



Effect of the Affordable Medicines Facility—malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data

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Summary

Background Malaria is one of the greatest causes of mortality worldwide. Use of the most effective treatments for malaria remains inadequate for those in need, and there is concern over the emergence of resistance to these treatments. In 2010, the Global Fund launched the Affordable Medicines Facility—malaria (AMFm), a series of national-scale pilot programmes designed to increase the access and use of quality-assured artemisinin based combination therapies (QAACTs) and reduce that of artemisinin monotherapies for treatment of malaria. AMFm involves manufacturer price negotiations, subsidies on the manufacturer price of each treatment purchased, and supporting interventions such as communications campaigns. We present findings on the effect of AMFm on QAACT price, availability, and market share, 6–15 months after the delivery of subsidised ACTs in Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda, and Tanzania (including Zanzibar).

Methods We did nationally representative baseline and endpoint surveys of public and private sector outlets that stock antimalarial treatments. QAACTs were identified on the basis of the Global Fund's quality assurance policy. Changes in availability, price, and market share were assessed against specified success benchmarks for 1 year of AMFm implementation. Key informant interviews and document reviews recorded contextual factors and the implementation process.

Findings In all pilots except Niger and Madagascar, there were large increases in QAACT availability (25·8–51·9 percentage points), and market share (15·9–40·3 percentage points), driven mainly by changes in the private for-profit sector. Large falls in median price for QAACTs per adult equivalent dose were seen in the private for-profit sector in six pilots, ranging from US\$1·28 to \$4·82. The market share of oral artemisinin monotherapies decreased in Nigeria and Zanzibar, the two pilots where it was more than 5% at baseline.

Interpretation Subsidies combined with supporting interventions can be effective in rapidly improving availability, price, and market share of QAACTs, particularly in the private for-profit sector. Decisions about the future of AMFm should also consider the effect on use in vulnerable populations, access to malaria diagnostics, and cost-effectiveness.

Funding The Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Bill & Melinda Gates Foundation.

Background

Malaria is a major cause of mortality in Africa. However, the use of artemisinin-based combination therapies (ACTs), the most effective treatment for uncomplicated malaria, remains far below that which is needed to fight the disease.¹ In 12 of 16 malaria endemic countries in Africa, less than 60% of antimalarial drugs used by febrile children under-5 were ACTs.^{2–4} Reasons for low ACT uptake include: unreliable public sector supply; high prices and limited availability in the private sector, which is a widely used source of treatment in many malaria endemic regions; and patient self-treatment with less expensive monotherapies.⁵ Additionally, there is growing concern about the emergence of artemisinin resistance, exacerbated by use of artemisinin monotherapies.⁶

In 2004, a global subsidy on the manufacturer price of medicines was proposed to increase ACT use through existing public and private sector distribution chains, and to reduce consumption of artemisinin monotherapies.⁷ Small-scale studies indicated that such a subsidy could increase ACT uptake,^{5,8,9} but data for large-scale implementation were scarce.^{10,11}

In 2008, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) agreed to host a pilot ACT subsidy, termed the Affordable Medicines Facility—malaria (AMFm). AMFm was launched in eight national-level pilots in seven countries: Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda, and Tanzania (mainland and Zanzibar) in 2010.¹² The programme has been highly controversial.^{13–16} For example, there was

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concern that the subsidies would be captured by intermediaries and not passed on to consumers, that monotherapies would continue to dominate market share because of their familiarity and perceived effectiveness, and that the poorest would not benefit because drugs are not free.

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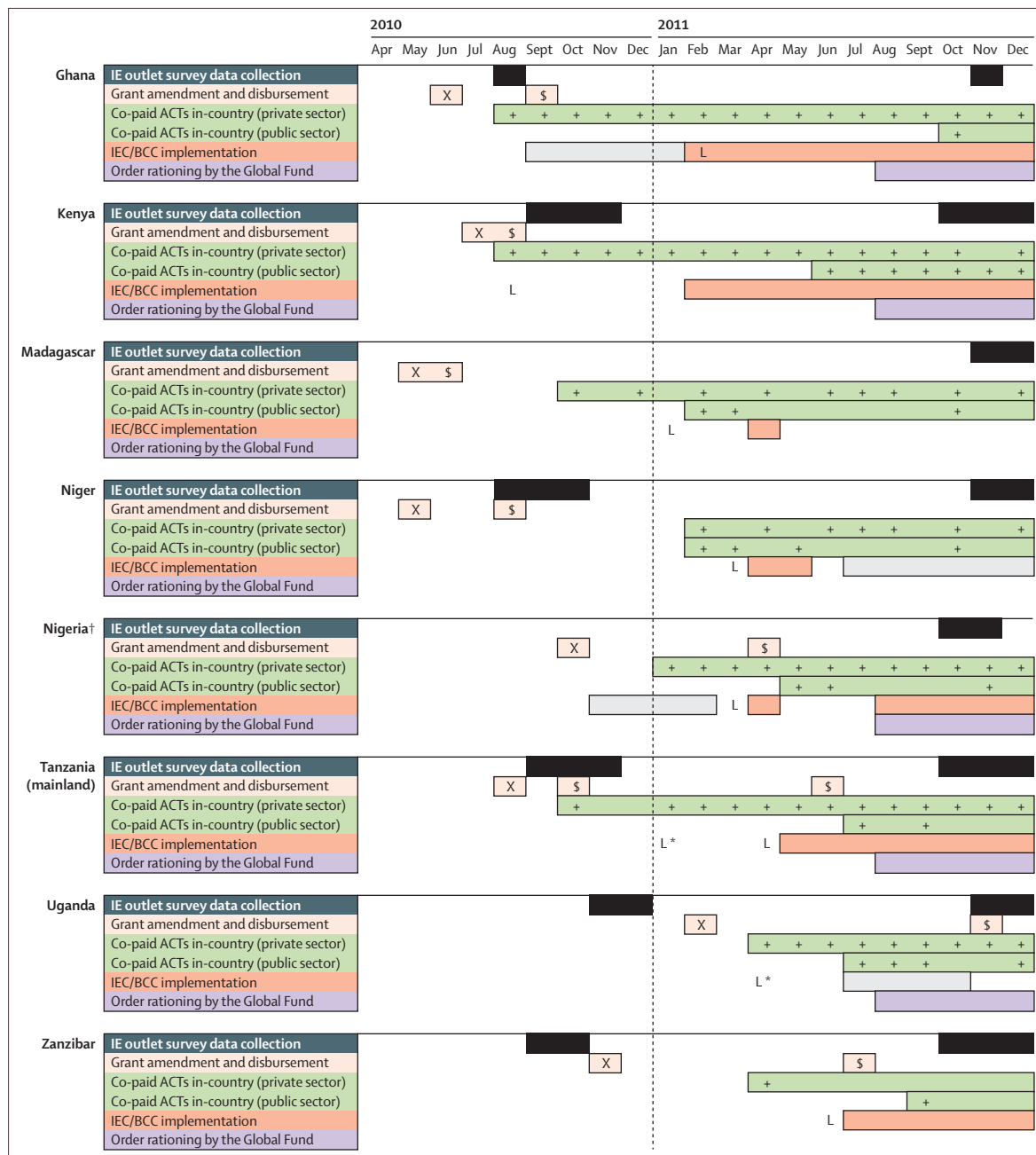


