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Subsidising artemisinin-based combination therapy in the private retail sector (Review)

Opiyo N, Yamey G, Garner P

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[Intervention Review]

Subsidising artemisinin-based combination therapy in the private retail sector

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ABSTRACT

Background

Malaria causes ill health and death in Africa. Treating illness promptly with artemisinin-based combination therapy (ACT) is likely to cure people and avoid the disease progressing to more severe forms and death. In many countries, ACT use remains low. Part of the problem is that most people seek treatment from the retail sector where ACTs are expensive; this expense is a barrier to their use.

The Global Fund and other international organisations are subsidising the cost of ACTs for private retail providers to improve access to ACTs. The subsidy was initially organised through a stand-alone initiative, called the Affordable Medicines Facility-malaria (AMFm), but has since been integrated into the Global Fund core grant management and financial processes.

Objectives

To assess the effect of programmes that include ACT price subsidies for private retailers on ACT use, availability, price and market share.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 1, *The Cochrane Library*, including the Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register); MEDLINE (OvidSP), EMBASE (OvidSP), CINAHL (EbscoHost), EconLit (ProQuest), Global Health (OvidSP), Regional Indexes (Global Health Library, WHO), LILACS (Global Health Library, WHO), Science Citation Index and Social Sciences Citation Index (ISI Web of Science) and Health Management (ProQuest). All databases were searched February 2015, except for Health Management which was searched November 2013, without any date, language or publication status restrictions. We also searched the International Clinical Trials Registry Platform (ICTRP; WHO), ClinicalTrials.gov (NIH) and various grey literature sources. We also conducted a cited reference search for all included studies in ISI Web of Knowledge, checked references of identified articles and contacted authors to identify additional studies.

Selection criteria

Randomised trials, non-randomised trials, controlled before-after studies and interrupted-time-series studies that compared the effects of ACT price subsidies for private retailers to no subsidies or alternative ACT financing mechanisms were eligible for inclusion. Two authors independently screened and selected studies for inclusion.

Data collection and analysis

Two review authors independently extracted data, assessed study risk of bias and confidence in effect estimates (certainty of evidence) using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Main results

We included four trials (two cluster-randomised trials reported in three articles and two non-randomised cluster trials). Three trials assessed retail sector ACT subsidies combined with supportive interventions (retail outlet provider training, community awareness and mass media campaigns). One trial assessed vouchers provided to households to purchase subsidised ACTs. Price subsidies ranged from 80% to 95%. One trial enrolled children under five years of age; the other three trials studied people of all age groups. The studies were done in rural districts in East Africa (Kenya, Uganda and Tanzania).

In this East Africa setting, these ACT subsidy programmes increased the percentage of children under five years of age receiving ACTs on the day, or following day, of fever onset by 25 percentage points (95% confidence interval (CI) 14.1 to 35.9 percentage points; 1 study, high certainty evidence). This suggests that in practice, among febrile children under five years of age with an ACT usage rate of 5% without a subsidy, subsidy programmes would increase usage by between 19% and 41% over a one year period.

The ACT subsidy programmes increased the percentage of retail outlets stocking ACTs for children under five years of age by 31.9 percentage points (95% CI 26.3 to 37.5 percentage points; 1 study, high certainty evidence). Effects on ACT stocking for patients of any age is unknown because the certainty of evidence was very low.

The ACT subsidy programmes decreased the median cost of ACTs for children under five years of age by US$ 0.84 (median cost per ACT course without subsidy: US$ 1.08 versus with subsidy: US$ 0.24; 1 study, high certainty evidence).

The ACT subsidy programmes increased the market share of ACTs for children under five years of age by between 23.6 and 63.0 percentage points (1 study, high certainty evidence).

The ACT subsidy programmes decreased the use of older antimalarial drugs (such as amodiaquine and sulphadoxine-pyrimethamine) among children under five years of age by 10.4 percentage points (95% CI 3.9 to 16.9 percentage points; 1 study, high certainty evidence).

None of the three studies of ACT subsidies reported the number of patients treated who had confirmed malaria.

Vouchers increased the likelihood that an illness is treated with an ACT by 16 to 23 percentage points; however, vouchers were associated with a high rate of over-treatment of malaria (only 56% of patients taking ACTs from the drug shop tested positive for malaria under the 92% subsidy; 1 study, high certainty evidence).

Authors' conclusions

Programmes that include substantive subsidies for private sector retailers combined with training of providers and social marketing improved use and availability of ACTs for children under five years of age with suspected malaria in research studies from three countries in East Africa. These programmes also reduced prices of ACTs, improved market share of ACTs and reduced the use of older antimalarial drugs among febrile children under five years of age. The research evaluates drug delivery but does not assess whether the patients had confirmed (parasite-diagnosed) malaria. None of the included studies assessed patient outcomes; it is therefore not known whether the effects seen in the studies would translate to an impact on health.

PLAIN LANGUAGE SUMMARY

Subsidising artemisinin-based combination therapy in drug shops and pharmacies

We conducted a review of the effect of subsidising artemisinin-based combination therapy (ACT) drugs for malaria. We searched for all relevant studies up to February 2015 and identified four. Our findings are summarised below.

Background

Malaria causes ill health and death in Africa, particularly in children under five years of age and poor rural populations. The World Health Organization recommends that people use ACT to treat malaria. ACT drugs are available at shops and pharmacies, but these drugs are expensive and people often choose cheaper, older, less effective drugs instead. The Global Fund and other international organisations have therefore decided to subsidise the cost of ACT drugs so that people can buy them from shops and pharmacies at prices similar to, or lower than, those of the older, less effective drugs.

What is the effect of delivery programmes that subsidise ACT prices?

We included four studies. One study looked at the effect of subsidising ACT drugs for children under five years of age and three studies looked at subsidising ACT drugs for people of all ages. All studies were from rural districts in East Africa (Kenya, Uganda and Tanzania). ACT price subsidies were accompanied with activities (such as staff training at shops and pharmacies, community awareness and mass media campaigns) to promote appropriate use of antimalarial drugs in all except one study. In all four studies, the effect of subsidising the drugs was compared to not subsidising the drugs. Price subsidies ranged from 80% to 95% of the actual price; vouchers to households were used in one study.

The findings from these studies indicate that ACT subsidy programmes:

(i) lead to a substantial increase in the number of children under five years of age who used ACTs when they had a fever (high certainty evidence);

(ii) lead to a substantial increase in the number of shops that stocked ACTs for children under five years of age (high certainty evidence); we could not draw any conclusion on the effect on the number of shops that stocked ACTs for patients of any age because the quality of evidence was very low;

(iii) lead to a substantial decrease in the price of ACTs for children under five years of age (high certainty evidence);

(iv) lead to a substantial increase in the market share of ACTs for children under five years of age (high certainty evidence); and

(v) lead to a decrease in the use of older, less effective antimalarials among children under five years of age (high certainty evidence).

None of the studies measured whether the subsidy programmes led to any harmful effects (such as the inappropriate use of ACTs, in other words people who receive ACTs but do not actually have malaria).

The review findings also showed that subsidising ACT prices using vouchers lead to an increase in the likelihood that an illness was treated with an ACT among people seeking treatment for fever or suspected malaria. However, vouchers also lead to an increase in inappropriate use of ACTs (high certainty evidence).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Effects of retail sector ACT subsidy programmes on ACT use, availability, price and market share

Population: Patients seeking treatment for suspected uncomplicated malaria
Settings: Rural districts in East Africa (Kenya, Uganda, Tanzania)
Intervention: Retail sector ACT price subsidies plus supportive interventions (retail outlet provider training, community awareness and mass media campaigns)
Comparison: Standard practice (no subsidies)

Outcomes	Illustrative comparative risks[a] (95% CI)		Absolute difference (95% CI)	Number of participants (studies)	GRADE certainty of the evidence
	Assumed risk	Corresponding risk			
	No ACT subsidy	ACT subsidy			
ACT use (percentage of children under 5 years receiving ACT on the same day or following day of fever onset) Follow-up: 1 year	5.3%[1]	30.3% (19.4% to 41.2%)[b,2]	25% (14.1% to 35.9%)[3,4,5]	2,662[6] (1 study)	⊕⊕⊕⊕ **High**
ACT availability (percentage of outlets stocking ACTs for children under 5 years) Follow-up: 1 year	<0.5%	32.4% (22.5% to 41.8%)[7]	31.9% (26.3% to 37.5%)	1 study (2 articles)	⊕⊕⊕⊕ **High**
ACT availability (percentage of outlets stocking at least one ACT for patients of any age) Follow-up: 1 year	0.5%	72.7% (65.5% to 79.8%	72.2% (65.0% to 79.3%)[8]	1 study	⊕○○○ **Very low**[9]
ACT price (change in ACT prices for children under 5 years)[c] Follow-up: 1 year	Median cost per ACT course: US$ 1.08[10]	Median cost per ACT course: US$ 0.24[11–14]	US$ 0.84 (IQR not estimable)	1 study	⊕⊕⊕⊕ **High**

ACT market share (volume of ACTs purchased as a proportion of all antimalarials purchased; all age groups) Follow-up period: 1 year	Range: 0% to 1.0%[15]	Range: 25.4% to 65.0%[16,17]	Range 23.6% to 63.0%	1 study (2 articles)	⊕⊕⊕⊕ **High**
Use of older antimalarials (amodiaquine, sulphadoxine-pyrimethamine; children under 5 years) Follow-up period: 1 year	34.4%[18]	24.0% (17.5% to 30.5%)[19]	-10.4% (-3.9% to -16.9%)	1 study	⊕⊕⊕⊕ **High**
Adverse effects (such as the number of people receiving ACTs who do not have malaria)	Not measured	Not measured	Not estimable	3 studies	Not estimable

ACT = artemisinin-based combination therapy; CI = confidence interval; IQR = interquartile range

[a]The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[b]This suggests that among febrile children with an expected ACT usage rate of 5% without subsidy, subsidy programmes would increase usage by between 19% and 41%

[c]Costs include only prices paid by patients to purchase ACTs. Costing based on US$-to-Kenyan shillings exchange rate for 1 November 2008

About the certainty of the evidence (GRADE)*

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high

*This is sometimes referred to as ' quality of evidence' or ' confidence in the estimate'

†Substantially different = a large enough difference that it might affect a decision

[1]Based on Kangwana 2011 baseline values.

[2]Based on Kangwana 2011. The second study, Talisuna 2012, reported an absolute change of 16%, but with no baseline data or confidence intervals. Using baselines from Kangwana 2011 (5.3%) gives 20.3% ACT use in Talisuna 2012, which is consistent with the findings of Kangwana 2011.

[3]Kangwana 2011: there was no correlation between socioeconomic status and use of artemether-lumefantrine (P = 0.875) or Tibamal (subsidised artemether-lumefantrine; P = 0.745).

[4]Talisuna 2012: **Children under 5 years of age:** odds ratio 10.0 (4.96 to 18.86); **All age groups**: patients in the intervention districts had a six-fold increase in ACT use relative to the control district (95% CI 4.22 to 8.44). Use of ACT was higher in the highest socioeconomic status stratum compared to the lowest stratum (odds ratio 2.4, 95% CI 1.72 to 3.35, p<0.001); the certainty of evidence was downgraded from low to very low due to likely selection bias (non-randomised design) and confounding by study site (only one control site included, results likely to be influenced by site-specific factors).

[5]Cohen 2015: Compared to an access rate of 19 percent in the control group, subsidies of 80 percent or more increased the likelihood that a malaria-like illness is treated with an ACT by 16 to 23 percentage points (i.e. 85 to 118 percent increase). However, subsidies were associated with overtreatment of malaria: only 56 percent of patients taking ACTs from the drug shop tested for malaria under the 92 percent subsidy.

[6]Total number of children surveyed at follow up at 12 months in Kangwana 2011. Data were collected on 2,749 children at baseline.

[7]Based on Kangwana 2011. The second publication Kangwana 2013 reported an absolute increase of 31.7% (22.0% to 41.3%).

[8]Based on Sabot 2009. Drug shops in population centres were more likely to stock ACTs than those in more remote areas (P <0.001).

[9]Downgraded from low to very low certainty evidence due to high likelihood of selection bias (non-randomised design) and confounding by study site (only one control site included; results likely to be influenced by site-specific (contextual) factors).

[10]Based on Kangwana 2011 baseline values. ACT treatment course: six tablets (children aged 3-35 months) and 12 tablets (children aged 36-59 months).

[11]Based on Kangwana 2011 follow-up (intervention site) data. 95.3% (SD 5.9%) of caregivers in the intervention arm at follow-up who bought Tibamal said they purchased it at the recommended retail price of US$ 0.25. Of the eight not paying this price, three paid less than US$ 0.25 and five paid between US$ 0.31 and 1.23.

[12]Kangwana 2013: In the mystery-shopper survey, at baseline there were only two doses of artemether-lumefantrine sold, at a cost of US$ 2.46 and 2.22. At follow-up, the 12 tab Tibamal was sold at a median price of US$ 0.25 (IQR 20-20), which was the recommended retail price. Of those not paying the recommended price, two paid US$ 0.37, another two paid US$ 0.49 because of buying two packs of the six tab to meet the required dose, and one paid US$ 0.74.

[13]Talisuna 2012: "Maximum recommended retail price was within 10% of the recommended ACT price". The recommended retail price for an adult course of treatment - US$ 0.47 - was not adhered to (the median price at the endline survey was US$ 1.96).

[14]Sabot 2009: **Children:** the mean price paid for ACTs (US$ 0.19) was less than for both sulphadoxine-pyrimethamine (US$ 0.51, P = 0.001) and amodiaquine (US$ 0.86, P <0.001); the price paid for ACTs did not vary by socioeconomic status or geographical location across all age groups; **All age groups:** the mean price for ACTs (US$ 0.58) did not differ from the price of sulphadoxine-pyrimethamine (US$ 0.67), but was higher than for amodiaquine (US$ 0.48, P <0.001).

[15]Based on baseline data from Kangwana 2011 and Kangwana 2013.

[16]Sabot 2009 reported a market share of 8.9% (-0.5% to 18.2%) for children under 5 years of age, and 35.3% (29.8% to 40.7%) for patients ≥ 16 years. **Children under 5 years of age:** purchases of sulphadoxine-pyrimethamine in the intervention districts decreased from 7.0% to 4.0% and remained the same at 9.0% in the control district. Purchases of amodiaquine in the intervention districts declined from 91.0% to 36.0%, and from 91.0% to 36.0% in the control district.

[17]Talisuna 2012: **All age groups:** market share for ACTs in the intervention group was 43% at baseline and 69% at follow-up (control data not reported).

[18]Based on Kangwana 2011 baseline data.

[19]Talisuna 2012: At follow-up, use of quinine was 44% in the control group and 37% in the intervention group (odds ratio 0.76, 95% confidence interval 0.54 to 1.08; no baseline data were reported).

BACKGROUND

Malaria is a major cause of ill health and death in Africa (WHO 2012). Uncomplicated *Plasmodium falciparum* malaria is the commonest form of the disease and accounts for most of the malaria cases and deaths (WHO 2012). The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria (WHO 2012). These drugs are highly effective and have the potential to reduce the development of antimalarial resistance. Unfortunately, despite the WHO's recommendation and substantial donor funding, only one in five antimalarial drugs used in malaria treatment in malaria-endemic countries are ACTs (WHO 2009). Reasons for the low use include high prices of ACTs in the retail sector (drug shops and pharmacies) where most people seek treatment for fever or suspected malaria (Patouillard 2010; Talisuna 2009). The price of ACTs is typically more than 10 times the price of older, less effective antimalarial drugs such as amodiaquine (AQ) and sulphadoxine-pyrimethamine (SP) in the retail sector (Morris 2014).

