALY by prophylaxis with CTX in pregnant women with HIV would cost approximately US\$ 12–34.9, whereas using SP with two or three doses would

cost between US\$ 9.8 and 30.03 depending on the degree of coverage of HIV detection (Table 3).

The average cost-effectiveness ratio for IPTp-SP was US\$ 2 for each DALY avoided; it was the most cost-effective intervention, followed by the administration of IPTp-SP in pregnant women with HIV. Administration of IPTp-SP throughout the community showed the highest cost per DALY avoided (US\$ 296.4), followed by administration of IPTp-MQ (Figure 3).

A meta-analysis of the incremental cost-effectiveness ratio (ICER) indicates that the monthly IPTp-SP scheme or administering two doses of SP, with IPTp-MQ, is the dominant strategy to avoid costs for the institution when compared with the management of each case of PAM, whereas treatment with artemether-lumefantrine and distribution by the community of IPTp-SP are interventions that imply the highest costs for each additional DALY avoided, although they were less than one GDP per capita in the countries analyzed (Figure 4).

4. Discussion

Most economic evaluations are from Africa, which is associated with malaria's global profile, where 90% of cases occur on this continent [1]. The highest academic and scientific output on PAM in Africa is consistent with the findings of this review, demonstrating a knowledge gap regarding the microeconomic impact of PAM in other regions, thus limiting decision-making possibilities based on scientific evidence and using available resources in interventions that maximise health benefits [9].

Partial economic evaluations were found in Brazil and Colombia, which demonstrate the economic burden of PAM, but do not relate the costs of managing it to the health gains, in which case full economic evaluations are more useful [46, 47]. In this sense, cost-effectiveness analysis was most frequently applied for PAM, comparing the monetary costs of different interventions with their effects on morbidity, mortality or disability, allowing the prioritisation of health actions [48].

The above applies to cost-effectiveness studies with good methodological quality. In this review, many studies did not provide an adequate