Figure 1: Timeline of AMFm phase 1 independent evaluation data collection, grant amendments and disbursements, arrival in-country of co-paid QAActs, launch events, IEC/BCC implementation, and order rationing by the Global Fund
 Black=Baseline and endpoint data collection for independent evaluation outlet surveys. Light red=Signing of the AMFm grant amendment required to commence AMFm activities in each pilot and Global Fund grant disbursements for implementation of supporting interventions. Green=Co-paid QAActs in-country (although not necessarily in continuous supply). +=co-paid QAActs delivered. Dark red=Implementation of AMFm public awareness (information, education and communication/behaviour change communication [IEC/BCC]) campaign at scale. Grey=Interim AMFm public awareness campaign—ie, Ghana: talk shows only; Niger: activities not at scale; Nigeria: stop-gap soft launch; Uganda: stop-gap radio. Purple=Application of Global Fund order rationing. X=grant amendment. \$=disbursement for implementation of supporting interventions. L=Launch. L*="Soft" launch; in Tanzania (mainland) a soft launch was held with a press conference on January 25, 2011; in Uganda a soft launch was held on April 29, 2011, linked to World Malaria Day celebrations; however, no IEC/BCC or trainings began until after endpoint data collection. †In Nigeria, baseline data were collected Sept–Nov, 2009.

AMFm is a financing mechanism incorporating three elements: price reductions through negotiations with manufacturers of quality-assured ACTs (QAACTs); a buyer subsidy, via a co-payment by the Global Fund to participating manufacturers, for purchases made by eligible public, private, and non-governmental organisation importers; and interventions to support AMFm implementation and promote appropriate antimalarial use.¹⁷ All medicines subsidised through AMFm have a green leaf logo on their packaging. Available funding to date has consisted of US\$336 million for drug co-payments and \$127 million for supporting interventions.

Negotiations with manufacturers led to reductions in manufacturer price for sales to private for-profit buyers of up to 29–78% depending on package size, bringing prices down to around the levels paid by public sector purchasers.^{18,19} Under AMFm, public and private importers paid manufacturers a subsidised price of between \$0.005 and \$0.220 per treatment course, representing 1–20% of the manufacturer price. The balance was paid to the manufacturer via the co-payment fund.

Between August, 2010, and the end of 2011, 155.8 million doses of QAACTs financed through AMFm were delivered to participating pilots. The main supporting interventions implemented were communication campaigns, recommended retail prices, and provider training. Implementation of supporting interventions trailed the arrival of the first co-paid drugs by 2–9 months. In

Madagascar, Niger, and Uganda, no large-scale sustained communications campaign had been established by the end of 2011 (figure 1).

An independent evaluation of AMFm was commissioned by the Global Fund to assess achievement of its four objectives of reducing QAACT prices and increasing availability, market share, and use.²⁰ Our paper reports on ACT price, availability, and market share. These results will be supplemented by secondary data for the use of QAACTs in children with fever from nationally representative household surveys, such as ACTwatch and Demographic and Health Surveys, when appropriately timed endpoint data become available.

Methods

Study design

Our evaluation had a non-experimental design, with before-and-after comparisons of price, availability, and market share in each pilot setting, and detailed documentation of implementation process and context.²¹

Nationally representative baseline and endpoint surveys of outlets stocking antimalarial treatment were done in each pilot. Methods for these surveys were adapted from the ACTwatch project.²² Baseline data collection took place between August and December, 2010, in most pilots, generally just before the first delivery of co-paid drugs, although in Kenya the first co-paid ACTs arrived a month before data collection (figure 1). Similar ACTwatch surveys undertaken in Nigeria in 2009 and in Madagascar in 2010 were used as a baseline.²³ Endpoint data collection took place in all pilots between October, 2011, and January, 2012.

All categories of outlets with the potential to stock antimalarial drugs in both public and private sectors were targeted. Since comprehensive lists of stockists were not available, outlets were selected with a cluster sampling approach, and all outlets with the potential to sell antimalarials in the cluster were visited. Clusters were generally administrative units with an average of 10 000–15 000 inhabitants, and were selected using probability proportional to size sampling, stratified by rural and urban domains. Independent samples were drawn at baseline and endpoint. A full census of outlets was done in Zanzibar because of the small population size.

A minimum sample size of 305 outlets that stock antimalarial drugs per urban or rural domain was needed to detect a 20 percentage point change in ACT availability at the 5% significance level with 80% power, assuming baseline availability of 40% and a design effect of 4. Sample size requirements at endpoint were calculated using baseline results for QAACT availability and design effect.

Public health facilities and registered pharmacies were oversampled, because previous surveys found few of these outlets in any given cluster.²³ For each sampled cluster, all public health facilities and pharmacies within a larger administrative area (eg, district) in which the cluster was located were also visited. Country-specific sampling details are available in the appendix.

See Online for appendix

Panel 1: AMFm benchmarks for success for 1 year of effective implementation, by objective

Availability

Benchmark 1: Increase of 20 percentage points from baseline to endpoint in the availability of quality-assured artemisinin-based combination therapy (QAACT) among all outlets stocking antimalarial treatment

Price*

Benchmark 2: Median price of one adult equivalent dose of AMFm co-paid QAACTs is less than three times the median price of one adult equivalent dose of the most popular antimalarial in tablet form that is not a QAACT† (calculated for private for-profit outlets only)

Benchmark 3: Median price of one adult equivalent dose of AMFm co-paid QAACTs is less than the median price of one AETD of oral artemisinin monotherapy tablets (calculated for private for-profit outlets only)

Market share

Benchmark 5: Increase in QAACT market share of 10 percentage points from baseline to endpoint

Benchmark 6: Decrease in market share of artemisinin monotherapy from baseline to endpoint

*Price success metrics are calculated for the private for-profit sector only, because in all pilot countries except Ghana ACTs were officially free at baseline in the public sector and in some private not-for-profit outlets. †The most popular antimalarial in tablet form that is not a QAACT is defined as the antimalarial, excluding QAACTs, with the highest sales volume measured in terms of adult equivalent doses sold in private for-profit outlets. Source: Success metrics developed for AMFm by the Evidence to Policy Initiative^{25,26} and adapted by the AMFm Independent Evaluation team. A success metric was also developed for ACT use (benchmark 4), but is not reported here since it is based on household survey data that are not yet available.

