Use of evidence to inform policy change: The case of Adequacy of antimalarial drug efficacy studies in Ethiopia

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Abstract

Malaria in Ethiopia is seasonal and unstable. Prompt malaria treatment with effective antimalarial drugs is the mainstay but often challenged by drug resistance. The need to ensure availability of effective antimalarial drugs is a public health priority. This paper describes the characteristics, findings and actions taken based on in vivo antimalarial drug efficacy studies on P. falciparum infections conducted in the Ethiopia. Published and unpublished in vivo antimalarial drug efficacy studies on P. falciparum infections conducted in Ethiopia were reviewed and scored based on nine indicators for study completeness, timeliness and representativeness compared to the WHO recommended standards. A combined score of at least 60% was set as a cut-off for study adequacy and study gaps identified in order to formulate recommendations for prospective studies. Of the 24 in vivo therapeutic efficacy studies on P. falciparum conducted from 1972 to 2010, only 2(8.3%) of the studies had a combined adequacy score of 66.7%. Most of the studies (91.7%, n=22) had a score of less than 60%. Retrospective chronological mapping of the antimalarial drug efficacy study findings indicate that chloroquine was replaced by sulfadoxine-pyrimethamine (SP) when its efficacy failure increased from 22% in 1985 to 65% in 1998. SP was replaced by artemether-lumefantrine (AL) when it efficacy failure increased from 7.7% in 1998 to 36% in 2004. Nearly eight years after the introduction of AL as the first-line treatment for P. falciparum, isolated studies show a decrease in its efficacy from 99% in 2003 to 93.3% in 2008. This study has shown that the adequacy of studies used for initiating policy change was not optimal; but is also emphasizes the fact that 20% of studies were useful in the implementation of change. This finding suggests that policy change process is beyond collecting the correct evidence at the right time, it should be based on an institutional mechanism managed by appropriate personnel who have the right skills.

Keywords: Malaria, anti-malarial drug efficacy, adequacy, policy, Ethiopia

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Introduction

Malaria in Ethiopia is seasonal and unstable (Adhanom et al. 2006), local and wide-spread epidemics are associated with major climatic changes (Abose et al, 2004) and disruption of malaria prevention and control activities (Negash et al, 2005). Prompt malaria treatment with effective antimalarial drugs is the mainstay but often challenged by drug resistance. The need to ensure availability of effective antimalarial drugs is a public health priority. Population movement to and from malaria endemic areas contributes to increased malaria incidence (Deressa, Ali & Berhane, 2006) and treatment of cases is critical as natural protective immunity to the diseases is low (Alamirew & Oqbaegzi, 1998) .

In the Ethiopian epidemiological setting, malaria control heavily relies on the availability and access to malaria early diagnosis and prompt treatment services (Federal Ministry of Health, 2004). A significant increase in the health service coverage has been attained over the last few years, and that has contributed to remarkable public health achievements such as the reduction in under five child and maternal mortality (Central Statistics Agency, Ethiopia, 2011), availability of good quality antimalarial drugs (WHO, 2011) and regular monitoring of the efficacy of antimalarial drugs. These are critical actions that need to be strengthened in order to maintain the public health gains in malaria control in Ethiopia that are contributing to the significant reduction in child mortality.

In the Ethiopian setting, the objectives, findings and relevance of antimalarial drug efficacy studies have never been reviewed to extract lessons to inform policy decisions; hence there was a need for a study to fill this gap. This paper describes the characteristics, findings and actions taken based on *in vivo* antimalarial drug efficacy studies on *P. falciparum* infections conducted in the Ethiopia in order to formulate recommendations and best practice approaches for future planning.

Methods

Study design and sampling procedure

The research design used for this study was a descriptive epidemiological analytical study design based on data extracted from published and unpublished reports and other relevant sources. Literature searches were conducted in major scientific databases such as Medline, Web of Science, Google Scholar, Sciencedirect, the National Centre for Biotechnology Information (NCBI) repository and others. The keywords used were: antimalarial drug, clinical studies, trials, Ethiopia.