Description of the intervention

From 2010 to 2012, the Global Fund established and operated a new global subsidy programme, termed the Affordable Medicines Facility-malaria (AMFm), funded by three donors (UNITAID, the UK government and the Bill & Melinda Gates Foundation). The programme operated in seven sub-Saharan African countries (Ghana, Kenya, Madagascar, Niger, Nigeria, mainland Tanzania and Zanzibar and Uganda). In November 2012, the Global Fund board decided to change the way in which the ACT subsidy scheme operated. Instead of being a 'stand alone' initiative at the Global Fund, the subsidy programme was incorporated into the Global Fund's core grant management and financial processes. The AMFm was renamed as the Private Sector Co-payment Mechanism. As of mid-2014, Ghana, Madagascar and Tanzania had integrated the Private Sector Co-payment Mechanism into existing Global Fund grants.

The aim of the AMFm subsidy is to reduce ACT retail prices to a level similar to older, less effective antimalarial drugs in order to increase demand and access for ACTs and displace artemisinin monotherapy and other sub-standard malaria treatments from the market, particularly among populations most vulnerable to malaria (children under five years of age and poor rural populations). Under the AMFm, 'first-line buyers' in the retail sector (those who buy ACTs directly from the manufacturer) pay about US$ 0.05 for a course of ACT rather than US$ 5.00 (the price paid before the AMFm; RBM 2007). The public sector can also purchase donor-subsidised ACTs, which may in turn broaden public sector ACT access. The subsidy programme is combined with supporting interventions (such as retail outlet provider training, community awareness and mass media campaigns) to facilitate effective delivery and appropriate use of ACTs.

How the intervention might work

The AMFm subsidy programme is designed to increase access to ACTs in the retail and public sector by subsidising the prices of ACTs at the manufacturer level (Arrow 2004; Laxminarayan 2009). The programme aims to lower consumer prices of ACTs, compared to older and less effective antimalarial drugs, available through the retail sector via two mechanisms: (1) negotiating with manufacturers of ACTs to reduce ACT prices; and (2) co-paying a proportion (about 90%) of the reduced ACT price directly to participating manufacturers, hence further lowering prices to eligible wholesalers of ACTs (Global Fund; Laxminarayan 2009). The wholesalers thus pay a lower price for ACTs and prices fall all along the supply chain, increasing affordability for the final consumer, while at the same time undercutting the price of resistance-inducing artemisinin monotherapy and competing with the prices for chloroquine and SP.

The pre-specified benchmarks of success of the AMFm pilot by the AMFm included: an increase in ACT use of 10 to 15 percentage points; increase in ACT availability of 20 percentage points; increase in ACT market share of 10 to 15 percentage points; and quality-assured ACT price less than 300% of the dominant non-quality-assured ACTs (chloroquine or SP; Table 1). The AMFm process is illustrated in Figure 1. In Figure 2 we provide a logic framework for this review, showing the theory of impact of the subsidies on malaria burden, potential influences on these steps and the outcomes that can be measured to evaluate the subsidy programmes.

Figure 1. Illustrative example of the AMFm process

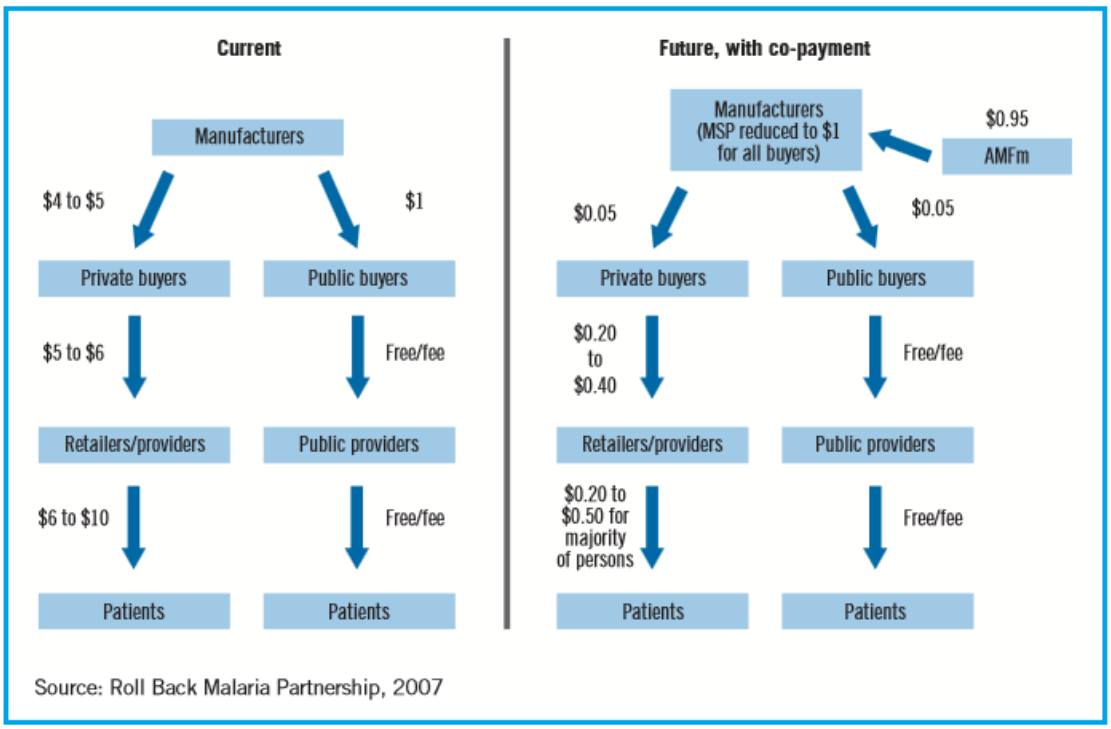
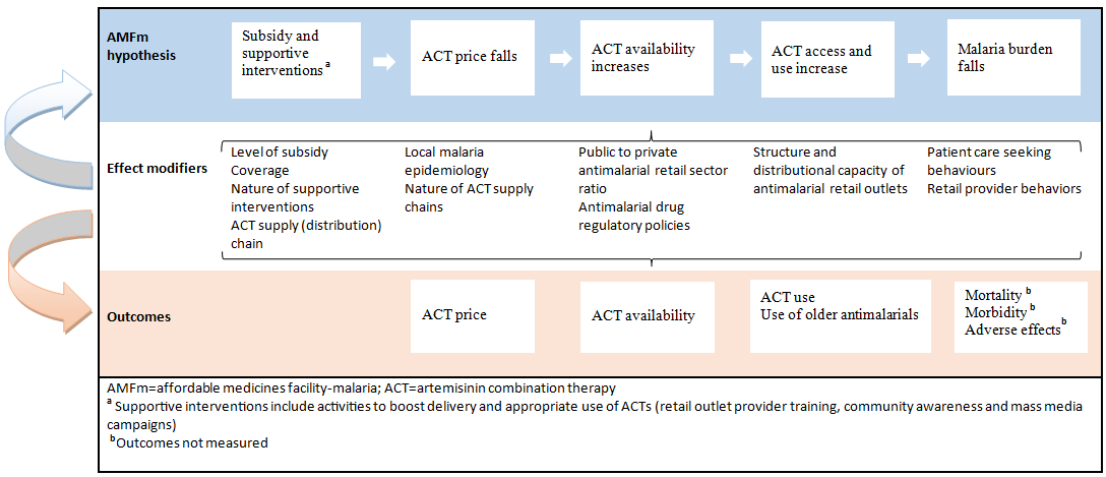


Figure 2. Logic framework for evaluating AMFm programme



Why it is important to do this review

ACT subsidy programmes are expensive. The initial costs of the AMFm pilot that ran from 2010 to 2012 were estimated at US$ 343 million: US$ 216 million for the subsidy and US$ 127 mil-

lion for the supportive interventions (Global Fund). It is therefore important to ensure that such programmes lead to intended outcomes: lower ACT prices; increased ACT availability and usage; crowding-out of older, less effective malaria drugs; and an end to the marketing of artemisinin monotherapy (such marketing might increase the development of *Plasmodium falciparum* resistance, rendering ACTs ineffective; Perkins 2008). It is also important to make sure these subsidies do not have unintended consequences (such as inappropriate use of ACTs among patients with non-malarial fevers leading to drug wastage and delay in care-seeking for appropriate treatment).

OBJECTIVES

To assess the effect of programmes that include ACT price subsidies for private retailers on ACT use, availability, price and market share.

METHODS

Criteria for considering studies for this review

Types of studies

Studies that assessed the effect of retail sector ACT price subsidies using the following designs were eligible for inclusion (Appendix 1).

- Randomised trials.
- Non-randomised trials.
- Controlled before-after studies.
- Interrupted-time-series studies (with a clearly defined point in time when the subsidy occurred, and at least three data points before and three after the subsidy intervention).

Types of participants

Studies involving the following groups of patients and units or channels of delivery of subsidised ACTs were eligible for inclusion.

- Consumers of retail sector subsidised ACTs (patients seeking treatment for fever or malaria; both children and adults).
- Private retailers of subsidised ACTs (pharmacies, franchised clinics, drug shops, general stores).

Types of interventions

Intervention

Studies assessing the effect of retail sector ACT price subsidies were eligible for inclusion.

- Retail sector ACT subsidy programmes (both for-profit and not-for-profit retail sectors).
- Retail sector ACT subsidy programmes with supportive interventions (e.g. retail outlet provider training, community awareness and mass media campaigns).

Comparisons

- Alternative ACT financing mechanisms aiming to achieve similar goals as retail sector ACT price subsidies (such as the generic Global Fund financing mechanism aiming to expand ACT availability in public health care facilities).
- Public sector interventions to increase ACT availability funded by the United States President's Malaria Initiative (PMI) (http://www.pmi.gov/).
- Usual ACT delivery mechanisms (non-subsidised ACT interventions).

Types of outcome measures

Primary outcomes

ACT use (defined as the percentage of patients with fever/confirmed malaria who received an ACT on the day that the fever started or on the following day; Global Fund).

Secondary outcomes

- ACT availability (proportion of all facilities stocking ACTs among outlets with any antimalarials in stock).
- ACT price (cost to patients of a full child or adult course of ACTs).
- ACT market share (total volume of ACTs sold or distributed as a proportion of the total volume of all antimalarials sold or distributed via outlets).
- Use of older antimalarial drugs (AQ, chloroquine, artemisinin monotherapy, SP).
- Adverse effects (such as the number of people receiving ACTs who do not have malaria).

All studies with eligible designs, participants and interventions were considered for inclusion irrespective of whether only the above outcome measures were reported.

Search methods for identification of studies

Electronic searches

We aimed to identify eligible published and unpublished studies. We searched the following databases and grey literature sources in February, 2015.

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 1, *The Cochrane Library*) including The Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register.
- MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE and OLDMEDLINE, 1946 to Present (OvidSP).
- Embase 1980 to 2015 Week 07 (OvidSP).
- CINAHL 1980 to present (EbscoHost).
- Regional Indexes (Global Health Library, WHO).
- LILACS (Global Health Library, WHO).
- Science Citation Index and Social Sciences Citation Index (ISI Web of Science).
- EconLit 1969 to current (ProQuest).
- Global Health 1973 to 2015 Week 07 (OvidSP).
- Health Management (ProQuest; searched 27/11/2013 because we no longer have access to this database).

The searches were done without any language, date or publication status restrictions. See Appendix 2 for all search strategies.

Searching other resources

Grey literature

- The Grey Literature Report from The New York Academy of Medicine Library (http://www.greylit.org/; searched 04/11/2013).
- Websites of the following institutions: the Global Fund, the Roll Back Malaria partnership, Malaria Consortium, Medicines for Malaria Venture, UNITAID, the Clinton Health Access Initiative, PMI, World Bank (Booster Program for Malaria Control in Africa), WHO Global Malaria Program, the United Nations Children's Fund (UNICEF), Drugs for Neglected Diseases Initiative, Centre de Recherche pour le Développement Humain, ACTwatch, Bill & Melinda Gates Foundation, UK Department for International Development, Management Sciences for Health Sustainable Drug Sellers Initiative, Oxfam International and Center for Health Market Innovations (searched 04/11/2013).

Trial registries

- WHO International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/; searched 04/11/2013).
- ClinicalTrials.gov, US National Institutes of Health (http://clinicaltrials.gov/; searched 04/11/2013).

Additional resources

We also:

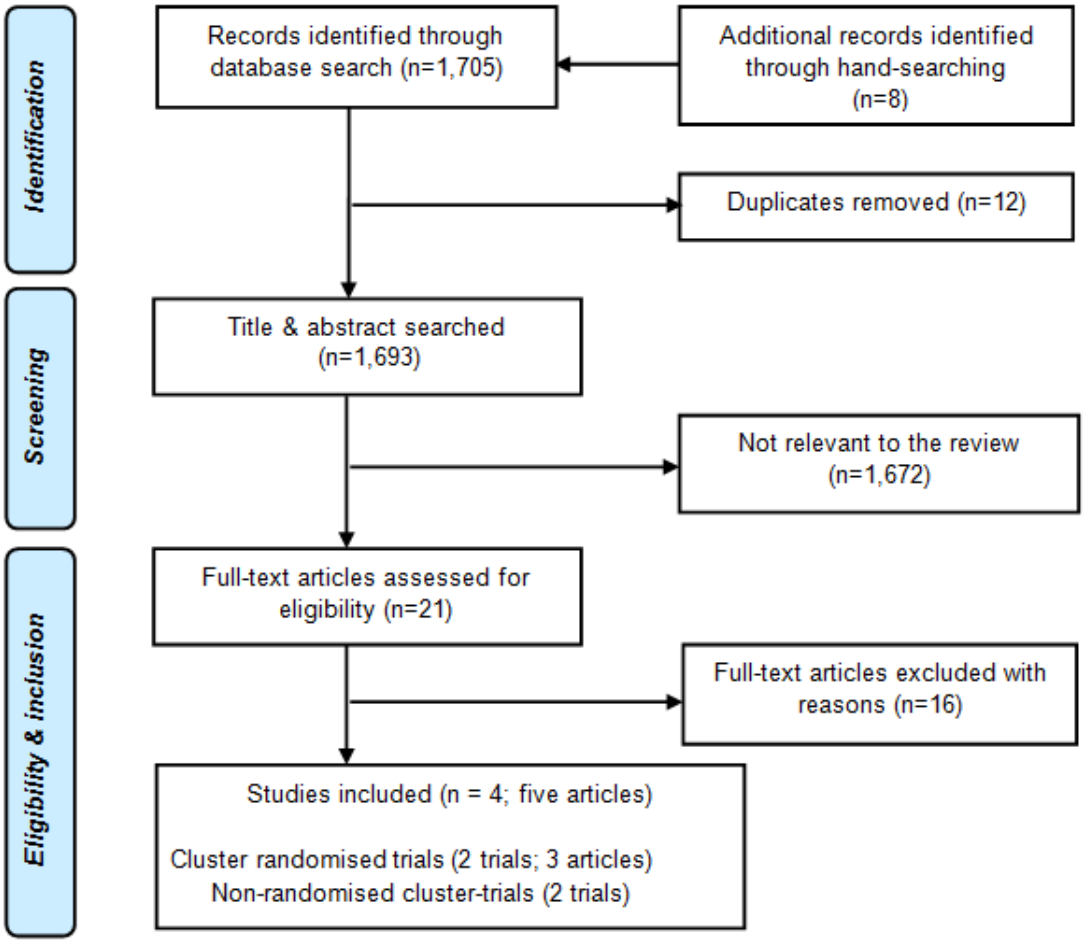
- hand searched relevant conference proceedings (e.g. Multilateral Initiative on Malaria; searched 04/11/2013);
- hand searched reference lists of relevant articles (technical reports, reviews; searched 04/11/2013);
- contacted authors of relevant articles regarding any further published or unpublished work; and
- conducted cited reference searches for all included studies in ISI Web of Knowledge (searched 19/02/2015).