A questionnaire was administered to respondents at outlets that had antimalarial drugs in stock on the day of the survey or had stocked them within the previous 3 months. The questionnaire covered outlet characteristics and the reported price and volume sold of each antimalarial product in stock. Informed oral consent was obtained from respondents.

Antimalarials were classified into non-artemisinin therapies, artemisinin monotherapies, and ACTs. Artemisinin monotherapies were further classified into oral and non-oral, the latter being recommended for treatment of severe malaria. ACTs were subdivided into QAACTs and non-quality-assured ACTs, with QAACTs identified based on the Global Fund's quality assurance policy²⁴ (appendix). At endpoint, the presence of the AMFm logo was used to identify AMFm co-paid QAACTs.

Antimalarial price and market share data are reported in terms of adult equivalent doses, defined as the amount needed to treat a 60 kg adult.²² In practice, many customers will obtain drugs for children or purchase incomplete doses, therefore obtaining less than an adult equivalent dose. Market share was calculated by dividing the number of adult equivalent doses of a particular antimalarial category sold by the total for all antimalarials sold. Price data were collected in local currencies and endpoint data were adjusted to 2010 prices using national consumer price indices. Prices were converted to US dollars using the average interbank rate for 2010.

Qualitative studies were done to document the context pre-intervention and post-intervention, and the process of AMFm implementation. Data were collected between November, 2011, and January, 2012, through key informant interviews and document review. Topics covered included registration of importers, ordering and distribution of co-paid ACTs, supporting interventions, and key contextual events. The findings were used to facilitate interpretation of study outcomes, and to discuss the extent to which recorded changes could plausibly be attributed to AMFm.

Ethics approval was obtained from all national ethics committees and Institutional Review Boards of ICF International and the London School of Hygiene and Tropical Medicine.

Statistical analysis

Analyses were done in Stata v11, R version 2.14.2, and SAS v9.2. All point estimates were weighted using survey weights and all standard errors calculated taking account of the clustered and stratified sampling strategy with the relevant suite of survey commands in the statistical packages. Within each pilot, differences in availability, price, and market share between baseline and endpoint surveys were calculated overall, by urban and rural location, and by outlet type. For availability and market share, the difference is expressed in terms of the percentage point change with a 95% CI. For prices, the difference in median price, interquartile

range, and p value from the Wilcoxon rank sum test of the hypothesis of no difference between baseline and endpoint are shown.

Changes in availability, price, and market share are assessed against benchmarks proposed by the Evidence to Policy Initiative on the basis of performance of similar programmes as reasonable achievements after 1 year of AMFm implementation from “the effective start date of AMFm at the country level” (panel 1).^{25,26} Statistical testing for benchmarks related to availability and market share was based on a one-sided unadjusted Wald test. For price, two types of statistical testing were done. Achievement of benchmark 2 was tested by comparing a test statistic (the ratio of the two median prices divided by the jackknife standard error of the ratio, calculated omitting one outlet at a time) to a standard normal curve. Achievement of benchmark 3 was tested by calculating a one-sided p value from the Wilcoxon rank sum test.

Role of the funding source

The evaluation was funded by the Global Fund, and The Bill & Melinda Gates Foundation funded outlet

	Selected clusters	Outlets visited*	Outlets screened	Eligible outlets†	Outlets interviewed	Outlets stocking antimalarials at the time of survey visit
Ghana						
Baseline	55	1241	1187	1167	1154	1144
Endpoint	54	1093	1002	974	968	957
Kenya						
Baseline	57	18 250	13 913	2625	2582	1916
Endpoint	57	13 376	11 386	2112	2088	1856
Madagascar						
Baseline	38	7221	6769	2642	2616	2414
Endpoint	46	10 723	10 041	2854	2806	2371
Niger						
Baseline	75	3745	3738	2444	2380	2031
Endpoint	64	3541	3292	2070	2034	1662
Nigeria‡						
Baseline	114	6089	5456	2210	2206	2113
Endpoint	124	8507	7939	1567	1562	1504
Tanzania (mainland)						
Baseline	48	3151	3120	710	660	631
Endpoint	49	3786	3709	799	798	787
Uganda						
Baseline	39	11 369	11 153	2590	2511	2420
Endpoint	44	16 521	16 207	3285	3227	3138
Zanzibar						
Baseline	..	2256	2231	322	321	313
Endpoint	..	4303	4221	374	374	342

*Outlets where at least basic descriptive information was collected. †Eligible outlets were outlets that had antimalarial drugs in stock on the day of the survey or had stocked them in the past 3 months. ‡Nigeria baseline data collection done in 2009.

Table 1: Survey sample breakdown—number of outlets visited and number stocking antimalarial treatment, according to country at baseline (2010) and endpoint (2011)

surveys in three countries. The funders played no role in data collection, analysis, interpretation of findings, or the decision to submit the manuscript. All authors were involved in the decision to submit the manuscript, and authors from the core independent evaluation team at LSHTM and ICF International had access to all country data.

Results

Table 1 shows the samples at baseline and endpoint; the sample breakdown by outlet type is shown in the appendix. Differences in the number of outlets visited reflect variation in the number of selected clusters across countries and data collection rounds, and cross-country variations in the sampling approach (appendix).

Response rates, as measured by the percentage of outlets visited that were screened, were 90% or above in all pilots except Kenya, reflecting more frequent visiting of permanently closed outlets. The percentage of eligible outlets that were interviewed exceeded 90% in all surveys. Item non-response ranged from 0% to 8% for the main QAACT availability and price outcomes and 3% to 30% for market share (data not shown).

Results for availability, price, and market share are presented for all sectors combined and separately for public health facilities and private for-profit outlets. Results are not shown separately for private not-for-profit outlets and community health workers due to low numbers. Results are not presented separately for urban and rural domains because the changes in rural and urban areas were generally similar to those observed overall (appendix).

In public health facilities, QAACT availability in facilities stocking antimalarials at baseline was over 90% in Zanzibar only, 80% to 89% in five pilots, and less than 50% in Niger and Nigeria (table 2). There were increases in QAACT availability in public health facilities in Kenya,

Madagascar, Niger, and Zanzibar. In the remaining pilots there was no evidence of change.