A data extraction tool designed to gather data for this study included the number of patients or cases enrolled, treatment outcomes (success and failure cases), drugs used and laboratory findings as well as the study period or and the follow-up duration.

The data so collected were pooled in to a Microsoft Excel (Microsoft Corporation, 2003) for analysis. The attributes that were considered for evaluating the studies were adequacy, completeness, representativeness and timeliness. In this context, representativeness meant that regardless of the statistical approaches to determine sample size, WHO (2009) recommends a minimum number of 50 subjects each in 4 to 8 study sites for an antimalarial efficacy study to be considered as complete. Based on this, studies have been scored based on a scale of 0 to 2 (Table 1). Completeness, meant, that the confirmation of infection in the patients enrolled through slides was cross-checked by examination of PCR, proof of quality of the antimalarial drug tested as well as tests to confirm absorption of the drug after administration being considered as the most critical elements for data completeness. Based on this, study completeness was rated in score scale of 0 to 3 (Table 1). Moreover, timeliness means that regular assessment of the efficacy of

antimalarial drugs should be performed every two years as per WHO (2009) recommendations. Based on this approach, timeliness was rated on a scale from 0 to 1 (Table 1) based on the time-lapse between two consecutive studies. Finally, the adequacy of a study to inform policy is a composite index meaning that a study that fulfils all the requirements for representativeness, completeness and timeliness as described above. However, considering the lack of widely available local capability in the Ethiopian setting at the time of the study, to conduct PCR based confirmation of malarial infection and drug quality and blood level concentration analysis, a score of 60% or above was set as a cut-off for adequacy.

Table 1 Antimalarial Drug Efficacy Study Adequacy Rating Criteria

Measure	Score	Attribute
Representativeness	0	Sample size below 50 and number of study sites less than four
	1	Meets at least one of the requirements (sample size above 50 or more than 4 study sites)
	2	Meets both requirements with sample size more than 50 each and more than 4 sites
Completeness	0	No blood film examination re-check, no drug quality analysis, and no blood level of drug administered determined
	1	Only one of the three tasks met
	2	Only two of the three tasks met
	3	All the three tasks completed
Timeliness	0	Study conducted after two years from the date of publication of the preceding study
	1	Study conducted within two years from the date of publication of the preceding study
Study adequacy to inform policy	Yes	Combined score for representativeness, completeness and timeliness of above 60%,
	No	Combined score for representativeness, completeness and timeliness of below 60%,

Study sample and population

The study sample and population was the same as what was considered and analysed in the studies conducted from 1972 to 2011. With the exception of two antimalarial efficacy studies conducted in the capital city of Addis Ababa, where local malaria transmission is rarely reported, most of the studies were conducted in malaria endemic areas where malaria transmission occurs. The subjects who were involved in the antimalarial efficacy study conducted in Addis Ababa were residents or short-time visitors to malaria-endemic localities in other parts of the country and most of the locations are towns along the frontier with Kenya and the Sudan.

Statistical analysis

A Microsoft Excel (Microsoft Office Excel 2003) based data entry and analysis was applied to calculate proportions, mean, median and range using the therapeutic efficacy data collected from the relevant studies. Statistical test such as comparison of proportions and determining the corresponding 95% CI (confidence interval) and P-values were also calculated for study findings that required comparison. For the purpose of statistical analysis, Statistical Package for Social

Sciences (SPSS) version 10 (SPSS Inc 2007) and MedCalc version 11.6 statistical software for biomedical research (MedCalc Software 1993-2011) were used as necessary.

Ethics approval

Ethical clearance approval to conduct the study was obtained from the Ethics committee of the Department of Health Studies at the University of South Africa.

