

Assessing Antimalarial Efficacy in a Time of Change to Artemisinin-Based Combination Therapies: The Role of Médecins Sans Frontières

Jean-Paul Guthmann*, Francesco Checchi, Ingrid van den Broek, Suna Balkan, Michel van Herp, Eric Comte, Oscar Bernal, Jean-Marie Kindermans, Sarah Venis, Dominique Legros, Philippe J. Guerin

During the 1990s, high levels of *Plasmodium falciparum* (*Pf*) resistance to common antimalarials were reported from malaria-endemic countries, raising questions about the efficacy of chloroquine (CQ), then the mainstay of antimalarial treatment. Drug resistance was considered a prime contributing factor to increased malaria mortality and morbidity across Africa [1,2]. The natural successor to CQ, sulfadoxine-pyrimethamine (SP), had a short therapeutic lifespan [3], and the choice of an effective first-line regimen emerged as a key issue in *Pf* malaria control. Artemisinin-based combination therapy (ACT), adopted in southeast Asia since the early 1990s, appeared to be the best available option [3].

Médecins Sans Frontières (Doctors Without Borders, or MSF) is a humanitarian medical aid organisation, dedicated to providing assistance to populations who lack access to health care. In the 1990s, antimalarial resistance was emergent in most countries where MSF was operating, but scientific evidence of this resistance was often lacking, and CQ or SP were still recommended by national malaria control programmes. Faced with a lack of data and the reluctance of international technical advisors and donors to review treatment strategies, MSF initiated *in vivo* studies to document the situation in its programme locations. While the

The Policy Forum allows health policy makers around the world to discuss challenges and opportunities for improving health care in their societies.

Summary Points

- More than 12,000 patients were enrolled in 43 efficacy studies in 18 countries of Asia and Africa between 1996 and 2004, accounting for one fourth of the overall research output in these countries.
- This has provided extensive evidence on the efficacy of most drug regimens currently in use for uncomplicated malaria, which was often used for treatment policy changes by the concerned countries.
- The greatest contribution was in conflict-affected countries of

sub-Saharan Africa, where studies represent the vast majority of available data and where “traditional” academic research institutions were not or barely represented.

- The vast majority of the studies were published in peer-reviewed journals, which shows that research performed in difficult settings can be of a high enough standard to ensure publication and to be useful in policy change.
- This work demonstrates the potential role of non-governmental agencies in collecting the necessary evidence to stimulate and inform policy change in international health.

Funding: Individual studies and the present desk-based analysis were financed by the different operational sections of MSF, who gave authorisation to compile the existing data in one single analysis for publication. The authors received no specific funding for this article.

Competing Interests: The authors have declared that no competing interests exist.

Citation: Guthmann J-P, Checchi F, van den Broek I, Balkan S, van Herp M, et al. (2008) Assessing antimalarial efficacy in a time of change to artemisinin-based combination therapies: The role of Médecins Sans Frontières. *PLoS Med* 5(8): e169. doi:10.1371/journal.pmed.0050169

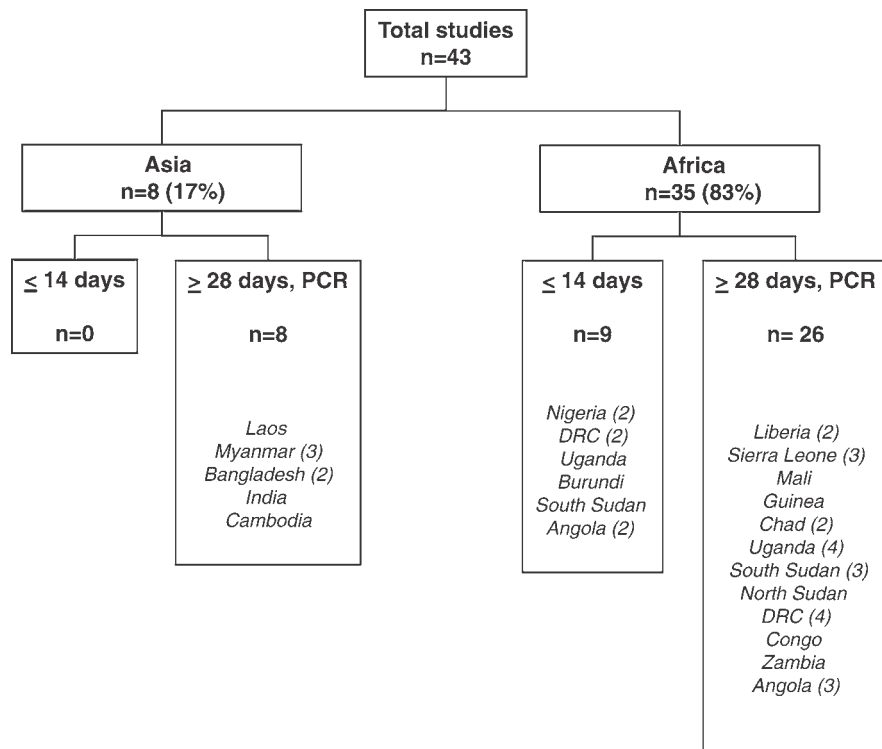
Copyright: © 2008 Guthmann et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abbreviations: ACT, artemisinin-based combination therapy; AQ, amodiaquine; AS, artesunate; CQ, chloroquine; DRC, Democratic Republic of the Congo; MSF, Médecins Sans Frontières; MQ, mefloquine; NGO, non-governmental organisation; *Pf*, *Plasmodium falciparum*; SP, sulfadoxine-pyrimethamine; WHO, World Health Organization

Jean-Paul Guthmann, Francesco Checchi, Ingrid van den Broek, Dominique Legros, and Philippe J. Guerin are with Epicentre, Paris, France. Jean-Paul Guthmann is also with the Département de Maladies Infectieuses, Institut de Veille Sanitaire, Saint Maurice, France. Francesco Checchi is also with the Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom. Ingrid van den Broek and Sarah Venis are with Médecins Sans Frontières, London, United Kingdom. Ingrid van den Broek is also with Médecins Sans Frontières, Amsterdam, The Netherlands, and the Centre for Infectious Disease Control, National Institute of Public Health and the Environment, Bilthoven, The Netherlands. Suna Balkan is with Médecins Sans Frontières, Paris, France. Michel van Herp and Jean-Marie Kindermans are with Médecins Sans Frontières, Brussels, Belgium. Eric Comte is with Médecins Sans Frontières, Geneva, Switzerland. Oscar Bernal is with Médecins Sans Frontières, Barcelona, Spain. Dominique Legros is also with Disease Control in Emergencies, Department of Epidemic and Pandemic Alert and Response, World Health Organization, Geneva, Switzerland.