Data collection and analysis

Selection of studies

Two review authors (NO, PG) independently screened titles, abstracts and full texts of identified articles and applied the pre-specified study eligibility criteria to select studies. GY reviewed all articles selected for inclusion. We resolved any disagreements by discussion. We documented the number of articles screened, assessed for eligibility and selected for inclusion in a PRISMA flow diagram (Figure 3; Moher 2009). Studies initially considered eligible but eventually excluded together with the reasons for exclusions are presented in the Characteristics of excluded studies.

Figure 3. Results of the literature search and studies selected



Data extraction and management

Two review authors (NO, PG) independently extracted outcome data at baseline and endline. We also extracted data on study settings (coverage), participants (patient age groups), retail outlets, interventions (level of price subsidy and duration of subsidy programme), ACT supply (distribution) mechanisms and nature of supportive interventions (Characteristics of included studies; Table 2). Data were entered into a pilot-tested data extraction form. We resolved any disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors (NO, PG) independently assessed the risk of bias in the included studies using the Cochrane EPOC 'Risk of bias' tool (EPOC 2014). Quality domains assessed included: allocation sequence generation, allocation concealment, similarity of baseline characteristics and outcome measurements, blinding (personnel and outcome assessors), handling of incomplete outcome data, protection against contamination, completeness of follow-up and reporting of outcomes. We also assessed the following additional cluster-specific sources of bias: recruitment bias, loss of clusters, incorrect analysis and comparability with individually randomised trials (Higgins 2011). Findings were classified into three categories: low (low risk of bias for key quality domains, i.e. allocation sequence generation and concealment), high (high risk of bias for one or more of the key domains) and unclear (unclear risk of bias for one or more key domains). We resolved any disagreements by discussion.

We did not exclude studies on the basis of their risk of bias ratings; rather, we used these findings to help us better understand weaknesses in the identified evidence. We took into account the

risk of bias ratings when synthesising and interpreting results. We report on the results of risk of bias assessment in the 'Risk of bias' tables and graphs (Figure 4; Figure 5).

Figure 4. Review authors' judgements about each risk of bias item for each included study

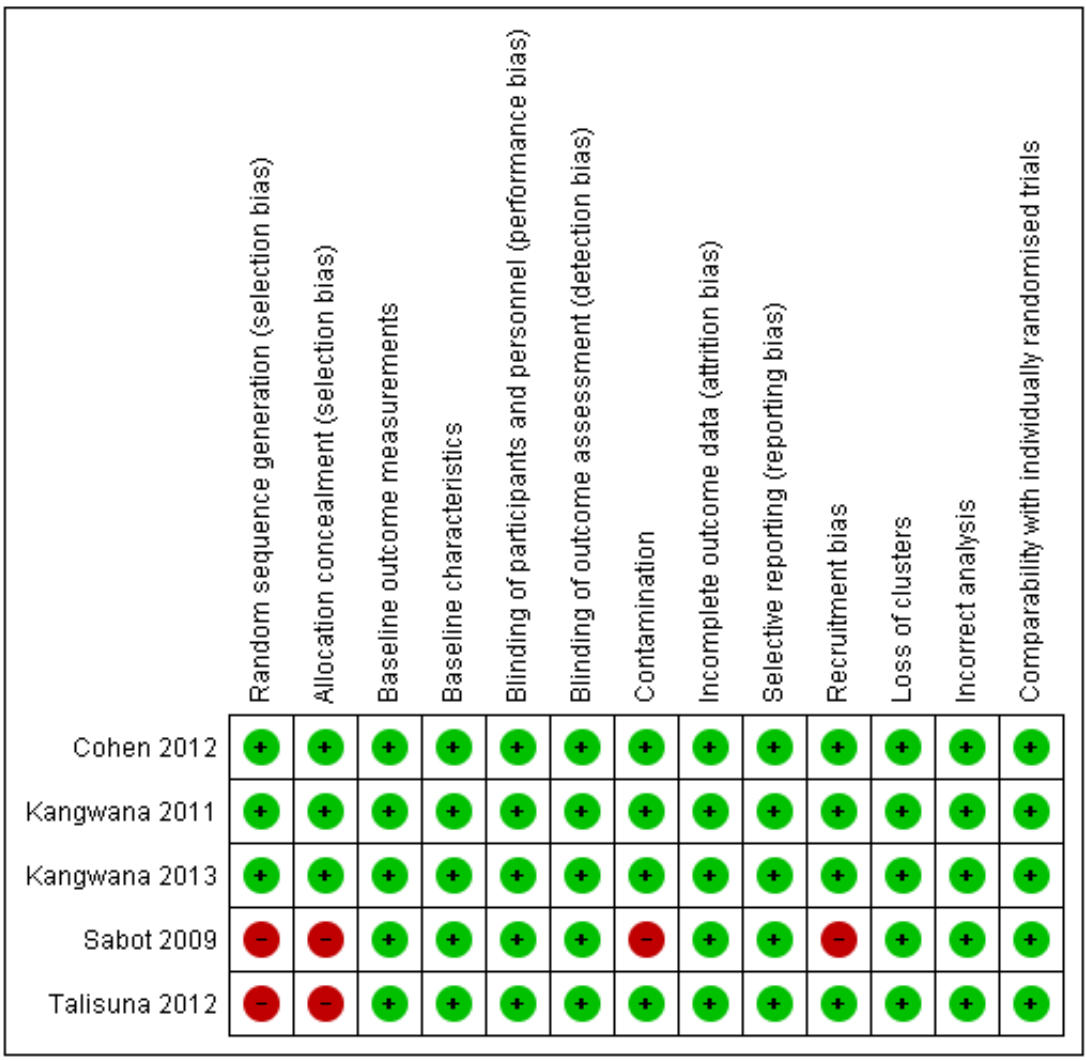
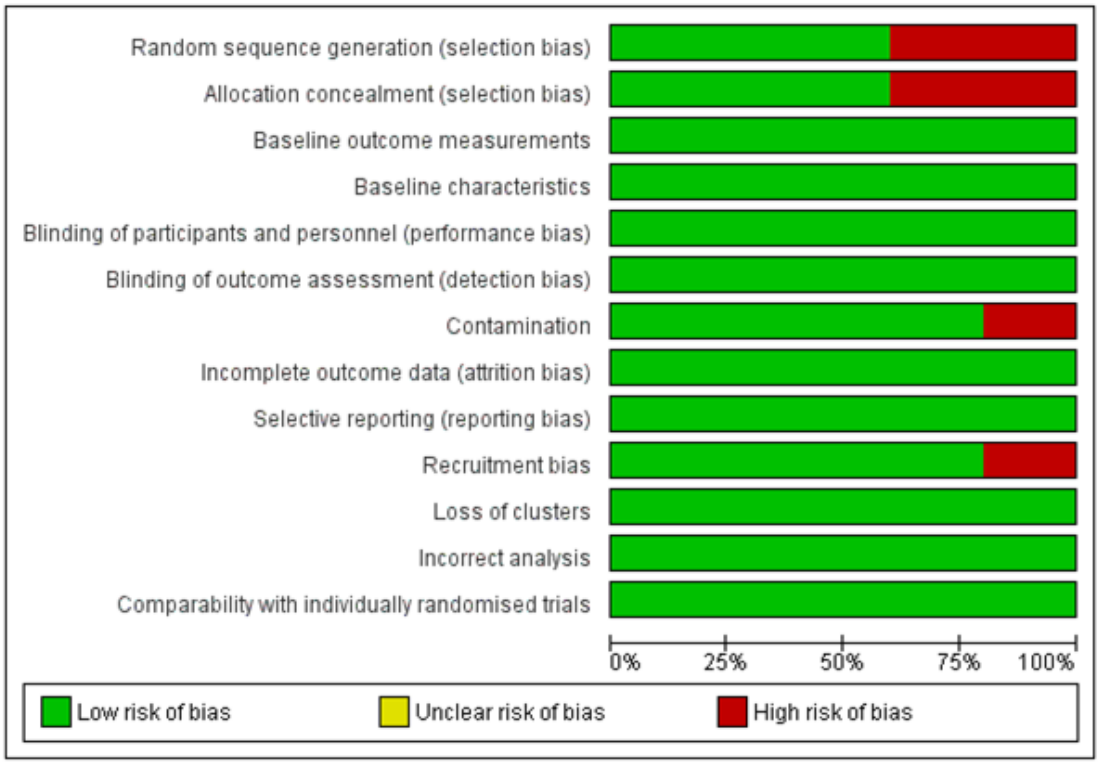


Figure 5. Review authors' judgements about each risk of bias item presented as percentages across all included studies



Measures of treatment effect

We have reported measures of subsidy effects as reported in the primary studies. We have presented absolute estimates of effects (percentage point differences, range and median effect sizes) with 95% confidence intervals (CIs) where estimable. For example, for the outcome of ACT use, we reported percentage changes in control and intervention sites from baselines and the absolute percentage point difference (cluster-adjusted) between the changes (i.e. 'difference-in-difference' estimates; Table 3).

Unit of analysis issues

We assessed whether appropriate analysis was conducted to adjust for clustering in estimating precision of effects in cluster trials (Higgins 2011).

Dealing with missing data

We contacted authors of primary studies where relevant data were missing or where we required further clarification on the reported data. Where data were not available from the authors, we reported the data as missing; we did not impute or extrapolate values.

Assessment of heterogeneity

We did not assess inconsistency between the results of individual studies using statistical methods; differences in studies precluded meta-analysis. We documented factors that could modify subsidy effects (such as programme coverage, level of price subsidy, ACT supply mechanism and nature of supportive interventions) in accordance with the established guidance for evaluating complex interventions (Shepperd 2009; Table 2).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Sterne 2011). Reporting biases comprise publication bias, time lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias and outcome reporting bias. We assessed potential selective reporting of outcomes as one component of risk of bias

assessment (we focused on the completeness of reporting of pre-specified outcomes). We did not create funnel plots as planned because of insufficient data (only four studies were included in the review) (Sterne 2011).

Data synthesis

The included studies utilised varied study designs (randomised cluster and non-randomised cluster trials), enrolled diverse populations (children and adults) and used different effect measures. We therefore did not combine results using statistical methods. We have described individual study results in the 'Effects of interventions' section.

'Summary of findings' table and assessing the certainty of evidence

We assessed the overall confidence in estimate of effect (certainty of evidence) for each outcome using GRADE (Guyatt 2008). This system classifies the certainty of evidence (defined as 'the extent to which one can be confident that an estimate of effect or association is correct') into four categories: very low, low, moderate or high. Data from randomised trials start at high quality while data from observational studies start at low quality. Quality of evidence from randomised trials can be downgraded in consideration of five factors: risk of bias or study limitations, directness, consistency of results, precision and publication bias. Similarly, quality of evidence from observational studies can be upgraded in consideration of three factors: magnitude of effect estimate, dose-response gradient and influence of residual plausible confounding.

Two review authors (NO, PG) independently assessed the certainty of evidence; we resolved disagreements by discussion. We did not assess the certainty of evidence for outcomes where there was insufficient data to permit reliable certainty rating. We did not exclude studies on the basis of GRADE ratings; we took into account the certainty of evidence when interpreting results.

We used GRADEpro software (GRADEpro 2015) to create 'Summary of findings' (SoF) tables for two comparisons: (1) 'retail sector ACT subsidies combined with supportive interventions versus no subsidies' (Summary of findings for the main comparison); and (2) 'ACT subsidy vouchers versus no subsidies' (Summary of findings 2). We included all the pre-specified outcomes in SoF table 1 and ACT access (defined as 'the share of illness episodes treated with ACTs') and targeting (defined as 'the share of ACT-takers who are malaria positive') in SoF table 2. We prioritised findings from randomised trials (data from non-randomised trials were incorporated as footnotes).

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analysis to investigate potential variation in subsidy effects by study design, nature of supportive interventions, socioeconomic status and scale of coverage of subsidies (sub-national versus national programmes). However, we did not perform any of the planned analyses because there was insufficient data to permit reliable analysis.

Sensitivity analysis

We intended to conduct sensitivity analysis to assess the impact of study quality on results (for example, whether effect estimates are robust to changes in study risk of bias). We did not perform this analysis as no meta-analysis was done.

RESULTS

Description of studies

Results of the search

We identified a total of 1705 articles from both the electronic and supplementary searches. We excluded 1684 articles following a review of the titles and abstracts. We retrieved the full texts of 21 articles for detailed eligibility assessment. We excluded 16 of the articles because of ineligible study designs. No ongoing studies were identified. Overall, four studies (five articles) fulfilled the review inclusion criteria (Cohen 2015; Kangwana 2011; Kangwana 2013; Talisuna 2012; Sabot 2009; Figure 3).

Included studies

We included four studies (five articles; Characteristics of included studies; Table 2)

Two studies (three articles) were cluster-randomised trials (Cohen 2015; Kangwana 2011; Kangwana 2013). The remaining studies were non-randomised cluster trials (Sabot 2009; Talisuna 2012). The studies were conducted in rural districts in Kenya (Cohen 2015; Kangwana 2011; Kangwana 2013), Uganda (Talisuna 2012) and Tanzania (Sabot 2009). One trial enrolled children under five years of age (Kangwana 2011; Kangwana 2013); both adults and children were studied in the other trials. One trial (Kangwana 2011; Kangwana 2013) reported adequate power (80%) for primary outcomes. Study power was not reported in the other three studies.

ACT price subsidies were accompanied with supportive interventions (including retail outlet provider training and community awareness campaigns lasting less than a year) in all except one study (Cohen 2015). The subsidy level was 95% in two studies (Kangwana 2011; Kangwana 2013; Talisuna 2012), 80% to 92% in one study (Cohen 2015) and 90% in the remaining study (Sabot 2009). Post-intervention data collection periods were varied: 4 months (Cohen 2015), 12 months (Kangwana 2011; Kangwana

2013; Sabot 2009) and 20 months (Talisuna 2012). Retail outlets comprised specialised and general drug stores in all the studies. Private clinics were included in one study (Talisuna 2012).

ACT supply and distribution chains were varied: a third party procured and delivered ACTs directly to trained outlets from which shopkeepers purchased the treatment at a wholesale price in two trials (Kangwana 2011; Kangwana 2013; Talisuna 2012). In one trial the project managers procured the ACTs directly from the manufacturing drug company (Novartis) and sold them to a wholesaler; drug shops purchased the ACTs from the wholesaler (Sabot 2009). Households were provided with vouchers to purchase subsidised ACTs from retail outlets in one trial (Cohen 2015).

Randomised cluster trials

Kangwana 2011 evaluated the impact of retail sector ACT (artemether-lumefantrine; AL) subsidies in febrile children aged 3 to 59 months in Kenya. Nine areas were randomly allocated to the intervention arm (ACT subsidy plus supportive interventions, retail provider training and communication awareness activities) and nine to the control arm, with a buffer zone of two areas between selected areas. Subsidised AL was provided to retail outlets from November 2008. Cross-sectional household surveys were conducted before (July to August 2008) and after (July to August 2009) the delivery of the intervention. The primary outcome was the proportion of children reporting fever in the previous two weeks who started treatment with AL on the same day as fever onset or the following day. Secondary outcomes were adequacy of AL doses obtained and consumed and the price paid per pack. Data were collected on 2749 children in the target age group at baseline and 2662 at one year follow-up.

Kangwana 2013 evaluated the impact of retail sector ACT subsidies using provider and mystery-shopper survey data collected as part of the randomised trial described above (Kangwana 2011). Data were collected at baseline (July to August 2008) and follow-up (July to August 2009) using provider and mystery shopper cross-sectional surveys. The mystery shopper survey assessed patient-provider interactions and aimed to provide data on actual rather than self-reported provider practice. Outcomes assessed included retail sector ACT availability, provider knowledge and provider dispensing practices. A total of 468 outlets were assessed at baseline and 639 at follow-up in the provider survey. 499 outlets were assessed at baseline and 653 at follow-up in the mystery shopper survey.

