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Malaria Medicines Landscape

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Abbreviations

ACT	artemisinin-based combination therapy
AETD	adult equivalent treatment dose
AL	artemether-lumefantrine
AMFm	Affordable Medicines Facility-malaria
AMT	artemisinin monotherapy
AMTR	Artemisinin Monotherapy Replacement Project
API	active pharmaceutical ingredient
AQ	amodiaquine
AQ+SP	amodiaquine+sulfadoxine-pyrimethamine
ASAQ	artesunate-amodiaquine
ASMQ	artesunate-mefloquine
ASPY	pyronaridine-artesunate
ASSP	artesunate sulfadoxine-pyrimethamine
AZCQ	azithromycin-chloroquine
A2S2	Assured Artemisinin Supply System
CAGR	compound annual growth rate
CHAI	Clinton Health Access Initiative
CQ	chloroquine
DFID	United Kingdom Department for International Development
DHA	dihydroartemisinin
DHA PPQ	dihydroartemisinin+piperaquine
DND*i*	Drugs for Neglected Diseases *initiative*
DRC	Democratic Republic of the Congo
EC	European Commission
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC	fixed-dose combination
FFCR	Four-Firm Concentration Ratio
FPP	finished pharmaceutical product
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMAP	Global Malaria Action Plan
GMP	good manufacturing practice
G6PD	glucose-6-phosphate dehydrogenase
ha	hectare
HIV	human immunodeficiency virus
INJAS	injectable artesunate
INN	nonproprietary name
IPTi	intermittent preventive treatment for infants
IPTp	intermittent preventive treatment for pregnant women
IQR	interquartile range
IVAS	intravenous artesunate
IVQ	parenteral quinine
K	thousand
kg	kilogram
LSHTM	London School of Hygiene & Tropical Medicine
M	million
MARC	Myanmar Artemisinin Containment Project
mg	milligram
mL	millilitre
MMK	Burmese (Myanmar) kyat
MMV	Medicines for Malaria Venture
MQ	mefloquine
nAT	non-artemisinin therapy
nQAACT	non-quality-assured ACT
oAMT	oral artemisinin monotherapy

P. falciparum	*Plasmodium falciparum*
PMI	United States President's Malaria Initiative
PPQ	piperaquine
PQ	primaquine
PQP	WHO Prequalification Programme
PQR	Global Fund Price and Quality Reporting
P. vivax	*Plasmodium vivax*
P4i	Procurement for Impact
QAACT	quality-assured ACT
QN	quinine
RAS	rectal artesunate
RDT	rapid diagnostic test
R&D	research and development
SMC	seasonal malaria chemoprevention
SP	sulfadoxine-pyrimethamine
SRA	stringent regulatory authority
SSA	semi-synthetic artemisinin
UNICEF	United Nations Children's Fund
US	United States
USD	United States dollar
WHA	World Health Assembly
WHO	World Health Organization
WMR	World Malaria Report

Executive summary

Introduction

This report is the second edition of the UNITAID *Malaria medicines landscape*. It is part of an ongoing initiative within UNITAID to describe and monitor the landscape for malaria commodities. It focuses on product, technology and market dynamics around antimalarial medicines, specifically artemisinin-based combination therapies (ACTs). It includes an overview of the current ACT technology and market landscape, and a high-level perspective on barriers to access and potential opportunities for market-based interventions to address these barriers. Information in this report was collected through a variety of methods, including desk research, literature reviews, dataset analyses and consultation with experts.

Public health problem

Despite the fact that malaria cases have decreased 30% since the peak number of cases in 2000 and mortality rates have decreased by 47%, malaria remains a substantial global health problem *(1)*. While gains have been made since the mid-2000s, the current trajectory is not sufficient to reach the World Health Assembly goals of 75% case reduction (to ~56 million [M] cases) and near zero deaths by 2015.

In 2013, there were an estimated 198M cases of malaria across 97 countries *(2)*. Africa has the highest burden and South-East Asia has the second-highest burden. Malaria mortality primarily impacts children, with 78% of cases occurring in children under 5 years old *(2)*. It is estimated that approximately 8M cases of uncomplicated malaria progress to severe malaria each year *(3)*. Although this represents only a minority of cases worldwide, reducing severe malaria is critical to reducing malaria mortality.

Commodity access issues

Significant progress has been made in scaling up access to ACTs since they were recommended in the 2006 World Health Organization (WHO) *Guidelines for the treatment of malaria*. By 2013, 79 of the 88 malaria endemic countries had adopted ACTs as the first-line treatment for *Plasmodium falciparum* and ACT delivery volumes have increased from 11M treatment courses in 2005 to 392M courses in 2013 *(2)*. Additionally, household surveys show that the proportion of febrile children treated with an ACT has increased in both the public and private sector, for example, in the private sector from 11% (~1–68%) in the earliest household surveys to 57% (~9–75%) in the most recent surveys *(2)*. However, as household surveys report that 40% of febrile children does not present for treatment, widespread access to ACTs remains an issue *(2)*. For example, the proportion of febrile children receiving an ACT for antimalarial treatment remains higher in the public sector than in the private sector where a large proportion of antimalarial medicine is purchased.

Given that a large proportion of malaria cases occurs in children under 5 years old, the availability of recommended antimalarials in formulations and dosage forms appropriate for use for children is a key consideration in evaluating access. In malaria specifically, it has been shown that crushing solid tablet

ACTs for use for children may make them unpalatable and lead to incorrect dosing *(4)*. There are limited options available for child-friendly medicines. Currently, as artemether-lumefantrine (AL) is the only taste-masked medicine available and for tenders that ask for dispersible AL products, there are limited options available *(5)*.

WHO updated severe malaria treatment guidelines in 2011, recommending injectable artesunate (INJAS) over quinine (QN) *(6)*. Uptake of this product was slow until 2012, but has increased notably in 2013. Between 2010 and 2013, approximately 12M vials of INJAS were procured, representing approximately 1.5–2M treatments for severe malaria in children under 5 years old *(7)*. This represents around 25% of the total volume needed to treat global annual cases. The uptake of rectal artesunate (RAS) for pre-referral treatment of severe malaria has been hindered by the absence of a WHO prequalified/stringent regulatory authority (SRA) product. The absence of a prequalified product may potentially threaten malaria mortality given that the risk of death from severe malaria is greatest in the first 24 hours.

Low coverage rates of chemotherapy interventions in sub-Saharan Africa impacts access to IPTp and IPTi despite the potential large population benefit e.g. around half of women attending antenatal clinics in 2011 received a second dose of SP for IPTp *(8)*, and the proportion of all pregnant women receiving a second dose of SP for IPTp was 22% *(8)*. Uptake of IPTi is also low but uptake may accelerate with new implementation guidance now available *(9)*. Since WHO released its policy statement on SMC in March 2012, several countries have initiated the process of incorporating SMC into malaria control policy. However current coverage remains low with only 3.4% of eligible children benefiting from this intervention in 2013.

Technology landscape

Currently available products

ACTs, non-artemisinin monotherapies (nATs) and artemisinin monotherapies (AMTs[1]) are used in the treatment of uncomplicated malaria *(10)*. nATs have been in the market for many years and are generally inexpensive, however, in specific geographic regions resistance has reduced their efficacy and they are no longer recommended for treatment of *Plasmodium falciparum* in the regions where resistance has been detected *(6)*. Chloroquine (CQ), however, is recommended as the first-line treatment of *Plasmodium vivax* in non-resistance settings where infections are still CQ sensitive and sulfadoxine-pyrimethamine (SP) is still recommended in intermittent preventive treatment for pregnant women (IPTp) and intermittent preventive treatment for infants (IPTi) *(6)*. Oral AMTs (oAMTs, e.g. artesunate; artemether; dihydroartemisinin) threaten the overall effectiveness of ACTs by selection for resistance. Despite WHO encouraging countries to prohibit the marketing and use of oral AMTs, they continue to be available in some settings. Injectable AMTs are still recommended for use in severe malaria, and intravenous artesunate (IVAS) is the recommended first-line treatment *(6)*.

ACTs are WHO recommended as the first-line treatment of *P. falciparum*. There are currently five different combinations available and recommended in the WHO *Guidelines for treatment of malaria (6)*:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (ASAQ)
- artesunate-mefloquine (ASMQ)
- artesunate sulfadoxine-pyrimethamine (ASSP) (in areas that are still SP sensitive)
- dihydroartemisinin + piperaquine (DHA PPQ).

ACTs are divided into quality-assured ACTs (QAACTs) and non-quality-assured ACTs (nQAACTs). Quality assurance, through the WHO Prequalification Programme (PQP) or by an SRA, is required before medicines can be purchased in the donor-funded market. There are 33 prequalified products from ten manufacturers with varying combinations and formulations, including 28 ACTs *(5)*.

1 AMTs include oral artemisinin monotherapies (oAMTs), injectable artemisinin monotherapies (INJAS) and rectal artemisinin monotherapies (RAS).

WHO recommends the use of fixed-dose combination (FDC) ACTs to treat malaria wherever possible because of the benefits they offer with respect to patient compliance and delayed development of parasite resistance *(6)*. AL, DHA PPQ, ASMQ and ASAQ are all available as FDCs. There are currently 22 prequalified FDC ACTs *(5)*. Pyronaridine-artesunate (APSY) has also been approved under the Article 58[2] scheme for one-time use in areas of high resistance. WHO identifies flexible solid dosage forms as the most suitable form of medicine for children under 5 years old in developing countries, including for the treatment of malaria *(11)*. Two products (from Novartis Pharma [hereinafter Novartis] and Ajanta Pharma Ltd [hereinafter Ajanta]) are prequalified for dispersible formulations of AL *(5)*.

Pipeline products

A strong research and development (R&D) pipeline of antimalarial medicines exists, including products to cure *P. vivax* hypnozoites (liver-stage infections) provide a single-dose treatment of malaria, offer paediatric formulations of existing ACTs and expand the range of medicines that can be used for chemoprevention *(12)*. Products in late-stage development that show high potential include *(13)*:

- artesunate intrarectal (Registration)
- amodiaquine + sulfadoxine-pyrimethamine (AQ + SP; Registration)
- arterolane maleate + PQP (Registration by the WHO PQP or SRA)
- tafenoquine (Phase III)
- APSY dispersible for paediatric use (Phase III)
- DHA PPQ for paediatric use (Phase IIb/III)
- OZ439 (Phase IIb)
- KAE609 (Phase IIa)
- KAF156 (Phase IIa).

Azithromycin-CQ (AZCQ) (Phase III) is no longer under development. With the development of this product ceasing, there are currently limited alternative therapy options in the pipeline specifically for use in IPTp *(13)*. Co-trimoxazole [Phase II]) is a potential candidate for IPTp but has limitations including daily administration and safety concerns in HIV-positive populations when taken in combination with SP. Piperaquine based combinations are also being evaluated. There are no drugs in development for use in IPTi, though some studies have recently taken place evaluating DHA PPQ for IPTi.

Market landscape

Since 2006, considerable efforts have been made to scale up access to ACTs. The volume of procured QAACTs has increased rapidly over time, from 11M treatment courses in 2005 to 392M in 2013. However, growth of the donor-funded portion of the ACT market is beginning to plateau. The market share of ACT volumes procured in the donor-funded market has been consistently greatest in the African Region: in 2012, 97% of ACTs procured by donors was for Africa.

The market share of ACT volumes procured in the donor-funded market remains highly concentrated on two FDC ACTs – AL and ASAQ – which accounted for 74% (290M treatments) and 26% (100M treatments) of ACTs delivered in 2013, respectively. FDCs now account for almost 100% of ACTs procured, equalling an approximate 80% growth over five years.

Between 2005 and 2012, the number of child-packs of AL delivered to the public and private sector has increased. In 2012, 68% of all AL procured was for children, but of this only 26% was the dispersible formulation. For ASAQ/AS + AQ, the proportion of child-packs of both FDC and co-blister has been more in favour of child-packs since 2008.

2 Article 58 is a procedure that allows the EMA's Agency's Committee for Medicinal Products for Human Use to scientifically assess medicines that are intended for markets exclusively outside the European Union and specifically used to prevent and treat diseases of major public health interest. In consultation with WHO, a scientific opion is adopted.

The AL market is becoming increasingly distributed across prequalified suppliers. In 2008, Novartis was the first and only SRA manufacturer and accounted for the greatest share of AL (85%) procured in the donor-funded market. By 2012, three generic manufacturers together had secured 73% of the AL market procured by international donors, compared to 27% for Novartis. While 2013 data are incomplete, they suggest that the Novartis market share decreased to around 12%.

In 2012, Sanofi accounted for approximately 98% of ASAQ volumes procured, and only one other manufacturer, Ipca Laboratories Ltd (hereinafter Ipca), received purchases from donors. Between June and November 2012, six more FDC ASAQ became prequalified by the WHO prequalification Program from two manufacturers (Ipca and Guilin Pharmaceuticals Co. Ltd (hereinafter Guilin)), however, these still represent very small portions of the market.

Although data available for 2013 are incomplete, the procurement price of AL between 2012 and 2013 decreased from US$ 1.59 (US$ 0.01–2.33) in 2012 to US$ 1.40 (US$ 1.17–2.15). The median price of 3x2 ASAQ has declined since first becoming prequalified in October 2008, from US$ 1.09 (US$ 0.69–1.09) in 2008 to US$ 0.94 in 2013.

A significant portion of market growth in recent years has been attributable to the Affordable Medicines Facility-malaria (AMFm) pilot, through which 122M ACTs were delivered through the private sector in 2012. In 2014, AMFm was integrated into the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) core grant mechanism. Going forward, the extent to which countries will utilize the Private Sector Co-payment Mechanism (Co-payment Mechanism) (formerly AMFm) to supply ACTs through the private sector at a subsidized price remains uncertain.

While not yet reflected in procurement transaction data, a key change to the market since the publication of the first edition of the *Malaria medicines landscape* in 2013 has been the reform of the Global Fund procurement model. Key elements of the new model include: (i) joint ACT forecasting between the Global Fund and PMI *(14)* and two-year forecasts for suppliers; (ii) longer-term contracts with suppliers established through a tender process; and (iii) volume guarantees for suppliers. A tender conducted under this new model took place in 2014, which is likely to impact both market share and price in the near future (a savings of 32% is estimated as a result of the 2014 tender).

At the facility level, ACT prices remain substantially higher than nATs. For example, in Uganda, the median patient price of ACTs was US$ 2.02, compared to US$ 0.51 for SP or US$ 0.65 for CQ. In addition, nATs still represent a significant proportion of total antimalarials distributed in both the public and private sectors. For example, in Nigeria, nATs represented 62% and 33% of all antimalarials distributed in the private and public sectors, respectively.

There is currently only one WHO prequalified IVAS product available (Guilin) for the treatment of severe malaria. Until 2012, uptake of INJAS was low but has continuously increased since WHO prequalification: quantities procured in 2012 were less than 25% of the total needed to treat global annual cases. Approximately 12M vials (roughly 1.5–2M treatments for children under 5 years old) were procured out of an estimated 48–50M vials that would be needed to treat global annual cases. Access to pre-referral treatment of severe malaria is also hindered by the lack of a WHO prequalified/SRA-approved product, although efforts are under way to have an RAS product submitted for WHO prequalification in 2015.

Both the WHO South-East Asia Region and Western Pacific Region are particularly important in the supply of antimalarial medicines: six of the nine manufacturers that supply WHO prequalified medicines are based across both of these regions. Five of these are based in India and the other in China. Furthermore, the vast majority of the natural artemisinin supply is grown both the WHO South-East Asia Region and Western Pacific Regions. Access to quality ACTs in both of these regions remains a problem even though there is substantial potential within these regions to expand quality ACT manufacturing. A key challenge will be to improve the quality of ACTs manufactured in this region to international standards without impacting the user price.

The proportion of the donor-funded ACT market directed to the WHO South-East Asia Region and Western Pacific Region has increased in the past two years. In 2012, 13.9% of ACT treatment courses was procured for these regions, compared to only 4.2% in 2011. While data for 2013 are incomplete, they suggest a further increase to nearly one quarter of all ACTs procured through donor funding.

The volumes of PQ procured with donor funding have increased significantly in recent times, particularly in the South-East Asia Region and Western Pacific Region. In 2012, 33M treatment courses were procured, compared to 4M in 2011. Data from 2013, while incomplete, suggest a further increase to at least 41M treatment courses.

The supply of agricultural artemisinin has been volatile in the past decade due to a number of factors, including the long lead times and uncertain demand forecasts, resulting in price volatility and cycles of undersupply and oversupply. Artemisinin prices fell in 2012, albeit from an artificially high level in the last quarter of 2011 and the beginning of 2012. Current reported spot market prices are around US$ 250/kg, which is less than the break-even point for artemisinin extractors (Figure 53). Low prices could impact the quantity of *Artemisia annua* harvested in 2014 as well as future plantings. A significant decline in cultivation in 2015 could lead to an artemisinin shortage and/or high market prices in 2016–2017.

The first delivery of ACTs produced with semi-synthetic artemisinin (SSA) to endemic countries occurred in 2014. SSA provides a complementary source of non-seasonal artemisinin with a shorter lead time, which could contribute to stabilizing the artemisinin market. The current price estimate, based on a "no profit, no loss" model, is approximately US$ 400/kg at high capacity usage. The total production capacity of SSA is approximately 60 tonnes per year, which is currently not being fully utilized due to the lack of ACT manufacturers (beyond Sanofi, the manufacturer of SSA) that have gone through the WHO prequalification process needed to supply SSA-based ACTs.

Market shortcomings for malaria medicines

Table 1. Summary of market shortcomings for antimalarial medicines

Category	Shortcoming	Reason
Availability	No alternative to PQ for treating the liver stage of *P. vivax*.	■ Research is ongoing (e.g. tafenoquine), but products are not yet available. ■ 8-aminoquinolines are the only class of drugs known to have anti-hypnozoite activity and all suffer from safety issues, especially G6PD-deficient patients. ■ Lack of incentives for manufacturers to invest in R&D due to uncertainties around future demand, market size and return on investment.
	No single-dose malaria medicines to reduce the current three-day dosing requirements of ACTs.	■ Two candidates for a single-dose cure for uncomplicated *P. falciparum* malaria are under development, but earliest availability is 2018. ■ Lack of incentives for manufacturers to invest in R&D due to uncertainties around future demand, market size and return on investment.
	Limited alternatives to SP for ITP.	■ The development of AZCQ ceased in late 2013. There are currently limited alternative therapy options in the pipeline specifically for use in IPTp (co-trimoxazole (Phase II) is a potential candidate for IPTp but there are concerns with daily administration and safety in HIV-positive populations when taken with SP. Piperaquine based combinations are currently being evaluated, as well as DHA PPQ for intermittent screening and treatment (ISTp)). ■ There are no drugs in development for use in IPTi, however, studies evaluating the efficacy of DHA PPQ have recently taken place.

Affordability	Varying ACT retail prices in countries where price subsidies have not been applied.	■ High ACT manufacturing costs, including expensive and variable raw material prices. ■ Despite an increase in the number of prequalified ACT suppliers in recent years, market share is still highly concentrated by a few manufacturers. ■ As private sector subsidies are no longer additional funding but instead are part of Global Fund country allocations, scope for expansion may be limited.
Quality	Although recently increasing, low private sector market share and availability of QAACTs, particularly of non-AMFm countries (which represent the majority of countries in sub-Saharan Africa and the Greater Mekong subregion).	■ Low demand for QAACTs in the out-of-pocket market due to higher cost (see Affordability above). ■ QAACT manufacturers have tight production capacity with low incentive for expansion due to uncertain future demand. ■ Lack of visibility on future orders and variability of raw materials prices. ■ Complexity and cost of prequalification process. ■ Weak and/or unharmonized regulatory standards in many endemic countries, which limit incentives for manufacturers to meet international drug quality standards. ■ Majority of QAACTs depend on agricultural artemisinin. The quality if the artemisinin extraction process greatly influences the API yield (i.e. the amount of impurities present in a yield), and has an overall effect on QAACT prices.
	High quality-control failure rates among non-prequalified ACTs.	■ Insufficient and weak local quality control, enforcement and low awareness. Weak regulatory systems that allow significant market penetration by substandard or non-proven therapies. ■ Technologies for on-the-spot quality control not widely used.
Acceptability/ adaptability	While ACTs are more widespread than in 2002–2006, their usage is still below that of non-recommended therapies.	■ Complex dosing regimen of ACTs compared to single-dose conventional therapies that are no longer recommended for use or are omitted from treatment guidelines in malaria endemic areas. Complex ACT dosing regimens has been cited by patients and providers as a key acceptability barrier to ACTs. ■ Limited palatable medicines for children, both for curative and preventive drug regimens.