The list of principal authors of individual studies is given at the end of the paper.

* To whom correspondence should be addressed. E-mail: jp.guthmann@invs.sante.fr



doi:10.1371/journal.pmed.0050169.g001

Figure 1. Flow Chart of Sites and Type of MSF *Pf* Efficacy Studies, 1996–2004

primary aim was optimising treatment strategies for MSF patients, results were often used to formulate national policy change. Studies followed World Health Organization (WHO) recommendations [4,5], were usually conducted in insecure or difficult-to-access sites where data were absent, and were generally supported by MSF's epidemiological unit, Epicentre, in collaboration with national Ministries of Health, WHO, and other partners.

Here, we describe the output of MSF's work in antimalarial efficacy assessment during the last decade, and place it within the broader context of studies leading to regimen change from monotherapies to mostly artemisinin-based combinations during a critical decade in malaria control. We also describe challenges and lessons learned whilst carrying out this research and discuss its role within antimalarial policy change.

Descriptive Analysis of Efficacy Studies

Review methods. We identified all malaria in vivo drug efficacy studies for which MSF was the main sponsor during 1996–2004, whether published in peer-reviewed journals or existing

as unpublished reports in MSF operational centres (Brussels, Paris, Amsterdam, Barcelona, and Geneva; unpublished reports are available upon request from epimail@epicentre.msf.org). Only *Pf* studies were considered. For every study, we compiled country and site, year of completion, treatment group(s) tested, drug allocation method, length of post-enrolment follow-up (14 days or less; more than 14 days, i.e., at least 28-day follow-up), and failure rate with 95% confidence intervals. A treatment group is defined as the regimen tested. Multi-centric studies simultaneously evaluating several treatment groups within the same country were treated as single studies.

We calculated the proportion of MSF study treatment groups among all treatment groups tested against *Pf* per country during 1996 to 2004 by consulting the Global Malaria Program database (<http://www.who.int/malaria/resistance.html>). We reviewed the WHO Global Antimalarial Drug Policy Database (<http://www.who.int/malaria/treatmentpolicies.html>) and reference document [6] to establish the occurrence and timing of changes in treatment policy for

uncomplicated malaria. We did not consider the introduction of CQ and SP in combination, as this was not a recommended option to replace either monotherapy [7]. We compared the new drug policy to findings and recommendations of the relevant MSF malaria studies and calculated the proportion of countries where recommendations made by MSF were concordant with subsequent national decisions regarding policy change.

To calculate the proportion of MSF papers among all published papers published in peer-reviewed journals, we searched PubMed to identify antimalarial studies published since 1996 until up to April 2007, performed in the countries in which MSF's studies had taken place, and reporting original in vivo efficacy data for treatment of uncomplicated *Pf* malaria in non-pregnant populations. Keywords were "malaria" and country of intervention (e.g., "Angola").

Study output. Between 1996 and 2004, MSF performed 43 efficacy studies or clinical trials in 18 countries, of which eight (17%) were in Asia (five countries) and 35 (83%) in Africa (13 countries) (Figure 1). Half of the studies took place in four African countries (21/43, 49%): Angola ($n = 5$), the Democratic Republic of the Congo (DRC, $n = 6$), Uganda ($n = 5$), and Sudan ($n = 5$). 12,145 patients were enrolled. Most studies (88%) were conducted between 2001 and 2004 and had a follow-up of 28 days or more ($n = 34$, 79%) with genotypic analysis of presumed failures/parasite recurrences to distinguish recrudescence from reinfection (Figure 2). Of studies with 28-day follow-up, 28/34 (82%) were published in peer-reviewed journals, and three out of 34 (9%) had been submitted to peer-reviewed journals at the time of writing; conversely, only three out of nine (33%) 14-day studies were published (Table 1).

Overall, nine (21%) studies were single arm, whereas 34 (79%) were comparative. Of the comparative studies, 22 (65%) were randomised. 117 treatment groups were investigated, of which 69 (59%) were monotherapies (SP, $n = 27$; CQ, $n = 24$; amodiaquine [AQ], $n = 15$; mefloquine [MQ], $n = 3$) and 48 (41%) were combinations. Most combinations (90%) were artemisinin-based (artesunate [AS]-SP, $n = 14$; AS-AQ, $n = 12$; AS-MQ, n

= 10, artemether-lumefantrine, $n = 5$; dihydroartemisinin-piperaquine, $n = 2$); the remaining five were quinine-SP ($n = 1$) or CQ-SP ($n = 4$). The number of ACT studies increased over time, from one in 1998 to 20 (80% of total) in 2004 (Figure 2).

Contribution of MSF Studies to the Evidence for Policy Change

Within these 18 countries and during 1996–2004, 455 treatment groups were investigated, 112 (25%) by MSF (Table 2). The proportion of study groups investigated by MSF was higher for ACTs (46%) than monotherapies (19%), and higher in Africa than in Asia, both for monotherapies (23% versus 9%) and ACTs (57% versus 29%). Recommendations made by MSF were concordant with subsequent national decisions regarding policy change in 13/18 (72%) of the countries of intervention (Asia: two out of five [40%]; Africa: 11/13 [84%]).