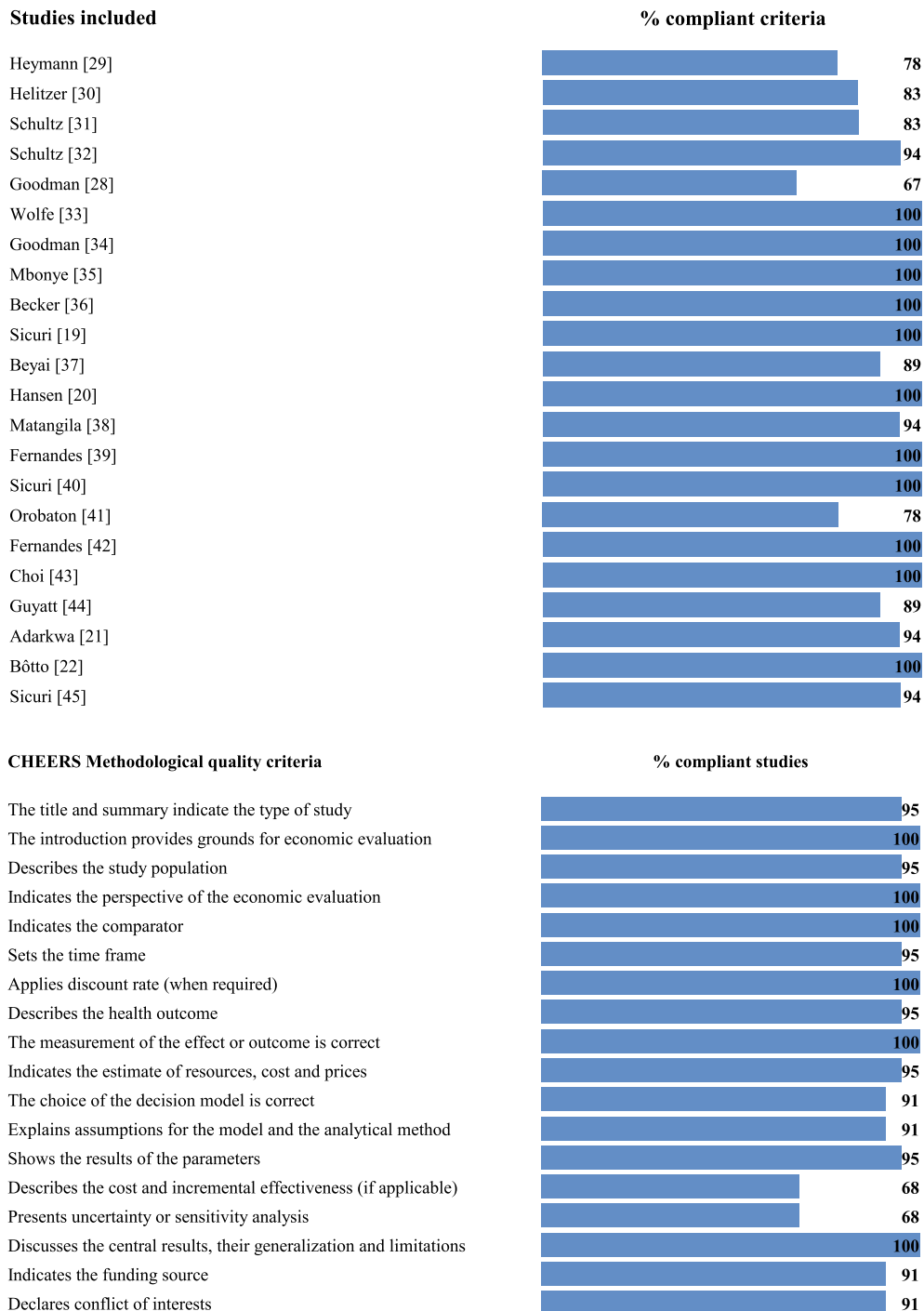


Figure 2. Evaluation of methodological quality according to CHEERS criteria.

description of the assumptions of the analytical model and did not present the incremental or sensitivity analysis, thus decreasing the internal and external validity of the conclusions, given that the analytical model identifies the health times and states analyzed. ICER informs the additional cost when choosing an intervention other than the one used routinely, and the uncertainty analysis allows to establish the degree of stability of the result in regard to changes in the model's parameters, which are key aspects for public policy decision makers [47, 49]. Furthermore, few studies include a comprehensive description in terms of weeks of pregnancy, number of previous pregnancies, coinfections, prenatal controls, follow-ups of fetal health and the product of the pregnancy, which should be considered for subsequent studies, given

that these variables are determinants for the maximisation of the economic resources destined to the prevention and caring for patients with PAM [4, 9, 50].

With respect to the interventions studied, the most frequent was IPTp-SP from the second trimester of pregnancy. This is related to the fact that in most endemic areas for malaria, pregnant women attend prenatal care during this quarter and prophylaxis with SP can only be administered after week 13 owing to its teratogenic effects in the first weeks of pregnancy. These findings show that little is known about the risk of infection, the consequences of malaria during the first trimester and the best interventions for PAM during this period, which should be improved in subsequent studies [4, 17, 51].

Table 2. Description of studies according to year, country, economic evaluation type, population, compared alternatives and outcomes.