Cohen 2015 studied the impact of ACT vouchers in three rural districts in Kenya. Four drug shops (in four market centres) were selected and all households in the catchment area (within a 4 km radius) of these shops were sampled. Households were randomly assigned to one of three groups: (1) 'No subsidy' group (received vouchers to purchase full price ACTs at the pre-AMFm retail price of Kenya shillings 500 (approximately US$ 6.25 in 2009)); (2) 'ACT subsidy only' group (received vouchers for ACT subsidies of between 80% and 92%); (3) 'ACT plus rapid diagnostic test (RDT) subsidy' group (received vouchers for both subsidised ACTs and RDTs. Two vouchers for ACTs (AL) and two vouchers for RDTs (where applicable) were distributed to each household following a baseline survey; 2789 (95%) out of the 2928 households sampled consented to the baseline survey. The trial was conducted between May and December 2009 (the endline survey was administered about four months after the vouchers had been distributed). We only extracted data on ACT access and targeting in the 'ACT subsidy' only and 'No subsidy' group. ACT access was defined as 'the share of illness episodes treated with ACTs'. ACT targeting was defined as 'the share of ACT-takers who are malaria positive'.

Non-randomised cluster trials

Sabot 2009 assessed the impact of AMFm in three rural districts in Tanzania. Since two of the selected districts were adjacent, randomisation was limited so that one of the adjacent districts served as the control. The selected districts were randomly assigned to receive ACT subsidy, ACT subsidy plus suggested retail price or no ACT subsidy (control). The intervention was implemented in 2007. Data were collected at baseline and during intervention using interviews with drug shop customers, retail audits, mystery shoppers and audits of public and non-governmental facilities. Most consumers interviewed in all districts were from the two least poor socioeconomic status quintiles (59% and 68%, respectively). A range of behaviour change communication (local radio advertisements and wall paintings) highlighting the importance of using ACTs and their availability in private shops was conducted by Population Services International. Outcomes assessed were ACT uptake, availability and price. A total of 216 drug shops (*duka la dawa baridi*) were studied. The report focuses on data collected between August 2007 and August 2008.

Talisuna 2012 evaluated the impact of retail sector ACT subsidies in Uganda. The pilot was implemented in 2008 and involved four intervention districts (purposefully selected to receive branded subsidised ACTs) and one control district. Supportive interventions included communication and training activities to improve awareness of the availability of subsidised ACTs and correct dispensing and use of ACTs. Outcomes assessed were ACT uptake, availability, price, purchase within 24 hours of symptom onset and market share. Reported data comprise 1162 interviews at baseline (September 2008) and 5181 interviews at endline (May 2010) from 783 outlets.

Excluded studies

We excluded 16 studies from the analysis because the study designs did not meet our inclusion criteria (uncontrolled pilots, pre-post surveys or qualitative assessments; Characteristics of excluded

studies). Some of the studies excluded were large country evaluations without control sites where the observed effects could be true effects or could be secular and not due to the subsidy intervention (Tougher 2012; Table 4). Details of some of the excluded studies are described below.

Tougher 2012 assessed the effect of AMFm in seven countries (Ghana, Kenya, Madagascar, Niger, Uganda, Nigeria and Tanzania (including Zanzibar)). Nationally representative baseline and endpoint surveys of public and private sector outlets that stock antimalarial treatments were conducted in each of the seven countries (eight national-level pilots). Clusters were selected using probability proportional to size sampling; independent samples were drawn at baseline and endpoint (a full census of outlets was done in Zanzibar because of the small population size). Outcomes assessed were ACT price, availability and market share. These outcomes were assessed against pre-specified success benchmarks after one year of AMFm implementation (Table 1). Data on the implementation process and contextual factors (e.g. supportive interventions, mechanisms of distribution of co-paid ACTs) were collected through key informant interviews and document reviews. Although this study provides important evidence on AMFm effectiveness at a national scale we did not include it because it used a before-after design with no comparator sites. The lack of control sites limits the degree to which observed effects can be attributed to AMFm (findings may have been influenced by secular trends in measured outcomes and concurrent malaria interventions).

We identified six national programmes to scale-up subsidised ACTs in Cameroon, Senegal, Cambodia, DRC, Madagascar and Rwanda (Table 4). Although the programmes report results indicative of the kind of effect ACT subsidies can have under 'real world' conditions, we did not include them because they lacked comparison groups. In addition baseline data were not available for five of the national programmes (such data were only available for Rwanda's national programme).

Risk of bias in included studies

We have presented findings on risk of bias assessment using 'Risk of bias' tables and graphs (Characteristics of included studies; Figure 4; Figure 5). The overall risk of bias was low in two trials (Cohen 2015; Kangwana 2011; Kangwana 2013); it was high in the other two (Sabot 2009; Talisuna 2012).

Random sequence generation and allocation concealment were judged to be adequate (indicating low risk of selection bias) in two trials (Cohen 2015; Kangwana 2011; Kangwana 2013); in the other two they were inadequate (high risk of selection bias). Baseline outcome measures and characteristics between study groups were comparable in all studies. Blinding of personnel (retail outlet providers) and data collectors (interviewers) was not possible in three studies given the public awareness campaigns around subsidised ACTs (Kangwana 2011; Kangwana 2013; Sabot 2009; Talisuna 2012). Performance and detection biases due to lack of blinding were considered low in all studies. The risk of contamination (potential leakage of subsidy intervention into control sites) was low in all except one trial (Sabot 2009), where it was high. None of the trials were at risk of attrition bias or selective outcome reporting. No additional source of bias was present for the cluster-specific domains except for possible recruitment bias in one trial (Sabot 2009).

Effects of interventions

See: **Summary of findings for the main comparison** ACT subsidies combined with supportive interventions versus no subsidies; **Summary of findings 2** ACT price vouchers versus no subsidies

We have presented effect estimates and certainty of evidence for each outcome in GRADE tables (Summary of findings for the main comparison; Summary of findings 2; Appendix 3; Appendix 4). We did not report the certainty of evidence for outcomes where there was insufficient data for GRADE assessment.

Comparison 1: ACT subsidies combined with supportive interventions versus no subsidies

Three studies were included in this comparison (Kangwana 2011; Kangwana 2013; Sabot 2009; Talisuna 2012).

Primary outcome

Two studies reported data on ACT use (Kangwana 2011; Talisuna 2012; Table 3). In the first study (Kangwana 2011), ACT subsidy programmes increased ACT usage in children under five years of age by 25 percentage points (95% CI 14.1 to 35.9 percentage points; high certainty evidence). This suggests that in practice, among febrile children under five years of age with an ACT usage rate of 5% without a subsidy, subsidy programmes would increase usage by between 19% and 41%. In the second study (Talisuna 2012), ACT subsidy programmes resulted in a ten-fold increase (95% CI 5.0 to 18.9) in ACT usage in children under five years of age and a six-fold increase (95% CI 4.2 to 8.4) in ACT usage in all age groups (very low certainty evidence).

Secondary outcomes

Two studies reported data on ACT availability (Kangwana 2011; Kangwana 2013; Sabot 2009; Table 5). In the first study (Kangwana 2011; Kangwana 2013), ACT subsidy programmes increased the percentage of retail outlets stocking ACTs for children under five years of age by 31.9 percentage points (95% CI 26.3 to 37.5 percentage points; high certainty evidence). In the second study (Sabot 2009), ACT subsidy programmes increased the percentage of retail outlets stocking ACTs for patients of any age by

72.2 percentage points (95% CI 65.0 to 79.3 percentage points; very low quality evidence).

Three studies reported data on ACT price outcomes (Kangwana 2011; Kangwana 2013; Sabot 2009; Talisuna 2012; Table 6). In the first study (Kangwana 2011), ACT subsidy programmes decreased the median price for ACT prescribed for children under five years of age by US$ 0.84 (median cost per ACT course without subsidy: US$ 1.08 versus with subsidy: US$ 0.24; high certainty evidence). In the second study (Talisuna 2012), "the maximum recommended retail price was within 10% of the recommended ACT price". In addition, the recommended retail price for an adult course of treatment (US$ 0.47) was not adhered to (the median price at the endline survey was US$ 1.96). In the third study (Sabot 2009), the mean price paid for paediatric ACTs (US$ 0.19) was less than for both SP (US$ 0.51, P = 0.001) and AQ (US$ 0.86, P < 0.001). The mean price for ACTs for any age (US$ 0.58) did not differ from the price of SP (US$ 0.67), but was higher than the price for AQ (US$ 0.48, P < 0.001).

Three studies assessed ACT market share outcomes (Kangwana 2011; Kangwana 2013; Sabot 2009; Talisuna 2012; Table 7). In the first study (Kangwana 2011; Kangwana 2013), ACT subsidy programmes increased market share of ACTs among children under five years of age by between 23.6 and 63.0 percentage points (high certainty evidence). In the second study (Talisuna 2012), the market share for ACTs for patients of any age in the intervention group was 43% at baseline and 69% at follow-up (control data not reported). In the third study (Sabot 2009), the market share for ACTs for children under five years of age increased by 8.9% (-0.5% to 18.2%), and 35.3% (29.8% to 40.7%) for patients aged at least 16 years.

Two studies reported data on use of older antimalarials (Kangwana 2011; Talisuna 2012; Table 8). In the first study (Kangwana 2011), ACT subsidy programmes decreased use of AQ and SP among children under five years of age by 10.4 percentage points (95% CI 3.9 to 16.9 percentage points; high certainty evidence). In the second study (Talisuna 2012), at follow-up, use of quinine was 44% in the control group and 37% in the intervention group (odds ratio 0.76, 95% CI 0.54 to 1.08; all age groups; no baseline data were reported).

None of the three studies measured adverse effects of ACT subsidy programmes.

Comparison 2: ACT vouchers versus no subsidies

One study assessed the effect of ACT vouchers to households on ACT access and targeting, among other outcomes (Cohen 2015). Compared to an access rate of 19% in the control group, subsidies of 80% or more increased the likelihood that a malaria-like illness was treated with an ACT by 16 to 23 percentage points (representing an 85% to 118% increase). However, subsidies were associated with a high rate of over-treatment of malaria: only 56% of patients taking ACTs from the drug shops tested positive for malaria under the 92% subsidy. The two lower subsidy levels were associated with much higher malaria positivity rates: "drug shop ACT-takers were 18 to 19 percentage points more likely to be malaria-positive under the 88 and 80 percent subsidies than under the 92 percent subsidy" (high certainty evidence).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Effects of ACT price vouchers on ACT accessibility and targeting

Patient or population: Patients seeking treatment for suspected uncomplicated malaria
Settings: Three rural malaria endemic districts in Western Kenya
Intervention: ACT subsidy (ACT vouchers to households; 80% to 92% subsidy)
Comparison: No subsidy (households received vouchers to purchase unsubsidised ACTs at the pre-AMFm retail price)

Outcomes	Effect	Number of participants (studies)	GRADE certainty of the evidence	Comments
ACT access (percentage of illness episodes treated with ACTs; all age groups) Follow-up: 4 months	Compared to an access rate of 19% in the control group, subsidies of 80% or more increased the likelihood that a malaria-like illness is treated with an ACT by 16 to 23 percentage points, that is, 85% to 118% increase	2,789 households (1 study)	⊕⊕⊕⊕ **High**	Cohen 2015
ACT targeting (percentage of ACT takers who are malaria positive; all age groups) Follow-up: 4 months	Subsidies were associated with a high rate of over-treatment of malaria (only 56% of patients taking ACTs from the drug shop tested positive for malaria under the 92% subsidy)	2,789 households (1 study)	⊕⊕⊕⊕ **High**	Cohen 2015

ACT: artemisinin-based combination therapy; AMFm: Affordable Medicines Facility-malaria

About the certainty of the evidence (GRADE)*
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high
*This is sometimes referred to as ' quality of evidence' or ' confidence in the estimate'
†Substantially different = a large enough difference that it might affect a decision

DISCUSSION

Summary of main results

This systematic review examined evidence from studies that evaluated the effect of subsidy programmes aimed at improving ac-

cessibility and use of ACT for treatment of malaria. Four trials (five publications) that included substantive subsidies for private retailers were included in the review. All the studies were carried out in three adjacent countries in East Africa (Kenya, Uganda and Tanzania), and had accompanying interventions, including retail outlet provider training, community awareness and mass media campaigns.

The findings indicate that programmes that include substantive price subsidies (90% or more) for private antimalarial drug retailers improve use of ACTs (by 25 percentage points) among children under five years of age with suspected malaria. In practice this suggests that, among febrile children with an ACT usage rate of 5% without a subsidy, subsidy programmes would increase usage by between 19% and 41%. The findings also indicate that subsidy programmes improve ACT stocking in retail outlets (by 32 percentage points) and lower ACT prices (by US$ 0.84 per dose) for children under five years of age with suspected malaria. The impact on ACT stocking for patients of any age is unknown because the certainty of evidence was very low. Subsidy programmes also improve ACT market share (by between 24 to 63 percentage points) among patients of any age and reduce the use of older antimalarials (by 10 percentage points) among children under five years of age.

The findings also show that retail-sector ACT subsidies using vouchers lead to substantial increases in ACT access among people seeking treatment for suspected malaria. However, these subsidies also increase inappropriate use of ACTs (that is, increase the proportion of people who receive ACTs but do not in fact have malaria).

Overall completeness and applicability of evidence

The data that were used in this review are from studies where malaria was mostly diagnosed based on the presence of fever in people seeking treatment for suspected malaria. The number of patients with confirmed (parasite-diagnosed) malaria was unclear in most of the studies; we therefore do not know whether subsidies resulted in over-treatment of malaria, except in the study of ACT vouchers where this was measured. None of the identified studies assessed mortality or other clinical outcomes. Furthermore, the studies did not examine patient adherence to subsidised ACTs. Thus, whether the observed improvement in ACT usage would translate into real health benefits remains uncertain. It is also unknown whether the impact of subsidies would vary by scale of coverage (sub-national vs. national subsidy programmes), ACT supply (distribution) mechanisms to retail outlets or socioeconomic status (there were insufficient data to explore effects across these subgroups).

All the included studies were conducted in rural communities in low-income countries where malaria remains prevalent. Review findings are mostly generalisable to similar settings. However, the small scale nature of the subsidy programmes included in this review, differences in the ACT supply mechanisms and retail sector distribution chains across settings may limit generalisability in some areas. Zambia, for example, has a more expansive public sector distribution chain compared to the private sector (Patouillard 2010).

Decisions to incorporate retail sector ACT subsidies into national malaria control programmes need to involve consideration of individual country contexts (which could include local malaria epidemiology, public sector to private sector antimalarial market ratio, diagnostic and distributional capacity of retail outlets, access to rapid malaria diagnostics and treatment seeking behaviours). In addition malaria subsidy policies need to balance the benefits of retail sector ACT subsidies and potential unintended adverse effects (for example, delaying the formal treatment-seeking that is needed for correct diagnosis and treatment of malaria and non-malarial fevers; under-treatment of malaria (under-dosing); failing to diagnose and treat co-morbid non-malarial fevers such as pneumonia; and over-treatment of malaria resulting from inappropriate use of subsidised ACTs in individuals with non-malarial fevers). Such use of ACTs may increase the likelihood of emergence of artemisinin resistance.

Quality of the evidence

The randomised trials provided high quality evidence on subsidy effects (Cohen 2015; Kangwana 2011; Kangwana 2013). The certainty of evidence for all outcomes reported in the three trials was judged to be high (i.e. the research provides a very good indication of the likely effect).

The findings from the other two studies were susceptible to bias (Sabot 2009; Talisuna 2012). We downgraded the certainty of evidence (for ACT stocking for patients of any age) in one study because of high likelihood of selection bias (non-randomised evaluation) and possible confounding by study site (only one control site included; results were likely to be influenced by site-specific factors; Sabot 2009).