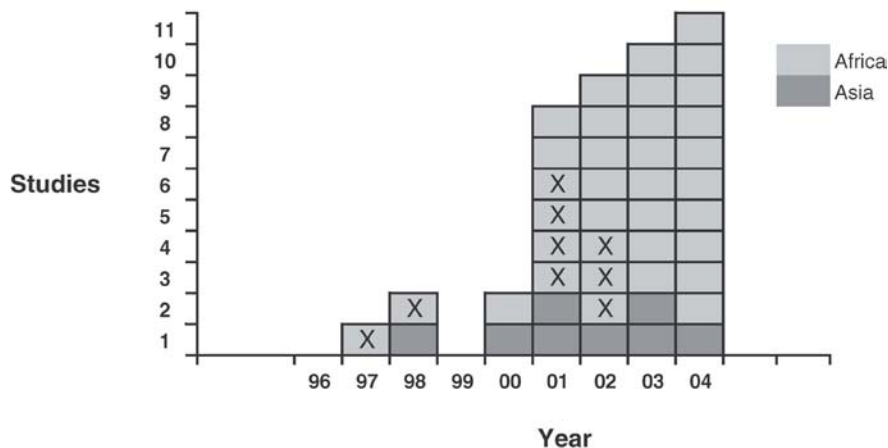
Of the 43 MSF studies, 31 (72%) were published in peer-reviewed journals. MSF studies accounted for 23% (31/137) of all articles published during this period in the 18 countries of intervention (Table 3).

MSF's largest output was in conflict-affected countries of sub-Saharan Africa, including Angola, Burundi, Chad, Liberia, Sierra Leone, and southern Sudan, where its studies represent the vast majority of available data, and where "traditional" academic research institutions were not or barely represented. Overall, MSF's study output accounted for one quarter of antimalarial drug efficacy research in 18 countries. Most studies were published in peer-reviewed journals.

Challenges and Lessons Learned

Generalisability of results obtained in crisis settings. With the exception of Sierra Leone, where a national multi-centric study was carried out, the MSF studies were not necessarily representative of national trends. Armed conflict, forced displacement in Maheba, Zambia and Kailahun, Sierra Leone (potentially leading to the introduction of more or less resistant strains), and conflict-induced nutritional crises (leading to lower immuno-competence and thus impaired host response) that had recently affected many of the study

Study treatment groups (n)										
Year	96	97	98	99	00	01	02	03	04	Tot
Mono	0	1	5	0	2	22	11	23	5	69
ACT	0	0	1	0	2	6	2	12	20	43
% ACT	0	0	16	0	50	21	15	34	80	38



doi:10.1371/journal.pmed.0050169.g002

Figure 2. Number of MSF *Pf* Efficacy Studies and Treatment Groups (Monotherapies and ACT) Per Year of Completion, 1996–2004

Cells with X represent studies of 14-day follow-up or less; empty cells represent studies of 28-day follow-up or more. Mono = monotherapies.

populations (Angola; Burundi; DRC; Lankien, Mapel, and Nuba, southern Sudan; Sierra Leone; Amudat and Bundibugyo, Uganda) may have resulted in systematic differences in local antimalarial efficacy compared to other regions of the country. Evidence suggests that malnourished children have an increased risk of treatment failure [8–10]. Organisations conducting studies in crisis-affected settings need to consider the generalisability of their data carefully in addition to the more general problem of extrapolating findings from individual sites to wider populations.

Planning and organisational strategy. MSF's contribution was not systematically planned but rather ad hoc, driven by its programmes. In retrospect, MSF's approach could have been more systematic, and more adherent to the standards of evidence-based medicine, in which randomised clinical trials are the primary tool by which inefficacious treatments are replaced once a more efficacious and equally safe alternative is identified. The approach shifted over time from measuring the efficacy of CQ and alternative potential partner drugs to combine with AS, to assuming that CQ was already inefficacious and focusing

on head-on comparisons of different ACT combinations. MSF's strategy thus wavered between building an evidence base to argue against continued CQ use, trying to establish the baseline resistance of typical partner drugs, and a more pragmatic approach of directly investigating combinations.

Logistical and implementation challenges. Carrying out field research in some of the remote settings proved extremely challenging. For example, Caala, Angola was under military siege and affected by a humanitarian emergency during the study period. In Bundibugyo, Uganda, security constraints due to rebel incursions necessitated innovative solutions to trace patients not attending follow-up, including field visits by clinicians and laboratory staff. Shabunda, DRC and most Sudanese sites were accessible only by plane or on foot. Laboratory facilities were usually established from scratch, without electricity and with the threat of possible sources of contamination and degradation of slides and blood samples. While most study personnel were from the country itself, it was necessary to either recruit qualified professionals from other areas of the country, or re-train local staff who had been unemployed for years

Table 1. MSF PfEfficacy Studies by Site, Year of Completion, Drug Tested, and Result