Baseline availability of QAACTs was markedly lower in private for-profit outlets than in public health facilities, ranging from 6% in Niger to 27% in Nigeria of outlets stocking antimalarials. There were large increases in QAACT availability in private for-profit outlets in all countries except Madagascar, where there was no evidence of change. The increase in availability among private for-profit outlets exceeded 50 percentage points in four pilots.

Across all sectors combined, there were large increases in QAACT availability (26–52 percentage points) in six pilots, driven mainly by changes in the private for-profit sector. Niger had a more modest increase of 10 percentage points, while in Madagascar there was no evidence of change.

Benchmark 1, a 20 percentage point increase in QAACT availability, was clearly met in five countries ($p < 0.0008$ in all cases), whereas in Nigeria, the statistical evidence that the benchmark was met was weak ($p = 0.14$) (table 2).

In public health facilities, the median QAACT price per adult equivalent dose was zero at baseline and endpoint in all pilots except Ghana, reflecting officially free provision, although there could have been other charges such as consultation fees (figure 2). In Ghana, the median price per adult equivalent dose fell from \$2.74 to \$0.94.

In private for-profit outlets at baseline, the median QAACT price per adult equivalent dose ranged from \$2.47 to \$5.99 across all pilots except Madagascar. Large falls in price were seen in this sector in six pilots, with the decline ranging from \$1.28 to \$4.82 (table 3). In Uganda, no substantial price change was noted. In Madagascar, there was an increase in median price from \$0.14 to \$0.60. The low median price at baseline indicates the presence of a national subsidy programme, whose products accounted for 48% of observations of QAACTs found in private for-profit outlets.

	Public health facilities			Private for-profit outlets			Total*			Test for achievement of benchmark (p value†)
	Baseline (%)	Endpoint (%)	Change (95% CI)	Baseline (%)	Endpoint (%)	Change (95% CI)	Baseline (%)	Endpoint (%)	Change (95% CI)	
Ghana	86.2	80.7	-5.5 (-14.5 to 3.5)	24.8	82.6	57.8 (51.7 to 63.8)	30.7	82.7	51.9 (46.2 to 57.7)	<0.0001
Kenya	87.5	97.0	9.5 (0.7 to 18.3)	21.2	60.2	38.9 (29.7 to 48.2)	31.2	65.8	34.6 (25.8 to 43.4)	0.0007
Madagascar	83.2	93.7	10.5 (4.7 to 16.4)	8.1	9.2	1.0 (-3.3 to 5.4)	23.4	28.1	4.6 (-7.2 to 16.5)	0.99
Niger	44.8	72.9	28.1 (16.9 to 39.3)	6.3	13.8	7.6 (4.6 to 10.6)	9.4	19.4	10.0 (7.0 to 13.1)	1.00
Nigeria	46.3	56.7	10.4 (-14.4 to 35.2)	26.6	52.9	26.3 (15.1 to 37.5)	27.7	53.5	25.8 (15.1 to 36.5)	0.14
Tanzania (mainland)	80.1	81.4	1.3 (-15.8 to 18.4)	10.8	66.4	55.6 (46.4 to 64.8)	25.5	69.5	44.0 (35.8 to 52.1)	<0.0001
Uganda	87.3	91.7	4.3 (-1.2 to 9.8)	11.3	65.5	54.2 (47.3 to 61.0)	21.0	67.1	46.2 (39.5 to 52.9)	<0.0001
Zanzibar‡	92.1	93.5	1.5	8.8	80.1	71.3	45.8	85.1	39.3	..

QAACT=Quality-assured artemisinin-based combination therapy. *Total includes community health workers and private not-for-profit facilities, which are not shown separately due to small numbers. †The reported p value is from a one-sided unadjusted Wald test, which is the probability that QAACT availability is at least 20 percentage points higher at endpoint than baseline. ‡No CIs or p values are presented for Zanzibar because a complete census of outlets was done.

Table 2: Availability of QAACTs in outlets stocking antimalarials at baseline and endpoint by sector, and achievement of benchmark 1 (20 percentage point increase from baseline in availability of all QAACTs)

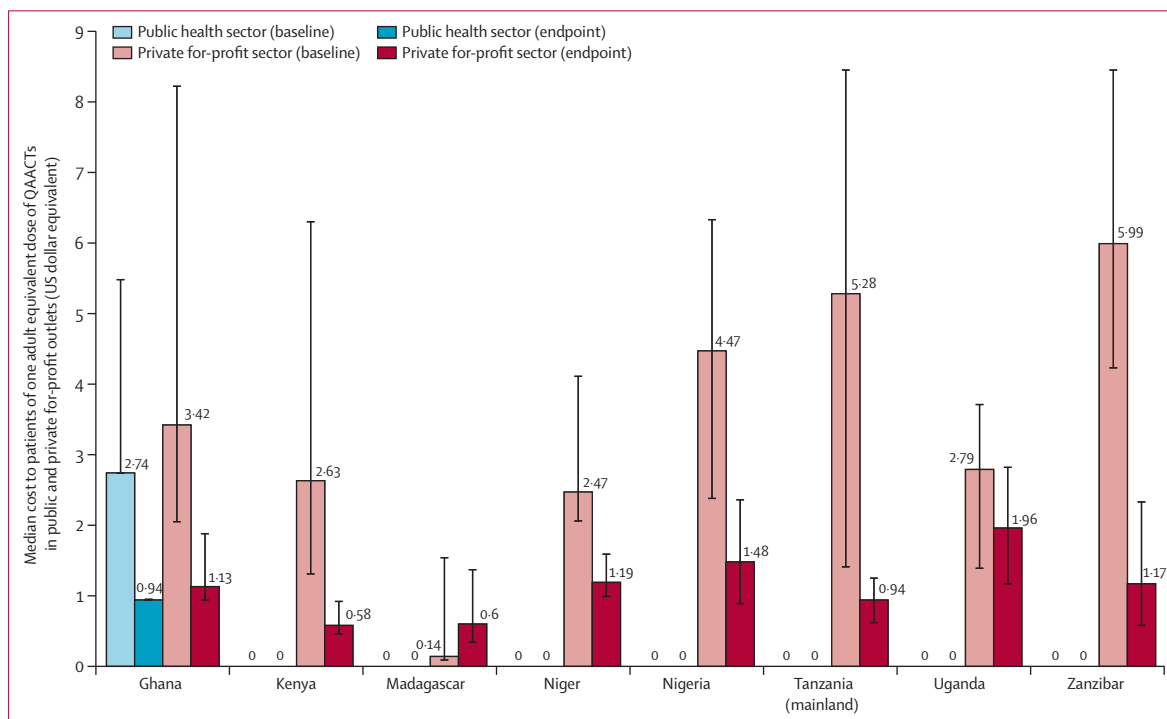


Figure 2: Median price to patients of one adult equivalent dose of quality-assured ACTs in public and private for-profit outlets (US dollar equivalent)
 Whiskers show the interquartile range (IQR) for the median price of quality-assured ACTs. In the countries where QAACTs were free in the public sector (all except for Ghana), the IQR is not visible for the public sector because the 25th and 75th percentiles were \$0.00 and \$0.00. In Ghana at endpoint the 25th and 75th percentiles are not visible because they were \$0.94 and \$0.95.