Results

In the period from 1974 to 2010, a total of 24 in vivo therapeutic efficacy studies on three antimalarial drugs for the treatment of uncomplicated *P. falciparum* malaria were conducted. Of these studies 13 (54.2%) were on chloroquine in the period from 1974 to 1998 followed by 7 (29.2%) studies on sulfadoxine-pyrimethamine from 1993 to 2005 and 4 (16.7%) studies on artemether-lumefantrine in the period from 2005 to 2010. A chronological listing of the studies and their score for completeness, representativeness, timeliness and adequacy is presented in Table 2.

The therapeutic efficacy studies on chloroquine had a follow-up duration of 7 to 28 days involving patients of all ages who met the inclusion criteria. The patient follow-up duration employed in the studies did not show any chronological pattern. The very early study had a 28 days follow-up. Of the 13 studies, seven studies (53.8%) had a follow-up period of seven days, three studies (23.1%) had 14 days and the remaining 3 studies (23.1%) for 28 days.

None of the chloroquine efficacy studies attained the minimum cut-off of 60% for study adequacy and had a mean score of 25% (range 0 - 50%). Three of the studies conducted during this period by the Ministry of Health (1998a, 1998b) were used to decide change of the first-line antimalarial drug from chloroquine to sulfadoxine-pyrimethamine in 1999. The studies had adequate representativeness involving more than four study sites across the nation while the study's completeness and timeliness were low. A study conducted by Teklehaimanot (1985) reported a therapeutic efficacy failure on chloroquine treatment of 22.4%. The time gap between the detection of high treatment failures as reported by Teklehaimanot in 1985 to the time a decision was made to replace chloroquine with the combination of sulfadoxine-pyrimethamine was 14 years. The replacement of chloroquine with sulfadoxine-pyrimethamine was done is 1999 when its failure rate had reached 65% (WHO, 2000).

The patient follow-up duration in the seven studies on sulfadoxine-pyrimethamine showed a chronological pattern with the earliest studies (2 or 28.6%) which had a follow-up period of 7 days; and the following four studies (57.1%) with a follow-up period for 14 days and 1 study (14.3%) with a follow-up period of 28 days. The mean adequacy score of all the studies on sulfadoxine-pyrimethamine was 35.7%, ranging from 16.7% to 66.7%. In fact, the study by Jima et al (2005a) that triggered an antimalarial treatment policy change had an adequacy score of 66.7% which was higher than the minimum cut-off of 60%. However, completeness of the data in terms of confirmation of infection, drug quality and blood level analysis was low. It is noteworthy that the level of treatment failure which was initially 7.7% (WHO, 2000), had reached 35.9% at the time it was replaced by artemether-lumefantrine 6 years in 2005 (Jima et al, 2005).

A total of 4(16.7%) studies conducted to assess the efficacy of artemether-lumefantrine for the treatment of *P. falciparum* in the period from 2005 to 2010 involved a follow-up period of 14 to 28 days. The study duration follow-up didn't show any chronological pattern with the studies conducted in 2005 being with a follow-up period of 28 days while the studies conducted in 2010 involved a follow-up period of 14 and 28 days. The study conducted by Jima et al (2005b) reported a therapeutic efficacy of 99.9% while the study conducted by Assefa et al (2010)

reported a therapeutic efficacy of 93.3%. Despite this slight decrease, artemether-lumenantrine continues to be used as the first-line antimalarial drug for the treatment for uncomplicated *P. falciparum* malaria.

Table 2 *In vivo* therapeutic efficacy study on *Plasmodium falciparum* and adequacy score of studies