Country	Site	Year	Drug	Failure Rate (%) ^a	95% Confidence Interval (%)	Reference ^b
At least 28-day follow-up: 34 studies						
Myanmar	Kachin	1998	CQ	79.2	68.4–87.6	[16]
			SP	80.8	69.9–89.1	
			MQ	23.0	14.0–34.2	
			MQ-AS ₃	20.5	12.0–31.6	
Laos	Sekong	2000	CQ	39.7	29.5–50.7	[17]
Uganda	Mbarara	2000	SP	59.3	51.3–67.0	[18]
			SP-AS ₁	54.0	44.4–63.3	
			SP-AS ₃	22.3	15.3–30.7	
South Sudan	Kajo Keji	2001	CQ	93.9	87.3–97.3	[19]
			SP	69.9	60.0–78.3	
			AQ	25.2	17.7–34.5	
Myanmar	Rakhine	2001	MQ ₁₅ -AS ₁	5.9	3.0–10.3	[20]
			MQ ₂₅ -AS ₁	3.6	1.5–7.4	
			MQ ₂₅ -AS ₃ un _{sup}	3.9	1.7–8.2	
			MQ ₂₅ -AS ₃ sup	0.0	0.0–2.1	
India	Assam & Karbi Anglong	2001	CQ	65.9	48.8–78.1	[21]
			SP	39.0	25.3–54.0	
			MQ ₁₅	4.4	0.54–15.1	
			MQ ₁₅ -AS	10.9	3.6–23.5	
India	Sonitpur	2001	CQ	95.8	83.5–98.7	[21]
			SP	57.1	42.2–71.2	
			MQ ₁₅	7.8	2.2–18.9	
			MQ ₁₅ -AS	1.8	0.5–9.9	
Sierra Leone	Matru	2001	CQ	61.8	52.1–70.8	Bachy C, Epicentre Internal Report 2002
			SP	22.4	14.1–32.7	
Bangladesh	Chittagong	2002	Qui-SP	12.9	8.1–17.7	[22]
Liberia	Harper	2002	CQ	84.0	70.9–92.8	[23]
			SP	69.7	57.1–80.4	
Liberia	Harper	2002	AQ	23.5	14.8–34.2	[24]
Zambia	Maheba	2002	SP-AS _{sup}	16.4	9.0–26.5	[25]
			SP-AS _{un^{sup}}	36.6	26.2–47.9	
Uganda	Bundibugyo	2002	SP	37.0	27.1–47.7	[26]
			AQ	20.6	11.7–32.7	
			CQ-SP	22.8	14.1–33.6	
Chad	Bongor	2002	CQ	23.7	14.7–34.8	[27]
			SP	16.3	9.4–25.5	
			AQ	6.4	2.1–14.3	
Uganda	Amudat	2003	CQ-SP	52.8	35.5–69.6	Grandesso F, Epicentre Internal Report 2004
			AQ-AS	14.3	4.0–32.7	
			SP-AS	7.9	2.6–17.6	
Bangladesh	Chittagong	2003	CQ-SP	37.6	48.8–37.4	[28]
			MQ-AS	0.9	0.0–3.5	
			A-L	2.9	0.6–8.4	
			SP-AS	8.8	2.9–19.3	
South Sudan	Nuba	2003	AQ-AS	7.3	2.0–17.6	[29]
			SP-AS	8.8	2.9–19.3	
Sierra Leone	Freetown ^c	2003	CQ	67.8	54.4–79.4	[30]
			SP	28.0	16.2–42.5	
			AQ	7.4	2.1–17.9	
Sierra Leone	Kabala	2003	CQ	39.5	25.0–55.6	[30]
			SP	23.2	13.9–34.9	
			AQ	18.2	9.8–29.6	
Sierra Leone	Kailahun	2003	CQ	78.8	65.3–88.9	[30]
			SP	46.1	35.4–57.0	
			AQ	29.8	20.3–40.7	
Sierra Leone	Makeni	2003	CQ	70.0	55.4–82.1	[30]
			SP	24.0	15.8–33.7	
			AQ	5.4	1.8–12.1	
Sierra Leone	Matru	2003	AQ	13.0	6.4–22.6	[30]
North Sudan	Malakal	2003	SP-AS	0.9	0.0–4.8	[31]
			AQ-AS	1.0	0.0–5.6	
Angola	Caala	2003	CQ	83.5	74.1–90.5	[32]
			AQ	17.3	10.0–27.2	
			SP	25.3	16.7–35.8	
Angola	Kuito	2003	AQ	21.6	14.3–30.6	[32]
			SP	38.8	28.4–30.6	
			AQ-AS	1.2	0.0–6.4	
			SP-AS	1.2	0.0–6.4	

Table 1. Continued

Country	Site	Year	Drug	Failure Rate (%) ^a	95% Confidence Interval (%)	Reference ^b
At least 28-day follow-up: 34 studies						
South Sudan	Mapel	2003	CQ	82.7	71.8–90.1	Bachy et al., Epicentre Internal Report 2003
			SP	15.7	9.3–25.1	
Chad	Koumra	2003	CQ	32.9	22.1–45.1	[27]
			SP	4.3	1.2–10.5	
			AQ	2.2	0.3–7.6	
Cambodia	Anglong Veng & Kvav	2003	Piperaq-DHA	2.5	0.7–6.2	[33]
			MQ-AS	2.5	0.7–6.2	
Guinea	Dabola	2004	SP-AS	1.0	0.0–5.5	[34]
			AQ-AS	1.0	0.0–5.3	
DRC	Kabalo	2004	SP	22.9	12.0–37.3	Bonnet et al., submitted
			SP-AS	0.0	0.0–7.3	
			AQ-AS	0.0	0.0–6.8	
DRC	Shabunda	2004	SP-AS	19.7	10.9–31.3	[35]
			AQ-AS	6.8	2.2–15.1	
Congo	Kindamba	2004	AQ-AS	1.5	0.0–8.0	[36]
			SP-AS	9.9	19.3–4.1	
			A-L	0.0	0.0–5.2	
Uganda	Mbarara	2004	A-L _{sup}	2.3	1.0–4.9	[37]
			A-L _{un-sup}	2.0	1.0–3.5	
Angola	Caala	2004	AQ-AS	0.0	0.0–5.6	[38]
			A-L	0.0	0.0–5.8	
Sierra Leone	Kailahun	2004	AQ-AS	15.5	9.3–23.6	[39]
Mali	Koumantou	2004	CQ	90.5	84.8–96.2	[40]
			SP	7.0	1.9–12.1	
DRC	Boende	2004	SP	43.4	32.2–55.2	Bonnet et al., submitted
			AQ	25.8	16.1–38.2	
			SP-AS	32.8	21.6–46.1	
			AQ-AS	19.0	10.3–31.8	
DRC	Kilwa	2004	SP-AS	9.8	3.6–22.2	Bonnet et al., submitted
			AQ-AS	18.2	9.5–31.3	
Myanmar	Rakhine	2004	Piperaq-DHA	0.6	0.2–2.5	[41]
			MQ-AS	0.0	0.0–1.2	
14-day follow-up: 9 studies						
Angola ^d	Mbanza Congo	1997	CQ	57.2	50.9–63.2	MSF, Internal Report 1997
Uganda	Mbarara	1998	CQ	81.1	68.0–90.5	[42]
			SP	25.0	15.0–37.4	
Burundi	Kayanza	2001	CQ	100.0	91.8–100	Legros D, Dantoine F, Epicentre Report 2001
			SP	74.8	65.7–82.2	
			CQ-SP	56.9	46.7–66.5	
Burundi	Karuzi	2001	CQ	97.8	86.8–99.9	Legros D, Dantoine F, Epicentre Report 2001
			SP	89.7	80.8–94.9	
DRC	Pweto	2001	SP	51.0	38.4–63.0	MSF, Internal Report 2001
DRC	Multi-centric	2001	CQ	45.4	40.1–50.8	[43]
			SP	7.5	5.0–11.0	
South Sudan	Lankien	2001	CQ	11.5	6.1–19.3	[44]
			SP	0.0	0.0–3.6	
			AQ	5.9	2.2–12.5	
Nigeria	Bayelsa	2001	CQ	70.5	61.8–78.2	Hardwick et al., MSF Internal Report 2001
Nigeria	Bayelsa	2002	AQ	8.6	4.0–15.6	MSF, Internal Report, 2002
Angola	Malange	2002	CQ	79.7	69.2–87.9	Prinseberg T, Broeder R, MSF Internal Report 2002
			SP	8.6	3.5–17.0	

^aThese are usually 28-day PCR corrected failure rates, except in 6 studies: [16,20,21,28,31,33], where failure rates are given at day 42 or 63.