Author	Year	Country	Population	Alternatives	Outcome
Cost-Effectiveness Analysis					
Heymann [29]	1990	Malawi	Pregnant women	Prophylaxis CQ	Case of malaria avoided
Helitzer [30]	1993	Malawi	Pregnant women	CQ + MSE, CQ + NMSE, CQCovered + NHEM, CQCovered + OHEM	Compliance with the intervention
Schultz [31]	1995	Malawi	Women in their 2nd or 3rd pregnancy	SP, SP/CQ, CQ/CQ	LBW
Schultz [32]	1996	Malawi	Women in their 2nd or 3rd pregnancy	SP, SP/CQ and CQ/CQ	Infant mortality
Goodman [28]	1999	Sub-Saharan Africa	Primigravida	IPTp-SP and CQ	LBW, DALYs
Wolfe [33]	2001	Sub-Saharan Africa	Women in their 2nd or 3rd pregnancy	SP2, SPmonth, HIV test + SP, case management	LBW, DALYs
Goodman [34]	2001	Sub-Saharan Africa	Primigravida	IPTp-SP and CQ	LBW, YLL
Mbonye [35]	2008	Uganda	Primigravida	Distribution of IPTp-SP by the community	Anaemia, Maternal malaria, LBW, DALYs
Becker [36]	2009	Congo	Pregnant women	ITM	LBW, Infant mortality, DALYs
Sicuri [19]	2010	Mozambique	Pregnant women	IPTp-SP	Maternal malaria, Neonatal mortality, DALYs
Beyai [37]	2010	Gambia	Multiple pregnancies	IPTp-SP	Anaemia, LBW, DALYs
Hansen [20]	2012	Uganda	Pregnant women (<27 weeks)	IPTp-SP, ITM, IPTp-SP + ITM	Anaemia, LBW, DALYs
Matangila [38]	2014	Congo	Pregnant women	Microscopy-RDT	Correctly diagnosed
Fernandes [39]	2015	Sub-Saharan Africa	Pregnant women	IPTp-SP	Maternal malaria, anaemia, LBW, DALYs
Sicuri [40]	2015	Sub-Saharan Africa	Pregnant women with and without HIV	IPTp-SP/IPTp-MQ, IPTp-MQ + CTX/CTX	Maternal malaria, anaemia, DALYs, non-obstetric hospital admission
Orobaton [41]	2016	Nigeria	Pregnant women	IPTp-SP distributed by the community	% compliance, head circumference in newborn, Infant mortality
Fernandes [42]	2016	West Africa	Women in their 1st or 2nd pregnancy	IPTp-SP, ISTp-AL	Maternal malaria, anaemia, LBW, DALYs
Choi [43]	2017	Sub-Saharan Africa	Pregnant women with HIV	Low 2-IPT, low 3-IPT, high 3-IPT, CTX	Maternal malaria, anaemia, LBW, DALYs
Costs of the disease					
Guyatt [44]	2002	Kenia	Pregnant women	ITM distributed by antenatal program	
Adarkwa [21]	2009	Ghana	PAM	Description of PAM costs	
Bóto [22]	2016	Brazil	PAM and postpartum	Description of PAM costs	
Sicuri [45]	2018	Colombia	PAM	Description of PAM costs	

OHEM: Original health educational message; **NHEM:** New health educational message; **CTX:** Cotrimoxazole; **RDT:** Rapid diagnostic test; **ISTp-AL:** Intermittent Screening and treatment of pregnant women with artemether-lumefantrine; **low 2-IPT:** IPTp-SP2 (two doses) or CTX; **low 3-IPT:** IPTp-SP3(three doses) or low coverage CTX; **high 3-IPT:** IPTp-SP3 or CTX with antiretroviral therapy.

Table 3. Average Cost-Effectiveness (ACE) for DALYs avoided with PAM interventions (costs deflated for 2018 and adjusted by PPP).