We excluded several studies because they used ineligible designs prone to bias. The ideal designs to assess the effects of large scale public health interventions such as ACT subsidy programmes are cluster-randomised trials with comparable control sites. However, such experimental designs are rarely feasible in practice. For example, cluster randomisation of regions in the included studies was limited by the need to use existing pharmaceutical retail distribution channels. Consequently, implementation of the subsidy interventions could not be restricted to certain areas as predicted by randomisation processes. Furthermore, identification of comparable control groups remains a challenge given inherent differences in contexts such as health systems arrangements in malaria-endemic settings. This challenge was addressed in one included study (Kangwana 2013) through documentation of the context and processes of subsidy implementation (in line with the rec-

ommendations for the evaluation of complex interventions; Craig 2008; Shepperd 2009).

Potential biases in the review process

We excluded many potentially eligible studies because of ineligible study designs. It is possible that some of these studies provide useful information that might complement findings from the four included studies. For example, positive effects observed in the included studies were replicated in one excluded study (Tougher 2012). Consistent findings from different study designs across varying malaria transmission and cultural contexts increase our confidence that observed improvements in ACT use, availability, prices and market share can be attributed to the studied subsidy programmes.

We intended to include only randomised trials, non-randomised trials, controlled before-after studies with at least two intervention and two control sites and interrupted-time-series studies (Appendix 1). These criteria were necessary to minimise possible confounding of subsidy effects by site-specific factors (such as ACT supply chains, regulatory policies and retail provider behaviours). However, we made a post-hoc decision to include two non-randomised cluster trials (Sabot 2009; Talisuna 2012) which compared intervention sites to only one control site. We therefore cannot rule out the possible influence of site-specific factors on observed subsidy effects (hence the decision to downgrade certainty of evidence in Sabot 2009). In addition, government regulatory interventions to phase out monotherapy (AQ/SP) may have contributed to the observed decline in the use of these drugs in Kenya and Uganda (Kangwana 2011; Talisuna 2012). We also did not assess effects on two outcomes as planned in our protocol: 'availability of alternative antimalarial drugs in all facilities, private and public (including informal outlets)' and 'prices of alternative antimalarial drugs (full adult or child courses)'; we used six outcomes included in the 'Summary of findings' tables.

Agreements and disagreements with other studies or reviews

We identified one related review and one study of the impact of ACT subsidy programmes (Morris 2014; Tougher 2012).

Morris 2014 assessed the impact of retail sector ACT subsidies on ACT use. The review included 40 studies, comprising 10 experimental subsidies in eight countries, non-AMFm programmatic subsidies in nine countries and AMFm subsidies in eight pilots. Reported findings were derived from four experimental subsidies, three programmatic subsidies and five of the eight AMFm pilot subsidies. ACT subsidies substantially increased use of ACTs among patients with suspected malaria: each US$1 decrease in price was linked to a 24 percentage point increase in the fraction of suspected malaria cases purchasing ACTs. There were no differences in ACT use among the poorest and richest groups, rural versus urban populations or children versus adults. The authors concluded that ACT price reductions can increase ACT use for suspected malaria, even within poorer, more remote populations that may be most at risk of malaria mortality.

Tougher 2012 assessed the effect of the AMFm in seven countries (Ghana, Kenya, Madagascar, Niger, Uganda, Nigeria and Tanzania (including Zanzibar)). The study used a before-after design with no comparator sites (see Excluded studies for details on study methods). The AMFm resulted in a large increase in quality-assured ACT (QAACT) availability (by 25.8 to 51.9 percentage points) in all pilots except Niger and Madagascar, and a large increase in ACT market share (by 15.9 to 40.3 percentage points), driven mainly by changes in the private for-profit sector. Median price for QAACTs per adult equivalent dose decreased substantially in the private for-profit sector in six pilots; the decrease ranged 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. The authors concluded that 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.

We did not conduct a quality assessment (risk of bias) for the evidence presented in the related review and study; these findings should therefore be interpreted with caution. However, despite differences in study designs, the conclusions in both studies are consistent with the findings of our review: ACT subsidies combined with supportive interventions increase ACT usage, availability and market share and lower ACT prices for people seeking treatment for suspected malaria.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review suggest that programmes that include substantive price subsidies (90% or more) for ACTs for private retailers combined with provider training and marketing improve use and availability of ACTs and lower ACT prices for children under five years of age with suspected malaria. This research has also shown that subsidy programmes improve market share of ACTs (volume of ACTs distributed as a proportion of total volume of all antimalarials distributed via outlets) and reduce use of older, less effective antimalarials for children. We could not draw any conclusion on the impact on ACT stocking for patients of any age because the certainty of evidence was very low.

Decisions to incorporate retail sector ACT subsidies into national malaria control programmes need to involve consideration of individual country contexts and weigh the benefits of subsidies against potential unintended consequences (such as over-treatment of

malaria resulting from inappropriate use of ACTs among patients with non-malarial fevers). Efforts to scale-up retail sector ACT subsidy programmes in malaria-endemic settings (for example, via licensed community based pharmacies) should be complemented with policies to strengthen health systems (for example, enhanced malaria diagnostics using subsidised rapid diagnostic tests to improve ACT targeting; improved antimalarial drug supply in the public sector; in-service malaria case management training; and routine monitoring and surveillance for safety and impact).

Implications for research

The number of patients with confirmed (blood-diagnosed) malaria was unclear in most of the included studies. Thus, future studies should investigate options to better target subsidised ACTs to patients who actually have malaria (for example, effectiveness of retail sector ACT subsidies combined with subsidies for rapid diagnostic tests). Optimal targeting of subsidised ACTs would increase the likelihood that non-malarial illness such as pneumonia (the symptoms of which are often similar to those of malaria) are promptly diagnosed, treated or referred. Such targeting would also reduce the likelihood of emergence of artemisinin resistance. These studies should ideally use cluster-randomised, interrupted-time-series or plausibility designs (Victora 2004).

Future studies should also investigate pharmacovigilance and the extent of under- and over-treatment of malaria resulting from inappropriate targeting of retail sector ACT subsidies. The cost-effectiveness and sustainability of subsidy programmes compared to alternative financing mechanisms and other approaches to expand access to subsidised malaria drugs (such as private retail sector-public partnerships and community based strategies) also need to be investigated.

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REFERENCES

References to studies included in this review

Cohen 2015 *{published data only}*
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Sabot 2009

Methods	Non-randomised controlled cluster trial
Participants	Country: Tanzania Setting (coverage): 2 intervention districts, 1 control district Outlets: Small drug shops *(duka la dawa baridi)* Age group: All age groups
Interventions	Intervention: Subsidised ACT (AL) Comparison: No ACT subsidy (control) Supportive interventions: Behavior change communication (e.g. local radio advertisements, wall paintings, themed cultural shows) emphasising the importance of using ACTs and their availability in private shops
Outcomes	ACT uptake, availability and price
Notes	The project managers procured AL from the manufacturer, Novartis, and sold them to a pharmaceutical wholesaler in Dar es Salaam at an average of US$ $0.11 per dose, 88% below the price offered to public buyers In one of the intervention districts (Kongwa), the suggested retail price intended to inform consumers of the maximum amount they should pay was set at 300, 600, 900, and 1200 Tanzanian shillings (0.25, 0.50. 0.75. and 1 USD respectively) for the four weight packs respectively; no suggested retail price was included on drugs distributed to Maswa in order to test its effect on price outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The selected districts were randomly assigned to one of the three arms in the study design: subsidy, subsidy plus suggested retail price, and no subsidy (control). As two of the qualified districts were adjacent, randomization was limited so that one of the adjacent districts served as the control" Comment: Non-randomised design
Allocation concealment (selection bias)	High risk	Quote: "The selected districts were randomly assigned to one of the three arms in the study design: subsidy, subsidy plus suggested retail price, and no subsidy (control). As two of the qualified districts were adjacent, randomization was limited so that one of the adjacent districts served as the control"

Sabot 2009 (*Continued*)

		Comment: Non-randomised design
Baseline outcome measurements	Low risk	Comment: No important differences across study groups on pre-specified subsidy outcome measures
Baseline characteristics	Low risk	Quote: "The selected districts were among the few roughly comparable across all indicators, with high malaria transmission, large numbers of private drug shops and, importantly, no malaria related trials (e.g. vaccines) underway"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not possible for study personnel and ACT providers due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was, however, unlikely to influence results as the outcomes assessed were objective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Blinding was not possible for data collectors due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was however unlikely to influence results as outcomes assessed were objective
Contamination	High risk	Quote: "As two of the qualified districts were adjacent, randomization was limited so that one of the adjacent districts served as the control"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: The number of drug shops closed or refusing to participate were 30 (13%) and 39 (15%) respectively
Selective reporting (reporting bias)	Low risk	Comment: Data on pre-specified outcomes reported
Recruitment bias	High risk	Quote: "The selected districts were randomly assigned to one of the three arms in the study design: subsidy, subsidy plus suggested retail price, and no subsidy (control). As two of the qualified districts were adjacent, randomization was limited so that one of the adjacent districts served as the control"

Sabot 2009 (*Continued*)

Loss of clusters	Low risk	Quote: "The total number of DLDB audited increased from 200 in August 2007 to 216 in August 2008 due to the opening of new shops, with 30 (13%) and 39 (15%) additional shops closed or refusing to participate at these two time periods respectively."
Incorrect analysis	Low risk	Quote: "To assess geographical variation in outcomes, the competition level of all DLDB was calculated using the fixed radius approach...The competitive space of each DLDB was defined as 1 kilometer and each shop was assigned to a competition index category between 0 and 5 based on the number of other DLDB within that radius." "A repeated measures multivariate regression model was used to compare differences in purchase price while controlling for potentially confounding factors and adjusting for clustering of multiple purchases in the same shops."
Comparability with individually randomised trials	Low risk	Comment: Included clusters comparable

Kangwana 2011

Methods	Cluster-randomised controlled trial
Participants	Country: Kenya Setting (coverage): 3 districts (9 sublocations allocated to intervention, 9 sublocations allocated to control) Outlets: Retail outlets (specialised drug shops and general shops) Age group: Children under 5
Interventions	Intervention: Tibamal (subsidised ACT: AL) plus supportive interventions Comparison: No subsidised ACT (control) Supportive interventions: Training of retail outlet staff, job aids, community awareness activities (e.g. workshops, posters and paintings on shops; these activities were designed to make the community aware of malaria, the availability of Tibamal, and the importance of adherence to the medication)
Outcomes	Primary outcome: proportion of children reporting fever in the past 2 weeks who started treatment with AL on the day or following day of fever onset. Secondary outcomes: adequacy of AL doses obtained and consumed and the price paid per pack

Notes	At the time of the study, AL had a retail price of around US$ 6.16 (500 Kenyan shillings) compared with an average of around US$ 0.37 for common, older antimalarials such as SP and AQ. The outlets were instructed to sell the packs at a retail price of US$ 0.25, which was printed on the drug packaging, providing a 150% retailer mark-up (exceeding that of AQ and SP, which generally had retail markups of 50% to 100%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: A random list of all eligible sublocations was formulated per district in Microsoft Excel. The first intervention sublocation was selected from the top of the list. In order to reduce the potential for contamination a "buffer zone" was created where all sublocations located within two sublocation boundaries of the selected sublocation were removed from the list. The list was reshuffled randomly and the first sublocation on the new list allocated to the control arm
Allocation concealment (selection bias)	Low risk	Comment: The same procedure as for random sequence generation (described above) was used; intervention allocation could not have been seen in advance
Baseline outcome measurements	Low risk	Comment: No important differences across study groups on pre-specified subsidy outcome measures
Baseline characteristics	Low risk	Comment: Baseline characteristics of study groups reported and comparable
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not possible for shopkeepers and community members due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was, however, unlikely to influence results as the outcomes assessed were objective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Blinding was not possible for data collectors due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was, however, unlikely to influence results as outcomes assessed were objective

Kangwana 2011 (*Continued*)

Contamination	Low risk	Quote: "No children in the control arm were reported to have received Tibamal (subsidised ACT) at follow-up. In addition, at follow-up 82% of caregivers in the intervention arm had heard of Tibamal, compared to only 7% in the control arm."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: In the control arm, of 1,679 households interviewed at baseline, 152 were lost to follow-up; in the intervention arm, Of 1,609 households interviewed, 114 were lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: Data on prespecified outcomes were reported
Recruitment bias	Low risk	Quote: "A random list of all eligible sublocations was formulated per district in Microsoft Excel. The first intervention sublocation was selected from the top of the list...The list was reshuffled randomly and the first sublocation on the new list allocated to the control arm."
Loss of clusters	Low risk	Quote: "We completed interviews in 2,319 homesteads at baseline (3,288 households), and 2, 204 homesteads at follow-up (3,182 households) .All randomised clusters included in the analysis. "
Incorrect analysis	Low risk	Quote: "A separate analysis allowing for clustering within homesteads was also conducted."
Comparability with individually randomised trials	Low risk	Comment: Included clusters comparable

Talisuna 2012

Methods	Non-randomised controlled cluster trial
Participants	Country: Uganda Setting (coverage): 4 intervention districts, 1 control district Outlets: Drug shops (private drug shops, private clinics, pharmacies) Age group: All age groups
Interventions	Intervention: Subsidised ACT plus supportive interventions Comparison: No ACT subsidy (control) Supportive interventions: Communication activities to improve awareness of the importance and availability of ACTs, and training activities to ensure correct dispensing and use of subsidised ACTs

Outcomes	ACT uptake, purchase of ACT within 24 hours of symptom onset and ACT price, availability and market share
Notes	There was better availability of ACT in the public sector in the control district because of: (1) new interventions initiated targeting the community level distribution of ACTs through the public sector; and (2) improvements in the procurement and distribution system in the public sector, based on a push instead of a pull system for the lower level health units The maximum recommended retail price for the subsidised ACT ranged from 200 Ugandan shillings to 800 Ugandan shillings (US$ 0.10 to 0.40), depending on the target age/doses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Four intervention districts were purposefully selected to receive branded subsidised medicines - 'ACT with a leaf', while the fifth district acted as the control." Comment: Non-randomised design
Allocation concealment (selection bias)	High risk	Quote: "Four intervention districts were purposefully selected to receive branded subsidised medicines - 'ACT with a leaf', while the fifth district acted as the control." Comment: Non-randomised design
Baseline outcome measurements	Low risk	Comment: No important differences across study groups on pre-specified subsidy outcome measures
Baseline characteristics	Low risk	Quote: "Some discordance was observed between the intervention and control districts at baseline in terms of drug consumption habits. Fortunately, the observed disparities did not include the use of ACT. Generating survey-adjusted outputs was intended to provide a more reasonable range of likely values that accounted for this prior to executing tests of significance"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not possible for drug shop personnel due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was, however, unlikely to influence outcomes as outcomes assessed were objective

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Possible interviewer bias minimised through a week long training to instil strict processes for conducting interviews, and to minimise deviation from the interview script. It was unlikely that the lack of blinding could influence outcomes as it was obligatory for the interviewer to observe and record the details of the actual medicine purchased."
Contamination	Low risk	Quote: "To limit leakage of the intervention to the control area, the control and intervention areas had two intervening buffer districts (Bukedea and Kumi) or a lake between them. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...the rate of refusal was generally small (not exceeding 10%) and any effect due to refusal probably did not impact significantly on the outcome measures." Comment: Of the 5,643 observations collected in the final evaluation survey, 5,181 observations resulting from visits to 783 outlets were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: Data on pre-specified outcomes reported
Recruitment bias	Low risk	Quote: "Four intervention districts were purposefully selected to receive branded subsidised medicines - 'ACT with a leaf', while the fifth district acted as the control."
Loss of clusters	Low risk	Quote: "Following the baseline survey, [Consortium for ACT Private Sector Subsidy] initiated the ACT subsidy for the intervention districts and four subsequent rounds of monitoring of cross-sectional surveys were administered in the same manner as the baseline survey, with the final round occurring during the period 20 April - 11 May, 2010 (Baseline: n=1,162; round 1: n=1044; round 2: n= 1794; round 3: n=1976 and final round 4: n= 5181). A minimum number of 5 interviews per outlet were respected in the final survey round, resulting in a significantly higher sample size."