Delivery	Risk of supply shortages and/or high market prices for artemisinin.	■ The long, complex and multi-actor upstream supply chain contributes to a volatile market and limits market responsiveness to sudden changes in demand. ■ SSA could help to stabilize the supply and price of artemisinin, but currently the 60 tonnes capacity is not being fully utilized. As demand for SSA increases, there may be supply risks associated with the fact that it is a single-source product with a defined production capacity. SSA could also have a destabilizing effect on the market if shortages arise from growers and extractors of plant-based artemisinin exiting the market.
	Long lead times to gain necessary regulatory approvals to bring new antimalarials to market.	■ Limited regulatory harmonization and capacity across countries and regions to register products. It should be noted that the East Africa Medicines Regulatory Harmonization Programme (EAC-MRH) *(15)*, which aims to harmonize medicines regulation systems and procedures in accordance with national and international policies and standards, is now operational and launched a request for proposals (RFP) for harmonized registration in December 2014. This represents an important step forward in streamlining the regulatory approvals process for medicines, including antimalarials.
	Limited diversification of first-line ACT treatments with continued dominance of AL and ASAQ.	■ While other prequalified ACTs are available, their use is limited due to a number of factors, including safety labels – e.g. the EMA label of DHA PPQ required ECG monitoring during treatment, higher costs and sole suppliers.
	Public sector stockouts of prequalified ACTs.	■ Delays in funding disbursements. ■ Demand uncertainty/unpredictability and episodic diversion from the public subsidized sector to the private for-profit sector. ■ Suboptimal in-country planning and supply management and forecasting as well as uncertainty on the effect of diagnostics on treatment demand (see below).
	Low availability of ACTs in private sector facilities, particularly outside AMFm countries.	■ Low private sector demand for ACTs, largely due to high ACT prices compared to non-artemisinin treatments. ■ Habitual purchasing behaviour; lack of awareness and education at the provider and consumer levels about the problems associated with the use of older (increasingly ineffective) antimalarial therapies.
	High rates of overtreatment with all antimalarials, including ACTs, particularly in the private sector.	■ Historical practice of presumptive treatment of fever with antimalarials. ■ Low uptake of quality, point-of-care diagnostic tools for malaria (e.g. RDTs), particularly in the private sector where presumptive dispensing prevails.
	Low uptake of INJAS for severe malaria until 2012, though an upward trend has been observed from 2013.	■ Inadequate advocacy, education and training, including poor communication around the superior efficacy, leading to poor acceptance by patients and providers. ■ High treatment prices (three times more than injectable QN) due in part to low volumes and lack of competition. ■ Only one prequalified product (Guilin), with buyer concerns over single-prequalified supplier (if the single supplier cannot meet the demand, then there is potential for stockouts). ■ Commercial interests around injectable QN, which is often procured from local manufacturers; behavioural issues around QN use.
	Unpredictable future demand.	■ Uncertainties around future funding, rate of scale-up of malaria RDTs and its impact, and the overall impact of prevention and control efforts on malaria epidemiology.

Market shortcomings for paediatric antimalarial medicines

Table 2. Summary of market shortcomings for paediatric malaria medicine

Category	Shortcoming	Reason
Availability	No RAS product has been WHO prequalified or approved by an SRA for the pre-referral treatment of severe malaria.	■ Work is under way to submit a dossier for RAS to the WHO PQP in 2015, but a decision is only expected in 2016. ■ Once an RAS product becomes available, there are likely to be market (e.g. single-source) and operational (e.g. community-based delivery) challenges to the scale-up of this product.
Availability	No taste-masked, dispersible AQ+SP tablets which would facilitate the administration of SMC; no alternative to AQ+SP for SMC which limits the use of this intervention to the Sahel region.	■ A prequalified, dispersible SMC regimen is not yet available. ■ Limited incentive for manufacturers to invest in R&D due to uncertainties around both future market size and return on investment for a low-margin product.
Quality	Limited supply of quality-assured SP and AQ, which has led to supply shortages of the AQ+SPSMC regimen, both in co-blister and bulk tablets, for the 2015 transmission season.	■ Rapid upsurge in demand for SP beyond supply-side forecasts ■ ASSP still prioritized in some countries though no longer promoted as treatment by WHO ■ The closing of a Chinese source of sulfadoxine API in 2014. ■ Parallel loss of Guilin API production capacity for both SP & AQ due to manufacturing site change combined with plant downtime needed to optimize process for SP to meet PQ standards. Late discovery of AQ API shortfall ■ Many generic versions of SP available, but with high quality control failure rates (28% across six sub-Saharan African countries).
Acceptability/ adaptability	Low uptake of child-friendly ACT formulations for children under 5 years old (26% of dispersible AL was procured in 2012).	■ Only one prequalified manufacturer of dispersible tablets until December 2012. ■ Although increased demand of dispersible AL has been reported (12M AL treatment courses were procured in the donor funded market in 2010 increasing to 33M in 2012), when compared to the demand of solid oral tablet for infants there is variable demand for dispersible tablets by different providers and caregivers. ■ Multiple non-prequalified paediatric formulations (e.g. suspensions) of unknown quality are available in local markets.

Potential opportunities for market interventions

- Ensure rational and appropriate use of ACTs and improve access to appropriate diagnostics testing and treatment, i.e. getting the rapid diagnostic test (RDT)/ACT ratio right
  Market shortcoming addressed: Delivery
- Support the sale of QAACTs at an affordable retail price that does not require a subsidy
  Market shortcomings addressed: Affordability, Quality, Delivery
- Monitor the antimalarial R&D pipeline and facilitate market entry and scale-up of important, cost-effective products
  Market shortcoming addressed: Availability
- Encourage further research for to develop new products for IPTp
  Market shortcoming addressed: Availability
- Support market approaches that strategically target scaling up medicines for *P. vivax* malaria and scaling up the testing requirements (e.g. G6PD testing) associated with certain therapies
  Market shortcoming addressed: Availability, Delivery

- Maintain and communicate up-to-date information on the future demand for ACTs
  Market shortcoming addressed: Delivery
- Collect and disseminate information on artemisinin supply and demand, and evaluate the need for additional targeted interventions to stabilize artemisinin prices and supply
  Market shortcomings addressed: Affordability, Delivery
- Encourage the uptake of INJAS for the treatment of severe malaria
  Market shortcomings addressed: Affordability, Delivery
- Catalyse the market for artesunate suppositories for the pre-referral treatment of severe malaria
  Market shortcomings addressed: Quality, Delivery
- Support a competitive market for child-friendly ACT formulations, especially for children under 5 years old
  Market shortcoming addressed: Acceptability/adaptability
- Support market intelligence on other antimalarial medicines
  Market shortcoming addressed: Delivery
- Support the scale-up of technologies to detect counterfeit and substandard medicines
  Market shortcoming addressed: Quality
- Support the scale-up of ASPY for artemisinin resistance containment
  Market shortcoming addressed: Availability, Delivery
- Explore whether targeted interventions are needed to scale up the use of newer, less widely used ACTs
  Market shortcoming addressed: Availability, Acceptability/adaptability
- Support increased global production capacity of quality-assured AQ + SP for use in SMC, and actively coordinate among funders/implementers of SMC programs to ensure timely information on overall demand.
  Market shortcoming addressed: Quality, Delivery

1. Introduction

This report is the second edition of the UNITAID *Malaria medicines landscape*. This landscape reflects an initiative within UNITAID to describe and monitor the disease, technology and market landscapes for commodities used in the prevention, diagnosis and treatment of malaria. This report focuses on malaria medicines, particularly antimalarial artemisinin-based combination therapies (ACTs), including the active pharmaceutical ingredients (APIs) and the artemisinin landscape. While ACTs are the focus, this report also covers other malaria medicines, for example, injectable artesunate (INJAS) for severe malaria.The UNITAID *Malaria diagnostics technology landscape* and the *Malaria vector control technology and market landscape* complement this report.

The primary objectives of this landscape are:

- to describe the current landscape of available antimalarial medicines as well as those in the research and development (R&D) pipeline ("technology landscape");
- to describe key characteristics of the malaria medicines market as well as trends over time ("market landscape");
- to identify market shortcomings and resulting opportunities to improve access through market-based approaches;
- to serve other stakeholders and the broader global health community interested in understanding the market for malaria medicines.

The *Malaria medicines landscape* is structured as follows:

Section 2: The methods section outlines the primary objectives of the landscape and describes the methods used to conduct the analysis.

Section 3: The public health problem and commodity access issues sections provide an overview of malaria disease burden and trends, as well as current treatment recommendations, the role of ACTs and the current levels of access for malaria medicines.

Section 4: The medicines technology landscape describes the currently available product technologies that are useful tools to treat malaria, as well as the medicine technology pipeline, looking at priorities for new medicine development that will address the current limitations of ACTs and other technology shortcomings.

Section 5: This section analyses the current ACT market, including the market size and market share of ACTs over time. It looks at the availability of medicines at facilities and at international quality-assured procurement practices. The malaria medicines market is also considered at a regional level, specifically assessing the procurement practices of the market in sub-Saharan Africa, where the burden of malaria is greatest, and Asia where the number of people at risk of malaria is high and resistance to effective therapy has been detected. Trends in the paediatric and severe malaria markets also are reviewed, and a high-level overview of the current market of chloroquine (CQ), primaquine (PQ) and quinine (QN) is provided. The landscape of the artemisnin market is also discussed in this section.

Section 6: This section identifies market shortcomings and their reasons. Findings from the market landscape are co-presented and explained in terms of the existing market barriers impeding access to malaria medicines. The shortcomings are arranged by five categories: quality; availability; affordability; acceptability/ adaptability; and delivery.

Section 7: The opportunities for market interventions section describes active, potential and exploratory market interventions to improve access to malaria medicines in the near and long term.

2. Methodology

Information in this report was collected in a variety of ways, including desk research, literature reviews, data analyses and through consultation with experts either individually or at meetings/conferences. A description of key data sources and methods is described below.

Medicines technology landscape methods

To obtain information for the technology landscape, a diverse set of publicly available sources was accessed to identify currently available products and products in the development pipeline. The World Health Organization (WHO) *Guidelines for the treatment of malaria* and the WHO Prequalification Programme (PQP) were used to describe the currently available products included in the technology landscape.

Review of published and unpublished reports (25 in total, Table 4), Google searches and the product development partnership Medicines for Malaria Venture (MMV) website were accessed for any information regarding antimalarial pipeline products. The MMV Interactive R&D Portfolio available from their website was used as the primary source to inform new antimalarial medicines under development. This tool reflects the global malaria portfolio and is updated quarterly. Interviews with MMV also took place to discuss the information available on their website and to learn of any new product developments that should be further investigated and described in the landscape.

Medicine market landscape methods

For the market landscape, a four-pronged approach was employed to retrieve evidence related to the market dynamics of malaria treatment commodities. The main approaches were literature reviews and data collection and analysis, which were supplemented by desk research and limited key informant consultation.

2.1 Literature review

First, a literature search was carried out to retrieve published and unpublished academic papers and grey literature that specifically referenced market drivers of antimalarial medicines. In order to identify published studies that were relevant to market-related aspects of malaria treatments, several MeSH terms on PubMed and OVID Medline were used. Key terms such as anti-malar*, treat*, med*, ACT* price, demand, supply, quality and market were used in conducting the initial search. Appropriate Boolean operators also were utilized to narrow the search and deliver more specific results, for example, anti-malarial* AND treat* OR med* AND market (Table **3**). Moreover, Google scholar returned grey literature included in this landscape, and also helped to crosscheck any missed academic publications. The reference lists of annotated publications also were reviewed to further ensure that any relevant publications were not missed.

Table 3. PubMed and OVID Medline: searched MeSH key terms

PubMed and OVID with Boolean operators						
malar*med*	AND	Artemisinin*	AND	econ*	AND	Publication date Jan 2013 – Jun 2014
				OR		
				market*		
				OR		
		OR		market share		
OR				OR		
				supply		
				OR		
		combination*		demand		
				OR		
malar*treat*				Access*		
				OR		
		OR		commod*		
				OR		
				Price*		
OR				OR		
		Combination therap*		Cost		
				OR		
				Drug cost		
				OR		
Anti-malar*		OR		Afford*		
				OR		
				qual*		
				OR		
		ACT*		private		
				OR		
				public*		

Selection criteria

As a comprehensive literature review was completed by UNITAID in preparation for the first edition of the *Malaria medicines and technology landscape*, in 2013, the search for this report was limited to English-language literature published between January 2013 and June 2014. First, the retrieved research studies that reported on key general market indicators such as price, market share, product availability and quality were selected for use. Preference was given to studies that reported data from more than two countries as they were considered to provide a broader analysis of the market. These studies were thus categorized as "general" in Table 4. To allow a more targeted market analysis, the remaining results were then filtered by region (west and central Africa; rest of Africa; Asia; rest of World). The regional divisions were determined by following the United Nations composition of macro geographical (continental) regions, geographical subregions, and selected economic and other groupings *(16)*. Single-country data for the regional analysis were included. Studies that were not specific to key market indicators, but were relevant for other sections of the landscape such as the technology landscape were excluded and put aside for use in their appropriate section. Finally, consumer demand-side issues such as willingness-to-pay were also excluded, but

were considered as supplementary information for insight into the broader market issues associated with commodity availability and access.

Publications were reviewed using the following strategy. First, publications retrieved through various search engines were screened according to their titles. Publication titles that did not refer to the market of malaria treatments were excluded. The publications that passed the initial stage were then screened for relevance according to their abstract. Publications that clearly articulated an emphasis on malaria medicine markets were then read and reviewed by two researchers. Independent cross-validation between the researchers ensured that the publications selected were directly related to malaria medicine markets and any discrepancies were resolved by consensus. Studies that alluded to methods, service delivery and commentaries on social and behavioural determinants of treatment uptake and acceptance were not included.

Results

Literature searches for the medicines landscape returned 147 relevant articles between January 2013 and June 2014. The search retrieved 79 multicountry and 68 single-country publications for malaria medicine. After the selection criteria were employed, 33 publications were found to present comprehensive findings on the overall malaria medicine market (Table 4). By topic area, the breakdown of the 33 studies shows: 7 related to artemisinin, 8 related to AMFm and 3 on the supply and demand of ACTs. Eight articles were found relating to quality, 4 studies were found for the market dynamics in the private sector and 2 were found regarding prices.

Table 4. Breakdown of results by relevant landscape section, category and regional breakdown

Landscape section	Category	Regional breakdown					
		General	West & central Africa	Rest of Africa	Asia	Rest of world	Total
Market landscape	Artemisinin	7					7
	AMFm	8	3	7			18
	Supply & demand	3	4	3	2	1	13
	Quality	8	2	1	1	2	14
	Private sector	4		2			6
	Price	3			1		4
	Total	33	9	13	4	3	62
Technology landscape	API & new technology	25					25
	Resistance	7	4	2	2	1	16
	Preventive medicines	6	2		1		9
	Subtotal	38	6	2	3	1	50
Commodity access & general background information	Treatment & policy guidelines	4	10	3	3	3	23
	Access/use	4	3	5			12
	Subtotal	8	13	8	3	3	35
Overall total		79	28	23	10	7	147

2.2 Data collection and analysis

Data presented in this landscape were retrieved from the following sources: (i) a collection of published reports publicly available on the Internet; ACTwatch reports and presentations; and (ii) the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) Price and Quality Reporting (PQR) transactional database aggregated with AMFm data.

Published reports

Published global malaria reports were retrieved through desk research and Internet searches. The reports from which data were found and presented in this landscape include: the annual WHO *World malaria report* (WMR); WHO *Guidelines for the treatment of malaria*; reports from the Global Malaria Programme policy recommendations; and the Roll Back Malaria Partnership. Experts from WHO were then contacted to obtain various pieces of global data regarding the volumes of ACT deliveries by sector, region and population groups.

Data from published UNITAID reports, the Assured Artemisinin Supply System (A2S2) *(17)*, the Demand Forecast for Artemisinin-based Combination Therapies, and ICF International *(18)* and the London School of Hygiene & Tropical Medicine (LSHTM) Independent Evaluation of the AMFm Phase 1 also are included in this landscape.

ACTwatch

ACTwatch is a multicountry research project implemented by Population Services International *(19)*. Standardized tools and approaches are employed to provide comparable data across countries and over time. Project countries include: Benin, Cambodia, the Democratic Republic of the Congo (DRC), Kenya, the Lao People's Democratic Republic, Madagascar, Myanmar, Nigeria, Thailand, Uganda, United Republic of Tanzania (currently mainland only, previous work in Zanzibar), Viet Nam and Zambia. The project is currently funded by the Bill & Melinda Gates Foundation, UNITAID and the United Kingdom Department for International Development (DFID) *(20)*. ACTwatch data include population-based household and outlet surveys conducted in 2009–2010, 2011 and 2013. Household surveys are conducted among consumers to document fever treatment-seeking behaviour. The surveys investigate the extent to which health care was sought, as well as common sources of care received. From 2008 through 2012, ACTwatch conducted 14 household surveys focused on fever treatment-seeking behaviour. Reports are available at www.actwatch.info, and a peer-reviewed publication has appeared in *Malaria Journal (21)*. Outlet surveys entail collecting quantitative data from all outlets and providers with the potential to sell or distribute antimalarials and/or provide malaria blood testing. These include health facilities, community health workers, pharmacies, drug shops, retail outlets, market stalls and mobile providers. A screening process identifies outlets that provide antimalarials and/or malaria blood testing. From 2008 through 2014, ACTwatch conducted 35 national outlet surveys across the 10 project countries.[3] Reports are available at www.actwatch.info, and peer-reviewed publications have appeared in *Malaria Journal (22)* and *The Lancet (23)*.

ACTwatch also uses the adult equivalent treatment dose (AETD) as the unit of analysis for price and market share indicators. One AETD is defined as the number of milligrams (mg) of an antimalarial drug required to treat an adult weighing 60 kg. For each antimalarial generic, the AETD is defined as the number of mg recommended in treatment guidelines for uncomplicated malaria in areas of low drug resistance issued by WHO. Where WHO treatment guidelines do not cover a specific generic, the AETD is defined based on peer-reviewed research or the product manufacturer's recommended treatment course for a 60 kg adult. While it is recognized that the use of AETDs may oversimplify and ignore many of the complexities of medicine consumption and use, this analytical approach was selected because it standardizes medication dosing across drug types and across countries (which may sometimes vary) thus permitting comparisons on both prices and volumes calculated on the basis of an AETD.

Information collected on drug strength and unit size as listed on the product packaging was used to calculate the total amount of each active ingredient found in the package. The number of AETDs in a unit was

3 Surveys in the DRC and Myanmar were subnational.

calculated. The number of AETDs in a monotherapy is calculated by dividing the total amount of active ingredient contained in the unit by the AETD (i.e. the total number of mg required to treat a 60 kg adult). The number of AETDs for a combination therapy was calculated by dividing the total amount of one active ingredient that was used as the basis for the AETD by the AETD. Artemisinin was used to calculate the AETD for all artemisinin combination therapies.

Market share

The total number of medicine units (package, ampoule, bottle) that was reportedly sold/distributed to individual patients/consumers is captured for each audited antimalarial. Based on the number of AETDs in each unit, the total number of AETDs sold/distributed for each medicine is calculated. These totals are summed across all audited medicines for a total market sales volume in AETDs. Relative market share is calculated for a given antimalarial medicine or outlet type by calculating the proportion of all AETDs distributed that was distributed for the given medicine/outlet.

Price

Median price is typically reported for the private sector as a whole and among specific private sector outlet types. The number of medicines audited that are contributing to this price estimate is reported as well as the interquartile range (IQR), or the 25th and 75th percentiles. The median price and IQR are weighted using sampling weights.

Global Fund PQR transactional database and AMFm

Analyses of datasets from the Global Fund PQR transactional database, the United Nations Children's Fund (14) ACT Scale-Up Initiative and AMFm were conducted to examine market trends, including market share, product availability, quality and price of antimalarial treatments. The PQR and AMFm databases represent historical transaction procurement information from principal recipients on key health products, including antimalarial medicine *(24)*. Data were disaggregated to reveal market indicators, for example: (i) procurement of ACT originator brands to generic brands; (ii) procurement of ACTs by the Global Fund versus AMFm; (iii) fixed-dose combination (FDC) formulations versus co-blistered formulations; (iv) dispersible formulations versus child-friendly tablets; (v) procurement by ACT (e.g. artemether-lumefantrine [AL] compared to artesunate-amodiaquine [ASAQ]); (vi) regional procurement practice breakdowns; and (vii) median price assessments. Median prices were used over weighted average prices to reduce the effect of extreme values, or outliers, and the 10th and 90th QRT were obtained where the lowest and highest points were discarded. Except where noted, analyses reflect transactions from 2008 to 2012.

In order to analyse data retrieved from AMFm, the Global Fund and the ACT Scale-Up Initiative, a master dataset was created to use in Tableau Software® compiling the records from each individual set. Data from the PQR and AMFm were downloaded on 23 May 2014. AMFm data was downloaded from the AMFm Co-paid Summary Report and included data reported up to 21 December 2013. As the Global Fund changed to a different financial reporting platform, no further data was incorporated into the report in the public domain after 21 December 2013. PQR transactions included data from 2005 to 2014. Five transactions from 2014 (3 million [M] treatment units,4 US$ 0.3M) were excluded from analyses as the small number of transactions reported and verified by the download date was not considered to represent 2014 purchasing trends. Entries listed with a null value and flagged as "pending verification" were also excluded (n = 71, evenly distributed over time). A total of 2025 procurements of malaria medicines, worth a total of US$ 321.3M for 650M treatment units, were included in the analyses presented here. Due to the lag in reporting and verification, complete data from 2013 were not expected to be available until December 2014: therefore, where results are presented for 2013, it is clearly indicated that these are based on partial data. AMFM data collected had procurement dates between 2010 and 2013. Due to the lag in reporting and verification, data from 2013 are not complete.