	All QAACTS		Median price at endpoint (IQR)				Benchmark 2		Benchmark 3		
	Median price at baseline (IQR)	Median price at endpoint (IQR)	Change	p value*	AMFm co-paid QAACTs	Most popular antimalarial that is not a QAACT†	Oral artemisinin monotherapy tablets‡	Ratio (95% CI)	p value§	Difference (95% CI)‡	p value¶
Ghana	3.42 (2.05 to 8.22)	1.13 (0.94 to 1.88)	-2.30	<0.0001	0.94 (0.94 to 1.88)	0.31 (0.31 to 0.50)	1.88 (1.88 to 2.19)	3.0 (2.9 to 3.2)	0.8127	-0.94 (-0.95 to -0.93)	<0.0001
Kenya	2.63 (1.31 to 6.30)	0.58 (0.46 to 0.92)	-2.05	<0.0001	0.52 (0.46 to 0.92)	0.52 (0.35 to 0.86)	..	1.0 (0.6 to 1.5)	<0.0001
Madagascar	0.14 (0.09 to 1.54)	0.60 (0.34 to 1.37)	0.46	0.0001	0.51 (0.34 to 1.03)	0.32 (0.32 to 0.32)	..	1.6 (1.6 to 1.6)	<0.0001
Niger	2.47 (2.06 to 4.11)	1.19 (0.99 to 1.98)	-1.28	<0.0001	1.19 (0.79 to 1.59)	0.48 (0.37 to 0.60)	..	2.5 (2.2 to 2.8)	<0.0001
Nigeria	4.47 (2.38 to 6.33)	1.48 (0.89 to 2.36)	-2.99	<0.0001	1.48 (0.89 to 2.36)	0.47 (0.35 to 0.89)	2.66 (2.36 to 2.83)	3.1 (3.1 to 3.2)	0.9998	-1.17 (-1.24 to -1.10)	<0.0001
Tanzania mainland	5.28 (1.41 to 8.45)	0.94 (0.62 to 1.25)	-4.34	<0.0001	0.94 (0.62 to 1.25)	0.94 (0.62 to 1.12)	..	1.0 (1.0 to 1.0)	<0.0001
Uganda	2.79 (1.39 to 3.71)	1.96 (1.17 to 2.82)	-0.83	0.2647	1.96 (1.17 to 2.82)	0.59 (0.59 to 0.78)	..	3.3 (3.3 to 3.3)	0.9999
Zanzibar	5.99 (4.23 to 8.45)	1.17 (0.58 to 2.33)	-4.82	..	1.17 (0.58 to 2.33)	0.79 (0.52 to 1.40)	7.46	1.5	..	-6.30	..

AMFm=Affordable Medicines Facility—malaria. QAACT=Quality-assured artemisinin-based combination therapy. IQR=interquartile range. *Two-sided p value from the Wilcoxon rank sum test implemented in the survey suite of commands in R. This is the p value for the test of no difference between baseline and endpoint. †The most popular antimalarial that is not a QAACT at endpoint was: sulphadoxine pyrimethamine in Ghana, Kenya, Nigeria, Tanzania (mainland), and Uganda; amodiaquine in Zanzibar; and chloroquine in Madagascar and Niger. ‡Not shown, because the benchmark is not relevant since the number of oral AMT products was very low at endpoint. §One-sided p value from a comparison of a test statistic (the ratio of the two median prices divided by the jackknife standard error of the ratio, calculated omitting one outlet at a time) to a standard normal curve. The p value is for the test that the ratio of the median price of AMFm co-paid QAACTs to the median price of the most popular antimalarial in tablet form that is not a QAACT is <3. ¶One-sided p value from the Wilcoxon rank sum test implemented in the suite of survey commands in SAS. The p value is for the test that the difference between the median price of AMFm co-paid QAACTs and the median price of artemisinin monotherapy tablets is negative. ||No CIs or p values are presented for Zanzibar because a complete census of outlets was done.

Table 3: Price of QAACTs in the private for-profit sector at endpoint in US dollars, and achievement of benchmark 2 (median price of AMFm co-paid QAACTs is less than 3 times the median price of the most popular antimalarial tablet that is not a QAACT) and benchmark 3 (median price of AMFm co-paid QAACTs is less than the median price of artemisinin monotherapy tablets)

At endpoint, the price of AMFm co-paid QAACTs in the private for-profit sector ranged from \$0.51 to \$1.96 (table 3). There is strong evidence that benchmark 2 (comparing QAACT price to the most popular antimalarial that was not a QAACT) was met in five pilots ($p < 0.0001$).

Median price per adult equivalent dose for oral artemisinin monotherapy tablets is presented only for the three pilots with at least 50 observations in this category (table 3). In all three pilots the price for AMFm co-paid QAACTs was lower than artemisinin

monotherapies tablets and thus benchmark 3 was met ($p < 0.0001$).

At baseline, QAACT market share in public health facilities ranged from 6% to 64% (figure 3). There were increases of 15–42 percentage points in Ghana, Nigeria, Uganda and Zanzibar. In the other four pilots, QAACT market share in public health facilities apparently decreased, but confidence intervals crossed the null (table 4).