No	Author	No of study sites	Sample size	Method and follow-up duration	Test drug	Outcome (% treatment failure)	Score of adequacy				Adequacy to inform policy	Recommended action
							Rep	Com	Tim	% Total Score		
1	Dennis et al 1974	1	41	*In vivo*, 28 days	CQ*	26.8	0	0	1	16.7	No	Further study
2	Armstrong et al 1976	4	99	*In vivo*, 6-11 days	CQ	0	1	0	1	16.7	No	Further study
3	Gebremariam et al 1982	1	21	*In vivo*, 7 days	CQ	0	0	0	0	0.0	No	Further study
4	Gebremariam et al 1986	11	136	*In vivo*, 7 days	CQ	0	2	0	0	33.3	No	Further study
5	Gebremariam et al 1986	11	115	*In vivo*, 28 days	CQ	0	2	0	0	33.3	No	Further study
6	Teklehaimanot et al 1985	1	98	*In vivo*, 28 days	CQ	22.4	1	0	1	33.3	No	Further study
7	Wezam 1993	1	23	*In vivo*, 7 days	CQ	0	0	0	0	0.0	No	Further study
8	Alene and Bennett 1996	36	1706	*In vivo*, 7 days	CQ	87.2	1	0	0	16.7	No	Further study and need to consider alternatives antimalarial drug
9	Tulu et al 1996	1	29	*In vivo*, 7 days	CQ	86.2	0	1	0	16.7	No	Further study
10	Assefa 19897	1	1	*In vivo*, 7 day	CQ	100	0	0	1	16.7	No	Further study
11	Ministry of Health 1998a	14	473	*In vivo*, 14 days	CQ	73.6	2	1	0	50.0	Yes	Treatment policy change
12	Ministry of Health 1998a	6	257	*In vivo*,14 days	CQ	63.4	2	1	0	50.0	Yes	Treatment policy change
13	Ministry of Health 1998b	4	107	*In vivo*,14 days	CQ	47.7	2	1	0	50.0	Yes	Treatment policy change
14	Wezam 1993	1	24	*In vivo*, 7 days	SP	0	0	1	0	16.7	No	Further study
15	Tulu et al 1996	1	80	*In vivo*, 7 days	SP	1.3	1	1	0	33.3	No	Further study
16	Ministry of Health 1998b	7	232	*In vivo*,14 days	SP	5.6	2	1	0	50.0	Yes	Treatment policy change
17	Degefa 2004	1	77	*In vivo*,14 days	SP	2.6	1	1	0	33.3	No	Further study
18	Worku et al 2005	1	86	*In vivo*,14 days	SP	45.3	0	0	1	16.7	No	Need to search for alternative drug
19	Kassa et al 2005	1	60	*In vivo*,14 days	SP	21.1	1	0	1	33.3	No	Further study
20	Jima et al 2005[a]	11	523	*In vivo*,28 days	SP	33.5	2	1	1	66.7	Yes	Treatment policy change
21	Jima et al 2005b	4	213	*In vivo*,28 days	AL	0.9	2	1	1	66.7	Yes	Treatment policy change
22	Kefyalew et al 2009	1	102	*In vivo*,28 days	AL	0	0	0	1	16.7	No	Continued monitoring
23	Seboxa et al 2010	2	105	*In vivo*,14 days	AL	0	1	1	0	33.3	No	Further study
24	Assefa et al 2010	1	81	*In vivo*,*28 days*	AL	6.7	1	0	0	16.7	No	Further study

Key Rep.=representativeness; Com.= completeness; Tim.= timeliness * single dose of 10 mg/kg (standard treatment is 25mg/kg administered over three days)

Discussion

The antimalarial drug efficacy studies on *P. falciparum* infections conducted in Ethiopia over a period of 36 years from 1974 to 2010 have had significant contribution to the scientific knowledge by providing critical information on the pattern of efficacy of the antimalarial drugs in the country. However, most of the studies (66.7%, n=16) recommended the need for additional studies to be conducted further as the findings were not conclusive and generalizable to initiate or indicate a need for antimalarial policy change.

It seems that the authors of these studies reserved their recommendations intuitively as this study demonstrates that the adequacy of the studies was not sufficient for informing antimalarial treatment policy decision. In fact, the scores for adequacy of the studies that influenced decision to change the first-line antimalarial drugs was never 100% with the highest being 66.7%. Interestingly, of the 24 studies conducted in the period from 1972 to 2010, only findings from 5 (20.8%) studies had been used to effect antimalarial treatment policy change.