4 A treatment unit is either a full course of an ACT, or a vial of an injectable.

Median prices per treatment course were derived using STATA, with the number of units in a purchase transaction as the weighting variable: the results were reloaded into Tableau Software for presentation purposes. AMFm prices are pre-subsidized prices.

Results

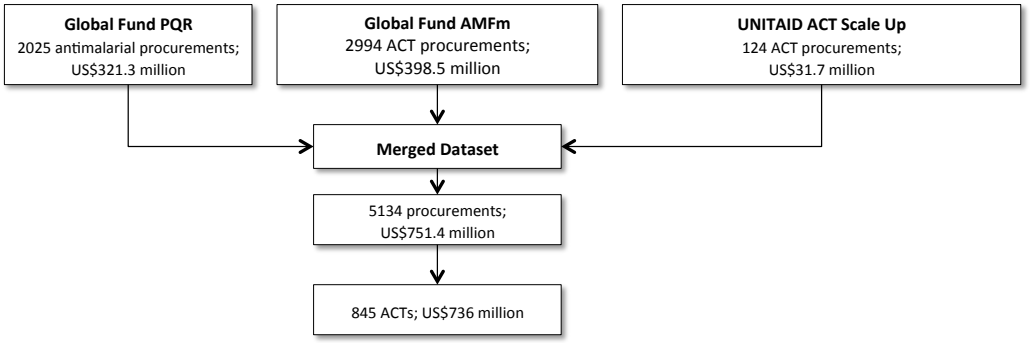
From the PQR, a total of 2025 procurements of malaria medicines, worth a total of US$ 321.3M and equalling 650M treatment units, were included in the analyses presented in this landscape. Total spending for 2013 as reported by 23 May 2014 was US$ 45.9M (113.7M treatment units purchased) from 236 transactions, compared with US$ 91.6M total spending (195M treatment units) from 441 transactions in 2012, i.e. around 50% of the 2012 total spending, and 58% of 2012 total volumes.

Data from AMFm comprised 2994 transactions worth a total of US$ 398.5M for 404.3M treatment units. Total spending for 2013 as reported by 23 May 2014, with data updated as of 21 December 2013, was US$ 63.6M (67.4M treatment units) from 728 transactions, compared with US$ 139.1M total spending (139.8M treatment units) from 1151 transactions in 2012, i.e. around 45% of the 2012 total spending. These figures are conservative compared to those presented in Figure 10, which represents data provided by eight manufacturers eligible for procurement from WHO/UNICEF and AMFm reports.

The UNICEF ACT Scale-Up Initiative was completed in June 2010 and the database is, therefore, static, comprising 124 transactions for 34.5M treatment units worth US$ 31.7M, procured between December 2007 and June 2010. The combination of the three datasets comprises a total of 5143 transactions, worth a total of US$ 751.4M and amounts to approximately 1.1 billion treatment units (Figure 1). Prior to the start of the ACT Scale-Up Initiative in 2008, there were minimal purchases recorded in the PQR (a total of 75 transactions for a total value of US$ 7.8M (23.4M treatment units) over the three years from 2005 to 2007). Our analyses are, therefore, based primarily on data from 2008 onwards.

For ACTs, the totals (excluding 2014) equalled: US$ 736M for 845M treatment courses, and for 2013 US$ 106M for 121.8M treatment courses (consisting of US$ 42.6M for 54.34M treatment courses from the PQR and US$ 63.6M for 67.4M treatment courses from AMFm).

Figure 1. Flow chart illustrating the merging of data source and total results



Based on the records retrieved from all three datasets, combined with desk research, the estimated coverage of the dataset of the donor-funded market was determined by calculating the total number of volumes reported in the Global Fund PQR and through AMFm, plus volume deliveries through the President's Malaria Initiative (PMI) that were retrieved from annual PMI reports. The total of the reported deliveries was then subtracted from the reported ACT volumes delivered by year as reported in the WMR. Excluding PMI, the merged dataset created from combining the Global Fund PQR records and the AMFm dataset represented approximately 49% of the donor market in 2009, 73% in 2010, 86% in 2011, 62% in 2012 and 35% in 2013 (Table 5).

Table 5. Estimated coverage of datasets collated for market share analysis

Year	Global Fund & AMFm[a]	PMI[b]	WMR (total donor market)[c]	Estimated coverage of Global Fund/AMFm dataset
2008	36 102 373	22 354 139		
2009	66 763 778	21 833 155	158 000 000	49%
2010	102 167 059	41 048 295	181 000 000	73%
2011	205 884 791	38 588 330	278 000 000	86%
2012	161 517 583	72 345 860	331 000 000	62%
2013[d]	121 800 000	48 433 634	392 000 000	35%

[a] Global Fund PQR.
[b] President's Malaria Initiative. Eighth Annual Report to Congress. Washington DC: US Agency for International Development; April 2014 (www.pmi.gov/docs/default-source/default-document-library/pmi-reports/pmireport_final.pdf?sfvrsn=14).
[c] Figures represent ACT volumes reported in the WHO WMRs.
[d] Approximate figure only; calculation based on total ACTs procured in the PQR database (4699 records), subtracted from the total of years 2008–2012.

Artemisinin market data

Data presented in the artemisinin market overview were derived from the API Market Dynamics Information Services (MDIS) project. Managed by a consortium consisting of the William Davidson Institute at the University of Michigan and Howard University, the MDIS project collects API market intelligence across HIV, tuberculosis and malaria therapeutic markets. Project methods include literature reviews, desk research, manufacturer interviews, analysis of data from third-party sources such as import and export data, and triangulation and modelling.

3. Public health problem

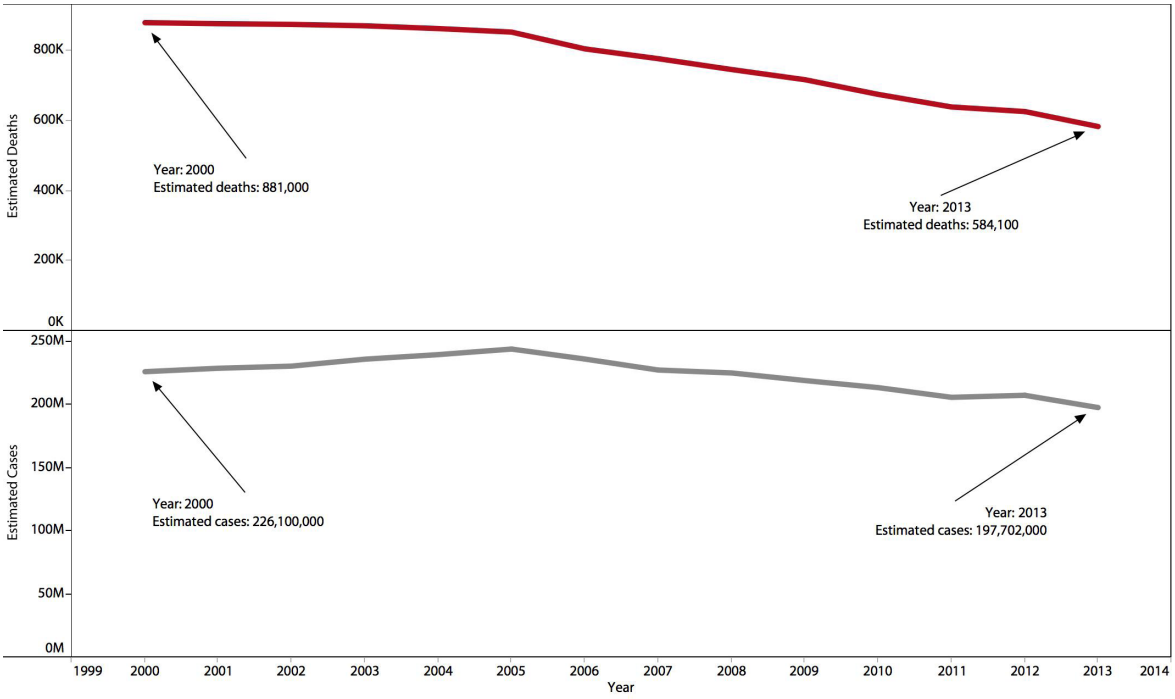
Key public health problem messages:

- More than 198M cases of malaria occurred in 97 countries in 2013.
- In 2013, 78% of malaria deaths was in children under 5 years old.
- Sub-Saharan Africa accounted for 90% of malaria deaths worldwide in 2013.
- Low- and lower-middle-income economies total 97% of malaria deaths and cases.
- Even though estimated malaria cases and deaths have been decreasing since the mid-2000s, the current trajectory is not sufficient to reach the World Health Assembly goals of 75% case reduction (to ~56M cases) and near zero deaths by 2015.

In 2005, the World Health Assembly set a goal to reduce the number of malaria cases by 75% with near zero deaths by 2015 *(25)*. The Roll Back Malaria Partnership Global Malaria Action Plan (GMAP), the targets set by the Millennium Development Goals *(26),(27)*, and scale-up of malaria control and case management strategies are leading to a reduction in the number of malaria cases and malaria deaths.

In 2013, there were an estimated 198M (range 124M–283M) cases of malaria across 97 countries, representing a 30% decrease in malaria cases between 2000 and 2013 (Figure 2) *(2)*. There were 584 000 deaths (range 367 000–755 000) from malaria in 2013, indicating a 47% decrease in mortality rates since 2000 (Table 2) *(2)*. Of these deaths, 78% (approximately 453 000) occurred in children under 5 years old *(2)*. Further to this, an estimated 8M cases of uncomplicated malaria progress to severe malaria each year *(28)*, that, when left untreated, leads to nearly 100% mortality *(6)*. Even though gains have been made since the mid-2000s, the current trajectory is not sufficient to reach the World Health Assembly goals of 75% case reduction (to 56M cases) and near zero deaths by 2015. Substantial variability exists in malaria disease burden across countries; for example, many countries are on track to meet or exceed the set incidence reduction targets, while some countries are reporting increases in malaria cases *(2, 3)*. Some countries have had success in progressing towards malaria elimination; for example, in 2013, 19 countries were in the pre-elimination and elimination phases *(3)*. Additionally, 55 countries with ongoing malaria transmission reported malaria reductions by 75% or more between 2000–2013, five countries with more than 1M cases in 2000 are on track to achieve reductions in reported malaria cases by 75% or more by 2015 *(2)*. Even though gains have been made since the mid-2000s, the current trajectory is not sufficient to reach the World Health Assembly goals of 75% case reduction (to 56M cases) and near zero deaths by 2015.

Figure 2. Malaria disease burden estimated deaths and estimated cases, 2000–2013



Source: World malaria report *2014 (2)*.

WHO African Region

The global malaria burden is highest in the WHO African Region, which accounted for 82% of cases in 2012 and 90% of worldwide deaths in 2013 (Figure 3). In this region, the DRC and Nigeria together accounted for approximately 40% of the global total of estimated malaria deaths in 2012 (Figure 4) *(2, 3)*. Overall, *Plasmodium falciparum* was identified as the infecting organism in 99% of estimated cases in the African Region *(2)*. Children under 5 years old bear a significant burden of malaria morbidity and mortality, accounting for 83% of estimated malaria deaths *(2)*. In addition, children in sub-Saharan Africa are significantly burdened by severe malaria, which is often the main reason for paediatric hospital admission *(29)*.

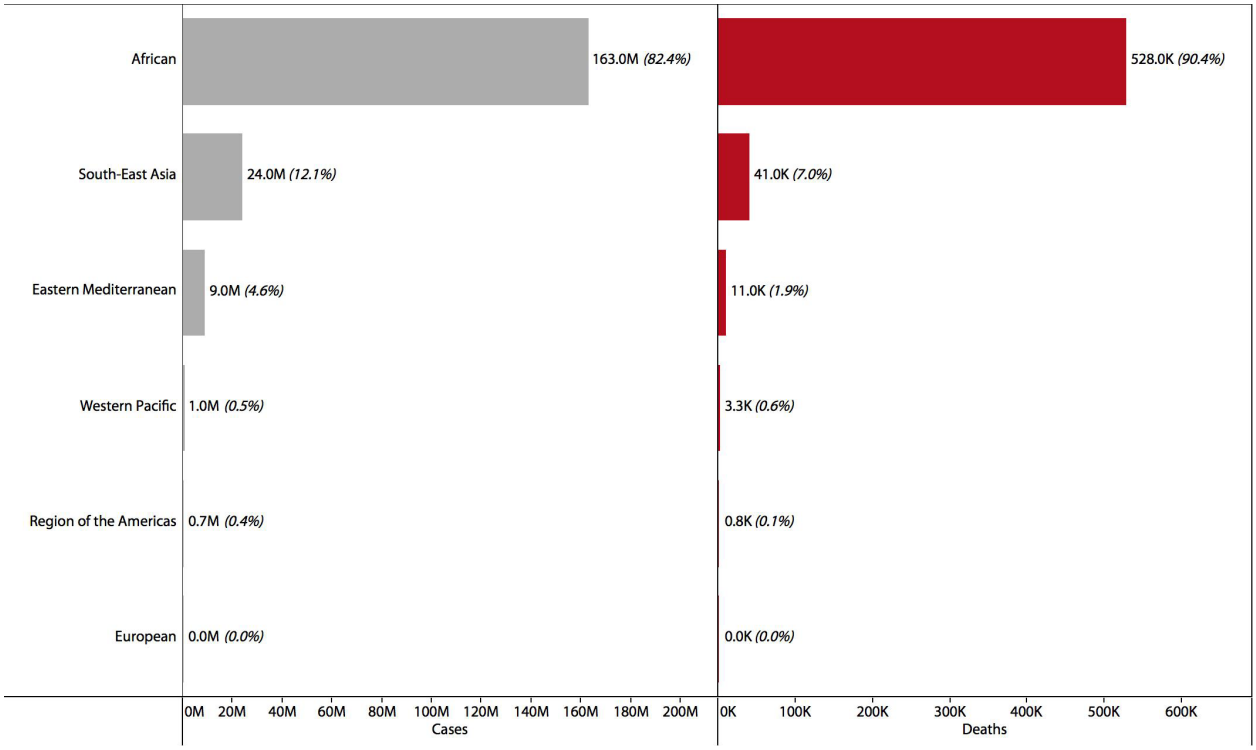
WHO South-East Asia Region and Western Pacific Region

The WHO South-East Asia Region had the second highest number of estimated cases (12%) and deaths (7%) after the WHO African Region (Figure 3). This region had an estimated 24M cases and 41 000 deaths in 2013 *(2)*. In 2013, around 9% of malaria cases occurred in India, making it the second highest burden country of global malaria cases (Figure 5). Additionally, throughout this region there are many diverse environments that cater to a diverse range of vectors. For example, in India and Pakistan, *Plasmodium vivax* and *P. falciparum* coexist and the epidemiology is fast changing between them due to a generation of resistant alleles *(30, 31)*. *P. falciparum* was identified in only 57% of cases, indicating this region has a higher burden of other forms of malaria parasites, particularly *P. vivax (2)*. Mortality in children under 5 years old accounted for only 29% of all malaria-related deaths *(2)*. This correlates with the WHO South-East Asia Region having less stable malaria transmission than the WHO African Region, resulting in decreased immunity in older children and adult populations and, therefore, increased mortality in these cohorts *(32)*. The geographical density of the WHO South East-Asia Region also impacts the stability of malaria. Severe malaria and the risk of death affect the broader population and not just young children.

Artemisinin resistance has also been identified in five countries in the Greater Mekong subregion (Cambodia, Myanmar, Thailand, Viet Nam and, most recently, the Lao People's Democratic Republic) *(33)*.

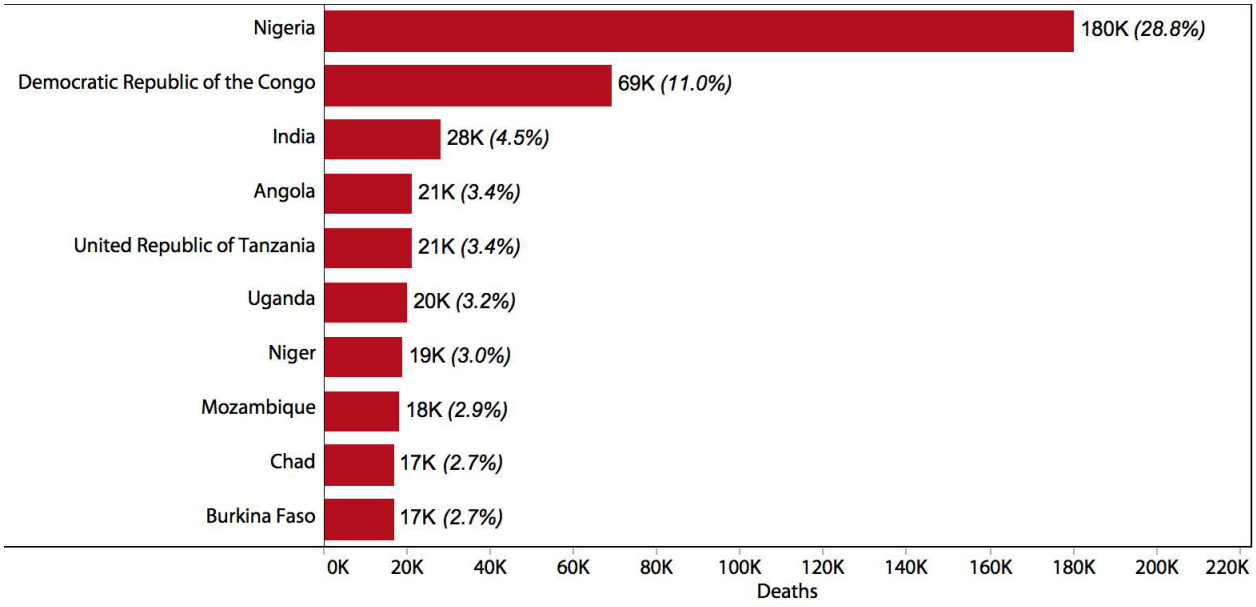
Resistance to artemisinin derivatives is of significant concern, especially given that alternative effective compounds to treat malaria will not be available for the next three years *(6)*.

Figure 3. Malaria cases (estimated) by WHO region, 2012; malaria deaths (estimated) by WHO region, 2013



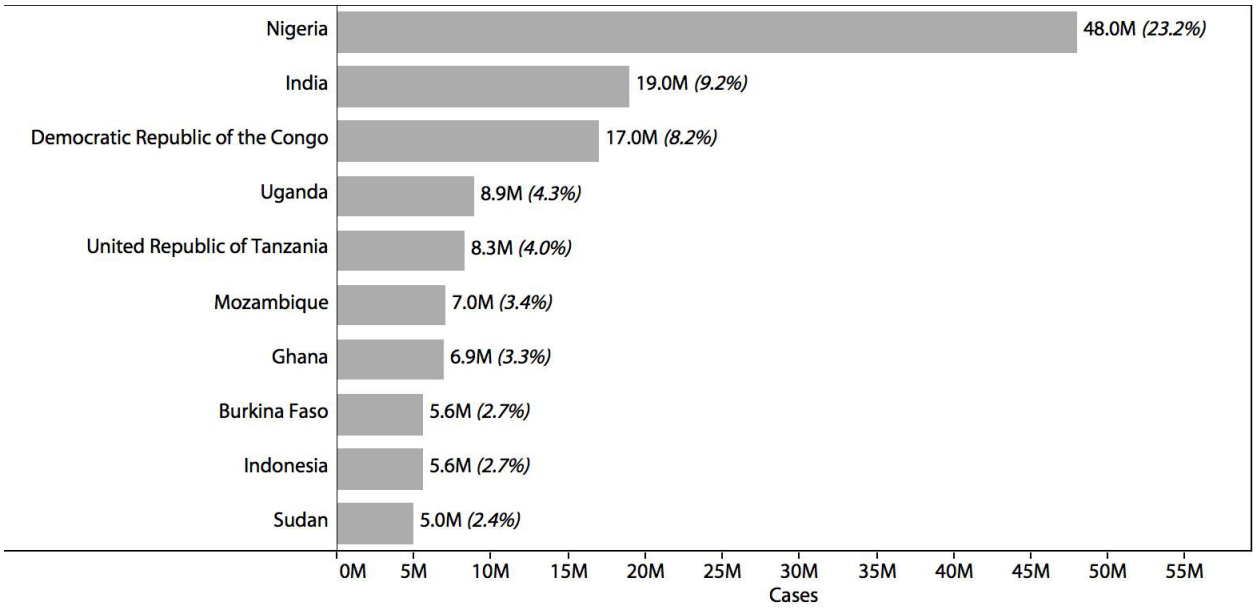
Source: World malaria report 2014 *(2)*.

Figure 4. Global malaria deaths in the 10 highest burdened countries, 2012



Source: World malaria report 2014 *(2)*.