^bUnpublished reports are available upon request from epimail@epicentre.msf.org.

^cStudy done by Concern Worldwide/Sierra Leone Ministry of Health/WHO, with MSF–Epicentre supervision.

^dIn this study, the follow-up was 7 days.

A-L, artemether-lumefantrine; AS₁, artesunate one day; AS₃, artesunate three days; AS_{sup}, artesunate supervised; AS_{un-sup}, artesunate un-supervised; MQ₁₅, mefloquine 15 mg/kg; MQ₂₅, mefloquine 25 mg/kg; Piperaq-DHA, piperazine-dihydroartemisinin; Qui, quinine.
doi:10.1371/journal.pmed.0050169.t001

because of health system collapse. The vast majority had no prior experience in research. Research procedures had to be adapted to programmes hitherto dedicated solely to emergency health

care provision. The greatest evidence gaps may well be in remote locations featuring the most difficult research conditions. Organisations must be prepared to be flexible, innovative,

and resourceful. Investment in basic infrastructure, training, and human resources is essential.

Follow-up and rescue treatment were also problematic. The WHO assessment

Table 2. Number of Studies Performed by MSF–Epicentre among Total Studies by Country and Drug (Monotherapy, ACT) and Concordance between MSF Recommendations and New Policy Subsequently Adopted by the Country

Country	MSF–Epicentre Studies/Total Studies				Year(s) of Study	ACT(s) Recommended by MSF	Year of Change	New Policy	Concordance between MSF Recommendations and New Policy		
	Monotherapies		ACT							Total	
	n/N	%	n/N	%	n/N	%					
Asia											
Bangladesh	0/4	0	2/2	100	2/6	33	2003	AS-MQ, A-L	2004	A-L	Yes
Cambodia	0/0	NA	2/17	12	2/17	12	2003	None	2000	AS-MQ	No
India	6/40	15	2/2	100	8/42	19	2001	AS-MQ	2004	SP, AS-SP	No
Laos	1/9	11	0/4	0	1/13	8	2000	None	2001	A-L	No
Myanmar	3/54	5	7/19	41	10/73	14	1998, 2001–04	AS-MQ	2002	AS-MQ, A-L	Yes
Total: Asia	10/107	9	13/44	29	23/151	15					
Africa											
Angola	8/16	50	4/4	100	12/20	60	1997, 2003–04	AS-AQ, A-L	2004	A-L	Yes
Burundi	4/8	50	0/4	0	4/12	33	2001	AS-AQ, A-L	2003	AS-AQ	Yes
Congo	0/5	0	3/3	100	3/8	37	2004	A-L, AS-AQ	No change		No
DRC	6/19	31	8/14	57	14/33	42	2001–04	A-L	2004	AS-AQ	No
Guinea	0/8	0	2/2	100	2/10	20	2004	AS-SP, AS-AQ	2004	AS-AQ	Yes
Mali	2/22	9	0/0	NA	2/22	9	2004	AS-SP, AS-AQ, A-L	2004	A-L	Yes
Nigeria	2/20	10	0/0	NA	2/20	10	2001–02	ACT, no precision	2004	A-L	Yes
Liberia	3/3	100	0/0	NA	3/3	100	2002	AS-AQ	2004	AS-AQ	Yes
Sierra Leone	15/17	88	1/1	100	16/18	89	2001–03–04	AS-AQ	2004	AS-AQ	Yes
Sudan	8/40	20	4/10	40	12/50	24	2001–03	AS-SP, A-L	2004	AS-AQ, AS-SP	Yes
Chad	6/7	86	0/0	NA	6/7	86	2002–03	AS-AQ	2004	AS-AQ	Yes
Uganda	5/48	10	6/6	100	11/54	20	98, 2000–02–03–04	AS-AQ, AS-SP, A-L	2004	A-L	Yes
Zambia	0/39	0	2/8	25	2/47	4	2002	A-L	2002	A-L	Yes
Total: Africa	59/252	23	30/52	57	89/304	29					
Total: All Countries	69/359	19	43/96	46	112/455	25					

A-L, artemether-lumefantrine; NA, not applicable.

doi:10.1371/journal.pmed.0050169.t002

protocol required investigators to withhold rescue treatment in case of asymptomatic parasite recurrence, which carries a high risk of avoidable morbidity [11]. Follow-up visits took place at one-week intervals, during which patients with known parasitaemia would remain without rescue treatment. On two occasions (two children treated respectively with AQ and CQ who were parasitaemic during follow-up and who did not come back for further visits), we believe this contributed to avoidable deaths from severe malaria. As a response, we instituted frequent home visits by field workers to detect any symptom progression.

Partly due to concerns about security-related interruptions to enrolment, a proportion of studies in the first half of the period were single arm or used sequential allocation procedures. Unplanned decisions to stop enrolment due to very high treatment failure were occasionally taken, thus exposing investigators to the criticism of having contravened the protocol; later, randomisation was introduced as the

standard, along with systematic early stopping rules.

Quality versus timeliness. Efforts were made to improve the quality of the studies, including establishment of routine laboratory quality control procedures (internal controls and review of slides by reference laboratories) and standard protocols and operating procedures for clinical and laboratory work. From 2003, follow-up was systematically extended to 28 days, and PCR genotyping analyses were always done to adjust failure rates for re-infections. This is broadly considered an appropriate method for assessing drug efficacy and therefore yielded realistic estimates for each site [12].