Talisuna 2012 (*Continued*)

Incorrect analysis	Low risk	Quote: "Based on the data-collection methods, a survey-adjusted logistic regression model was used. The outlets were treated as the population sampling units within five strata - the five pilot districts."
Comparability with individually randomised trials	Low risk	Comment: Included clusters comparable

Kangwana 2013

Methods	Cluster-randomised controlled trial
Participants	Country: Kenya Setting (coverage): 3 districts (9 sublocations allocated to intervention, 9 sublocations allocated to control) Outlets: Retail outlets (specialised drug shops and general shops) Age group: Children under 5
Interventions	Intervention: Tibamal (subsidised ACT: AL) plus supportive interventions Comparison: No subsidised ACT (control) Supportive interventions: Training of retail outlet staff, job aids, community awareness activities (e.g. workshops, posters and paintings on shops; these activities were designed to make the community aware of malaria, the availability of Tibamal, and the importance of adherence to the medication)
Outcomes	AL uptake (provider behaviour), availability of older antimalarials, AL price, AL stocking, provider knowledge, and provider dispensing practices. Generally, outlets that received subsidised AL plus training and job aids performed better than those receiving one or none of these intervention components
Notes	At the time of the study, AL had a retail price of around US$ 6.16 (500 Kenyan shillings) compared with an average of around US$ 0.37 for common, older antimalarials such as SP and AQ. The outlets were instructed to sell the packs at a retail price of US$ 0.25, which was printed on the drug packaging, providing a 150% retailer mark-up (exceeding that of AQ and SP, which generally had retail markups of 50% to 100%). Generally, outlets that received training and job aids performed better than those receiving one or none of these intervention components

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: A random list of all eligible sublocations was formulated per district in Microsoft Excel. The first intervention sublocation was selected from the top of the list. In order to reduce the potential for contamination a "buffer zone"

		was created where all sublocations located within two sublocation boundaries of the selected sublocation were removed from the list. The list was reshuffled randomly and the first sublocation on the new list allocated to the control arm
Allocation concealment (selection bias)	Low risk	Comment: The same procedure as for random sequence generation (described above) was used; intervention allocation could not have been seen in advance
Baseline outcome measurements	Low risk	Comment:No important differences across study groups on pre-specified subsidy outcome measures
Baseline characteristics	Low risk	Quote: "To control for potential confounders the covariates considered were outlet type (specialized drug store or general store), distance of shop to nearest road, whether any staff had clinically related training, and district. All covariates significant at a p-value of <0.2 were retained in the regression model."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not possible for shopkeepers due to the public information campaign around the subsidied drugs in the intervention arm. Lack of blinding was, however, unlikely to influence results as the outcomes assessed were objective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Blinding was not possible for data collectors due to the public information campaign around the subsidised drugs in the intervention arm. Lack of blinding was, however, unlikely to influence results as outcomes assessed were objective
Contamination	Low risk	Quote: "It is also possible that there was some contamination of the control arm outlets, which could have heard some of the communication activities. However, results indicated that such exposure was low, with only 1% of control arm respondents saying that they had attended the Tibamal training, 14% having heard of Tibamal, and no outlets stocking Tibamal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In both the provider and mystery-shopper surveys, at baseline and also at follow-up, less than 10% of outlets were not interviewed either

Kangwana 2013 (*Continued*)

		because the respondent refused to be interviewed or the outlet was closed during visits."
Selective reporting (reporting bias)	Low risk	Comment: Data on pre-specified outcomes were reported
Recruitment bias	Low risk	Quote: "A random list of all eligible sublocations was formulated per district in Microsoft Excel. The first intervention sublocation was selected from the top of the list...The list was reshuffled randomly and the first sublocation on the new list allocated to the control arm."
Loss of clusters	Low risk	Quote: "We completed interviews in 2,319 homesteads at baseline (3,288 households), and 2, 204 homesteads at follow-up (3,182 households) .All randomised clusters included in the analysis. "
Incorrect analysis	Low risk	Quote: "A separate analysis allowing for clustering within homesteads was also conducted."
Comparability with individually randomised trials	Low risk	Comment: Included clusters comparable

Cohen 2015

Methods	Cluster-randomised controlled trial
Participants	Country: Kenya Setting (coverage): Three rural districts (Busia, Mumias and Samia in Western Kenya) Outlets: Retail outlets (drug shops) Age group: All age groups
Interventions	Households were randomly assigned to one of three groups: (1) "No subsidy" group ("received vouchers to purchase unsubsidized ACTs at the market price of KSh (Kenyan shillings) 500 (just under $6.25). This treatment arm was meant to capture the no-subsidy status quo that prevailed in Kenya prior to the AMFm pilot, in which over-the-counter ACTs were expensive and RDTs were not available in drug shops.") (2) ACT subsidy only group (3) 'ACT plus RDT' subsidy group (received vouchers for both subsidised ACTs and RDTs) The ACT used in the study was Coartem (AL). Supportive interventions: None.
Outcomes	Outcomes of interest to current review: ACT accessibility ("the share of illness episodes treated with ACTs"); ACT targeting ("the share of ACT-takers who are malaria positive")

Notes	"Within the two ACT subsidy groups ('ACT subsidy only' and 'ACT+RDT subsidy') , households were randomly assigned to an ACT subsidy level of 92, 88 or 80 percent (corresponding to $0.50, $0.75 and $1.25 for an adult dose, respectively). The 92 percent subsidy level corresponds to the Kenyan government's target retail price of KSh 40 under the AMFm."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization of households was done using a computerized random number assignment algorithm and was stratified by drug shop, by the household's distance to the drug shop (in quartiles) and by the presence of children in the household."
Allocation concealment (selection bias)	Low risk	Comment: The same procedure as for random sequence generation (described above) was used; selection bias due to foreknowledge of treatment allocation is considered unlikely
Baseline outcome measurements	Low risk	Quote: "There are no significant differences across treatment groups, other than for the number of acres owned and the age distribution in the household. In particular, our control group has slightly older household heads, with, as a consequence, a significantly higher fraction of adults. Since age is highly correlated with malaria positivity, a lack of balance across treatment groups in the age composition of households could confound estimates of treatment assignment on uptake and targeting, even though the magnitude of the age differences is not large. Therefore, unless otherwise noted, we control for the age of the household head in all of our results. "
Baseline characteristics	Low risk	Quote: "There are no significant differences across treatment groups, other than for the number of acres owned and the age distribution in the household. In particular, our control group has slightly older household heads, with, as a consequence, a significantly higher fraction of adults. Since age is highly correlated with malaria positivity, a lack of balance across treatment groups in the age composition of households could confound estimates of treatment assignment on uptake and targeting, even though the magnitude of the age differences is not large. Therefore, un-

		less otherwise noted, we control for the age of the household head in all of our results."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Lack of blinding considered unlikely to impact on outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Lack of blinding considered unlikely to impact on outcomes
Contamination	Low risk	Comment: Households were provided with vouchers for subsidised and non-subsidised ACTs; cross-group contamination is considered unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Only five percent of households surveyed at baseline were not reached at endline, and attrition was balanced across treatment arms."
Selective reporting (reporting bias)	Low risk	Comment: Data on pre-specified outcomes were reported.
Recruitment bias	Low risk	Quote: "We selected four drug shops, in four rural market centers and sampled all households in the catchment area (within a 4km radius) of each of these shops." "The randomization of households was done using a computerized random number assignment algorithm and was stratified by drug shop, by the household's distance to the drug shop (in quartiles) and by the presence of children in the household."
Loss of clusters	Low risk	Quote: "Only five percent of households surveyed at baseline were not reached at endline, and attrition was balanced across treatment arms."
Incorrect analysis	Low risk	Comment: Multivariable regression analysis allowing for clustering used (e.g. "If more than one household member got sick simultaneously, we include all concurrent first episodes, and therefore cluster the standard errors in all illness episode regressions at the household level."
Comparability with individually randomised trials	Low risk	Comment: Included clusters comparable

ACT = artemisinin-based combination therapy

AL = artemether-lumefantrine
AQ = amodiaquine
RDT = rapid diagnostic test
SP = sulphadoxine-pyrimethamine

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Laxminarayan 2006	Not an RCT, NRCT, CBA or ITS: mathematical modelling study comparing impact of introduction of ACT subsidy with scenarios in which artemisinin monotherapy and partner drug monotherapy are used in a small proportion of patients in the absence of ACTs
MENTOR 2010	Not an RCT, NRCT, CBA or ITS: uncontrolled pilot of ACT implementation in two municipalities
Alba 2010	Not an RCT, NRCT, CBA or ITS: annual census of drug shops, retail audits of public, mission and private outlets complemented with demographic surveillance system data
Cohen 2010	Not an RCT, NRCT, CBA or ITS: pre/post survey examining equity and spatial distribution of outcomes in the delivery of subsidised private sector ACTs
Yeung 2011	Not an RCT, NRCT, CBA or ITS: documentation of programmatic experience of implementation of subsidised ACT in the private sector
Smith 2011	Not an RCT, NRCT, CBA or ITS: census of public and private facilities, chemists, pharmacies, other malaria medicine retailers
Rutta 2011	Not an RCT, NRCT, CBA or ITS: pre/post program evaluation (approximately one year after the introduction of subsidised AL in accredited drug dispensing outlet)
Tougher 2012	Not an RCT, NRCT, CBA or ITS: before-and-after design with no comparator sites
Yadav 2012	Not an RCT, NRCT, CBA or ITS: periodic retail audits of accredited drug dispensing outlets to examine availability and price of subsidised ACT during the first year of the AMFm
Yamey 2012	Not an RCT, NRCT, CBA or ITS: 'mixed-methods' design, triangulating data from a literature review with information from interviews with experts
Davis 2013	Not an RCT, NRCT, CBA or ITS: interview study of ACT availability and use in the private sector of five AMFm phase 1 countries
O Meara 2013	Not an RCT, NRCT, CBA or ITS: study examines factors associated with retailers' likelihood of stocking subsidised AL and the association between price and sales for AL, quinine and sulphadoxine-pyrimethamine
Kedenge 2013	Not an RCT, NRCT, CBA or ITS: qualitative study (focus group discussions) to understand the impact of subsidising ACTs in the retail sector

(*Continued*)

Malm 2013	Not an RCT, NRCT, CBA or ITS: document review of policies, guidelines, reports, meeting minutes, and Internet search of literature on implementation of AMFm
Fink 2013	Not an RCT, NRCT, CBA or ITS: periodic household and retail outlet surveys
Tougher 2014	Not an RCT, NRCT, CBA or ITS: before-and-after design with no comparator sites

ACT = artemisinin-based combination therapy
AL = artemether-lumefantrine
AMFm = Affordable Medicines Facility-malaria
CBA = controlled before-after
ITS = interrupted time series
NRCT = non-randomised controlled trial
RCT = randomised controlled trial

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Guidelines for success benchmarks at 1 and 2 years after effective start date of the AMFm Phase 1 at the country level

Outcome	Year 1	Year 2
Availability (The proportion of all facilities, private and public (including informal outlets), stocking QAACTs, among outlets with any antimalarials in stock at the time of the survey)	Increase of **20 percentage points** from baseline	Increase of **40 percentage points** from baseline
Market share (Total volume of QAACTs sold or distributed as a proportion of the total volume of all antimalarials sold or distributed in the last 7 days via outlets that will be included in the Independent Evaluation's outlet surveys)	Increase in ACT market share of **10 to 15 percentage points** from baseline *and* Decrease in market share of AMT from baseline	Increase in ACT market share of **15 to 20 percentage points** from baseline *and* Decrease in market share of AMT from baseline
Use[a] (Proportion of children under age 5 with fever who received a QAACT on the day that the fever started or on the following day)	Increase of **5 to 10 percentage points** from baseline	Increase of **10 to 15 percentage points** from baseline
Price (Adult equivalent treatment dose)	**QAACT price < 300%** of the price of the dominant non-QAACT (in most countries this is CQ or SP)[b] *and* Price of AMFm co-paid QAACT < price of AMT (this is useful but not sufficient to determine success)	**QAACT price < 150%** of the price of the dominant non-QAACT (in most countries this is CQ or SP) *and* Price of AMFm co-paid QAACT < price of AMT (this is useful but not sufficient to determine success)

ACT = artemisinin-based combination therapy; AMT = artemisinin monotherapy
AMFm = Affordable Medicines Facility-malaria
CQ = chloroquine
QAACT = quality-assured artemisinin-based combination therapies
SP = sulphadoxine-pyrimethamine
[a]The denominator for ACT use is 'fever episodes in children under age 5' (not 'parasitologically confirmed malaria cases'). The Independent Evaluation relies on national surveys (e.g. demographic and health surveys, multiple indicator cluster surveys, malaria indicator surveys and ACTwatch surveys), which use the denominator 'fever episodes in children under age 5' due to a lack of proper malaria diagnosis in many countries
[b]Price change was the indicator with the weakest empirical basis for setting a 1-year expectation
Source: Yamey 2012

Table 2. Characteristics of included studies

Study Design	Country Age group	Intervention[a]	Co-intervention	Outlet	Coverage	Data collection	Price subsidy	Duration
Cohen 2015 Cluster-RCT	Kenya All age groups	Subsidised AL	None	Drug shops	3 rural districts	Household surveys	80% to 92%	4 months
Kangwana 2011 Cluster-RCT	Kenya Children under age 5	Subsidised AL	Training of retail outlet staff Job aids Community awareness activities	Specialised and general drug stores[b]	3 rural districts (9 intervention and 9 control sublocations)	Household surveys	95%	1 year
Kangwana 2013 Cluster-RCT	Kenya Children under age 5	Subsidised AL	Training of retail outlet staff Job aids Community awareness activities	Specialised and general drug stores[b]	3 rural districts (9 intervention and 9 control sublocations)	Provider surveys Mystery shopper surveys	95%	1 year
Sabot 2009 Non-randomised cluster trial	Tanzania All age groups	Subsidised AL	Behaviour change communication (local radio advertisements, wall paintings, themed cultural shows)	Small drug shops (*duka la dawa baridi*)	3 rural districts (2 intervention and 1 control)	Outlet exit interviews Mystery shoppers Outlet audits Public facility audits	90%	1 year
Talisuna 2012[c] Non-randomised cluster trial	Uganda All age groups	Subsidised AL	Training of drug shop attendants Branding ('ACT with a leaf') Communication activities	Drug shops Private clinics Pharmacies	5 districts (4 intervention and 1 control)	Outlet exit interviews Outlet audits	95%	20 months

ACT = artemisinin-based combination therapy
AL = artemether-lumefantrine
NGO = non-governmental organisation

RCT = randomised controlled trial

[a] All studies: no ACT subsidy interventions were implemented in the control sites; malaria diagnosis was predominantly presumptive based on the presence of fever; exemption was granted for ACTs to be provided over the counter in the intervention sites; AL was repackaged in weight specific packs and marked with recommended retail prices to inform consumers the maximum amount they should pay

[b] Specialised drug stores (registered or unregistered pharmacies) and general stores (which sold medicines alongside general household goods)

[c] There was better availability of ACT in the public sector in the control district because of improvements in the procurement and distribution system, and supply by one NGO

Table 3. Percentage of children with fever who received ACT on the same day or following day of fever onset

Study	Design	Age group	Control		Intervention		Absolute difference (95% CI)	Relative effect (95% CI)
			Baseline	Follow-up	Baseline	Follow-up		
Kangwana 2011	Cluster-RCT	Children under age 5	5.3%	19.9%	4.7%	44.9%	25.0% (14.1% to 35.9%)[a]	NR
Talisuna 2012	Non-randomised cluster trial	Children under age 5	NR	2%	NR	18%	16.0%[b]	OR 10.0 (4.96 to 18.86)[c]