Figure 5. Global malaria cases in the 10 highest burdened countries, 2012



Source: World Malaria Report 2013 *(2)*.

Country burden by World Bank income level[5]

Lower-middle-income countries and low-income countries[6] had the highest malaria disease burden, together accounting for more than 97% of estimated malaria cases (44% and 53%, respectively) in 2010, and 97% of malaria deaths *(34)*. Upper-middle-income economies accounted for around 2% of malaria cases and deaths, while high-income economies accounted for less than 1% of estimated malaria cases and deaths *(34)*.

3.1 Global malaria guidelines and policy recommendations for treatment

As shown in Figure 6, recommended treatments for malaria are specific to the type of *Plasmodium* and the level of endemic and drug resistance in the region *(6, 10)*. In addition to the updated WHO treatment guidelines of 2010, a further update was produced in 2011 to reflect new guidance of the use of IVAS. A revised version of the guidelines is anticipated in the first half of 2015. A brief outline of recommended treatments is provided below. For a more detailed overview, refer to the first edition of the UNITAID *Malaria medicines landscape* and the WHO *Guidelines for the treatment of malaria*.

Uncomplicated malaria treatments

ACTs

WHO recommends ACTs as the first-line treatment of uncomplicated *P. falciparum (10)*. ACTs are also recommended as the first-line treatment of acute blood-stage *P. vivax* infections in areas that are no longer CQ sensitive because of resistance, except in combination with sulfadoxine-pyrimethamine (SP) due to pyrimethamine resistance *(10)*. Preferable ACT formulations are FDCs and dispersible formulations for children, and ACTs are still known to be safe and effective for pregnant women in the second and third trimesters of pregnancy.

5 Analysis of disease burden by World Bank income level is based on malaria disease estimates published in 2010. Country-level disease estimates for 2012 were not available at the time of publication, but will be included in the next update.

6 The World Bank classifies the economies of its member countries as low-income, middle-income (subdivided into lower-middle and upper-middle) or high-income based on gross national income (GNI) per capita. The latest per capita GNI levels and corresponding classifications are: low-income economies ≤US$ 1025; lower-middle-income economies US$ 1026–4035; upper-middle-income economies US$ 4036–12 475; and high-income economies ≥US$ 12 476. Country-level classification is updated yearly as new economic indicator data become available.

CQ

CQ is recommended as the first-line treatment of *P. vivax* in non-resistance settings where infections are still CQ sensitive *(6)*. Importantly, CQ is no longer recommended for *P. falciparum* due to resistance development. CQ is recommended to treat both *Plasmodium ovale* and *Plasmodium malariae*.

QN

QN is recommended to treat *P. falciparum* in pregnant women during their first trimester *(6)*.

PQ

For both *P. vivax* and *P. ovale*, particularly in the South-East Asia Region, PQ is recommended after treatment with CQ or an ACT to clear the dormant liver stages and to prevent relapse *(6)*.

For the use of PQ to treat *P. falciparum* malaria cases, in 2012 the Malaria Policy Advisory Committee recommended low-dose PQ (0.25 mg base/kg) in conjunction with an ACT as an anti-gametocytocide in pre-elimination and elimination settings. However, a recent Cochrane review reported that the appropriate dose levels remain uncertain for the use of PQ for malaria transmission blocking *(35)*.

Severe malaria and pre-referral treatments

INJAS

Intravenous artesunate (IVAS) is the first choice of treatment of severe malaria in adults and children *(6)*. If intravenous access cannot be achieved, artesunate should be given via intramuscular injection *(6)*. Intravenous artemether and QN are acceptable alternatives if artesunate is unavailable. INJAS and injectable QN are also recommended for pre-referral treatment.

Rectal artesunate (RAS)

In situations where parenteral medication is not possible and when the referral time is greater than six hours, WHO recommends the use of a single dose of RAS for pre-referral treatment *(6)*.

Preventive chemotherapy antimalarial agents

WHO also recommends strategies for the use of antimalarial medicines for the prevention of malaria.

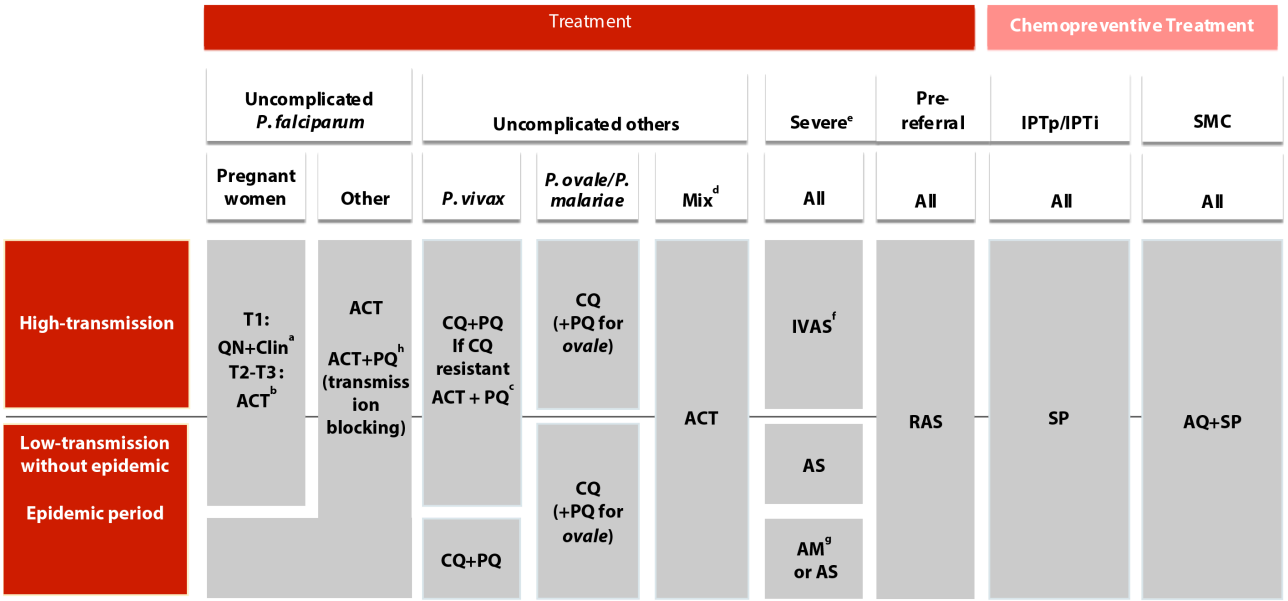
SP

WHO recommends SP for intermittent preventive treatment for pregnant women (IPTp) and intermittent preventive treatment for infants (IPTi) *(36, 37)*. IPTp-SP is recommended for all pregnant women at each scheduled antenatal care visit (a schedule of four antenatal care visits are recommended). The first IPTp-SP dose should be administered as early as possible during the second trimester of gestation. Each SP dose should be given at least one month apart. The last dose of IPTp with SP can be administered up to the time of delivery without safety concerns *(36, 38)*. IPTi-SP is the administration of a full therapeutic course of SP. It is recommended to be geographically limited to countries in sub-Saharan Africa with a moderate-to-high malaria transmission *(14)*.

Amodiaquine+sulfadoxine-pyrimethamine (AQ+SP)

In 2012, WHO recommended AQ + SP for seasonal malaria chemoprevention (SMC) in areas of highly seasonal malaria transmission across the Sahel subregion of Africa and where AQ + SP remains > 90% effective *(39, 40)*. It is recommended for monthly use for children under 5 years old for up to four months during the transmission season *(39)*.

Figure 6. Summary of WHO treatment guidelines for malaria



QN, quinine; Clin, clindamycin; ACT, artemisinin-based combination therapy; CQ, chloroquine; AQ, amodiaquine; PQ, primaquine; AS, artesunate; AM, artemether; INJAS, injectable artesunate
a Or ACTs where QN+clindamycin are not available.
b If effective – alternatives are AS+clindamycin or QN+clindamycin.
c Except artesunate sulfadoxine-pyrimethamine (ASSP) for *P. vivax*.
d Including *P. falciparum* or not.
e Mainly *P. falciparum*, very few cases of severe *P. vivax* treated like severe *P. falciparum*.
f AM and QN can be used if no AS; for pregnant women, AS and AM are preferred to QN for the second and third trimester.
g Intramuscular artemether.
h Effective and safe dose to be determined.
Sources: Image adapted from the Boston Consulting Group medicines market landscape (unpublished). Information derived from the WHO Guidelines for the treatment of malaria 2006 (10) and the WHO Guidelines for the treatment of malaria (second edition) 2010 *(6)*.

3.2 Commodity access issues in treatment

Key commodity access issues in treatment messages:

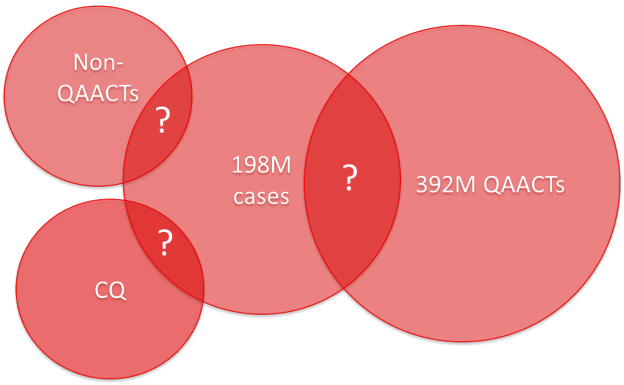
- Across 22 household surveys from nine African countries, ACTs comprise approximately 68% of antimalarials given to febrile children in the public and private sector combined (3).
- The proportion of febrile children treated with an ACT has increased in both the public and private sector, e.g. in the private sector from 11% (~1–68%) in the earliest household surveys to 57% (~9–75%) in the most recent surveys.[1]
- The proportion of febrile children receiving an ACT for antimalarial treatment remains higher in the public sector than in the private sector where 21 of the 22 household surveys reported higher rates in the public sector.[2]

1 Household surveys, 2006–2012, from nine African countries (Angola, Liberia, Madagascar, Malawi, Nigeria, Rwanda, Senegal, United Republic of Tanzania, Uganda) *(3. World Health Organization. World Malaria Report. Geneva: World Health Organization; 2013*.
2 Household surveys, 2006–2012, from nine African countries (Angola, Liberia, Madagascar, Malawi, Nigeria, Rwanda, Senegal, United Republic of Tanzania, Uganda) *(3. Ibid*.

Since the WHO malaria treatment recommendations in 2006, considerable efforts have been made to scale up access to ACTs. By the end of 2012, 79 of the 88 countries with endemic *P. falciparum* had adopted national treatment policies listing ACTs as the first-line treatment *(3)*. The number of ACTs delivered by manufacturers also has increased substantially, from 11M in 2005 to 76M in 2006, 278M in 2011 and reaching 392M in 2013 *(2)*. This increase is due largely to scaled-up investments from international donors, with an increase in 2011 due mainly to AMFm, (an innovating financing mechanism designed to expand affordable access to ACTs primarily in the private sector and to reduce the use of less effective therapies that promote drug-resistant malaria), while increased deliveries in 2012 primarily came from public sector procurement *(2)*.

It is very difficult to estimate access to appropriate antimalarial treatment. There were around 392M QAACT treatments procured for approximately 198M cases of malaria in 2013 (Figure 7). It is difficult, however, to determine the overlap between confirmed malaria cases and people who actually received a QAACT. In some settings, the lack of accessible diagnostic testing can mean that many fever cases are erroneously treated for malaria *(21)* . In addition, there are limited data on access to CQ (which is still recommended for *P. vivax*), and other ACTs (which are not approved by the WHO PQP or a stringent regulatory authority [SRA]) that can also be of acceptable quality that are used to treat confirmed malaria.

Figure 7. Approximation of QAACT coverage compared to annual malaria cases, 2013



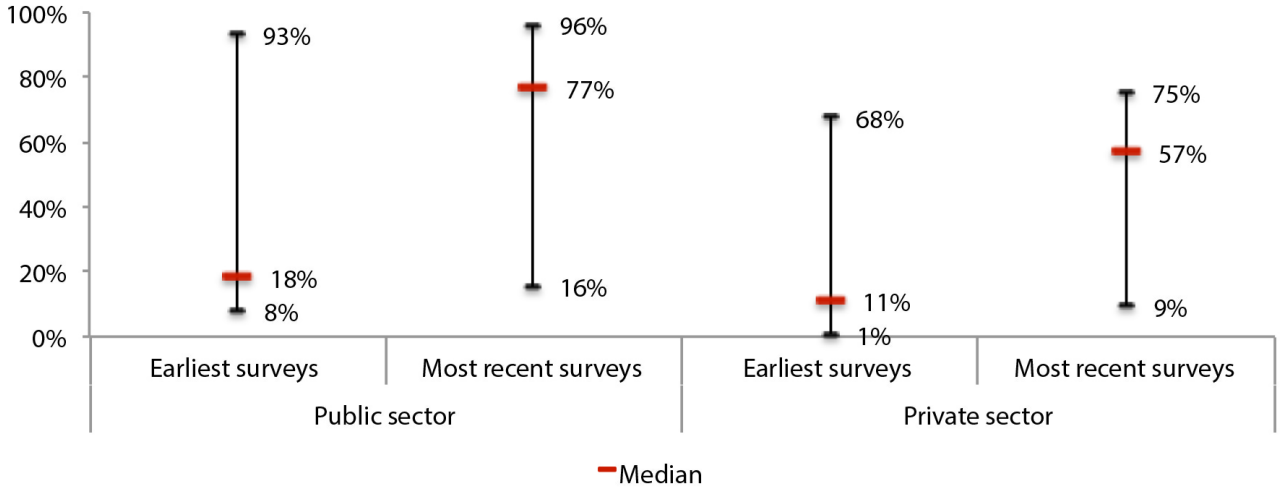
Access to ACTs has seen marked increases in both the public and the private sector in recent years. However, despite considerable progress in scaling up the use of ACTs and the overall increase in access, access between sectors continues to remain an issue. In the most recent household surveys from nine African countries, ACTs comprise approximately 68% of antimalarials given to febrile children (across both the public and private sector combined) *(2)*. Comparing the initial data collected to the most recently collected data of 22 household surveys during 2006–2012 (Figure 8) show that the proportion of all antimalarials that were ACTs given to febrile children in the public sector[7] has increased over time from less than 20% (~8–93%) to around 77% (~16–96%), with a wide range observed.

Additionally, access to ACTs in the private sector[8] has grown distinctly between survey rounds. The most recent surveys depict that 57% (~9–75%) of all antimalarials given to febrile children in the private sector are ACTs compared to around 11% (~1–68%) in initial surveys *(2)*. While this shows progress in achieving greater access to ACTs in the private sector, this indicator only reflects ACT use among febrile children accessing antimalarial treatment. The *World Malaria Report 2014* stated that approximately 40% of febrile children does not present for treatment *(2)*. Through scaled-up international funding, including AMFm, progress has been made in increasing access to ACTs, slowing the emergence of artemisinin resistance and reducing malaria cases and deaths *(18)*. Additional efforts are needed to address current gaps in access to ACTs across both sectors in order to ensure high malaria cure rates, reduce transmission and control the spread of drug resistance.

7 Includes government, non-profit facilities and community health workers.

8 Includes private clinics and providers, pharmacies, shops and traditional providers. Four out of five countries where surveys were collected were a part of the AMFm pilot (Madagascar, Nigeria, United Republic of Tanzania, Uganda).

Figure 8: Proportion of ACTs among antimalarial treatments given to febrile children, by health sector, nine African countries with at least two household surveys, 2006–2012



Notes: To show trends over time, the earliest and the most recent surveys collected from nine African countries with household surveys during 2006–2012 were used to create the graph. The top and bottom horizontal lines represent the minimum and maximum values; the red horizontal line represents the median value. Public health sector includes government and non-profit facilities and community health workers; private sector includes private clinics and providers, pharmacies, shops and traditional providers.[9]
Source: Adapted from the World Malaria Report 2013 *(3)*.

3.2.1 Child-friendly ACT formulations

Key child-friendly ACT formulations messages:

- Crushing solid tablet ACTs for use for children may make them unpalatable and lead to incorrect dosing *(4)*.
- Limited data from AMFm show that the availability of dispersible tablet ACTs in registered pharmacies is low (11–14%), and is substantially lower than that of paediatric packs of solid tablets (42–48%) *(41)*.

As children under 5 years old bear a significant proportion of the malaria disease burden (78%), it is important that effective antimalarials be available in formulations that facilitate their use for children *(2)*. WHO has identified flexible solid dosage forms as being most suitable for developing countries and appropriate for many of the medicines necessary to treat the major causes of mortality and morbidity in children under 5 years old, including malaria *(11)*.

Crushing ACT tablets for use for children affects their palatability, causing a reluctance to take the medication and can lead to incorrect dosing and waste *(4)*. Dispersible tablet formulations of ACTs, therefore, offer advantages for children in terms of palatability and dosing *(4)*. For prequalified purchases of dispersible AL products, there are limited options available and the options of paediatric formulations that are available for procurement in the donor market have not changed since December 2012 *(5)*. Additionally, dispersible AL is the only taste-masked medicine available in this category. Two WHO prequalified dispersible tablet formulations of AL are available *(5)* ; however, data indicate that uptake has been somewhat limited. Specifically, limited data from AMFm show that their availability in registered pharmacies compared to solid-oral formulations is low (11–14%), and is lower than that of paediatric packs of solid tablets (42–48%) *(41)*.

9 Household surveys, 2006–2012, from nine African countries (Angola, Liberia, Madagascar, Malawi, Nigeria, Rwanda, Senegal, United Republic of Tanzania, Uganda) *3. World Health Organization. World Malaria Report. Geneva: World Health Organization; 2013.*

3.2.2 Severe malaria treatments

Key severe malaria treatments messages:

- Between 2010–2013, approximately 12M prequalified INJAS vials were procured, amounting to approximately 1.5–2M treatments for severe malaria in children under 5 years old *(7)*. This represents around 25% of the total volume needed to treat global annual cases.
- The absence of a WHO prequalified/SRA agency-approved RAS has limited access and hampered widespread use of this pre-referral treatment of severe malaria *(2)*.

Since 2011, when WHO recommended INJAS as the preferred treatment of severe malaria *(6)*, uptake of INJAS has been increasing, but is still limited. From November 2010, when the first INJAS became prequalified, to December 2013, quantities procured were less than 25% of the total needed to treat global annual cases. While other sources of INJAS were available to purchase, approximately 12M prequalified vials (roughly 1.5M–2M treatments for children under 5 years old) were procured out of an estimated 48–50M vials that would be needed to treat global annual cases *(7)*. Reasons for low-level procurement of INJAS include unfamiliarity with the product, a higher price over parenteral quinine (IVQ) and buyer concerns about a single-prequalified supplier. In December 2012, UNITAID granted an MMV consortium US$ 34M to scale up the use and access of INJAS in high-burden countries *(12)*. This funding has contributed to the development of strategic programmes that are currently being implemented by MMV and its partners in six high-burden countries. These programmes are targeted at enhancing INJAS access in the highest burden countries of severe malaria, the DRC and Nigeria. Through this initiative, MMV is also currently collaborating with partners to secure at least one new generic manufacturer of WHO prequalified INJAS to diversify global supply of this medicine *(7)*.

Given that the risk of death from severe malaria is greatest in the first 24 hours, access to pre-referral treatment is also important to "buy time" for patients who are in transit to a facility where they can receive intravenous treatment. In situations where parenteral medication is not possible and when the referral time is greater than six hours, WHO recommends the use of a single dose of RAS for pre-referral treatment *(6)*. However, the lack of a WHO prequalified product or approval by an SRA has limited access and hampered widespread use of this product. Recognizing this, a proportion of the funding that was granted by UNITAID to the MMV consortium has been allocated to an RAS product receiving prequalification by 2016.

3.2.3 Preventive chemotherapy

Key preventive chemotherapy treatments messages:

- Access to IPTp in sub-Saharan Africa remains low: approximately half (43%) of women attending antenatal clinics in 2013 received a second dose of SP for IPTp amongst 31 reporting countries *(2)*, and the proportion of all pregnant women receiving a second dose of SP for IPTp was less than 30% *(2)*.
- Uptake of IPTi is low and only one country has adopted a national policy but uptake may accelerate with new implementation guidance now available *(2)*.
- SMC programs are slowly being adopted into national malaria control policy and implementation is only at its infancy in some African countries *(2)*.

Of the 840 million persons at risk of malaria in endemic countries in sub-Saharan Africa in 2013, an estimated 35 million women who become pregnant each year could benefit from IPTp, a large proportion of the estimated 26 million infants born each year could benefit from IPTi, and an estimated 25 million children aged 3-59 months living in the Sahel sub-region could benefit from SMC *(3)* . However, coverage rates of preventive chemotherapy interventions remain low. Approximately half (43%) of women attending antenatal clinics in 2013 received a second dose of SP for IPTp *(2)*. Household survey data show that among all pregnant women, the proportion receiving a second dose of SP for IPTp was around 30% (weighted average) *(2)*. This is primarily due to low coverage rates in large countries such as Nigeria and the DRC. While 36 countries in sub-Saharan Africa had adopted a national policy of IPTp with SP by the end of 2011, only Burkina Faso has adopted a national policy on IPTi since it was recommended by WHO in 2009 *(2)*. Slow uptake of IPTi may be partially due to the lack of implementation guidance at the time the policy recommendation was made. As such guidance is now available *(14)*, implementation may accelerate. Decisions made by counties to adopt SMC may also be impacting the likeliness of a country to adopt IPTi policies.