However, these analyses required the involvement of partner institutions (usually academic laboratories in Europe). Due to the heavy workload of these laboratories, PCR genotyping sometimes yielded considerable delays in releasing final results. In situations where treatment failure was severe, this raised an ethical dilemma of balancing the release of final results with the need for action. A common approach

was to release preliminary, unadjusted failure rates based on 14-day follow-up, especially when these already warranted an urgent change of the current first-line therapy. This however often led to confusion, especially when subsequent 28-day results overturned the initial impression that other cheap non-ACT regimens were still efficacious (particularly SP, for which failures tend to occur late). Furthermore, MSF field officers mediating between study investigators and local stakeholders did not always have the technical expertise to discuss genotyping adjustment. With more complex methods, the extra time involved in ensuring that data are accurate must be weighed against the urgency of action in each setting. However, our experience shows that in order to avoid confusion it is preferable to await final results, as long as the delay is acceptable (to be determined on a case-by-case basis).

Ethical Issues

These studies presented ethical dilemmas common to research in crisis-affected populations [13]. Local

clinicians had strong anecdotal evidence of poor drug efficacy, but lack of scientific evidence hindered advocacy to review treatment policies. Communities were particularly vulnerable to the effects of antimalarial drug resistance since they had poor access to health care, no recourse to efficacious second-line treatments, and limited civil rights and governance structures within which to voice their patient perspective. Furthermore, patients' or caregivers' ability to decide whether to participate in the study was severely constrained: the study venue was often their sole health care option, and their familiarity with biomedical concepts may have been insufficient to properly consider the risks and benefits of participation. Adhering to the strict follow-up schedule was also challenging, potentially entailing days of missed work.

In many countries there was no institutional review board (IRB), and protocols were approved by Ministry of Health directorates for research, as well as local health authorities. We considered that even in the absence of formal IRB review, generating evidence on antimalarial efficacy was essential to stimulate policy change. The assessment protocol was standardised and recommended by WHO; regimens were non-experimental; and patients' risk of untoward outcomes was lower than in routine care due to the systematic follow-up and availability of second-line regimens in case of treatment failure. These considerations persuaded us that the harm–benefit ratio was favourable. This experience suggests that ethical risks of conducting research should always be weighed against the consequences of inaction. Measures to minimise risk include standardising protocols, ensuring locally appropriate, understandable consent procedures, developing alternative structures for ethics review, and involving the community.

Future Research Challenges

Recently, several players have become involved in antimalarial efficacy assessment, and there are global initiatives to co-ordinate studies [14]. Today's challenges are different: (1) to detect resistance to ACTs as early as possible, best done by combining molecular and *in vivo* studies, and defining strategic surveillance sites

Table 3. Number and Proportion of Articles Published in Peer-Reviewed Journals, 1996–2007

Country	Total Articles (n)	MSF Articles (n)
Angola	3	3
Liberia	2	2
Sierra Leone	2	2
Chad	2	2
Bangladesh	7	2
Burundi	3	0
Uganda	24	4
Sudan	15	4
Myanmar	5	3
Guinea	1	1
DRC	2	2
Cambodia	5	1
India	15	1
Laos	9	1
Congo	5	1
Mali	4	1
Nigeria	27	0
Zambia	6	1
Total	137	31 (23%)

doi:10.1371/journal.pmed.0050169.t003

where resistance is more likely to arise *de novo* or be introduced from other regions; and (2) to demonstrate that new regimens (e.g., dihydroartemisinin-piperazine) are at least as efficacious as current first-line ACTs and carry additional benefits in terms of safety, cost, or feasibility: this would require non-inferiority rather than comparative trial designs [15].

Conclusions

Our analysis shows that research can be performed in difficult settings to a high enough standard to ensure publication and to be useful in policy change.

MSF's work shows that non-governmental organisations (NGOs) can provide extensive evidence on the efficacy of most antimalarial regimens. This evidence probably affected malaria treatment policy decisions, as suggested by the high number of countries where recommendations and decisions were the same. However, this conclusion has to be drawn with caution: factors leading to policy change are many and difficult to measure, as are reasons for adopting one regimen over another.

As part of their mandate, medical NGOs should be prepared to fill gaps in evidence, including evaluating current tools to control tropical diseases in hard-to-reach populations, and demonstrating the effectiveness of alternatives. Dissemination of findings

in peer-reviewed journals is crucial to bolster the validity of such research and inform international policy and advocacy. While operational research can successfully be undertaken by NGOs, national malaria control programmes, WHO, and other major international disease control partnerships hold the primary responsibility for initiating such studies. Had such institutions stimulated a systematic process of monitoring antimalarial efficacy from the onset of reports of drug resistance, change might have occurred earlier. Finally, it is important that complacency does not set in. Artemisinin resistance may well arise, and countries, international bodies, and NGOs need to prospectively monitor the situation to avoid history repeating itself. ■

Acknowledgments

We thank Pascal Ringwald (Global Malaria Programme/WHO) for sharing the databases compiled by WHO and for helpful advice and comments. We thank all authors and partner institutions of the individual studies (some of which provided helpful comments), who unfortunately cannot all be listed in this paper. Thank you to Christa Hook for her important work as the Coordinator of the MSF Malaria Working Group. We are grateful to Elizabeth Ashley (Epicentre) and Rebecca Freeman Grais (Epicentre) for helpful comments on final versions of the manuscript. Thank you to Nick White (Wellcome Trust), François Nosten (Wellcome Trust), and Piero Olliaro (TDR-WHO) for their constant support

during all these years.

List of principal investigators (or first author of paper/report) of individual studies:

C. Bachy, M. Bonnet, P. Campbell, F. Checchi, E. Depoortere, X. de Radiguès, F. Grandesso, J. P. Guthmann, B. Janssens, S. Hamour, R. Hardwick, D. Legros, P. Piola, T. Prinsberg, G. Priotto, F. Smithuis, E. Stivanello, T. Swarthout, I. van den Broek.