Author and Intervention	Costs	DALYs avoided	ACE
Wolfe [33] –Case management	875	140	6,2
Fernandes [42]- Detection + Intermittent with artemeter-lumefantrine	2.962	156	19,0
Wolfe [33] - IPTp-SP monthly	2.687	71	37,8
Sicuri [40] -IPTp-MQ	1.081	9	120,1
Mbonye [35]- IPTp-SP distributed throughout the community	328.955	1.110	296,4
IPTp-SP			
Hansen [20]	381	558	0,7
Fernandes [39] (2 doses)	837	151	5,5
Fernandes [39] (3 doses)	994	442	2,2
Wolfe [33]	1.687	100	16,9
Fernandes [42]	573	556	1,0
Sicuri [19]	301	571	0,5
ITM			
Becker [36] (R. of the Congo)	149.380	9.897	15,1
Hansen [20] (Uganda)	832	541	1,5
IPTp-SP + MTI			
Hansen [20] (Uganda)	1.202	590	2,0
Beyai [37] (Gambia)	15.839	58	271,2
Pregnant womenwith HIV			
Sicuri [40] - IPTp-SP + MQ + CTX(HIV)	3.581	603	5,9
Wolfe [33] – HIV test + IPTp-SP	4.374	277	15,8
CTX (HIV)			
Choi [43] (Tanzania)	122.590	3.516	34,9
Choi [43] (Mozambique)	182.901	15.240	12,0
Choi [43] (Kenya)	184.650	5.339	34,6
Choi [43] (Malawi)	144.536	11.317	12,8
Choi [43] (Ghana)	138.042	9.312	14,8
IPTp-SP2 Low coverage of HIV detection			
Choi [43] (Ghana)	137.653	12.055	11,4
Choi [43] (Malawi)	143.512	14.671	9,8
Choi [43] (Kenya)	183.073	7.000	26,2
Choi [43] (Mozambique)	183.720	16.424	11,2
Choi [43] (Tanzania)	121.512	4.364	27,8
IPTp-SP3 Low coverage of HIV detection			
Choi [43] (Malawi)	143.878	14.563	9,9
Choi [43] (Kenya)	183.597	6.934	26,5
Choi [43] (Mozambique)	184.850	16.022	11,5
Choi [43] (Tanzania)	122.380	4.327	28,3
Choi [43] (Ghana)	137.786	11.912	11,6
IPTp-SP3 High HIV detection			
Choi [43] (Tanzania)	122.693	4.231	29,0
Choi [43] (Malawi)	145.481	12.382	11,7
Choi [43] (Kenya)	185.629	6.183	30,0
Choi [43] (Mozambique)	184.957	15.997	11,6
Choi [43] (Ghana)	138.265	11.434	12,1

Regarding costs, it should be mentioned that in most endemic countries, medicines for the treatment or prevention of PAM are distributed and financed by governments or international organisations [51], and the most expensive items correspond to the implementation of interventions on site and care of pregnant women [20, 36] as well as the indirect costs associated with travel to health centers, downtime, etc. This is worsened when PAM and poverty are intimately related and constitute a vicious circle that exacerbates social inequalities and hinders social development [52]. This calls for state intervention through high-coverage preventive treatment and control measures that would allow pregnant women and the health system to save the costs of treating the disease and its associated complications [9, 37, 45, 53], apart from improving the dynamics of families and the macroeconomies of the affected countries [52].

The most relevant clinical outcomes of PAM were included in this review, highlighting the avoided DALYs as a combined measure of morbidity, mortality and disability, which allows us to differentiate the current health status and an ideal health situation in which the entire population lives up to old age free of disease and disability [54, 55]. Based on this outcome, according to the WHO threshold, all the alternatives were found to be highly cost-effective, although with important differences according to the use of medications, the need for training, new distribution routes, supervision protocols [35, 40], duration of the intervention and the level of adherence that is related to the efficacy and development of parasitic resistance [10, 19, 33] which are key variables for decision makers, given that they would determine the success of health-related actions in the affected areas [47, 49].

Alternative	Costs in USD-PPP 2018	DALYs avoided (LBW)	Average Cost-Effectiveness Ratio
Case management	875	140	6.2
IPTp-SP	795	396	2.0
IPTp-SP + Low HIV detection	154,196	10,827	14.2
IPTp-SP3 + Low HIV detection	154,498	10,752	14.4
ITM	75,106	5,219	14.4
IPTp-SP3 High HIV detection	155,405	10,045	15.5
CTX - HIV	154,544	8,945	17.3
Artemether-lumefantrine	2,962	156	19.0
IPTp-SP + ITM	8,520	324	26.3
Monthly IPTp-SP	2,687	71	37.8
IPTp-MQ	1,081	9	120.1
IPTp-SP distributed throughout the community	328,955	1,110	296.4

Figure 3. Average Cost-Effectiveness Ratio (cost per DALY avoided) in the interventions identified from the institutional perspective.