Since WHO released its policy statement on SMC in March 2012, several countries have initiated the process of incorporating SMC into malaria control policy and as of 2013 6 countries had adopted national SMC policies *(2)*. In 2014, UNITAID committed US$67.4M for ACCESS-SMC, a project led by the Malaria Consortium. The project aims to create a well-structured market by implementing SMC at scale in seven countries in the Sahel and thereby addressing key supply-side and demand-side barriers to current scale-up efforts.

4. Medicines technology landscape

Key product landscape messages:

- The range of antimalarials that are currently available represents a powerful set of tools for the treatment of malaria but unmet needs still exist.
- Products with significant public health potential have recently entered the market (e.g. INJAS for severe malaria), but new products often require targeted support to scale up use.
- A strong pipeline of products exists, with several high-potential products in late-stage development, including a single-dose cure for radical cure of vivax (i.e. clearance of liver-stage hypnozoite infections), a single-dose cure for uncomplicated falciparum malaria and paediatric formulations *(13)*.
- Azithromycin-chloroquine (AZCQ) has ceased development meaning there are currently no novel compound therapies in the R&D pipeline specifically for use in IPTp *(13)*, As populations in areas where resistance to SP is growing, new IPT therapies are urgently needed.

4.1 Overview of current products on the market

Medicines used in the treatment of uncomplicated malaria can be divided into three categories: artemisinin-based combination therapies (ACTs); artemisinin monotherapies (AMTs[10]); and non-artemisinin therapies (nATs). Each of these categories is described further below.

ACTs

In 2006, WHO recommended that all countries use ACTs as the first-line treatment of uncomplicated *P. falciparum (10)*. ACTs were adopted by WHO as the preferred treatment in response to the threat of increasing resistance to existing antimalarial medicines, thus global efforts are currently directed at supporting the introduction, use and maintenance of ACTs in endemic countries where they are still effective. There are currently five different combinations available and recommended in the WHO treatment guidelines (Table **6**) *(6)*.

Table 6. Available ACT combinations recommended by WHO

ACT combination	Recommended dose	Treatment course
artemether/lumefantrine (AL)	1.4–4 mg/kg/dose 10–16 mg/kg/dose	Twice daily for three days
artesunate+/amodiaquine (AS+AQ, ASAQ)	2–10 mg/kg/day 7.5–15 mg/kg/day	Daily for three days
artesunate+/mefloquine (AS+MQ, ASMQ)	4 mg/kg/day (2–10 mg/kg/day) Total dose of 25 mg/kg	Daily for three days Divided daily for three days
artesunate+sulfadoxine-pyrimethamine (AS+SP)[a]	4 mg/kg/day (2–10 mg/kg/day) 25 mg/kg (S) (25–70 mg/kg (S))	Daily for three days Once on day-1
dihydroartemisinin+piperaquine (DHA PPQ)	4 mg/kg/day (2–10 mg/kg/day) 18 mg/kg/day (16–26 mg/kg/day)	Daily for three days

a In areas that are still SP sensitive. S, sulfadoxine; P, pyrimethamine.

10 AMTs include oral artemisinin monotherapies (oAMTs), injectable artemisinin monotherapies (INJAS) and rectal artemisinin monotherapies (RAS).

For an ACT to be eligible for purchase in the donor-funded market, it needs to be included in the WHO treatment guidelines *(24)*. It also needs to be quality assured through either the WHO PQP, or from an SRA such as the United States Food and Drug Administration (FDA) and the European Medicines Agency *(42)* or to become available in the donor-funded market *(24)*. Therefore, ACTs are often divided into those that are quality assured through one of the abovementioned mechanisms (QAACTs) and those that are non-quality-assured ACTs (nQAACTs). There are many nQAACTs that may be purchased directly by endemic countries or other market participants (typically wholesalers) that are not prequalified. For example, in Nigeria, approximately 450 ACT products are registered to market, but only 30 were quality assured by the WHO PQP *(43)*. Even though some products are GMP certified[11], they are not eligible for purchase in the donor-funded market. While not all nQAACTs are of substandard quality, nQAACTs have been found to have a 60% quality-control failure rate compared to less than 4% for prequalified ACTs *(44)*.

To date, WHO has prequalified 33 malaria products from 10 manufacturers with varying combinations and formulations, of which 28 are ACTs (Appendix 1) *(5, 45)*. There are a further 22 ACT products currently under assessment by the WHO PQP (Appendix 2) *(45)*.

New products in the ACT market

Apart from the two main ACT combinations – AL and ASAQ – multiple new ACT formulations have entered the market.

Dihydroartemisinin piperaquine (DHA PPQ) *(46)*: Developed by Sigma-Tau under the brand name Eurartesim, DHA PPQ was approved by the EMA in October 2011. Holley-Cotec produced another version of DHA PPQ (trade name Duo-Cotecxin), also available in many countries, but which is not prequalified/approved by an SRA. DHA PPQ offers once-a-day dosing (three doses of three tablets over three days) and does not require co-administration with food. This provides clear benefits in terms of patient compliance and tolerability. The longer half-life of piperaquine relative to lumefantrine and other partner drugs may also provide a prophylactic effect and lower the rate of reinfection, making this product suitable for use in regions pursuing malaria elimination. There are also three DHA PPQ products currently under assessment by the WHO PQP. A child-friendly granule formulation has been developed and is currently in Phase III trials *(13)*. However, there is currently only one supplier of prequalified DHA PPQ, and the current EMA label advises an electrocardiogram (ECG) is obtained before the last of the three daily doses[12] *(48)*. However, the recent Cochrane review reported that DHA PPQ is generally safe, where patients who presented with ECG changes were resolved within one week without serious consequence *(47)*.

Pyronaridine-artesunate (ASPY) *(46)*: The Shin Poong Pharmaceutical Co. Ltd version Pyramax® was approved by the EMA in February 2012. This product is efficacious against both *P. falciparum* and the blood stage of *P. vivax* and, therefore, could have a strong potential market in areas where both species of the parasite exist (e.g. Greater Mekong subregion. It is also once-a-day dosing for three days, potentially facilitating patient compliance. While ASPY is not included in the WHO treatment guidelines, WHO separately called for its use as a potential tool in containing artemisinin resistance in Cambodia *(49)* where it has recently been registered for use in both *P. falciparum* and *P. vivax (50)*.

Artesunate-mefloquine (ASMQ) *(46)*: ASMQ, developed by Drugs for Neglected Diseases *initiative* (DND*i*)/Cipla Ltd, was prequalified in September 2012. This product is also produced by Farmanguinhos for use in Brazil. Studies have shown this product to have high cure rates and the ability to achieve lower rates of gametocyte carriage, providing strong post-treatment suppression of falciparum malaria coupled with effective suppression of blood-stage *P. vivax*.

Since 2006, WHO has recommended that wherever possible, FDC tablets should be used to treat malaria *(24)*. FDCs offer several major benefits, including increased individual compliance to the full treatment course, reduced pill burden, delayed development of parasite resistance (for example, AL and DHA PPQ

11 While GMP certified products are available, they are not quality assured to the standrards of the ICH or to international SRA/WHO PQP standards. For this reason the quality of these products is uncertain.

12 A recent Cochrane review has found that DHA PQP was associated with more frequent prolongation of the QTc interval (low quality evidence), but no cardiac arrhythmias were reported *(47)*.

have only ever been available as an FDC, therefore, there is generally a lower level of resistance to the partner medication) and reduced risk of medication errors. There are currently 22 FDC ACTs prequalified by WHO, including AL, ASAQ, ASPY and ASMQ, and DHA PPQ is also approved by EMA, an SRA *(5)*. In addition, there are a number of ACTs that have not been co-formulated into FDCs, including co-blistered formulations of AS + AQ, artesunate + sulfadoxine-pyrimethamine (AS + SP) and AS + MQ. Under the Global Fund new tender process (Procurement for Impact [P4i] initiative, see Section 5.1), only FDCs will be eligible for procurement in the donor-funded market.

WHO has identified flexible solid dosage forms as being the most suitable form of medicine for children under 5 years old in developing countries, including the treatment of malaria *(51)*. As children bear a significant burden of malaria morbidity and mortality, and palatabilty and ease of administration are challenges in access to malaria medicine *(4)*, child-friendly formulations are an important technology in the overall antimalarial landscape. In general, child-packs for antimalarial medicines are based on weight bands, where pack sizes are tailored for infants (4–8 kg), toddlers or young children (9–15 kg) and children (16–35 kg). Over 35 kg is considered to be an adult-pack size.

Table **7** outlines the pack types by weight band and pack types for AL and ASAQ/AS + AQ. In addition to AL FDC, dispersible AL is also available in all pack types at the same strength as solid oral formulations, but the focus for scaling up dispersible tablets has been targeted at children under 5 years old due to the burden of disease within this population group. There are now two prequalified products available from different manufacturers for dispersible formulations of AL *(5)*. In addition, the prequalified FDC version of ASAQ is soluble in water (but not flavour masked). Additional child-friendly formulations are under development; these are described in the following section.

Table 7. Available AL and ASAQ formulations and pack types recommended by WHO

ACT	FDC or co-blister	Strength	Weight band	Pack type
artemether/lumefantrine (AL)	FDC	20/120 mg	Adult >35 kg	6x4
			Child 25–35 kg	6x3
			Child 15–25 kg	6x2
			Infant <15 kg	6x1
artesunate/amodiaquine (ASAQ)	FDC	100/270 mg	Adult >35 kg	3x2
		100/270 mg	Child 18–35 kg	3x1
		50/135 mg	Child 9–17 kg	3x1
		25/67.5 mg	Infant 4–8 kg	3x1
artesunate+amodiaquine (AS+AQ)	Co-blister	50/153 mg	Adult >35 kg	12+12
			Child 18–35 kg	6+6
			Child 9–17 kg	3+3
			Infant 4–8 kg	3+3 (half-tablet)

AMTs

The use of oAMTs (for example, artesunate, artemether and dihydroartemisinin) threatens the long-term usefulness of ACTs by selecting for resistance. An additional concern is that resistance can develop over a short period of time *(49)*. Artemisinin resistance has now been identified in five countries in the Greater Mekong subregion and is suspected in two countries in South America *(33)*. If *P. falciparum* develops resistance to the artemisinin derivatives, then there will be no alternative effective compounds to treat *P. falciparum* malaria over the next three years (see Section 4.2); this will have a significant impact on the population control of malaria *(6)*. In May 2014, the WHO Global Malaria Programme called for intensified efforts to withdraw oAMTs and ban the marketing of and their use as a monotherapy from the global market *(33)*. Despite these efforts, oAMTs continue to be available, and there are some endemic countries still

allowing them to be marketed *(49)*. In 2008, for example, 37 pharmaceutical companies were producing monotherapies that were marketed in 29 countries *(52)*.

AMTs in injection form remain the WHO-recommended first-line treatment of patients with severe malaria *(6)*. In 2010, an INJAS product, developed by Guilin Pharmaceuticals Co. Ltd (hereinafter Guilin), was prequalified by WHO with the help of MMV *(12)*. A goal of UNITAID and MMV is to encourage more manufacturers and recently there seems that there is hope of more INJAS suppliers entering the market in the coming years, for example, a second applicant is expected to submit a dossier to the WHO PQP is anticipated in 2015. RAS suppositories are also recommended for pre-referral treatment of severe malaria *(6)*. While an RAS product is yet to be quality assured by an SRA or WHO prequalified, two manufacturers have committed to achieve prequalification of RAS by 2016.

nATs

Traditional therapies for treating malaria include the use of CQ, QN and SP for *P. falciparum,* and PQ for *P. vivax*. There has, however, been a rapid emergence of resistance to these medicines, reducing their efficacy in clinical settings *(53)*. As a result, these therapies have not been recommended for at the least the past 10 years as the first-line therapy for *P. falciparum (6)*.

However, some nATs are recommended as the first-line treatment of uncomplicated *P. vivax*; for example, CQ plus PQ is recommended for *P. vivax* in non-resistance settings where infections are still CQ sensitive *(6)*. WHO also now recommends the use of low-dose PQ alongside an ACT for blocking the transmission of malaria, however, a recent Cochrane review reported that an effective and safe dose remains uncertain *(35, 56)*. For both *P. ovale* and *P. malariae*, CQ also is recommended as the standard regimen, as these two species are still generally considered to be CQ sensitive as well *(6)*.

Additionally, SP monotherapy is recommended by WHO for IPTp and IPTi. The use of SP for IPT is also threatened by increasing levels of resistance to SP in treating acute *P. falciparum* malaria. In 2012, WHO confirmed that SP remains effective for IPTp, even in areas with a high proportion of *P. falciparum* parasites carrying quintuple mutations associated with in vivo therapeutic failures to SP *(38)*. WHO, therefore, recommends that IPTp should still be administered to women in such areas. The use of SP for IPTi, however, is only recommended where parasite resistance to SP is not high *(14)*.

4.2 Pipeline

While the landscape of existing antimalarial medicines represents a powerful set of tools for malaria treatment, there is still a need for improvements to existing products as well as for the development of new products. For example, new products, as well as new drug categories, are needed that specifically address the current limitations of ACTs, including *(55)*:

- artemisinin market volatility;
- complex dosing regimens that challenge patient adherence;
- resistance to partner medications used in ACTs that have been used as monotherapies in the past, such as amodiaquine (56), mefloquine, piperaquine (PPQ) and SP;
- lack of child appropriate treatment courses and poor palatability of paediatric formulations;
- relatively short shelf-life.

Additional needs in malaria treatment include:

- quality RAS formulations for pre-referral treatment in cases of severe malaria when patients may experience over six hours of delay before parenteral treatment can begin;
- single-dose malaria medicines that can treat all types of malaria;
- substitutes for artemisinin, and more broadly ACTs, as a result of emerging resistance;
- alternatives to PQ for treatment and relapse prevention of *P. vivax* malaria given the substantial compliance (requires a 14-day treatment course) and safety issues associated with eight aminoquinolines *(54)*;

- alternatives to SP for use for IPTp and IPTi, considering the growing exposure to resistance to SP;[13]
- suitable medications for chemoprevention in infants and children with characteristics, including a long half-life, appropriate formulations and reasonable palatability;
- medicines that can block the transmission of malaria through activity against the gametocytes for disease elimination programmes; it has been proposed that an ideal medicine for elimination needs to combine transmission-blocking and anti-hypnozoite activity (e.g. ACT + PQ) *(58)*.

The future of global malaria control and elimination depends on the ability of R&D efforts to deliver a steady output of "next generation interventions" to replace those losing their effectiveness due to resistance. To guide these R&D efforts, a recent article has outlined the characteristics of an ideal new drug candidate *(59)*. Key characteristics include availability in oral form and as a single dose in order to maximize compliance, and immediate onset of action so as to rapidly clear parasite load. The ideal drug candidate would result in a clinical response of greater than 95%, and would have an effective concentration of less than 1000 mg as lower doses are less expensive and generally produce fewer gastrointestinal effects. Additionally, there must be a wide margin of safety between the dose required to produce a clinical effect and the point at which the dosing starts to cause adverse effects. The ideal drug candidate also would have bioavailability greater than 50%, since molecules with bioavailability less than 20% tend to vary in exposure and require larger doses. It would not interact with food, other antimalarials, antiretrovirals or tuberculosis medications as co-morbidities are present in a portion of patients and these patients are often taking multiple medications. The ideal candidate would pose no enhanced risk to G6PD-deficient individuals, as significant haemolysis has been observed with other antimalaria medications in G6PD-deficient patients. Finally, manufacturing prices must be similar to other antimalarial medications, ideally costing less than US$ 0.25 for adults and US$ 0.05 for infants under 2 years old.

Since it may not be possible to achieve an ideal drug, compromises likely will have to be made. For this reason, the *minimally acceptable* characteristics of a new drug candidate also have been described *(59)*. Characteristics include availability in oral form as one to three doses, with a clinical response of greater than 50%. Effective concentration should be less than 1000 mg, and there must be an acceptable margin of safety between the dose required to produce a clinical effect and the point at which the dosing starts to cause adverse effects. A new drug candidate should have greater than 30% bioavailability and should have no unmanageable risks in terms of interactions with other drugs. The new drug candidate should pose no enhanced risk to G6PD-deficient individuals based on animal model studies and should have pricing comparable to other antimalarial medications, costing less than US$ 0.5 for adults and US$ 0.1 for infants under 2 years old.

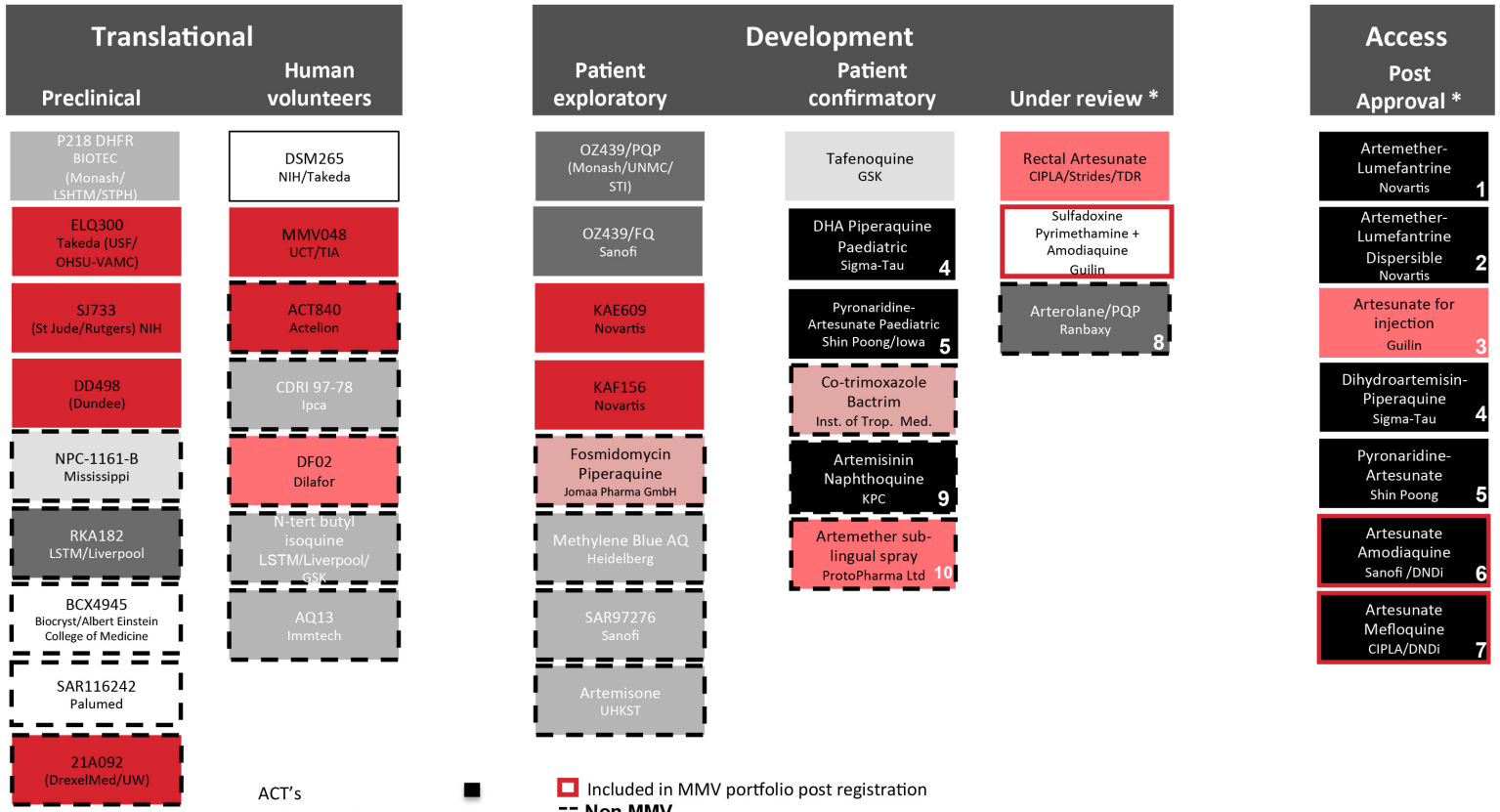
Global funding for malaria R&D

Global funding for all malaria R&D in 2011 was US$ 610M, accounting for around one fifth of the total global funding for neglected disease R&D *(60)*. Funding for overall malaria R&D comes from a variety of sources, with the top 12 funders accounting for 90% (US$2.7 billion) of all malaria R&D funding over the period 2007–2011, and the top five funding organizations (the Bill & Melinda Gates Foundation, the United States National Institutes of Health, the pharmaceutical industry, the European Commission and the United States Department of Defense), accounting for three quarters (74.1%) of total funding *(60)*. Drug development for malaria accounted for around 37% total funding in 2011 *(60)*. Global funding for malaria drug R&D has steadily received around US$ 190–250M each year since 2007 *(60)*. Drug funding has also come from varied sources across the public sector and industry and philanthropic donations. Looking forward, it has been estimated that between 2013 and 2022 malaria drug R&D funding will require around US$ 110–270M per year *(60)*.