ACT = artemisinin-based combination therapy

CI = confidence interval

NR = not reported

OR = odds ratio

RCT = randomised controlled trial

[a] There was no correlation between socio-economic status and use of AL (p=0.875) or Tibamal, subsidised AL (p=0.745)

[b] Estimated assuming similar baseline values in control and intervention groups

[c] All age groups: patients in the intervention districts had a six-fold increase in ACT use relative to the control district (95% CI 4.22 to 8.44). Use of ACT was higher in the highest socio-economic status stratum compared to the lowest stratum (OR 2.4, 95% CI 1.72 to 3.35, p<0.001); estimated from available data

Table 4. National ACT subsidy programmes[a]

Country	Lead organisation	Launch year	Age group	Outlets	Coverage	Outcome: ACT availability	Outcome: ACT price
Cambodia	PSI	2002	All age groups	Pharmacies Drug shops	17 of 20 malaria-endemic provinces	At 1 year: very low in private facilities (22% stocked adult ACTs, 6% stocked child ACTs)	At 1 year: mean consumer price for adult ACTs (US$ 1.07) 70% higher than RRP (US$ 0.63)

Table 4. National ACT subsidy programmes[a] (*Continued*)

Cameroon	Government	2007	All age groups	Public and private health facilities	National	At 1 year: low availability of subsidised ACTs at public and private facilities, monotherapies widely available	At 1 year: adherence to RRP strong in only one province (Yaoundé Centre)
DRC	PSI	2006	Children < age 5	Pharmacies	Limited to some districts	At 2 years: ACTs available in 20.2% (public facilities), 25.8% (part 1 pharmacies), 20% (drug shops), 8.6% (other private outlets); 66.4% of facilities stocked non-ACTs, 47.8% stocked AMT	At 2 years: median price of ACTs: US$ 2.75 (public health facilities), US$ 2.29-4.58 (private facilities), US$ 3.89 (all facilities selling ACTs); ACT price 60% higher than price of the most common antimalarial in outlets selling ACTs
Madagascar	PSI	2003	Children < age 5	Pharmacies Private providers Community agents	National	At 5 years: 85.6% (public facilities), 47.5% (part 1 pharmacies), 20% (drug shops), 0.1-16.5% (other private outlets); 34.4% of facilities stocked non-ACT, 0.5% stocked AMT	At 5 years: median price of ACTs in facilities selling ACTs was US$ 4.04 (ACTs free in public facilities); ACTs 11.3 times more expensive than the most common antimalarial in outlets selling ACTs
Rwanda	PSI	2007	Children < age 5	Pharmacies	National	At 18 months: high	Data unavailable

Table 4. National ACT subsidy programmes[a] *(Continued)*

						ACT availability in private pharmacies (80-90% stocked child ACTs compared with 10% at baseline) ; monotherapies effectively banned	
Senegal	Government	2006	All age groups	Pharmacies	National	At 1 year: proportion of all facilities (public and private) stocking ACTs was 44.8% (adult dose), 58.2% (child), 46.3% (infant) ; monotherapies widely available	At 1 year: strong adherence to RRP in private outlets (observed mean retail price = US$ 1.34; RRP = US$ 1.31)

ACTs = artemisinin-based combination therapies
AMFm = Affordable Medicines Facility-malaria
AMT = artemisinin monotherapy
PSI = Population Services International
RRP = recommended retail price
[a]These programmes were rolled out before the 2010-11 AMFm pilot. Two countries - Cambodia and Madagascar - have also been included in the AMFm pilot phase and the results from the pilot are due to be reported in 2012
Source: Yamey 2012

Table 5. Percentage of retail outlets stocking ACTs

Study	Design	Age group	Control		Intervention		Difference (95% CI)
			Baseline	Follow-up	Baseline	Follow-up	
Kangwana 2011	Cluster-RCT	Children under age 5	0.5%	5.5%	2.4%	37.6%	31.9% (26.3% to 37.5%)
Kangwana 2013	Cluster-RCT	Children under age 5	0.5%	5.2%	1.5%	36.8%	31.7% (22.0% to 41.3%)

Table 5. Percentage of retail outlets stocking ACTs (*Continued*)

Sabot 2009	Non-randomised cluster trial	All age groups	1.0%	0%	0%	72.2%	72.2% (65.0% to 79.3%) [a]

ACT = artemisinin-based combination therapy
CI = confidence interval
RCT = randomised controlled trial
[a] Drug shops in population centres were more likely to stock ACTs than those in more remote areas (P < 0.001)

Table 6. Change in ACT price to patients

Study	Design	Age group	Outcome definition	Group	Baseline costs [a]	Follow up cost[a]	Data collection method
Kangwana 2011	Cluster-RCT	Under age 5	Median cost per ACT course	Control Intervention	US$ 1.08 (US$ 0.18) US$ 0.9 (US$ 0.15)	US$ 0.84 (US$ 0.14) US$ 0.24 (US$ 0.04)	US$ 0.84 per ACT course (IQR not estimable)[b,c]
Kangwana 2013	Cluster-RCT	Under age 5	Cost per ACT course (2 doses)	Control Intervention	NR 2 doses each US$ 2.46 and US$ 2.22	NR US$ 0.25	Not estimable
Sabot 2009	Non-randomised cluster trial	Under age 5[d]	Mean price for ACT Mean price for SP Mean price for AQ	Intervention	NR	US$ 0.19 US$ 0.51 US$ 0.86	Not estimable
Talisuna 2012	Non-randomised cluster trial	Under age 5	'Retail price for ACT'	Control Intervention	NR	"Maximum recommended retail price was within 10% of the recommended ACT price)"[e]	Not estimable

ACT = artemisinin-based combination therapy
AQ = amodiaquine
IQR = interquartile range
NR = not reported
RCT = randomised controlled trial
SP = sulphadoxine-pyrimethamine
[a] ACT treatment course: six tablets (for children aged 3-35 months) and 12 tablets (for children aged 36-59 months) - cost estimates based on ACT course for children aged 3-35 months

[b] Difference between baseline cost per ACT course (control group: US$ 1.08) and follow-up cost per ACT course (intervention group: US$ 0.24)
[c] At follow-up, 95.3% of caregivers in the intervention arm who bought subsidised AL said they purchased it at the recommended retail price of US$ 0.25. Of the eight not paying this price, three paid less than US$ 0.25 and five paid between US$ 0.31 and US$ 1.23
[d] All age groups: the mean price for ACTs (US$ 0.58) did not differ from the price of SP (US$ 0.67), but was higher than for AQ (US$ 0.48, P < 0.001)
[e] The recommended retail price for an adult course of treatment - US$ 0.47 - was not adhered to (the median price at the endline survey was US$ 1.96)

Table 7. ACT purchases, sales or market share

Study	Design	Age group	Outcome definition	Control		Intervention		Difference (95% CI)
				Baseline	Follow-up	Baseline	Follow-up	
Kangwana 2011	Cluster-RCT	Children < age 5	Total volume of AL dispensed at general stores	0%	0%	0%	63.0%	63%[a]
			Total volume of AL dispensed in specialised drug stores	1.0%	11.0%	0%	65.0%	55%[a]
Kangwana 2013	Cluster-RCT	Children < age 5	Total volume of AL sold to mystery shoppers	0.5%	1.8%	0%	25.4%	23.6% (18.7% to 28.6%)
Sabot 2009	Non-randomised cluster trial	Adults ≥ age 16	Total volume of ACTs purchased	0%	0%	1.0%	35.0%	35.3 % (29.8% to 40.7%)[b,c]
		Children < age 5	Total volume of ACTs purchased	0%	6.0%	0%	53.0%	8.9% (-0.5% to 18.2%)[d]
Talisuna 2012	Non-randomised cluster trial	All age groups	Total volume of ACTs purchased as a proportion of the total volume of all	NR	NR	43%	69%	NR

Table 7. ACT purchases, sales or market share (*Continued*)

			anti-malarials purchased via outlets					
			Total volume of ACTs purchased	1.8%	5.6%	0.8%	26.2%	21.6%[a,e]

ACT = artemisinin-based combination therapy
AL = artemether-lumefantrine
AQ = amodiaquine
CI = confidence interval
NR = not reported
RCT = randomised controlled trial
SP = sulphadoxine-pyrimethamine
[a]95% CI not estimable from the reported data
[b]There was no correlation between the socio-economic status of the consumer and the likelihood of buying ACTs
[c]Purchases of SP and AQ in the intervention districts declined from 68.0% to 51.0% and 26.0% to 11.0% respectively. Purchases of SP in the control district increased from 62.0% to 83.0% while for AQ declined from 33% to 16.0%
[d]Purchases of SP in the intervention districts decreased from 7.0% to 4.0% and remained the same at 9.0% in the control district. Purchases of AQ in the intervention districts declined from 91.0% to 36.0%, and from 91.0% to 36.0% in the control district
[e]The market shares for chloroquine and quinine were 5% and 24% respectively at the end of the pilot; Children less than five years had subsidised ACTs purchased for them more often than those aged above 5 years

Table 8. Use of older antimalarials

Study	Design	Age group	Outcome definition	Control		Intervention		Difference (95% CI)	Relative effect (95% CI)
				Baseline	Follow-up	Baseline	Follow-up		
Kangwana 2011	Cluster-RCT	Children < age 5	Use of antimalarial monotherapy[a]	29.8%	22.8%	39.0%	12.4%	-10.4% (-3.9% to -16.9%)	NR
Talisuna 2012	Non-randomised cluster trial	All age groups	Use of quinine	NR	44%	NR	37%	NR	OR 0.76 (0.53 to 1.08)

CI = confidence interval
NR = not reported
OR = odds ratio
RCT = randomised controlled trial
[a]amodiaquine, suphadoxine-pyrimethamine and quinine

APPENDICES

Appendix 1. EPOC review study designs

Suggested terms	Definition	Exclusions
Randomised controlled trial (RCT) OR, preferably, randomised trial	An experimental study in which people are allocated to different interventions using methods that are random	**Studies with only one intervention or control site** We recommend only including cluster randomised trials, non-randomised cluster trials, and CBA studies with at least two intervention sites and two control sites In studies with only one intervention or control site the intervention (or comparison) is completely confounded by study site making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables
Non-randomised controlled trial (NRCT) OR, preferably, non-randomised trial	An experimental study in which people are allocated to different interventions using methods that are not random	
Controlled before-after (CBA) study	A study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not	
Interrupted-time-series (ITS) study	A study that uses observations at multiple time points before and after an intervention (the 'interruption'). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time	**Studies that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention**
Repeated measures study (RMS)	An ITS study where measurements are made in the same individuals at each time point	

Appendix 2. Search strategies

CENTRAL, Cochrane Library

#1	MeSH descriptor: [Artemisinins] this term only and with qualifier(s): [Economics - EC, Supply & distribution - SD]	16
#2	MeSH descriptor: [Sesquiterpenes] this term only and with qualifier(s): [Economics - EC, Supply & distribution - SD]	5
#3	#1 or #2	18
#4	MeSH descriptor: [Artemisinins] this term only	657
#5	MeSH descriptor: [Sesquiterpenes] this term only	412

(*Continued*)

#6	(artemisinin or artemisinins or artemisinine or artemisinines or artemisin or artemisins or artemisine or artemisines or arteannuin or "ching hao su" or chinghaosu or ginghaosu or qinghaosu or quinghaosu or quinhaosu or sesquiterpenes or sesquiterpene or artemether or artemetero or artemetherum or artenam or arthemether or paluther or "co artem" or "co artemether" or coartem or coartemether or riamet):ti,ab,kw	1007
#7	#4 or #5 or #6	1007
#8	MeSH descriptor: [Cost Sharing] this term only	25
#9	MeSH descriptor: [Cost Allocation] this term only	16
#10	MeSH descriptor: [Drug Costs] this term only	1689
#11	MeSH descriptor: [Economics, Pharmaceutical] this term only	236
#12	MeSH descriptor: [Commerce] this term only	112
#13	MeSH descriptor: [Financial Management] this term only	14
#14	MeSH descriptor: [Budgets] this term only	65
#15	MeSH descriptor: [Rate Setting and Review] this term only	0
#16	MeSH descriptor: [Marketing of Health Services] this term only	43
#17	MeSH descriptor: [Social Marketing] this term only	137
#18	MeSH descriptor: [Financial Support] this term only	20
#19	MeSH descriptor: [Financing, Government] this term only	56
#20	MeSH descriptor: [Financing, Organized] this term only	22
#21	MeSH descriptor: [Fees and Charges] this term only	66
#22	MeSH descriptor: [Fees, Pharmaceutical] this term only	25
#23	(subsidy or subsidies or subsidis* or subsidiz*):ti,ab,kw	143
#24	(financing or funding):ti,ab,kw	2733
#25	(co next pay* or copay*):ti,ab,kw	87

(*Continued*)

#26	(pocket near/3 pay*):ti,ab,kw	13
#27	(voucher or vouchers):ti,ab,kw	272
#28	(financial or monetary) near/3 (support or assistance or help or aid or backing):ti,ab,kw	153
#29	(reduce* or lower* or limit* or share or shared or sharing or cut or cutting) near/3 (cost or costs or price or prices or payment* or spending or expenditure):ti,ab,kw	3383
#30	(drug or drugs or medicine* or medicament* or pharmaceutic*) near/3 (econom* or cost or costs or fee or fees or budget* or affordable or marketing):ti,ab,kw	5562
#31	(#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)	11904
#32	MeSH descriptor: [Private Sector] this term only	41
#33	MeSH descriptor: [Public-Private Sector Partnerships] this term only	8
#34	privat*:ti,ab,kw	2215
#35	retail*:ti,ab,kw	118
#36	(#32 or #33 or #34 or #35)	2324
#37	(#31 or #36)	14025
#38	(#3 or (#7 and #37)) in Trials	41

MEDLINE, OvidSP

#	Searches	Results
1	Artemisinins/ec, sd [Economics, Supply & Distribution]	178
2	Sesquiterpenes/ec, sd [Economics, Supply & Distribution]	42
3	or/1-2	187
4	Artemisinins/	4435

(*Continued*)

5	Sesquiterpenes/	11844
6	(artemisinin or artemisinins or artemisinine or artemisinines or artemisin or artemisins or artemisine or artemisines or arteannuin or ching hao su or chinghaosu or ginghaosu or qinghaosu or quinghaosu or quinhaosu or sesquiterpenes or sesquiterpene or artemether or artemetero or artemetherum or artenam or arthemether or paluther or co artem or co artemether or coartem or coartemether or riamet).ti,ab	9803
7	or/4-6	17929
8	"Cost Sharing"/	2004
9	"Cost Allocation"/	1945
10	Drug Costs/	12407
11	Economics, Pharmaceutical/	2550
12	Commerce/	18154
13	Financial Management/	15422
14	Budgets/	9877
15	"Rate Setting and Review"/	2474
16	Marketing of Health Services/	14065
17	Social Marketing/	2076
18	Financial Support/	3039
19	Financing, Government/	18745
20	Financing, Organized/	5804
21	"Fees and Charges"/	8196
22	Fees, Pharmaceutical/	1141
23	(subsidy or subsidies or subsidis* or subsidiz*).ti,ab.	4892
24	(financing or funding).ti,ab.	39957
25	(co pay* or copay*).ti,ab.	1557

(*Continued*)

26	(pocket adj3 pay*).ti,ab.	571
27	voucher?.ti,ab.	1052
28	((financial or monetary) adj3 (support or assistance or help or aid or backing)).ti,ab	4544
29	((reduce* or lower* or limit* or share or shared or sharing or cut or cutting) adj3 (cost? or price? or payment? or spending or expenditure)).ti,ab	38933
30	((drug or drugs or medicine? or medicament? or pharmaceutic*) adj3 (econom* or cost or costs or fee or fees or budget? or affordable or marketing)).ti,ab	11651
31	or/8-30	190651
32	Private Sector/	7513
33	Public-Private Sector Partnerships/	1171
34	privat*.ti,ab.	63212
35	retail*.ti,ab.	6482
36	or/32-35	73669
37	randomized controlled trial.pt.	384812
38	controlled clinical trial.pt.	88618
39	pragmatic clinical trial.pt.	109
40	multicenter study.pt.	179454
41	non-randomized controlled trials as topic/	11
42	interrupted time series analysis/	16
43	controlled before-after studies/	25
44	(randomis* or randomiz* or randomly or random allocat*).ti,ab	586424
45	groups.ab.	1414883
46	(trial or multicenter or multi center or multicentre or multi centre).ti	156461