Author contributions. J-PG co-ordinated the project, compiled the studies, wrote the plan of analysis, analysed the data, and wrote the paper. FC had a crucial role in the analysis and interpretation of results and gave significant input in the writing of the paper. IvdB, SB, MvH, EC, OB, and J-MK compiled data from their MSF section and contributed in data interpretation. SV participated in the analysis and interpretation of part of the data and had a crucial role in paper writing. DL had an important role in the conception, analysis, and interpretation of several individual studies and had an important intellectual contribution to the overall intervention, to which he gave important epidemiological input. PJG contributed in the conception of the project, in the interpretation of results, and in the writing of the paper. All authors participated intellectually in this project and in the writing of the paper.

References

1. Trape JF (2001) The public health impact of chloroquine resistance in Africa. *Am J Trop Med Hyg* 64 (1-2 Suppl): 12-17.
2. Zucker JR, Ruebush TK II, Obonyo C, Otieno J, Campbell C (2003) The mortality consequences of the continued use of chloroquine in Africa: Experience in Siaya, Western Kenya. *Am J Trop Med Hyg* 68: 386-390.
3. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, et al. (1999) Averting a malaria disaster. *Lancet* 353: 1965-1967.
4. World Health Organization (1996) Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission. Available: http://www.who.int/drugresistance/malaria/en/Assessment_malaria_96.pdf. Accessed 7 July 2008.
5. World Health Organization (2003) Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Available: <http://www.who.int/malaria/docs/ProtocolWHO.pdf>. Accessed 7 July 2008.
6. World Health Organization (2005) Susceptibility of *Plasmodium falciparum* to antimalarial drugs. Report on global monitoring, 1996-2004. Available: http://www.who.int/malaria/rbm/Attachment/20041108/SusceptibilityPlasmodium_report.pdf. Accessed 7 July 2008.
7. World Health Organization (2003) Position of WHO's Roll Back Malaria Department on malaria treatment policy. Available: <http://www.who.int/malaria/treatmentguidelines.html>. Accessed 7 July 2008.
8. Hess FI, Iannuzzi A, Leafasia J, Cowdrey D, Nothdurft HD, et al. (1996) Risk factors of chloroquine resistance in *Plasmodium falciparum* malaria. *Acta Trop* 61: 293-306.
9. Hamel MJ, Holtz T, Mkandala C, Kaimila N, Chizani N, et al. (2005) Efficacy of trimethoprim-sulfamethoxazole compared with

- sulfadoxine-pyrimethamine plus erythromycin for the treatment of uncomplicated malaria in children with integrated management of childhood illness dual classifications of malaria and pneumonia. *Am J Trop Med Hyg* 73: 609-615.
10. Olanrewaju WI, Johnson AW (2001) Chloroquine-resistant *Plasmodium falciparum* malaria in Ilorin, Nigeria: Prevalence and risk factors for treatment failure. *Afr J Med Med Sci* 30: 165-169.
11. Olliaro P, Pinoges L, Checchi F, Vaillant M, Guthmann JP (2008) Risk associated with asymptomatic parasitaemia occurring post-antimalarial treatment. *Trop Med Int Health* 13: 83-90.
12. Guthmann JP, Pinoges L, Checchi F, Cousens S, Balkan S, et al. (2006) Methodological issues in the assessment of antimalarial drug treatment: Analysis of 13 studies in eight African countries from 2001 to 2004. *Antimicrob Agents Chemother* 50: 3734-3739.
13. Committee on Population, National Research Council (2002) Research ethics in complex humanitarian emergencies: Summary of a workshop. National Academy Press. Available: http://books.nap.edu/catalog.php?record_id=10481. Accessed 7 July 2008.
14. Price R, Dorsey G, Ashley E, Barnes K, Baird JK, et al. (2007) World Antimalarial Resistance Network I: Clinical efficacy of antimalarial drugs. *Malar J* 6: 119.
15. Stepniewska K, White NJ (2006) Some considerations in the design and interpretation of antimalarial drug trials in uncomplicated falciparum malaria. *Malar J* 5: 127.
16. Smithuis F, Shahmanesh M, Kyaw MK, Savran O, Lwin S, et al. (2004) Comparison of chloroquine, sulfadoxine/pyrimethamine, mefloquine and mefloquine-artesunate for the treatment of falciparum malaria in Kachin State, North Myanmar. *Trop Med Int Health* 9: 1184-1190.
17. Guthmann JP, Kasparian S, Phetsouvanh R, Nathan N, Garcia M, et al. (2002) The efficacy of chloroquine for the treatment of acute, uncomplicated, *Plasmodium falciparum* malaria in Laos. *Ann Trop Med Parasitol* 96: 553-557.
18. Priotto G, Kabakyenga J, Pinoges L, Ruiz A, Eriksson T, et al. (2003) Artesunate and sulfadoxine-pyrimethamine combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria in Uganda: A randomized, double-blind, placebo-controlled trial. *Trans R Soc Trop Med Hyg* 97: 325-330.
19. Stivanello E, Cavailler P, Cassano F, Omar SA, Kariuki D, et al. (2004) Efficacy of chloroquine, sulphadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in Kajo Keji county, Sudan. *Trop Med Int Health* 9: 975-980.
20. Smithuis F, van der Broek I, Katterman N, Kyaw MK, Brockman A, et al. (2004) Optimising operational use of artesunate-mefloquine: A randomised comparison of four treatment regimens. *Trans R Soc Trop Med Hyg* 98: 182-192.
21. Campbell P, Baruah S, Narain K, Rogers CC (2006) A randomized trial comparing the efficacy of four treatment regimens for uncomplicated falciparum malaria in Assam state, India. *Trans R Soc Trop Med Hyg* 100: 108-118.
22. van den Broek IV, van der Wardt S, Talukder L, Chakma S, Brockman A, et al. (2004) Drug resistance in *Plasmodium falciparum* from the Chittagong Hill Tracts, Bangladesh. *Trop Med Int Health* 9: 680-687.
23. Checchi F, Durand R, Balkan S, Vonhm BT, Kollie JZ, et al. (2002) High *Plasmodium falciparum* resistance to chloroquine and sulfadoxine-pyrimethamine in Harper, Liberia: Results in vivo and analysis of point mutations. *Trans R Soc Trop Med Hyg* 96: 664-669.