In private for-profit outlets, QAACT market share at baseline ranged from 2% to 12%. There were increases

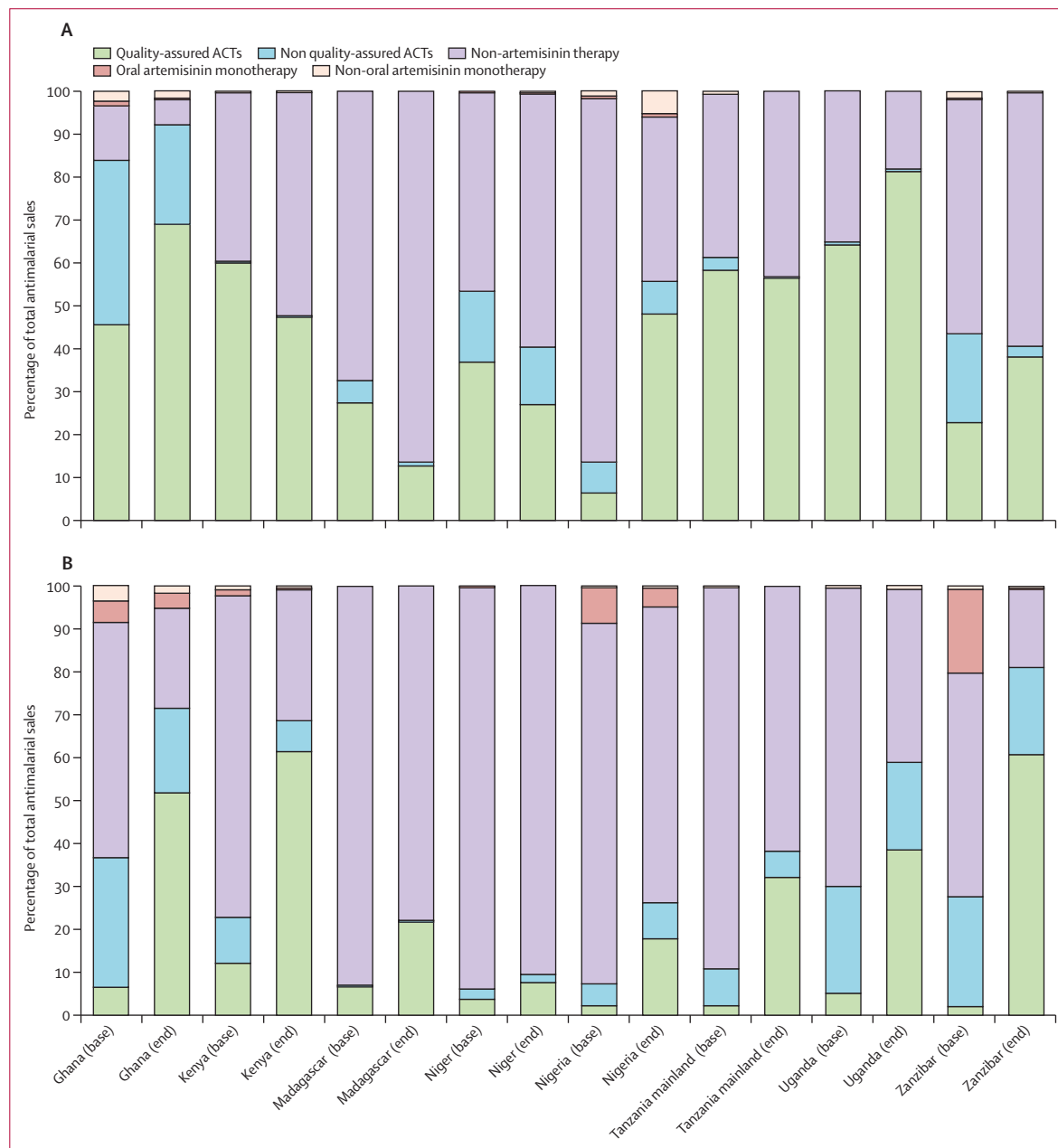


Figure 3: Market share of antimalarials sold in (a) public health facilities and (b) private for-profit outlets by antimalarial type at baseline (2010) and endpoint (2011)

	Public health facilities			Private for-profit outlets			Total*			Test for achievement of benchmark (p value)
	Baseline (%)	Endpoint (%)	Change (95% CI)	Baseline (%)	Endpoint (%)	Change (95% CI)	Baseline (%)	Endpoint (%)	Change (95% CI)	
Benchmark 5: 10 percentage point increase from baseline in the market share of all QAACTs†										
Ghana	45.6	69.0	23.3 (7.9 to 39.1)	6.5	51.8	45.3 (40.3 to 50.4)	17.3	57.6	40.3 (33.0 to 47.6)	<0.0001
Kenya	60.0	47.6	-12.4 (-52.8 to 27.9)	12.1	61.4	49.3 (39.5 to 59.1)	25.8	57.1	31.3 (12.7 to 49.9)	0.0125
Madagascar	27.4	12.7	-14.7 (-37.0 to 7.5)	6.8	22.0	15.1 (5.6 to 24.6)	12.1	20.7	8.6 (-0.6 to 17.9)	0.62
Niger	36.9	27.0	-10.0 (-26.8 to 6.9)	3.7	7.6	3.9 (1.4 to 6.4)	18.4	9.6	-8.8 (-18.0 to 3.8)	1.0
Nigeria	6.4	48.1	41.7 (26.5 to 56.8)	2.2	17.8	15.6 (12.1 to 19.1)	2.4	20.1	17.7 (13.6 to 21.8)	0.0002
Tanzania (mainland)	58.3	56.6	-1.8 (-37.7 to 34.2)	2.2	32.1	30.0 (21.9 to 38.1)	26.3	42.2	15.9 (0.1 to 31.7)	0.23
Uganda	64.2	81.3	17.1 (4.2 to 30.0)	5.1	38.5	33.4 (26.0 to 40.8)	40.0	56.7	16.8 (7.1 to 26.5)	0.08
Zanzibar‡	22.8	38.1	15.3	2.0	60.7	58.7	9.7	57.8	48.1	..
Benchmark 6: Decrease in market share of oral artemisinin monotherapies										
Ghana
Kenya
Madagascar
Niger
Nigeria	0.6	0.8	0.2 (-0.6 to 1.0)	8.3	4.4	-3.9 (-7.9 to 0.1)	8.1	4.1	-3.9 (-7.9 to 0.0)	0.0258
Tanzania (mainland)
Uganda
Zanzibar‡	0.1	0.0	-0.1	19.5	0.2	-19.3	12.2	0.2	-12.0	..

Missing values not shown because the number of oral artemisinin monotherapy products was very low at baseline; *Total includes community health workers and private not-for-profit facilities, which are not shown separately due to small numbers. †The sample size was not powered to detect a 10 percentage point increase in Madagascar, Uganda, or Tanzania (mainland). ‡No CIs or p values are presented for Zanzibar because a complete census of outlets was done.

Table 4: Market share of QAACTs by sector and achievement of benchmark 5 and benchmark 6

in all pilots, exceeding 30 percentage points in five. Over 87% of QAACTs sold in this sector at endpoint were AMFm co-paid in all pilots except Niger.

The increase in QAACT market share across all sectors combined was large in all pilots except Madagascar and Niger (table 4). There was strong evidence that benchmark 5 of a 10 percentage point increase in QAACT market share was met in four pilots ($p < 0.0126$ in all cases). This benchmark was not met in Niger. In Madagascar, Tanzania (mainland), and Uganda, the evidence that the benchmark was met was weak ($p = 0.62$, $p = 0.23$, and $p = 0.08$, respectively), but the sample size was not powered to detect a 10 percentage point increase.