(*Continued*)

47	(intervention* or controlled or control or compare or compared or (before adj5 after) or (pre adj5 post) or pretest or pre test or posttest or post test or quasiexperiment* or quasi experiment* or evaluat* or effect or impact or time series or time point? or repeated measur*).ti,ab	7687512
48	or/37-47	8282037
49	exp Animals/	17689330
50	Humans/	13699500
51	49 not (49 and 50)	3989830
52	review.pt.	1937353
53	meta analysis.pt.	53160
54	news.pt.	166715
55	comment.pt.	612267
56	editorial.pt.	369594
57	cochrane database of systematic reviews.jn.	10975
58	"comment on".cm.	612267
59	(systematic review or literature review).ti.	57183
60	or/51-59	6788530
61	48 not 60	5826774
62	3 and 61	76
63	7 and (31 or 36) and 61	192
64	62 or 63 [Artemisinin AND subsidy or private AND Methods]	216

Embase, OvidSP

#	Searches	Results
1	artemisinin/	4920
2	artemisinin derivative/	2097
3	sesquiterpene/	5893
4	sesquiterpene derivative/	2636
5	artemether/	2243
6	artemether plus benflumetol/	1792
7	(artemisinin or artemisinins or artemisinine or artemisinines or artemisin or artemisins or artemisine or artemisines or arteannuin or ching hao su or chinghaosu or ginghaosu or qinghaosu or quinghaosu or quinhaosu or sesquiterpenes or sesquiterpene or artemether or artemetero or artemetherum or artenam or arthemether or paluther or co artem or co artemether or coartem or coartemether or riamet).ti,ab	13715
8	or/1-7	20543
9	("Health Policy, Economics and management" or "36").ec.	467908
10	drug cost/	60104
11	commercial phenomena/	27879
12	drug marketing/	26589
13	social marketing/	2703
14	financial management/	102311
15	budget/	20306
16	fee/	14380
17	medical fee/	11634
18	pharmacoeconomics/	6029
19	(subsidy or subsidies or subsidis* or subsidiz*).ti,ab.	5621
20	(financing or funding).ti,ab.	47405

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21	(co pay* or copay*).ti,ab.	2279
22	(pocket adj3 pay*).ti,ab.	709
23	voucher?.ti,ab.	1226
24	((financial or monetary) adj3 (support or assistance or help or aid or backing)).ti,ab	5864
25	((reduce* or lower* or limit* or share or shared or sharing or cut or cutting) adj3 (cost? or price? or payment? or spending or expenditure)).ti,ab	50681
26	((drug or drugs or medicine? or medicament? or pharmaceutic*) adj3 (econom* or cost or costs or fee or fees or budget? or affordable or marketing)).ti,ab	18354
27	or/9-26	708923
28	public-private partnership/	2922
29	privat*.ti,ab.	76514
30	retail*.ti,ab.	7520
31	or/28-30	85785
32	Randomized Controlled Trial/	359286
33	Controlled Clinical Trial/	390010
34	Quasi Experimental Study/	2249
35	Pretest Posttest Control Group Design/	220
36	Time Series Analysis/	14920
37	Experimental Design/	10689
38	Multicenter Study/	114984
39	(randomis* or randomiz* or randomly or random allocat*).ti,ab	761973
40	groups.ab.	1772331
41	(trial or multicentre or multicenter or multi centre or multi center).ti	202335

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42	(intervention* or controlled or control or compare or compared or (before adj5 after) or (pre adj5 post) or pretest or pre test or posttest or post test or quasiexperiment* or quasi experiment* or evaluat* or effect or impact or time series or time point? or repeated measur*).ti,ab	9136496
43	or/32-42	9809305
44	(systematic review or literature review).ti.	67987
45	"cochrane database of systematic reviews".jn.	3776
46	Nonhuman/	4447094
47	or/44-46	4517005
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Science Citation Index and Social Sciences Citation Index (ISI Web of Science)

Citation search for all 4 included studies

Kangwana 2011

Kangwana BP, Kedenge SV, Noor AM, Alegana VA, Nyandigisi AJ, Pandit J, Fegan GW, Todd JE, Brooker S, Snow RW, Goodman CA. The impact of retail-sector delivery of artemether-lumefantrine on malaria treatment of children under five in Kenya: a cluster randomized controlled trial. PLoS Med 2011;8(5):e1000437.

Kangwana 2013

Kangwana BP, Kedenge SV, Noor AM, Alegana VA, Nyandigisi AJ, Pandit J, Fegan GW, Todd JE, Snow RW, Goodman CA. The effect of an anti-malarial subsidy programme on the quality of service provision of artemisinin-based combination therapy in Kenya: a cluster-randomized, controlled trial. Malar J 2013;12(81).

Sabot 2009

Sabot OJ, Mwita A, Cohen JM, Ipuge Y, Gordon M, Bishop D, Odhiambo M, Ward L, Goodman C. Piloting the global subsidy: the impact of subsidized artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. PLoS One 2009;4(9):e6857.

Talisuna 2012

Talisuna AO, Daumerie PG, Balyeku A, Egan T, Piot B, Coghlan R, Lugand M, Bwire G, Rwakimari JB, Ndyomugyenyi R, Kato F, Byangire M, Kagwa P, Sebisubi F, Nahamya D, Bonabana A, Mpanga-Mukasa S, Buyungo P, Lukwago J, Batte A, Nakanwagi G, Tibenderana J, Nayer K, Reddy K, Dokwal N, Rugumambaju S, Kidde S, Banerji J, Jagoe G. Closing the access barrier for effective anti-malarials in the private sector in rural Uganda: consortium for ACT private sector subsidy (CAPSS) pilot study. Malar J 2012;11: 356.

EconLit, ProQuest

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4	1 and 2 and 3	114

Health Management, ProQuest

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The Grey Literature Report from The New York Academy of Medicine Library

Combination of "artemisinin-based combination therapies, artemether, coartem, private sector, retail sector, retailers, drug shops, pharmacies, public-private sector partnerships, Affordable Medicines Facility - malaria, AMFm, subsidies, co-payment, financing, vouchers."

International Clinical Trials Registry Platform (ICTRP), WHO

Combination of "artemisinin-based combination therapies, artemether, coartem, private sector, retail sector, retailers, drug shops, pharmacies, public-private sector partnerships, Affordable Medicines Facility - malaria, AMFm, subsidies, co-payment, financing, vouchers."

ClinicalTrials.gov, NIH

Combination of "artemisinin-based combination therapies, artemether, coartem, private sector, retail sector, retailers, drug shops, pharmacies, public-private sector partnerships, Affordable Medicines Facility - malaria, AMFm, subsidies, co-payment, financing, vouchers."

Appendix 3. GRADE evidence profile: ACT subsidies combined with supportive interventions versus no subsidies

Effects of retail sector ACT subsidy programmes on ACT use, availability, price and market share
Population: Patients seeking treatment for suspected uncomplicated malaria
Settings: East Africa (Kenya, Uganda, Tanzania)
Intervention: Retail sector ACT price subsidies plus supportive interventions (retail outlet provider training, community awareness and mass media campaigns)
Comparison: Standard practice (no subsidies)

Quality assessment							Effect			GRADE quality of the evidence	Importance
Number of participants (studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With ACT subsidy	No ACT subsidy	Absolute difference (95% CI)		
ACT use (percentage of children under 5 years of age receiving ACT on the same day or following day of fever onset)											
2,662 (1 study)	Cluster-RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30.3% (19.4% to 41.2%)	5.3%	25% (14.1% to 35.9%)	⊕⊕⊕⊕ High	CRITICAL
ACT availability (percentage of outlets stocking ACTs for children under 5 years of age)											
1 study reported in 2 articles	Cluster-RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	32.4% (22.5% to 41.8%)	<0.5%	31.9% (26.3% to 37.5%)	⊕⊕⊕⊕ High	CRITICAL
ACT availability (percentage of outlets stocking at least one ACT for patients of any age)											
1 study	Non-randomised cluster trial	Serious [a]	No serious inconsistency	No serious indirectness	Serious [a]	None	72.7% (65.5% to 79.8%	0.5%	72.2% (65.0% to 79.3%)	⊕◌◌◌ [a] Very low	CRITICAL
ACT price (change in ACT price for children under 5 years of age) Median cost per ACT treatment course (6-12 tablets)											
1 study	Cluster-RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	US$ 1.08	US$ 0.24	US$ 0.84	⊕⊕⊕⊕ High	CRITICAL

(*Continued*)

ACT market share (volume of ACTs purchased as a proportion of all antimalarials purchased)											
1 study reported in two articles	Cluster-RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Range 25.4% to 65.0%	Range 0% to 11.0%	Range 23.6% to 63.0%	⊕⊕⊕⊕ High	CRITICAL
Use of older antimalarials (amodiaquine, sulphadoxine-pyrimethamine) among children under five years of age											
1 study	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	24.0% (17.5% to 30.5%)	34.4%	-10.4% (-3.9% to -16.9%)	⊕⊕⊕⊕ High	CRITICAL
Adverse effects (such as the number of people receiving ACTs who do not have malaria)											
None of the three studies of ACT subsidies combined with supportive interventions assessed adverse effect outcomes											

ACT = artemisinin-based combination therapy; RCT = randomised controlled trial
[a] Downgraded from low to very low due to high likelihood of selection bias (non-randomised design) and confounding by study site (only one control site included; results likely to be influenced by site-specific factors)

Appendix 4. GRADE evidence profile: ACT vouchers versus no subsidies

Effects of ACT price vouchers on ACT accessibility and targeting
Population: Patients seeking treatment for suspected uncomplicated malaria
Settings: Three rural malaria endemic districts in Western Kenya
Intervention: ACT subsidy (ACT vouchers to households; 80 to 92% subsidy)
Comparison: No subsidy (households received vouchers to purchase unsubsidised ACTs at the pre-AMFm retail price)

Quality assessment							**Effect**	**GRADE quality of the evidence**	**Importance**
Number of participants (studies)	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
ACT access (percentage of illness episodes treated with ACTs; all age groups; follow-up: 4 months)									

(*Continued*)

2, 789 households (1 study)	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Compared to an access rate of 19% in the control group, subsidies of 80% or more increased the likelihood that a malaria-like illness is treated with an ACT by 16 to 23 percentage points, that is, an 85% to 118% increase	⊕⊕⊕⊕ High	IMPORTANT
ACT targeting (percentage of ACT takers who are malaria positive; all age groups; follow-up: 4 months)									
2, 789 households (1 study)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Subsidies were associated with a high rate of overtreatment of malaria (only 56% of patients taking ACTs from the drug shop tested positive for malaria under the 92% subsidy)	⊕⊕⊕⊕ High	IMPORTANT

ACT = artemisinin-based combination therapy; AMFm = Affordable Medicines Facility-malaria

Appendix 5. Planned methods not used in the review

Unit of analysis issues

We will assess whether appropriate analysis was conducted to adjust for clustering in estimating precision of effects in cluster randomised trials and controlled before-after studies. Where clustering has not been accounted for, we will contact study authors, and if possible work with them to re-analyse the results using standard approaches incorporating measures of intra-cluster correlation coefficients (ICCs) (Higgins 2011). If re-analysis is not possible (e.g. due to lack of estimates of ICCs) we will report effect sizes without measures of precision.

Assessment of heterogeneity

For a subset of studies where meta-analysis is considered appropriate (e.g. where study designs and interventions are sufficiently similar), we will also explore heterogeneity using Chi^2 tests (Cochran's Q) and the I^2 statistic following guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions. Where heterogeneity is detected, we will explore and report plausible explanations for observed differences.

Data synthesis

We will consider combining results of subsets of studies using meta-analysis (random-effects method) where between-study differences are considered unlikely to explain variability in treatment effects. We will present data used in the synthesis alongside observed results using tables.

Where relevant, dichotomous data will be summarised using risk (or rate) ratios (with 95% confidence intervals (CIs)), while continuous data will be summarised using mean differences (with 95% CIs). Where relevant data can be obtained, inappropriately analysed interrupted-time-series' will be re-analysed using time series regression to account for secular trends and potential autocorrelation (in time) of data; the best fit pre-intervention and post-intervention line will be estimated using linear regression or autoregressive integrated moving average techniques (Lagarde 2012; Ramsay 2003).

Subgroup analysis and investigation of heterogeneity

We anticipate the number of eligible studies will be small so we have therefore limited the subgroup analysis. We will explore consistency of intervention effects in stratified analyses to examine whether the intervention indeed is pro-poor: participant socioeconomic status (SES; low versus high SES quintiles; we will consider the poor as those in the lower three SES quintiles or those living on less than $2 (purchasing power parity) per day (World Bank 2014). The following variables will be explored as possible explanations for heterogeneity:

- Study designs
- Nature of supportive interventions (e.g. malaria diagnostics)
- SES
- Coverage of interventions (sub-national versus national programmes)

Sensitivity analysis

We will conduct sensitivity analysis narratively or statistically (for a subset of studies where meta-analysis is considered appropriate) to investigate the influence of study quality.

CONTRIBUTIONS OF AUTHORS

NO, GY and PG designed the review methodology and undertook study identification and selection. NO extracted data. NO and PG assessed study quality and analysed data. NO prepared the first draft of the review. All authors participated in the interpretation of results and writing of the final manuscript.

DECLARATIONS OF INTEREST

GY led the San Francisco 'hub' of the Evidence-to-Policy initiative (E2Pi; www.e2pi.org), an independent, non-profit policy think tank based at the University of California, San Francisco during the writing of this review. E2Pi is funded by a core grant from the Bill & Melinda Gates Foundation, which was one of the funders of the pilot phase (Phase 1) of the AMFm. E2Pi was also contracted and funded by the Global Fund to estimate benchmarks of success for the AMFm Phase 1 (the final paper is published at http://www.theglobalfund.org/documents/amfm/E2PI˙EstimatingBenchmarksInAMFm˙Report˙en/). GY was on a fixed salary at UCSF.

PG is a member of the WHO Malaria Treatment Guidelines Panel that recommended a global shift to ACTs in 2006. PG is corresponding author of an analysis published in the Lancet in 2004 that provided some of the evidence underpinning the WHO decision.

NO has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- KEMRI-Wellcome Trust Research Programme, Kenya.

External sources

- Effective Health Care Research Consortium, UK.
- Cochrane Effective and Practice and Organisation of Care Group, Norway.
- Evidence-to-Policy initiative (E2Pi), Global Health Group, University of California, USA.
- UKAid (Department for International Development), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We intended to include only randomised trials, non-randomised trials (with at least two intervention and two control sites), controlled before-after studies (with at least two intervention and two control sites) and interrupted-time-series studies (Appendix 1). We, however, made a post-hoc decision to include two non-randomised cluster trials (Sabot 2009; Talisuna 2012) that compared intervention sites to only one control site (we downgraded the certainty of evidence in Sabot 2009 and acknowledged possible confounding associated with these designs).

We added adverse effects (unintended consequences of ACT subsidies) as a secondary outcome.

We did not consider two pre-specified secondary outcomes: availability of alternative antimalarial drugs in all facilities, private and public (including informal outlets); and prices of alternative antimalarial drugs (full adult or child courses; we prioritised direct outcomes presented in the summary-of-findings table).

A number of methods planned in the protocol were not implemented in the review. These methods could be relevant for future updates of this review and are summarised in Appendix 5.