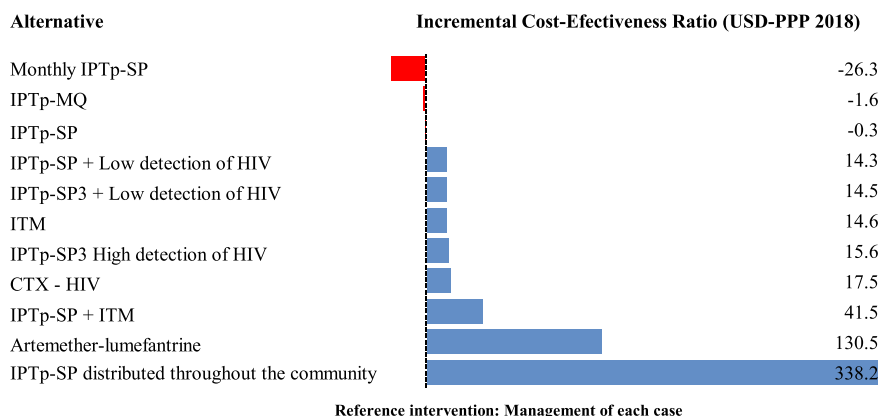


Figure 4. Meta-analysis of the Incremental Cost-Effectiveness Ratio (additional cost per DALY avoided) in the interventions identified from the institutional perspective.

It is striking that the simultaneous use of IPTp-SP with ITMs can lower its cost-effectiveness. This has been explained by the reduction in coverage and longer implementation or follow-up time and that pregnant women may consider using ITMs less important when they receive SP, and this could lead to an incorrect or lower use, thus reducing their effectiveness [20, 56]. However, WHO recommends distributing ITMs together with IPTp-SP because it protects pregnant women from the first trimester, as well as the newborn [51]. Artemether-lumefantrine is recommended in areas of high incidence of malaria and resistance to SP to control malaria during pregnancy, maternal anaemia and LBW [42, 57].

WHO also recommends IPTp-SP in pregnant African women to reduce the incidence of PAM, anaemia, complicated malaria, LBW and maternal and infant mortality [37, 51]. Added to this is the review which shows that this intervention saves resources for the health provider, patients and their families and constitutes a dominant strategy in the cost-effectiveness plan. Although the IPTp-MQ scheme is also highly cost-effective, low drug tolerance with multiple side effects does not favour its use as a preventive treatment [40]. Active detection of malaria cases in low endemic regions outside the African continent is recommended [58, 59, 60, 61]; however, research on the efficacy and cost-effectiveness of this strategy should be improved to lower the complications of PAM in the epidemiological, parasitological and economic aspects as well as in each country's health system coverage.

Interventions with IPTp-SP3 and CTX for pregnant women with HIV were highly cost-effective, constituting important evidence considering the negative feedback of PAM-HIV coinfection, whose intervention would reduce the negative effects of both. HIV potentiates the consequences of PAM by increasing the parasitic density, anaemia, cerebral

and placental malaria, preterm delivery, LBW and neonatal death; PAM, in turn, increases viraemia, the progression to AIDS and the risk of vertical transmission of HIV [4, 62, 63, 64]. However, the cost-effectiveness of this intervention depends, to a large extent, on close adherence to the daily dose (>80%) [43, 65].

The main limitations of this study which, in turn, become recommendations for subsequent studies or public policy measures, are related to the need to standardize the social and institutional costs of PAM and the measures of effectiveness to increase the number of studies that evaluate interventions other than that involving IPTp-SP mainly for the first trimester of pregnancy and, outside Africa, to perform uncertainty analysis and to increase the number of evaluations from the social perspective. Furthermore, the studies were not exhaustive in the description of the socioeconomic, clinical, and parasitological characteristics of the pregnant women studied, which should be improved in subsequent studies. The fact of not having registered online the search and selection protocol of the studies should also be declared as a limitation of this review; as well as the few data on Francophone Africa.

5. Conclusions

Published studies are scarce and restricted to Africa, which shows lack of knowledge of the economic impact of PAM and more cost-effective interventions in other endemic countries. Despite the high heterogeneity of impact measures, the costing systems used, interventions and populations studied and all alternatives identified were highly cost-effective. This demonstrates the importance of including resources for preventing and controlling PAM and providing care for patients with PAM as a priority in the health budget to reach the goal of

eliminating the disease, as demanded by WHO [58], promoting social progress and overcoming poverty in endemic areas.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This work was supported by Colciencias Colombia, Project 111577757447, Contract 755-2017, University of Antioquia.

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2020.e04558>.

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