The market share of oral artemisinin monotherapies across all sectors was very low at baseline everywhere but Nigeria (8%) and Zanzibar (12%). In both pilots, oral artemisinin monotherapies market share decreased meaning both pilots met benchmark 6 ($p < 0.0259$ in both cases).

Discussion

Large changes were recorded from baseline to endpoint in QAACT availability, price, and market share in most of the eight pilots after implementation of the AMFm programme. Success benchmarks were clearly met in five pilots for availability, five for QAACT price relative to the most popular treatment that is not a QAACT, and four for QAACT market share. These 1-year benchmarks

were met, although all pilots had less than 12 months of full implementation of supporting interventions (figure 1). Where benchmarks were met, the countries often substantially exceeded them. Although the statistical evidence is weak, Nigeria might also have met the benchmark for availability, and Tanzania (mainland) and Uganda might have met the benchmark for QAACT market share. Additionally, Ghana nearly met the benchmark comparing the price of co-paid ACTs to the most popular antimalarial that is not a QAACT.

Even at baseline, market share for oral artemisinin monotherapies was less than 4% in Ghana and less than 1% in Kenya, Madagascar, Niger, Tanzania (mainland), and Uganda. In Nigeria and Zanzibar, where oral artemisinin monotherapy market share was somewhat higher at baseline, large falls were seen, and benchmark 6 was met, possibly because of a combination of AMFm and, particularly in Zanzibar, regulatory measures.

The effect of AMFm in Niger and Madagascar was limited, with low AMFm ACT orders. Explanations could include: the predominance of general stores or itinerant vendors in the private for-profit sector that are not allowed to stock antimalarials; an unfavourable context in terms of political and economic instability and, in Niger, severe weather; and the lack of full-scale public awareness campaigns, which also seemed to hinder performance in Uganda. Given these challenging contexts it is unclear whether AMFm would have been

effective in these pilots if supporting interventions had been fully implemented.

In all other pilots, AMFm likely had a dramatic effect on the private for-profit market, through large increases in QAACT availability and market share, and decreases in prices (except in Uganda). These changes were substantial and achieved in only a few months, which showed the power of tapping into the distributional capacity of the private sector. The private sector response was similar in rural and urban areas (appendix) and similar increases in availability and falls in price have been seen in remote rural areas of Tanzania.²⁷ The substantial improvements seen in the private for-profit sector in the AMFm pilots are consistent with the results from previous small-scale trials of ACT subsidy schemes (panel 2). The results from this evaluation provide evidence that the positive changes seen in small-scale pilot studies can be replicated at national scale.

AMFm led to fewer fundamental changes to public health facility QAACT supply. This finding is unsurprising since, although the financing mechanism changed

under AMFm, the Global Fund has provided a substantial share of funding for QAACTs purchased for public health facilities both before and during AMFm in all pilots. Moreover, QAACT supply for public health facilities had substantial ordering delays stemming from problems with procurement and grant requirements that persisted after the start of AMFm. Although there were increases in public sector QAACT market share in four pilots, stock-outs remained widespread in several pilots. There was generally no change in public sector QAACT prices, since most countries provided QAACTs for free at baseline. The exception was Ghana, where prices for public sector QAACTs fell because of a reduction in the antimalarial reimbursement rate provided by the National Health Insurance Fund.

Our study had several limitations. In view of the complex nature of the AMFm intervention and its use of existing pharmaceutical distribution channels, we were unable to restrict implementation to certain areas of countries. The lack of comparable control areas constrains the ability to assess precisely the degree to which the changes are attributable to AMFm. In line with recommendations for the evaluation of complex interventions,²¹ we addressed this issue by systematically examining the context and process of AMFm implementation in each pilot. There was substantial evidence that in pilots where QAACT market share increased, this change was accompanied by strong implementation of the AMFm package: large quantities of co-paid ACTs were delivered; co-paid QAACTs accounted for a high proportion of market share at endpoint; and supporting interventions were widely implemented, albeit with delays in most settings. Moreover, changes in market share were accompanied by increases in availability and decreases in price, as would be expected if market share increases were associated with AMFm. Documentation of country context identified a range of factors that could also have improved AMFm outcomes, including bilateral ACT donations for public health facilities in many pilots; expansion of home-based care of malaria in Ghana; an on-going malaria communications campaign in Tanzania; and complementary regulatory measures in Zanzibar. Aside from regulatory enforcement in Zanzibar we concluded these contextual factors were unlikely to have been responsible for the scale of the changes seen in the private for-profit sector.

We also assessed the potential to compare our findings with changes in African countries not participating in AMFm. Data for QAACT price, availability, and market share collected at similar times to the baseline and endpoint surveys were available from Benin and Zambia only. The results present a mixed-picture.^{28–31} In both countries, there was no change in QAACT availability or price in public health facilities, but there was an increase in public health facility market share of 14·4 percentage points in Benin and 24·6 percentage points in Zambia (results of statistical testing not available). Private for-profit

Panel 2: Research in context

Systematic review

We searched PubMed for studies of subsidy schemes for antimalarials involving distribution in the private sector using the term “antimalarials” in the title, abstract or as a medical subject heading (MeSH) term in combination with “subsid*” in the title or abstract. We included peer reviewed publications assessing the effect of a subsidy programme on antimalarial availability, price, or market share, using a controlled design, a pre-post design, or a pre-post design which included a control. Two studies of small-scale trials of subsidies for artemisinin-based combination therapies (ACTs) were identified, covering 18 sub-locations in Kenya and three districts in Tanzania.^{5,8} Availability of artemether-lumefantrine increased by 32 percentage points in retail outlets in Kenya, and ACT availability increased by 72 percentage points among drug stores in the Tanzania pilot. In both pilots, availability was substantially higher and price lower at endpoint compared to baseline, and the intervention areas improved more than the control areas. Data on changes in market share were available for the Tanzanian pilot only, where at endpoint ACT market share among drug stores was 60% in the intervention sites but remained negligible in the control area. Two studies of national ACT subsidy programmes were identified but excluded from the review, as baseline data were not collected before the start of the subsidy programme.^{11,27}

Interpretation

Our research provides evidence on the effect of national-scale subsidy programmes on price, availability, and market share of quality-assured ACTs (QAACTs) in eight pilots. There were large improvements in QAACT availability, price, and market share in all pilots except for Madagascar and Niger, where AMFm had a limited effect. The changes we observed were mainly driven by the private-for-profit sector in all other pilots, through dramatic increases in QAACT availability and market share, and decreases in price (except Uganda). AMFm led to fewer fundamental changes to the supply of QAACTs in the public sector. This evaluation shows that the positive changes seen in small-scale pilot studies can be replicated at scale. Aside from regulatory enforcement in Zanzibar we did not identify other factors likely to be responsible for changes of this magnitude. However, AMFm might not have been responsible for all of the changes observed during the evaluation, since some improvements were seen in two non-AMFm countries over the period of AMFm implementation, and before AMFm in Madagascar and Uganda.