MMV, a product development partnership, is a major recipient of global funding, receiving over US$ 67.2M in 2011 and US$ 58.0M in 2012 *(12)*. The majority of the molecules and products in the current global malaria medicine MMV Interactive R&D portfolio are being developed with support from MMV.

13 Many generic versions of SP are available, with varying quality. A recent WHO study of the quality of antimalarial medicines in six sub-Saharan African countries found a 28% quality control failure rate for SP *(57)*.

Figure 9. Global malaria medicines pipeline



1 Brand name: Coartem®, Generics by Ajanta, Cipla, Ipca, Strides, Macleods Pharma Ltd, Mylan Laboratories
2 Brand name: Coartem® Dispersible, Generic by Ajanta
3 Brand name: Artesun®
4 Brand name: Eurartesim®
5 Brand name: Pyramax®
6 Brand names: Coarsucam™, ASAQ/Winthrop®, generics by Ajanta, Ipca, Guilin, Cipla, Strides (co-blistered)
7 Also Acino/Mepha product (co-blistered)
8 Brand name: Synriam™
9 Brand name: ARCO®
10 Brand name: ArTiMist™

Source: Adapted from MMV. Defeating malaria together: interactive global R&D portfolio, global malaria portfolio at the end of the 2nd quarter 2014 (www.mmv.org/research-development/rd-portfolio, accessed July 2014).

The global malaria medicine pipeline is more extensive than it has ever been (Figure **9**). Products currently in registration include an RAS formulation for pre-referral treatment of severe malaria *(13)*. These medicines are listed in further detail below.

These medicines are listed in further detail below.

- **Artesunate I.R. (Registration)**
  A rectally administered artemisinin derivate for severe malaria reduces risk of death or permanent disability if severe malaria cannot be treated orally or access to injectable solutions is not available within six hours *(6)*. With support from UNITAID, MMV is working with the Special Programme for Research and Training in Tropical Diseases (TDR) and pharmaceutical partners to support the submission of an RAS dossier to the WHO PQP in 2015 *(13)*.
- **AQ + SP (Launched; WHO PQP-approved in October 2014)**
  A co-blistered combination of AQ + SP (153 mg + 525 mg) for SMC was prequalified in October 2014 *(45)*. MMV, working with the manufacturer and Médecins sans Frontières, developed user-friendly packaging to ensure proper patient use and patient cards to help ensure correct dispensing by community health-care workers *(13)*. The tablets that are manufactured at present are not ideal for use in infants, as they would require tablets to be individually cut, and a lack of taste masking is likely to pose challenges, particularly as AQ has a very bitter taste. However, a dossier for an infant pack (75 mg + 262.5 mg) was submitted to the WHO PQP in 2013 *(61)*. In addition, MMV is working with the same manufacturer to evaluate a dispersible formulation of AQ + SP *(61)*.
- **Arterolane maleate + PPQ (Approved by the Drug Controller General of India, yet to be submitted to an SRA)**
  Arterolane is the first fully synthetic, non-artemisinin, oral antimalarial compound with rapid parasitical activity. This component has been found to also provide fast relief from malaria symptoms including fever *(62)*. Developed as an FDC of arterolane with piperaquine, this therapy has a simplified once daily for three days dosing regimen for the treatment of acute, uncomplicated *P. falciparum* in adults *(62)*. This drug was approved in 2011 by the Drug Controller General of India, but has yet to be submitted for approval by an SRA *(62)*.

A variety of products in Phases II and III represent ACTs, endoperoxides, synthetic endoperoxides, aminoquinolines, antibiotics and natural products *(13, 55)*. Several of these products show high potential for public health and market impact including:

- **tafenoquine (Phase III)**
  This 8-amiloquinoline is the only molecule in the pipeline with published activity against *P. vivax* hypnozoites *(13)*. In contrast to PQ, this medicine has a long half-life that would reduce treatment from 14 days (as required with PQ, the only medicine recommended today for liver-stage cure) to a single-dose cure, thus enhancing treatment compliance *(13)*. As with PQ, there are safety concerns for patients who carry the G6PD deficiency, and G6PD screening will be a necessary step before drug administration *(13)*. The Phase III trial began in April 2014. The FDA has granted breakthrough status for tafenoquine and the launch of this product could be expected as early as 2017 *(61)*.
- **ASPY dispersible for paediatric use (Phase III)**
  A granule formulation has been developed specifically for use for children and is currently in late phase trials. This ACT offers once-a-day dosing for three days and shorter fever and parasitic clearance times. A dossier for the granule presentation has been submitted to EMA for approval via Article 58, the same regulatory route that was used for the approval of the solid tablet version of this medicine in 2012 *Medicines for Malaria Venture (13)*.

- **DHA PPQ for paediatric use (Phase IIb/III)**
  Development is under way for a dispersible formulation of this drug whose solid tablet formulation was approved by EMA in 2011. The dossier is expected to be submitted to EMA in 2015 *(61)*. DHA PPQ is dosed once a day for three days and provides longer protection from new malaria infections compared to other ACTs because of the relatively long half-life of PPQ *(13)*.
- **OZ439 (Phase IIb)**
  This product is a fully synthetic peroxide under development by MMV, and could provide an alternative to the currently available artemisinin derivatives *(13)*. Studies have suggested that OZ439 is fast acting, has a good safety profile, might have greater efficacy at lower doses and has potential to be developed as a single-dose combination. There is potential for this drug to enter the market as a single-dose cure for uncomplicated *P. falciparum* malaria *(61)*. It is currently in Phase II trials that will help determine an optimal partner drug (either ferroquine or piperaquine) with which it will be coupled as an FDC. It should be cost competitive with ACTs, but it is not expected to be approved as an FDC formulation before 2018, with market launch expected in 2018 *(61)*.
- **KAE609 (Phase IIa)**
  Spiroindolone KAE609 is a synthetic antimalarial molecule with a novel mechanism of action with the potential to inhibit *P. falciparum* and *P. vivax (63)*. Its chemistry and mode of action differ from those of artemisinin derivatives; it is, therefore, highly unlikely that it is cross-resistant to them. This candidate is fast acting and has the potential to be part of a single-dose FDC cure *(13)*, and a possible partner for OZ439 *(61)*. It is one of a few molecules with the ability to cure a *Plasmodium berghei* model of blood-stage malaria, and it is the first molecule with a novel mechanism of action to enter Phase IIa studies for malaria in the last 20 years *(13)*.
- **KAF156 (Phase IIa)**
  KAF156 is from the novel class of antimalarial compounds imidazolopiperazines, and has been identified to have the potential to treat, prevent and block the transmission of *P. falciparum (56)*. KAF156 also has favourable properties for once daily dosing. This compound is currently in clinical trial to identify suitable dosages to take it forward, and is moving towards clinical development. While drug-resistant mutations of KAF156 are thought to be rare, it has been found that resistance can be easily acquired with a few single-nucleotide polymorphisms *(56)*. For this reason, the identification of suitable drug partner will be crucial to the development of KAF156.

There are also numerous new chemical entities currently in the transition and development pipeline, which are necessary for addressing parasite resistance to all existing malaria classes *(55)*. Of the 16 candidates in Pre-clinical and Phase I (research and translational) stages of development, 4 are currently on hold *(13)*. One specifically targets *P. vivax* and one targets severe malaria. Additionally, only two candidates have potential for transmission blocking (ELQ300 and MMV048).

Drug candidates removed from the pipeline

Importantly, AZCQ has been removed from the pipeline since publication of the first edition of the UNITAID *Malaria medicines landscape (61)*. MMV was working with Pfizer and LSHTM to develop an FDC tablet of this medicine to replace SP for IPTp, however, development of this product has ceased *(61)*. Now, there are currently limited alternative therapy options in the pipeline specifically for use in IPTp. Co-trimoxazole (Phase III) is a potential candidate for IPTp, however there are concerns with daily administration and safety in HIV-positive populations when taken with SP *(64)*. Piperaquine based combinations are currently being evaluated, as well as DHA PPQ for intermittent screening and treatment (ISTp) *(65)*. Additionally, there are no new drugs in development for use in IPTi, but studies have recently taken place to evaluate the potential of DHA PPQ for IPTi *(66)*. As populations in areas where resistance to SP is growing, new IPT therapies are urgently needed.

5. Market landscape

Key malaria market landscape messages:

- The volume of procured quality-assured ACTs (QAACTs) has increased rapidly over the past decade, from 11M treatment courses in 2005 to 392M in 2013, however, growth is now beginning to plateau.
- The market share of ACT volumes procured in the donor-funded market remains highly concentrated on AL and ASAQ, which together accounted for 74% and 26% of ACTs delivered in 2013, respectively.
- The AL market is becoming increasingly distributed across prequalified suppliers. In 2012, three generic manufacturers together had secured 67% of the AL market procured by international donors, compared to 27% for Novartis Pharma (hereinafter Novartis). While 2013 data are incomplete, they suggest that Novartis' market share decreased to around 12%.
- In 2012, Sanofi accounted for approximately 98% of ASAQ volumes procured. Between June and November 2012, six more FDC ASAQ became prequalified from two manufacturers (Ipca Laboratories Ltd [hereinafter Ipca] and Guilin), however, these still represent very small portions of the market.
- Between 2005 and 2012, the number of child-packs of AL delivered to the public and private sector has increased. In 2012, 68% of all AL procured was for children, but of this only 26% was the dispersible formulation. For ASAQ/AS+AQ, the proportion of child-packs of both FDC and co-blister has been more in favour of child-packs since 2008.
- A significant portion of market growth in recent years is attributable to AMFm). As AMFm is now integrated into the Global Fund core grant mechanism, the extent to which countries will request funding for private sector price subsidies remains uncertain.
- In 2014, the Global Fund reformed its procurement model. The tender conducted under this new model is likely to impact both market share and price in the near future (e.g. a cost savings of 32% is estimated).
- The private sector is still a channel where many people access malaria treatment (approximately 40%), yet a gap remains between ACT penetration in the private sector and the public sector.
- At the facility level, ACT prices remain substantially higher than nATs, and these therapies still represent a significant proportion of total antimalarials distributed in both the public and private sectors.
- The uptake of INJAS remains low, but is growing. Access to pre-referral treatment of severe malaria is also hindered by the lack of a WHO prequalified/SRA-approved product, although efforts are under way to have a product submitted to the WHO PQP in 2015.
- The proportion of the donor-funded ACT market directed at the WHO South-East Asia Region and Western Pacific Region is increasing. Available data suggest that it represented approximately one quarter of the donor-funded ACT market in 2013.
- Donor-funded PQ procurement volumes have increased significantly, particularly in the South-East Asia Region and Western Pacific Region. Currently, available data indicate that procured volumes were at least 41M treatment courses in 2013, compared to only 4M in 2011.
- Artemisinin spot market prices are around US$ 250/kg, which is less than the break-even point for artemisinin extractors. Low prices could impact the quantity of *A. annua* harvested in 2014 as well as future plantings. A significant decline in cultivation in 2015 could lead to an artemisinin shortage and/or high market prices in 2016-2017.
- The first delivery of ACTs produced with semi-synthetic artemisinin (SSA) to endemic countries occurred in 2014. The total production capacity of SSA is approximately 60 tonnes per year, which is currently not being fully utilized due to the lack of ACT manufacturers (beyond Sanofi) that have gone through the WHO prequalification process needed to supply SSA-based ACTs.

5.1 Growth and evolution of the ACT market

In the early 2000s, ACTs represented only a small proportion of the total antimalarial market. At that time, malaria was generally treated using "traditional therapies" such as CQ, QN, SP, etc. These therapies have been readily available and generally affordable in the markets of most endemic countries. When, in 2006, WHO published their first malaria treatment guidelines recommending ACTs, the nascent ACT market encountered several challenges, or *market shortcomings*, that needed to be addressed in order to scale up access. The market challenges included:

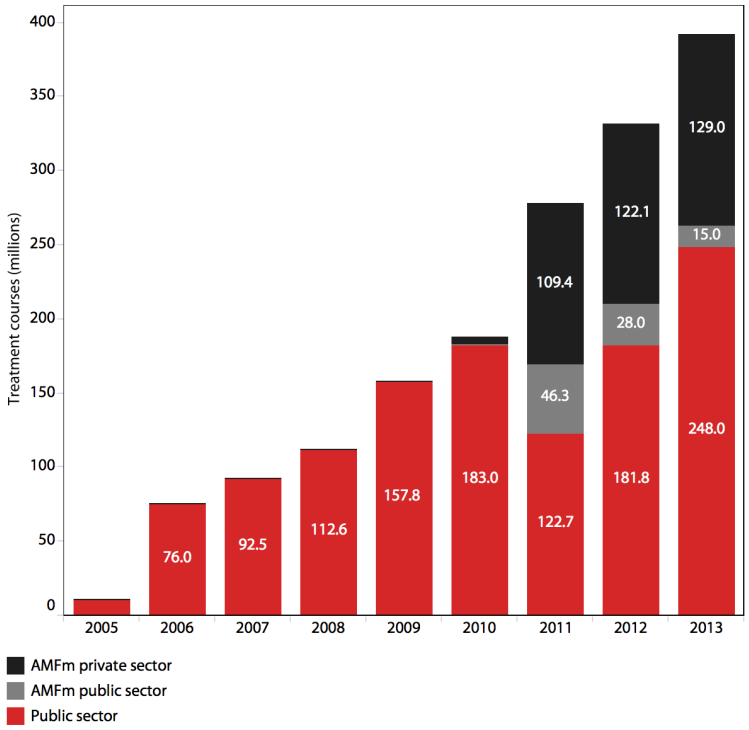
- the availability of *quality*-assured products;
- the *affordability* of quality ACTs;
- the *delivery* mechanisms to both the public and private sectors;
- the *acceptability* and *adaptability* of ACTs that were available in the market (e.g. limited FDCs and dispersible products for children, more complex dosing regimens).

For more information on the market shortcomings listed above, refer to the first edition of UNITAIDs *Malaria medicines landscape*.

Since 2006, considerable efforts have been made to scale up access to ACTs and to respond to the market shortcomings detailed above. The volume of procured QAACTs has increased rapidly over time, from 11M treatment courses in 2005 to 76M in 2006, 278M treatment courses in 2011, 331M in 2012 and reaching 392M in 2013 (Figure 10) *(2)*. In parallel to international efforts, national policy adoption by endemic countries also has increased whereby, at the end of 2013, 79 of the 88 countries with endemic *P. falciparum* had adopted national treatment policies listing ACTs as the first-line treatment *(2)*.[14] Domestic funding has also been increasing, particularly in the WHO African Region where investments have grown at an average rate or 4% since 2005 *(2)*. If endemic countries continue to increase their funding towards malaria control, there may be an upward impact on future ACT volumes.

14 Data provided by eight manufacturers eligible for procurement from WHO/UNICEF and AMFm reports.. Routine ACT public sector deliveries monitored 2005–2012; AMFm-facilitated public and private sector deliveries through the AMFm monitored deliveries 2010–2012, in 2010 by AMFm reports and in 2011–2012 by reports of manufacturers. ACT deliveries through non-AMFm private sector channels are not monitored, but are estimated to be a small fraction (approximately 5–10%) compared to public sector deliveries.

Figure 10. ACT deliveries, by health sector and initiative status, 2005–2013



Sources: World malaria report 2014 *(2)*.

Global interventions also have had a key role in tackling the market shortcomings limiting access to ACTs, particularly in relation to the high prices of ACTs. These interventions include: increased international donor funding for malaria control; the UNICEF ACT Scale-Up Initiative; incorporation of ACTs in the WHO PQP; the introduction of AMFm; and the Artemisinin and ACT Demand and Supply Forecasting service. AMFm is described in detail below and the other interventions are described in further detail in the first edition of the UNITAID *Malaria medicines landscape*.

AMFm

An important part of the evolution of the ACT market was the introduction of AMFm, an innovating financing mechanism designed to expand affordable access to ACTs and to reduce the use of less effective therapies that promote drug-resistant malaria *(18)*. AMFm was introduced into the donor-funded ACT market to enhance access and to address affordability barriers, particularly due to the size, quality and opaque nature of the private antimalarial market. Hosted by the Global Fund, AMFm was launched as a pilot in 2010 in eight malaria endemic countries (Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda and the United Republic of Tanzania) *(67)* and was integrated into the Global Fund grant mechanism at the end of 2013.

Along with scaled-up investments from international donors and increased procurements for routine public sector deliveries, medicines procured through AMFm contributed to the increase of ACT volumes delivered in both the public and private sectors in 2012 *(3)*. Through the AMFm novel price subsidy co-payment, ACTs were made available in the private sector at a lower price in the eight AMFm pilot countries. Also, through the AMFm subsidy and negotiations with manufacturers, private importers paid up to 80% less than they did in 2008–2009, and with the supporting interventions component ACT awareness and use increased *(67)*. In particular, programmes where the subsidy worked alongside supporting interventions had been effective in rapidly improving availability *(67)*.

The future of the donor-funded ACT market

In November 2012, the Global Fund Board decided to integrate AMFm into the core Global Fund grant management and financial processes following an orderly transition period in 2013 *(68)*. With that decision, AMFm is now (as of 2014) included with the Global Fund indicative funding process rather than as supplementary funding to country grants. Therefore, the private sector co-payment is no longer limited to countries that participated in the AMFm pilot, and is also open for health commodities beyond just those intended for the use in malaria treatment. As funding is now incorporated into the regular grant mechanism, countries will need to allocate a proportion of funding from their overall allocation *(68)*. Whereas, through AMFm, funding for the private sector co-payment was provided in addition to countries' regular grant portfolio.

The Global Fund has also made two core changes to the management of finances and procurement processes that have been implemented in parallel to each other. These changes will likely influence the ACT market, but to what extent is still unknown. First, the Global Fund has implemented a new funding model, named the Investment for Impact, for recipients of donor funds for 2014–2016. Under this model, countries are now assigned an indicative amount of funds according to their malaria burden and their ability to pay for malaria control. At a global level, malaria programmes have been allocated approximately 30% of the total amount of funds disbursed by the Global Fund *(69)*. Of this 30%, lower-income, higher-burdened countries have been allocated 76% (58% to sub-Saharan Africa and 7% to South-East Asia[15]), and higher-income, higher-burdened countries have been allocated 15% (12% to sub-Saharan Africa and 3% to South-East Asia) of malaria funding for 2014–2016 *(69)*.

Moreover, the Global Fund has also revised their procurement model. The P4i, has been designed to deliver efficiencies and to improve impact *(70)*. There are five elements of this new strategy that will have a direct impact on the ACT donor-funded market looking forward:

1. joint ACT forecasting between the Global Fund and PMI will deliver two-year forecasts for suppliers;
2. longer-term contracts with suppliers established through a tender process;
3. a balanced approach to both originators and generic manufacturers to support and reward innovation;
4. volume visibility for suppliers;
5. encourage local manufacturing.

One mechanism incorporated into P4i is the Global Fund Procurement and Supply Management (PSM) process. In March 2014, the Global Fund held a Supplier Conference to discuss P4i and Procurement and Supply Management that have now both been implemented *(70)*. Under the new initiative, the Voluntary Pooled Procurement has been renamed the Pooled Procurement Mechanism and AMFm is now called the Private Sector Co-Payment Mechanism (Co-payment Mechanism) *(70)*. The architecture of the new process requires suppliers to bid under a competitive tender. Successful bidders will receive an allocated volume across both the Pooled Procurement Mechanism and the Co-payment Mechanism. Additionally, the Global Fund will only procure FDCs and the new process will also see the introduction of supplier volume caps set at *(70)*:

- 40% for AL non-dispersible products;
- 75% for AL dispersible products;
- 40% for ASAQ products.