24. Checchi F, Balkan S, Vonhm BT, Massaquoi M, Biberson P, et al. (2002) Efficacy of amodiaquine for uncomplicated *Plasmodium falciparum* malaria in Harper, Liberia. *Trans R Soc Trop Med Hyg* 96: 670-673.
25. Depoortere E, Guthmann JP, Pressé J, Sipilanyambe N, Nkandu E, et al. (2005) Efficacy and effectiveness of the combination of sulfadoxine/pyrimethamine and a 3-day course of artesunate for the treatment of uncomplicated falciparum malaria in a refugee settlement in Zambia. *Trop Med Int Health* 10: 139-145.
26. Checchi F, Piola P, Kosack C, Ardizzone E, Klarkowski D, et al. (2004) Antimalarial efficacy of sulfadoxine-pyrimethamine, amodiaquine and a combination of chloroquine plus sulfadoxine-pyrimethamine in Bundi Bugyo, western Uganda. *Trop Med Int Health* 9: 445-450.
27. Grandesso F, Bachy C, Donam I, Ntambi J, Habimana J, et al. (2006) Efficacy of chloroquine, sulfadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated *Plasmodium falciparum* malaria among children under five in Bongor and Koumra, Chad. *Trans R Soc Trop Med Hyg* 100: 419-426.
28. van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, et al. (2005) Efficacy of chloroquine + sulfadoxine-pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat *Plasmodium falciparum* malaria in the Chittagong Hill Tracts, Bangladesh. *Trans R Soc Trop Med Hyg* 99: 727-735.
29. Hamour S, Melaku Y, Keus K, Wambugu J, Atkin S, et al. (2005) Malaria in the Nuba Mountains of Sudan: Baseline genotypic resistance and efficacy of the artesunate plus sulfadoxine-pyrimethamine and artesunate plus amodiaquine combinations. *Trans R Soc Trop Med Hyg* 99: 548-554.
30. Checchi F, Roddy P, Kamara S, Williams A, Morineau G, et al. (2005) Evidence basis for antimalarial policy change in Sierra Leone: Five in vivo efficacy studies of chloroquine, sulphadoxine-pyrimethamine and amodiaquine. *Trop Med Int Health* 10: 146-153.
31. van den Broek I, Amsalu R, Balasegaram M, Hepple P, Alemu E, et al. (2005) Efficacy of two artemisinin combination therapies for uncomplicated falciparum malaria in children under 5 years, Malakal, Upper Nile, Sudan. *Malar J* 4: 14.
32. Guthmann JP, Ampuero J, Fortes F, van Overmeir C, Gaboulaud V, et al. (2005) Antimalarial efficacy of chloroquine, amodiaquine, sulfadoxine-pyrimethamine, and the combinations of amodiaquine + artesunate and sulfadoxine-pyrimethamine + artesunate in Huambo and Bie provinces, central Angola. *Trans R Soc Trop Med Hyg* 99: 485-492.
33. Janssens B, van Herp M, Goubert L, Chan S, Uong S, et al. (2007) A randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia. *Trop Med Int Health* 12: 251-259.
34. Bonnet M, Roper C, Félix M, Coulbaly L, Kankolongo GM, et al. (2007) Efficacy of antimalarial treatment in Guinea: In vivo study of two artemisinin combination therapies in Dabola and molecular markers of resistance to sulphadoxine-pyrimethamine in N'Zérékoré. *Malar J* 6: 54.
35. Swarthout TD, van den Broek IV, Kayembe G, Montgomery J, Pota H, et al. (2006) Artesunate + amodiaquine and artesunate + sulphadoxine-pyrimethamine for treatment of uncomplicated malaria in Democratic Republic of Congo: A clinical trial with determination of sulphadoxine and pyrimethamine-resistant haplotypes. *Trop Med Int Health* 11: 1503-1511.

36. van den Broek I, Kitz C, Al Attas S, Libama F, Balasegaram M, et al. (2006) Efficacy of three artemisinin combination therapies for the treatment of uncomplicated *Plasmodium falciparum* malaria in the Republic of Congo. *Malar J* 5: 113.
37. Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, et al. (2005) Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: A randomised trial. *Lancet* 365: 1467-1473.
38. Guthmann JP, Cohuet S, Rigutto C, Fortes F, Saraiva N, et al. (2006) High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola. *Am J Trop Med Hyg* 75: 143-145.
39. Grandesso F, Hagerman A, Kamara S, Lam E, Checchi F, et al. (2006) Low efficacy of the combination artesunate plus amodiaquine for uncomplicated falciparum malaria among children under 5 years in Kailahun, Sierra Leone. *Trop Med Int Health* 11: 1017-1021.
40. de Radiguès X, Diallo KI, Diallo M, Ngwakum PA, Maiga H, et al. (2006) Efficacy of chloroquine and sulfadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria in Koumantou, Mali. *Trans R Soc Trop Med Hyg* 100: 1013-1018.
41. Smithuis F, Kyaw MK, Phe O, Aye KZ, Htet L, et al. (2006) Efficacy and effectiveness of dihydroartemisinin-piperaquine versus artesunate-mefloquine in falciparum malaria: An open-label randomised comparison. *Lancet* 367: 2075-2085.
42. Legros D, Johnson K, Houpijian P, Makanga M, Kabakyenga JK, et al. (2002) Clinical efficacy of chloroquine or sulfadoxine-pyrimethamine in children under five from south-western Uganda with uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 96: 199-201.
43. Kazadi WM, Vong S, Makina BN, Mantshumba JC, Kabuya W, et al. (2003) Assessing the efficacy of chloroquine and sulfadoxine-pyrimethamine for treatment of uncomplicated *Plasmodium falciparum* malaria in the Democratic Republic of Congo. *Trop Med Int Health* 8: 868-875.
44. van den Broek IV, Gatkoï T, Lowoko B, Nzila A, Ochong E, et al. (2003) Chloroquine, sulfadoxine-pyrimethamine and amodiaquine efficacy for the treatment of uncomplicated *Plasmodium falciparum* malaria in Upper Nile, south Sudan. *Trans R Soc Trop Med Hyg* 97: 229-235.