QAACT prices fell in both countries, remaining well above medians in all AMFm pilots at endpoint in Zambia (\$4·97), but similar to median price in Uganda at endpoint in Benin \$2·00). There was no change in private for-profit QAACT market share in Zambia, but a small increase in Benin of 8·7 percentage points (results of statistical testing not available). These countries might not be ideal comparators because of contextual factors, such as the relatively small role of private for-profit outlets in Zambian antimalarial supply compared with the AMFm pilots.^{29,30}

We also identified AMFm pilots where comparable outlet survey data were available before the baseline used in this evaluation, to assess trends pre-AMFm. Such data were available only for Uganda and Madagascar in 2008–2009, and showed some evidence of an upward trend in quality-assured ACT market share before AMFm implementation, although increases among private for-profit outlets were small (3 percentage point increase from 2009 to 2010 in Uganda, and 2 percentage points from 2008 to 2010 in Madagascar).^{32,33} Given the improvements seen in non-AMFm countries, and those seen before implementation of the programme of in our pilot countries, AMFm might not have been responsible for all the improvements recorded during this evaluation.

The evaluation took place after a fairly short period of AMFm implementation. In four pilots, endpoint outlet surveys were done at least 12 months after the arrival of the first co-paid drugs in-country. However, in most settings drug orders were low at first and full implementation of supporting interventions lagged several months behind drug arrival. In four pilots there were fewer than 10 months between arrival of the first co-paid ACTs and the midpoint of endpoint data collection, and in three pilots no full-scale communications campaign had been implemented by endpoint. How the results would have changed if a longer period of sustained implementation had been possible is unclear. Moreover, since mid-2011 the Global Fund has been rationing orders to some countries because of financial constraints, meaning that AMFm outcomes could have deteriorated in some settings.

Outlet survey data could be subject to reporting bias. For example, respondents might conceal antimalarial drugs they are not allowed to stock, underestimate sales volumes if they are concerned about possible tax implications, or report lower prices than they actually charge, especially if they are aware of recommended retail prices. We aimed to minimise such behaviours by reassuring interviewees about confidentiality and emphasising that we were not connected with regulatory authorities.

The evaluation did not measure health outcomes. The ultimate objective of AMFm is to reduce malaria mortality and delay the spread of artemisinin resistance. This paper assessed the effect on quality-assured ACT price, availability and market share only, which are intermediate to the ultimate objectives. Moreover, data are not yet available on ACT use, particularly by vulnerable populations, which will provide an important link between

the indicators measured here and health outcomes. As secondary data about use become available from appropriately timed endpoint household surveys, we will need to reassess conclusions about AMFm's effect on access to effective treatment. Other important questions and concerns about AMFm implementation beyond the scope of the evaluation include whether co-paid drugs are targeted at those with parasitaemia; patient adherence to dosing regimens; effect on global artemisinin supplies; effect on prevalence of counterfeit products; and re-export of co-paid drugs to non-AMFm countries.

In summary, our evaluation has shown that subsidies applied to manufacturer price, when partnered with supporting interventions such as communications campaigns, can be an effective mechanism to rapidly improve the availability, price, and market share of QAACTs, particularly in the private for-profit sector. Although care should be taken in extrapolating these results to countries with very different antimalarial markets, positive results were achieved across a range of malaria transmission, economic, and cultural contexts. Decisions about the future of AMFm should take into account evolving malaria epidemiology and control, availability of financial resources, improving access to malaria diagnostics, and the cost-effectiveness of an ACT subsidy relative to other possible interventions to improve access to effective treatment.

Collaborators

The ACTwatch Group: *ACTwatch Central*—Population Services International, Nairobi, Kenya (Gatakaa H, Poyer S, Njogu J, Evance I, Littrell M, Chavasse D, O'Connell K [Principal Investigator], and Shewchuk T); *ACTwatch Central*—London School of Hygiene and Tropical Medicine, London, UK (Palafox B); *ACTwatch National Level*—Kenya: Population Services International (Toda M); Madagascar: Population Services International/Madagascar (Raharinjatovo J, Rahariniaina J); Nigeria: Society for Family Health (Anyanti J, Arogundade E); Tanzania: Population Services International (Michael D); and Uganda: PACE (Buyungo P, Kuala H).

Contributors

The overall design of the Independent Evaluation of AMFm was conceived by FA, KH, YY, CG, and ST. The design of the outlet surveys drew heavily on data collection and analysis methods developed by the ACTwatch group. Adaptation of outlet survey data collection methods for the Independent Evaluation was led by ST, CG, KH, YY, FA, and RR, and development of procedures for outlet survey data analysis was led by AM, ST, BW, CG, KH, and YY with significant contributions from HG and SP of the ACTwatch group and with inputs from many other authors. Outlet survey data collection and analysis was led by the ACTwatch group in Kenya (MW, BM, MT, KOC, IE, SP, JN, TS, HG), Madagascar (JR, JR, JN, SP), Nigeria (EA, JA, KOC, IE, HG, JN), Uganda (PB, HK, JN, IE, SP, KOC, HG), and Zanzibar (DM, JN, HG); by the Ifakara Health Institute (RT, BJ, AK, MT, CF, KB) in Tanzania mainland; by the Drugs for Neglected Diseases initiative (DNDi)/Research and Development Unit, Komfo Anokye Teaching Hospital (JA, GD, SBN, DA) in Ghana; by the Centre de Recherche pour le Développement Humain/Centre International d'Etudes et de Recherches sur les Populations Africaines (SN, IAK, MS, OM) in Niger; and the African Population and Health Research Centre (MW, BM) at endpoint in Kenya. Analysis of changes over time in outlet survey indicators was conducted by AM, ST, BW, and RR. The process and context study component was designed by ST, KH, CG, FA, and YY, with data collection and analysis undertaken by EJ, AA, STR, DD, CA, CG, ST, and YY. FA was the project director for the Independent Evaluation. KH led the Independent Evaluation team at the

London School of Hygiene and Tropical Medicine. The first draft of the paper was written by ST, with inputs from many authors. All authors have read and approved the final manuscript.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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