Some key market objectives of this new strategy are to achieve price reductions across products based on a weighted average price and to assist suppliers of both artemisinin and ACTs with supply and demand forecasting. This strategy aims to enable loner term production planning and stabilizing raw material prices by cascading demand forecast from the final pharmaceutical product producers to the raw material

15 Based on Global Fund geographic regions and Asia and includes south Asia, east Asia and the Pacific.

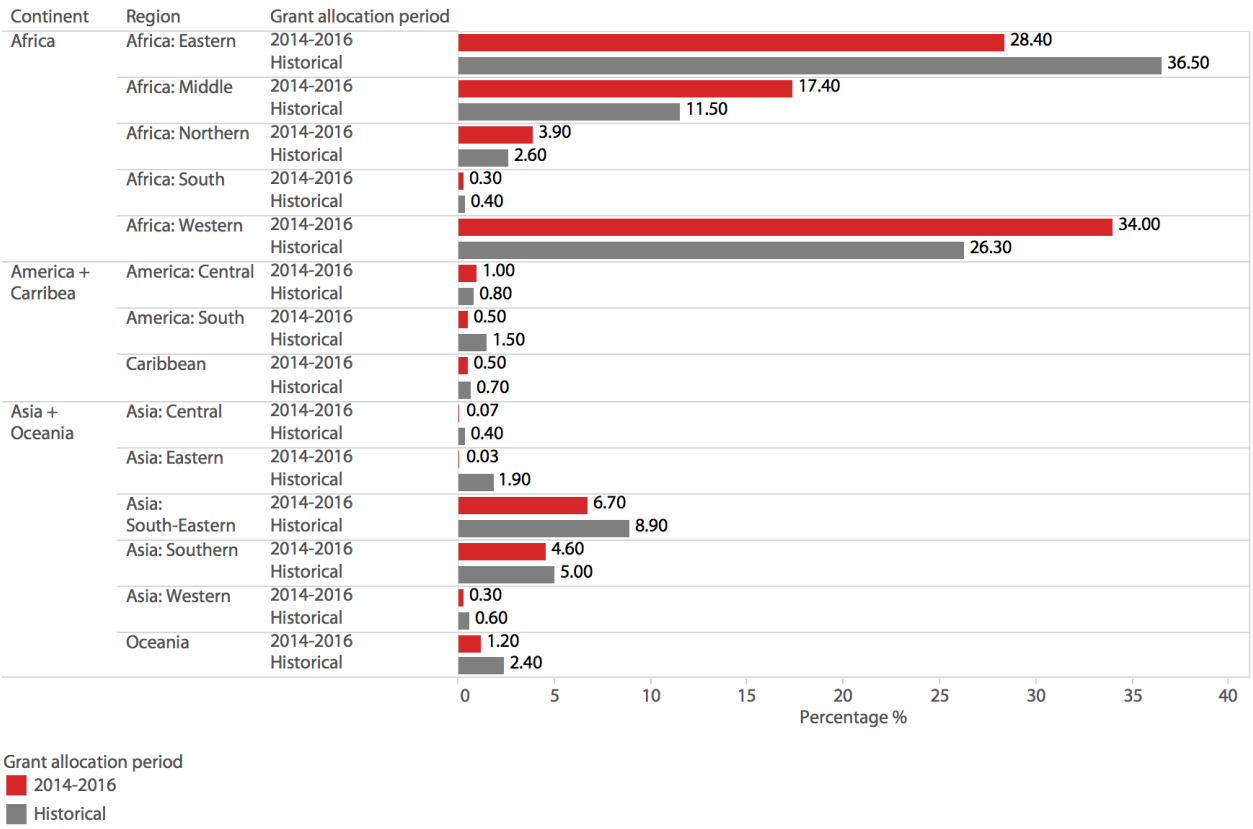
producers (farmers and extractors). The Global Fund suggests that overall the new process has delivered approximately 32% savings (US$ 102M over two years) *(71)*. However, as these changes commenced at the beginning of 2014, the longer-term impact this will have on private sector availability, price and, therefore, ACT access is still to be determined.

Over time, the ACT donor market is likely to be influenced by the concurrent scaling up of rapid diagnostic tests (RDTs). This is because of the wide use of ACTs to treat suspected and confirmed malaria cases. If RDTs are used increasingly in the coming years, with good adherence to test results, the need for malaria treatment may reduce substantially *(2)*. There are several scenarios, however, under which ACT demand may increase with RDT scale-up, including: (i) the more people are tested for malaria, the more likely they will receive an ACT compared to other antimalarial medicines; (ii) RDT negative results may still be treated with an ACT; and (iii) as household surveys have found that approximately 40% of febrile children does not present for treatment, there may be a period where ACT demand increases if RDT projects target this specific population *(2)*.

International donor funding

External expenditure on malaria control has expanded over the past 10 years, with international disbursements rising steeply from less than US$ 100M in 2000 to US$ 2.18 billion in 2013 *(2)*. However, international funding figures represent approximately 52% of the annual estimated funding requirements *(2)*. The Global Fund has consistently been the biggest source of malaria control funding, accounting for approximately 50% of disbursed funds in 2013 *(2)*. International disbursements have slowed in recent years, growing at around 3–4% per year from 2009 to 2013 compared to an increase average of 43% per year between 2005 and 2009 *(2)*. Under the new funding model, Global Fund grant allocations for malaria programmes for 2014–2016 amounted to approximately US$ 4.3 billion *(69)*. There is also a notable shift in the proportion of Global Fund grant allocations directed to specific regions under the new funding model. For example, allocations to Africa have increased by 6%, from 78% (2004–2013) to 84% (2014–2016) (Figure 11) *(69)*. Grants allocated to Asia have decreased by approximately 5%, from 19% (2004–2013) to 14% (2014–2016) *(69)*. The extent to which these shifts in grant allocations will impact future ACT procurement volumes remains unclear *(3)*.

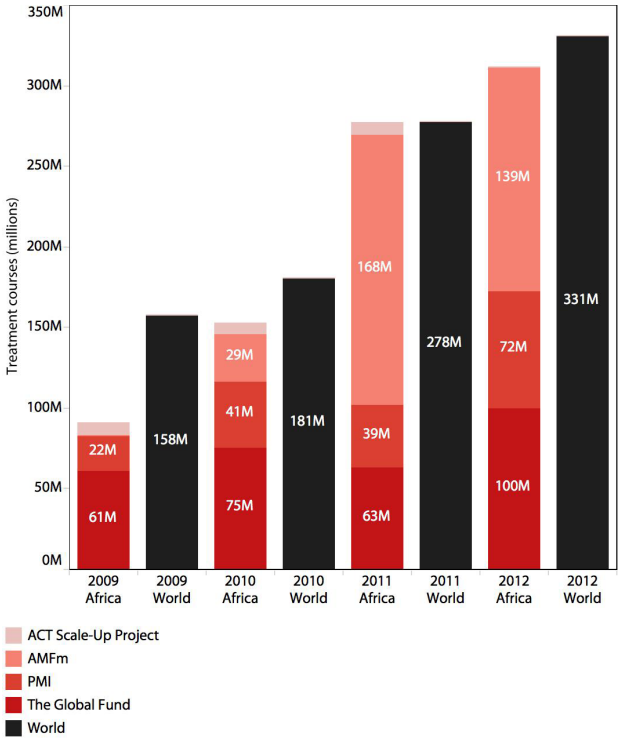
Figure 11. Global Fund malaria programme grant allocations over time, by United Nations geographical regions (2004–2016)



Note: Historical grant allocations are based on the Global Fund cumulative confirmed commitment amount from 2004 to 2013.
Source: Derived from the Global Fund 2014 *(69)*.

Most malaria donor funding has gone to sub-Saharan Africa and has mainly been allocated to malaria prevention (42%) and treatment (31%) *(1)*. The donor community is responsible for purchasing the majority of ACTs in Africa (Figure 12), which is aligned geographically with the greatest disease burden. International funding for ACTs in sub-Saharan Africa has been highly concentrated by two donors – the Global Fund, including AMFm, and PMI. A large number of countries rely on Global Fund financing for procuring ACTs, and public sector procurement using Global Fund grants contributes to more than one third of the global ACT market *(1)*.

Figure 12. Number of ACTs procured for Africa compared to total donor procurement (world), 2009–2012



Note: Total donor market ("World" bars in the figure) reflects ACT procurement volumes reported in the *World Malaria Report 2013*.
Sources: Calculated from transactions reported in the *World Malaria Report 2013*, Global Fund PQR data, AMFm data and published PMI annual reports.

5.2 UNITAID and scaling up ACTs

UNITAID strategic funding for specific interventions, together with constructive engagement with the international community, has been instrumental in supporting the scale-up of QAACTs. Over the last seven years, UNITAID made two major investments specifically targeting the scale-up of ACTs in both the private and the public sector. These include:

- Private sector ACT scale-up initiatives – UNITAID invested US$ 211M in AMFm between 2009 and 2013 *(72)*. UNITAIDs investment contributed to the delivery of 472.9M ACT treatment courses *(67, 73)*;
- Public sector ACT scale-up initiatives – UNITAID committed US$ 78.9M over the timeframe of December 2007 to June 2010 to the UNICEF ACT Scale-Up Initiative. By December 2010 had delivered 37.7M treatment courses *(67, 73, 74)*. The ACT Scale-Up Project was initiated in 2007 to provide quality ACTs to eight countries and helped increase access to ACTs by establishing a sustainable financing model. UNITAID also supported the Global Fund Round 6, Phase 1 project and committed US$ 21.5M to the project from 2007 to 2010. This project facilitated the delivery of 4.5M treatment courses in 13 countries by the end of 2012 *(67,73)*.

Overall, by 2013, over 516M ACT treatment courses had been delivered through UNITAID support *(67,73)*.

Addressing other antimalarial market gaps, UNITAID invested over US$ 104M in the WHO PQP for 2006–2016 *(75)*. This programme has been instrumental in enabling governments and the donor community to access high-quality medicines for procurement. UNITAID also invested in A2S2, which provided market intelligence on the artemisinin supply to improve stability in the market. UNITAID committed US$ 9.2M to A2S2, and 36 tonnes of the plant artemisinin (15% of global demand) have been secured by brokering contracts between growers and extractors to produce ACTs (76). UNITAID also supports artemisinin and

ACT demand and supply forecasting. From 2009 to 2013, UNITAID invested US$ 1M in this initiative *(77)*. A full description of these projects and other commitments made by UNITAID can be found in the first edition of the UNITAID *Malaria medicines landscape*.

5.3 Current ACT market

Reference to ACTs throughout this section refers to prequalified ACTs unless otherwise stated.

5.3.1 Market size

5.3.1.1 Market size by volume

Three major delivery channels have determined the overall market size for ACTs: (i) the public sector (including the AMFm public sector procurers); (ii) the AMFm private sector; and (iii) to a lesser extent, the premium private sector (unsubsidized not engaged with AMFm).

Market size of the donor-funded public sector

The public sector has been a key channel for ACT scale-up efforts. Delivery volumes in this sector grew from 11M treatment courses in 2005 to 183M treatment courses in 2010 (Figure 10) *(2)*. Total public sector (including the AMFm public sector) ACT volumes decreased from 183M treatment courses in 2010 to 169M in 2011. Approximately 17% (46M) of 2011 volumes was delivered by the AMFm public sector *(2)*. In 2011–2012, total public sector deliveries increased by around 7% (from 169M to 181M courses procured). During that time, the proportion of the AMFm public sector volumes decreased to 28M *(2)*.

Market size of the donor-funded private sector

It is estimated that 40% of malaria patients worldwide seek treatment in the private sector, and in some countries it may be greater, making this an important source of treatment of malaria in many countries *(2)*. Between 2010 and 2013, AMFm was the primary mechanism for donor intervention in the private sector antimalarial market. Of the total number of ACT treatment courses delivered by donors in 2011, approximately 39% (109M) was delivered by the AMFm private sector (Figure **10**) *(2)*. In 2012, volumes of procured ACTs delivered by the AMFm private sector increased to 122M. Engaging the private sector, however, remains difficult because of higher ACT prices that are often prohibitive compared to less effective monotherapies *(78)*. While the AMFm private sector volumes in the eight participating pilot countries represent a substantial proportion (approximately 37% in 2012) of ACTs delivered, they represent a small proportion of the total antimalarial private sector market. Overall, ACT penetration in the private sector remains limited, and has been inhibited by prices that are higher than monotherapies and are often unaffordable. Additionally, the impact that the transition of AMFm to the private sector Co-payment Mechanism will have on the private market is unknown and needs to be monitored closely. These issues are discussed in more detail in Section 5.4.2 and Section 5.4.3.

Delivery and demand in the overall private sector

The overall demand for all antimalarials (ACTs, nATs and AMTs) includes confirmed malaria cases and unconfirmed malaria cases due to a lack of diagnostic testing of febrile patients. Because of this, the size of the total antimalarial market in the private sector is estimated to be much larger than the number of actual malaria cases that occur each year *(78)*. One study estimated that, in 2010, 655M antimalarial treatments were delivered through the private sector in Africa, compared to 174M estimated malaria cases *(78)*. Together with a substantial public sector market, the total annual demand for antimalarials could possibly exceed 1 billion treatment courses *(78)*. nATs have been available in both the public and private markets of most endemic countries for many years, have a lower production cost than ACTs, are often produced by local manufacturers in malaria endemic countries, and may not be quality assured. In the private sector specifically, nATs are generally inexpensive and, therefore, readily available and affordable compared to ACTs *(79)*.

Forecasted market volume trends of donor-funded ACTs

For 2014, actual delivery volumes are still to be determined. While in 2013 there was an increase in ACT treatment courses procured from 2012 (Figure 10), donor-funded ACT deliveries are expected to decrease in 2014 *(77)*.

Looking ahead, there is significant uncertainty around procurement levels for QAACTs stemming from several factors:

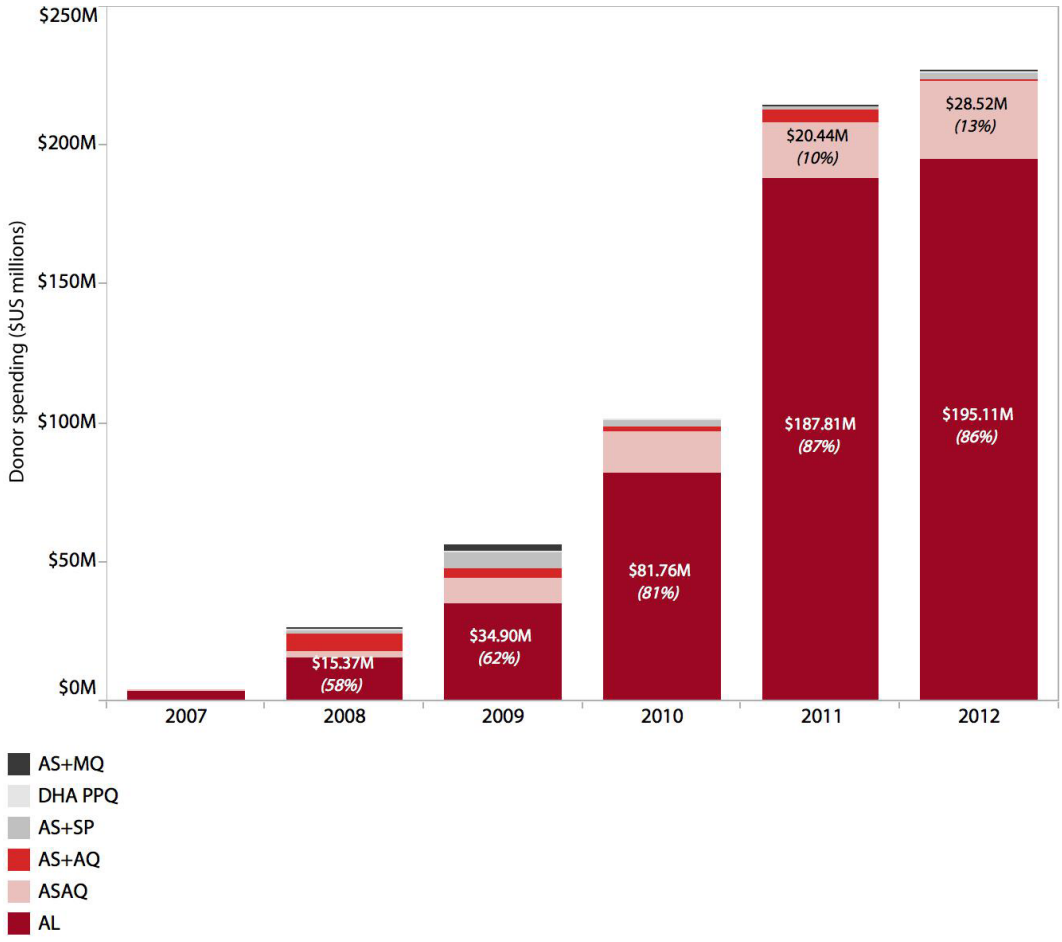
- In the short term, the effect of AMFm being integrated into Global Fund indicative funding for private sector ACT procurements and the effect of the Global Fund P4i on overall procurement volumes.
- The effect of the level of replenishment on future Global Fund grants and the timing of when these funds will become available.
- In the longer term, the effect of scaled-up RDTs potentially reducing the demand for malaria treatments. Currently, malaria test positivity rates in the WHO African Region are below 50% and, therefore, the ratio of diagnostic tests to ACTs should be at least two if all suspected cases receive a test *(2)*. If RDTs were effectively scaled up in the coming years, then the need for malaria treatment may be reduced.
- The impact of future malaria elimination programmes, e.g. potential mass drug administration campaigns *(80)*, and the impact of increased efforts to target *P. vivax* in endemic areas.

Market value of donor-funded ACTs

While the total value of donor-funded ACTs is unknown, data from the Global Fund and AMFm can give some indication as these sources represented approximately 73% in 2010, 86% in 2011 and 62% in 2012 of the ACT donor market by volume (excluding PMI volumes) (Table **5**). Using these data, the value of all ACTs (AL, ASAQ, AS + AQ, AS + MQ, AS + SP and DHA PPQ) procured in the donor market has grown since 2008, where the value of ACTs procured by the international community was approximately US$ 26M, hitting a peak in 2012 of a total market value of US$ 226M (Figure 13).[16] This represents a compound annual growth rate (CAGR) of 115% between 2008 and 2012.

16 The value of the donor-funded ACT market has been estimated using the merged results from the Global Fund PQR AMFm database.

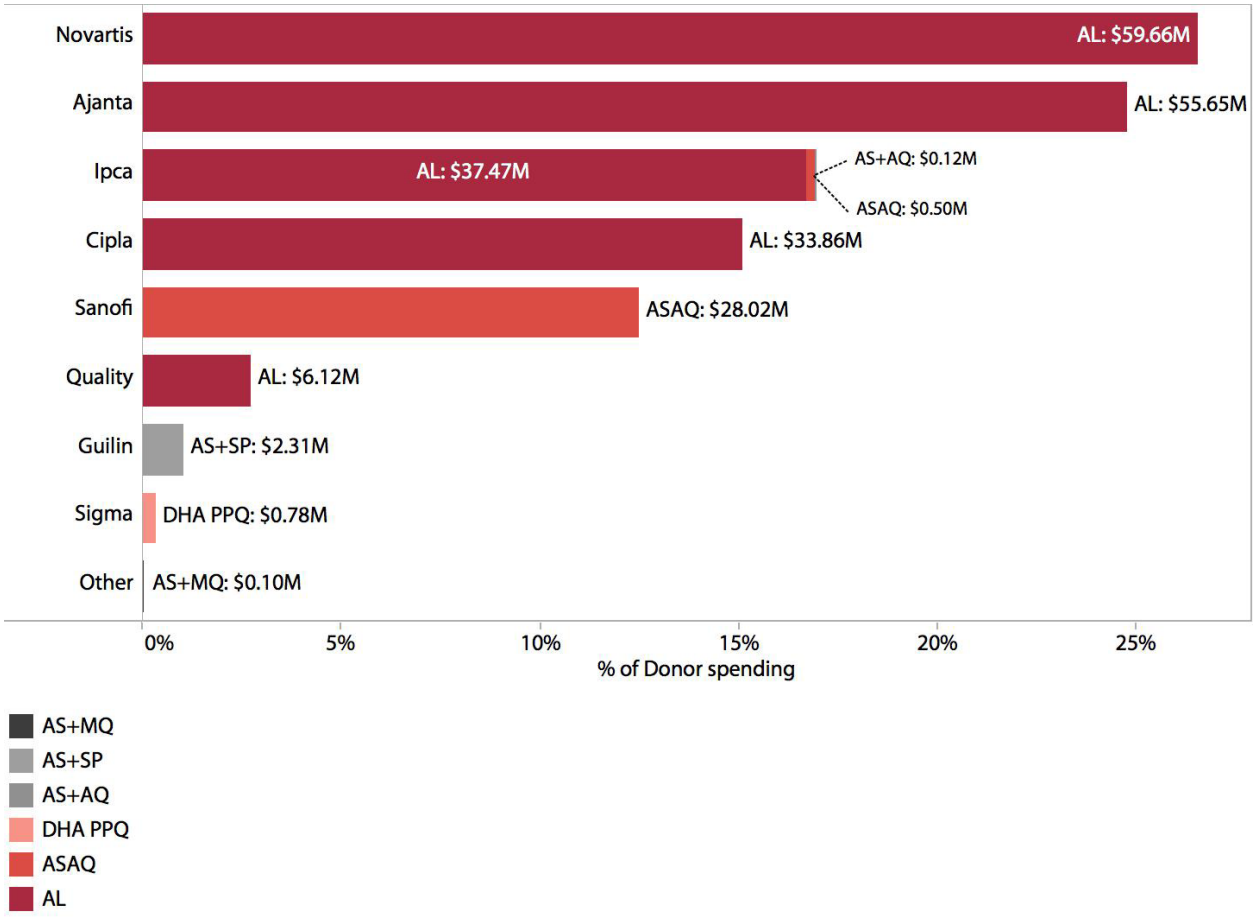
Figure 13. Value of the donor-funded prequalified ACT market over time, by ACT, 2007–2012



Note: The figures represented are indicative of all ACTs and all pack types procured via the Global Fund and AMFm from 2007 to 2012; this includes: AL; ASAQ; AS+AQ; AS+MQ; AS+SP; and DHA PPQ.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

There are currently nine manufactures that produce prequalified ACTs, and the manufacturers supplying AL account for the largest procurement value in the donor market. The value of the AL market in the donor-funded environment amounted to around US$ 193M in 2012 Novartis (US$ 59M) and Ajanta Pharma Ltd (hereinafter Ajanta) (US$ 55M) accumulated the greatest values through procured ACTs in 2012. While ASAQ/AS + AQ is the second most procured ACT in the donor market, the procurement value was approximately US$ 28M in that same year (Figure 14). Novartis (US$ 59M) and Ajanta Pharma Ltd (hereinafter Ajanta) (US$ 55M) accumulated the greatest values through procured ACTs in 2012. While ASAQ/AS + AQ is the second most procured ACT in the donor market, the procurement value was approximately US$ 28M in that same year.