Although the data collected was not adequate to the highest level expected, treatment policy changes were introduced partly due to increasing frequency and magnitude of malaria epidemics particularly with the advent of major malaria epidemics in the country in 1998 (Federal Ministry of Health, 1998a) and 2003 (Negash et al, 2005). Another contributing factor for implementing change of drug regimens was the effect of international programs such as Roll-Back Malaria (Nabarro, 1999).

In is our considered view that the lack of institutional mechanisms and initiatives to collect and appraise findings of antimalarial drug efficacy studies is one of the major gaps besides the absence an established culture of using evidence in decision-making in the public sector; as well as the lack of human resources capacities and skills. Hence, the findings from relevant studies were not tracked and reviewed in order to take timely corrective actions and recommend the performance of prospective studies.

The development of appropriate antimalarial drug efficacy protocols adapted to the malaria epidemiology of the endemic countries has been delayed and this seems to be as one of the major hindrances in timely adoption of policy changes. For instance, the antimalarial drug efficacy assessment protocol that has been in use until 2003 was primarily developed for areas with high transmission (WHO, 1996) and the protocol for areas with low to moderate malaria transmission was made available in 2003 (WHO, 2003).

For malaria-endemic countries such as Ethiopia where malaria transmission is seasonal and unstable, it is important to have up-to-date protocols for the conduct of studies, the use of evidence and for malaria treatment guidelines. Beyond these policy issues, the management of the supply chain of malaria medicines, commodities and laboratory supplies is also critical in ensuring that adopted changes are implemented correctly and effectively (Jaberidoost et al, 2013).

Besides the political will as shown by the Ethiopian authorities, the interventions require the availability of qualified, trained and motivated workforce that is well organised in appropriate technical teams and working groups at all levels of governments (Freudenberg and Tsui, 2014).

It should be noted that Artemisinin resistance was first detected in localized *foci* in the Thai-Cambodia border and has been expanding to wider geographic areas ever since (WHO 2009). Although resistance to artemisinin has not yet been reported in Africa, the early symptoms of declining responsiveness have been confirmed in Kenya by Borrmann et al (2011).

The decline in the efficacy of the first-line antimalarial drug, artemether-lumefantrine, in Ethiopia from 99.5% in 2003 (Jima et al 2005) to 93.7% in 2008 (Assefa et al, 2010), is a clear signal of the need to strictly monitor efficacy of the drug in order to timely gather evidence and allow identification of suitable alternatives.

Antimalarial drug efficacy monitoring should be conducted on regular basis of every two years, involving 4 to 8 representative study sites and involvement of statistically representative number of patients as recommended by the WHO (2009). The use of an appraisal process to check and confirm the appropriateness of the study plans during the ethical review process currently implemented by the Ethiopian Science and Technology Agency (2005) is also an important mechanism in place that can be used to ensure that studies are of the expected standards.

Although WHO (2009) recommends the initiation of malaria treatment policy change when the treatment failure rate of the first-line antimalarial drug in use exceeds 10%, Williams et al (2004) emphasizes that factors that influence antimalarial treatment policy change process such as safety, efficacy, cost and availability of the replacement drug should be well understood and agreed beforehand.

The above discussion should be considered taking into consideration the fact that this was a retrospective study based on the review of literature available at the time the study was conducted. Hence, newer and other studies may have provided a different picture of the situation.

Conclusions

The success in malaria prevention and control in Ethiopia will continue to depend on the availability of safe, effective, affordable and accessible antimalarial drugs.
This study has shown that the adequacy of studies used for initiating policy change was not optimal; but is also emphasizes the fact that 20% of studies were useful in the implementation of change. This is a step in the right direction.
This finding suggests that policy change process is beyond collecting the correct evidence at the right time, it should be based on an institutional mechanism managed by appropriate personnel who have the right skills. Malaria-endemic countries such as Ethiopia should endeavour to put technical team and groups in place to conduct studies, review and use evidence to effect meaningful policy changes.

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