Figure 14. Value of donor-funded ACT market in 2012, by manufacturer ($US)



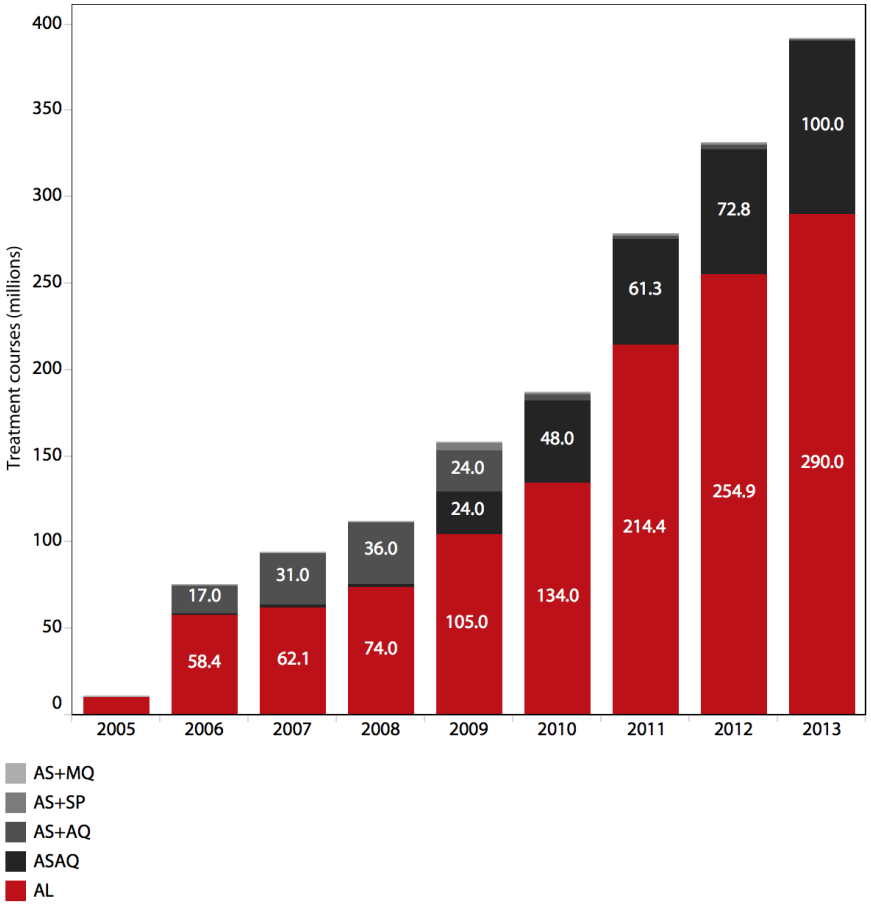
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.3.2 Market share

5.3.2.1 Donor-funded market share by product

The market share of ACT volumes procured in the donor-funded market remains highly concentrated on two ACTs – AL and ASAQ – which accounted for 74% (290M treatments) and 26% (100M treatments) of ACTs delivered in 2013, respectively (Figure 15) *(2)*. For this reason, analysis of the market share in the donor-funded market is focused on these two ACTs unless otherwise stated.

Figure 15. ACT deliveries to the public and private sector, 2005–2013

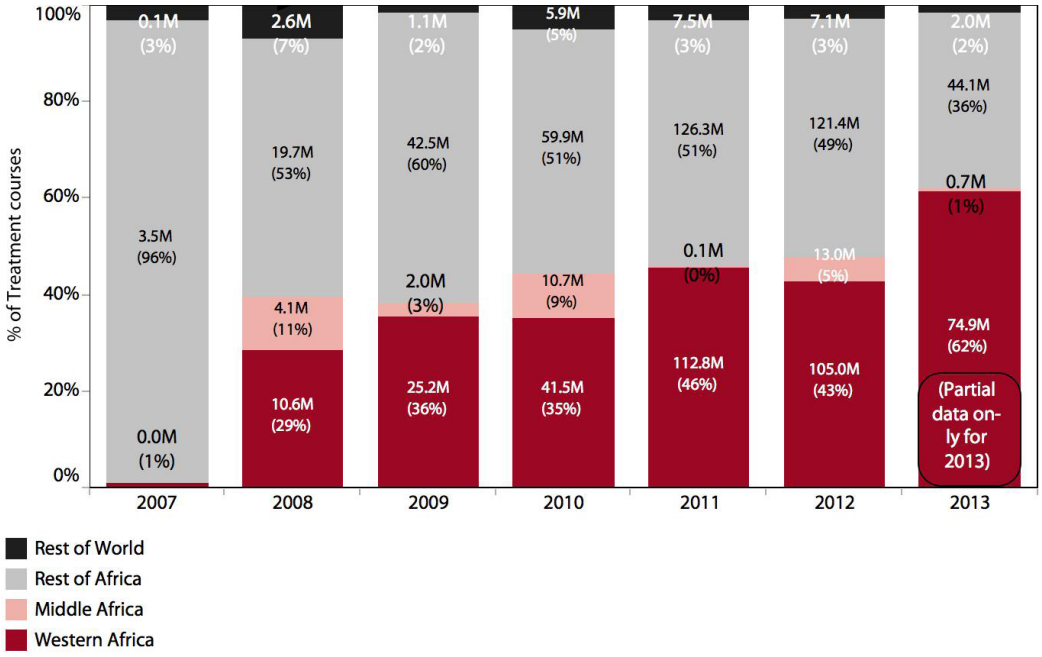


AL, artemether-lumefantrine; AQ, amodiaquine; AS, artesunate; MQ, mefloquine; SP, sulfadoxine-pyrimethamine.
Sources: World malaria report 2014 (2).

5.3.2.2 Donor-funded market share by region

The market share of ACT volumes procured in the donor-funded market has been consistently greatest in the African region. This trend is aligned with Africa bearing the greatest burden of malaria cases (82%) and deaths (90%) *(2)*. For example, in 2012, 97% of ACTs procured by donors was for Africa with the majority of volumes procured for eastern/southern Africa (49%) and western Africa (43%) (Figure 16). As the proportion of Global Fund grant allocations has increased for middle and western Africa for 2014–2016, the market share of ACT volumes procured for these regions may increase accordingly *(69)*.

Figure 16. ACTs procured in the donor-funded market by United Nations geographical region, 2007–2013



Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

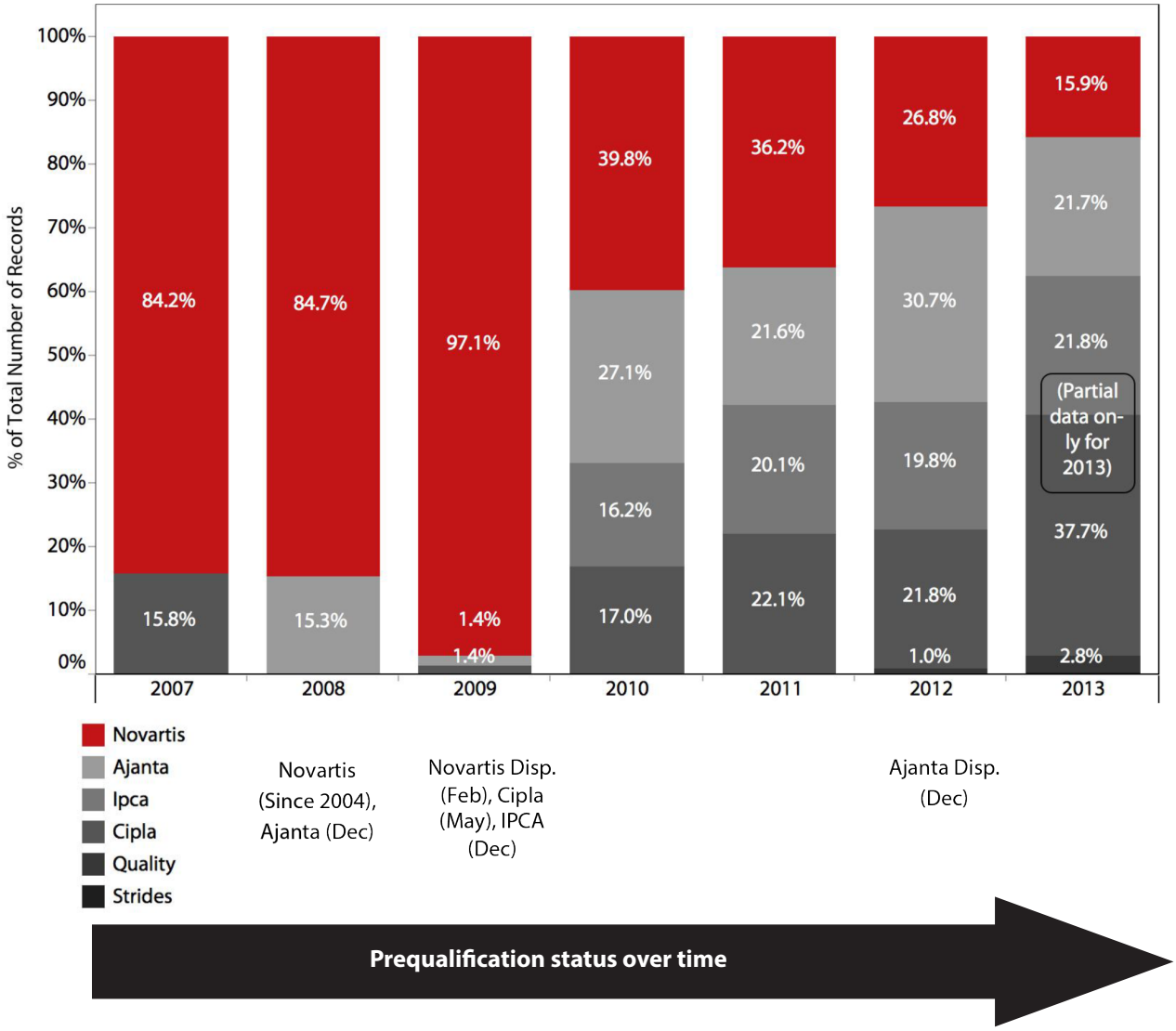
5.3.2.3 Donor-funded market share by product and manufacturer

Data from the PQR and AMFm show that since 2008, the proportion of donor-funded AL procurement volumes purchased from generic manufacturers has been growing. As more manufacturers have received prequalification (Annex 1),[17] there has been an increase in market entrants and the market share has changed, however, the ASAQ market is still highly concentrated by a few manufacturers (Figure 18). In 2011, generic medicines accounted for 52% of total AL and ASAQ/AS + AQ donor-funded procurement volumes. In 2012, however, the market share of generic manufacturers decreased to around 43%. This was likely the result of the increase in market share obtained by Sanofi with ASAQ (FDC).

In 2008, Novartis accounted for the greatest share of AL (85%) procured in the donor-funded market, likely given that Novartis had the only AL formulation approved by the WHO PQP at that time (Figure 17). By 2012, three generic manufacturers, Ajanta, Cipla Ltd and Ipca, together had secured 73% of the AL market procured by international donors (or 31%, 22% and 20%, respectively), compared to 27% for Novartis. While the 2013 dataset is incomplete, currently available data suggest that Novartis' market share decreased to around 16%. In that same year, the Cipla Ltd share grew to 38%.

17 Novartis AL prequalified in 2004, Ajanta AL prequalified in 2008, Novartis AL Dispersible prequalified in 2009, Cipla AL prequalified in 2009, Ipca AL prequalified in 2009, Ajanta AL Dispersible prequalified in 2012.

Figure 17. Market share by volume of AL by manufacturer, 2007–2012

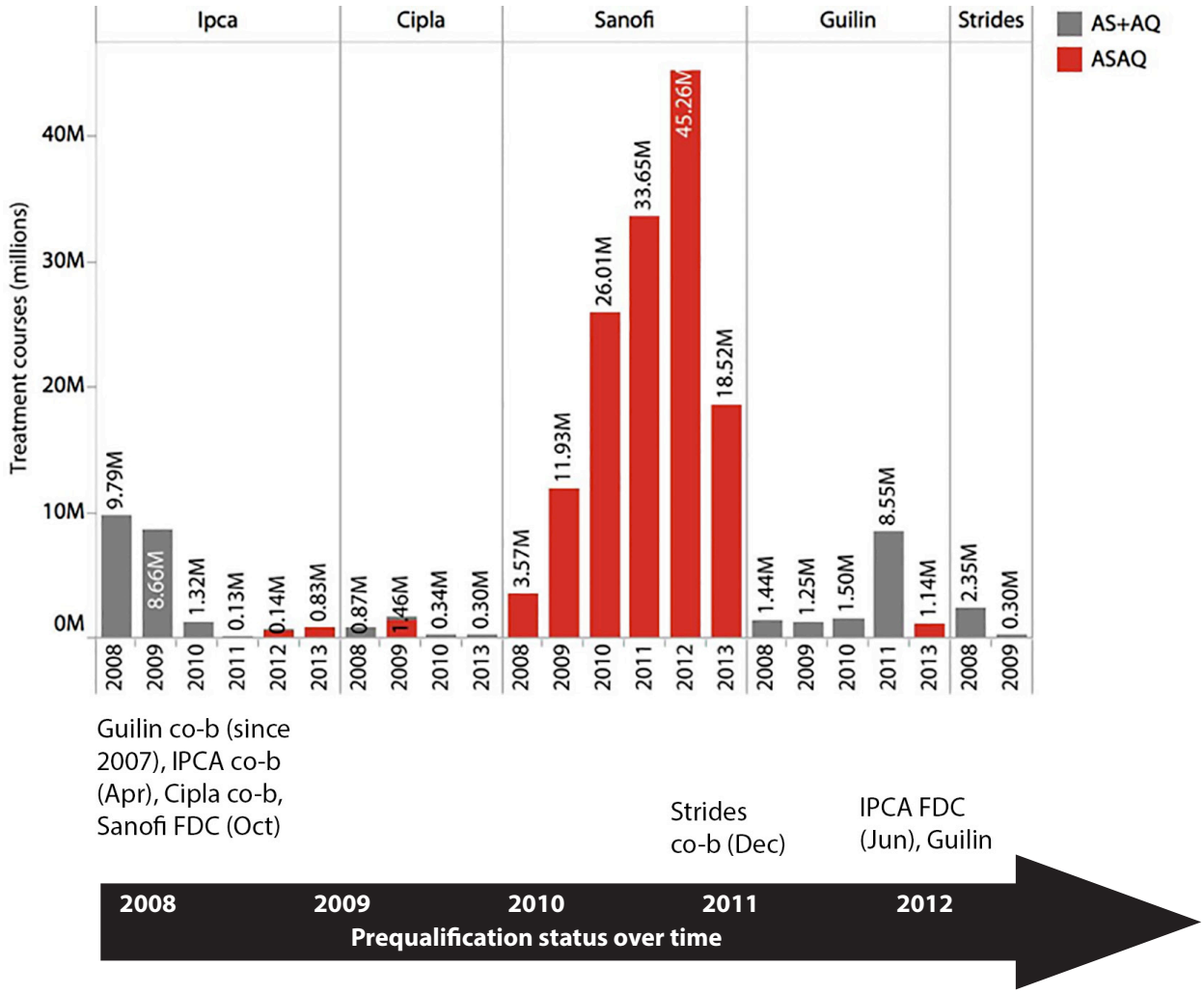


Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

The market share of ASAQ manufacturers has evolved differently to that of AL. One reason for this is that until 2011 there was only one prequalified FDC (Annex 1),[18] manufactured by Sanofi. Since 2009, Sanofi procurement volumes have exceeded all other ASAQ and AS + AQ manufacturers (Figure 18). Following prequalification of the Sanofi FDC ASAQ in October 2008, its market share has grown substantially. In 2012, Sanofi accounted for approximately 98% of volumes procured, and only one other manufacturer, Ipca, received purchases from donors. Between June and November 2012, six more FDC ASAQ became prequalified from two manufacturers (Ipca and Guilin). From the partial data available for 2013, Ipca's ASAQ procurement volumes accounted for 4% of the donor-funded market and Guilin's ASAQ accounted for 6% of volumes procured in the donor-funded market. Sanofi's ASAQ procurement volumes were around 90% of the ASAQ/AS + AQ market in 2013.

18 Guilin co-blister prequalified in 2007, Ipca co-blister prequalified in 2008, Cipla co-blister prequalifed in 2008, Sanofi FDC prequalified in 2008, Strides Arcolab Ltd co-blister prequalified in 2009, Ipca FDC prequalified in 2012, Guilin FDC prequalified in 2012.

Figure 18. Market share by volume of ASAQ and AS+AQ by manufacturer, 2008–2012



co-b, co-blister

Notes: Cipla Ltd FDC procurement volumes and Ipca 2009 volumes reported in 2008 and 2009 are unclear. Procured volumes are reported for both these manufacturers in this figure even though these manufacturers did not have product available to procure in the donor-funded market. 2013 data are only partial.

Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.3.2.5 Concentration of competition

Efforts to bring more manufacturers into the QAACT market have increased competition in the donor market and seem to have diluted the concentration of manufacturers in the market. The Herfindahl Index (HHI) and the Four-Firm Concentration Ration (FFCR) can show the level of competition between companies within an industry and the percentage of the market share held by the four largest firms. For an in-depth explanation of these concepts, refer to the first edition of the UNITAID *Malaria medicines landscape*. Using the HHI, the donor-funded ACT market over the last seven years has moved from being highly concentrated (0.52 in 2007) to a moderate concentration of competition, ranging from 0.24–0.18 between 2008 and 2013, and the number of competitors in the market has been consistently increasing since 2009 (Table 8).

When analysing the top four firms that together accounted for the greatest volumes of procured ACTs in the donor market, the figures in Table 8 show that competition from 2007 to 2012 in the ACT market ranged from an oligopoly to a monopoly (82–100% range). The four firms that had a predominate share

of the ACT market between 2008 and 2009 were: Guilin; Cipla Ltd; Novartis; and Sanofi. By 2012, the top four firms in the ACT market were: Sanofi; Ajanta; Novartis; and Cipla Ltd. This trend is aligned with AL having the largest market share of the donor market and Sanofi being the largest ASAQ supplier.

Table 8. Competition dispersion of the ACT market, 2007–2013

Year	Herfindahl Indexa	FFCRb,c
2007	0.52	100%
2008	0.24	81%
2009	0.33	88%
2010	0.21	83%
2011	0.20	82%
2012	0.19	82%
2013	0.18	63%

Note: Includes all ACTs available for procurement in the donor-funded market: AL; ASAQ; AS+AQ; AS+MQ; DHA PPQ; and AS+SP.
[a] Moderate concentration (decreasing).
[b] Medium concentration from 50% to 80%. An industry in this range is likely an oligopoly. High concentration from 80% to 100%. This category ranges from oligopoly to monopoly.
[c] Guilin, Ipca, Novartis, Sanofi.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Specifically analysing competition in the market of the most commonly donor-funded procured drugs, the donor-funded AL market over five years (2008–2012) moved from high concentration towards moderate concentration (range 0.80–0.28) (Table 9). The ASAQ market has remained highly concentrated throughout the same 2008–2012 time period (range 1.00–0.97), with only one prequalified supplier, Sanofi, until 2012. The AS + AQ market has seen the opposite trend where the market has moved from moderate levels of concentration to a highly concentrated market (range 0.50–1.00), for 2008–2012. This is likely due to the uptake of the FDC ASAQ in the donor market and the phasing out of co-blister volumes procured.

When analysing the top four firms that accounted for the greatest volumes of procured AL, ASAQ and AS + AQ in the donor market, the figures in Table 10 show that the competition from 2008 to 2012 ranged from oligopoly to a monopoly where the largest manufacturers in the market hold a significant market share (AL: 87%–100% ASAQ: 100%–100%; AS + AQ: 100%–100%).

Table 9. HHI dispersion of the AL, ASAQ and AS+AQ markets, 2008–2012

Drug	2008	2009	2010	2011	2012
AL	0.80	0.80	0.98	0.31	0.28
ASAQ	1.00	0.81	1.00	1.00	0.97
AS+AQ	0.50	0.70	0.41	0.97	1.00

Table 10. FFCR dispersion of the AL, ASAQ and AS+AQ markets, 2008–2012

Drug	2008	2009	2010	2011	2012
AL	100%	100%	87%	100%	98%
ASAQ	100%	100%	100%	100%	100%
AS+AQ	100%	100%	100%	100%	100%

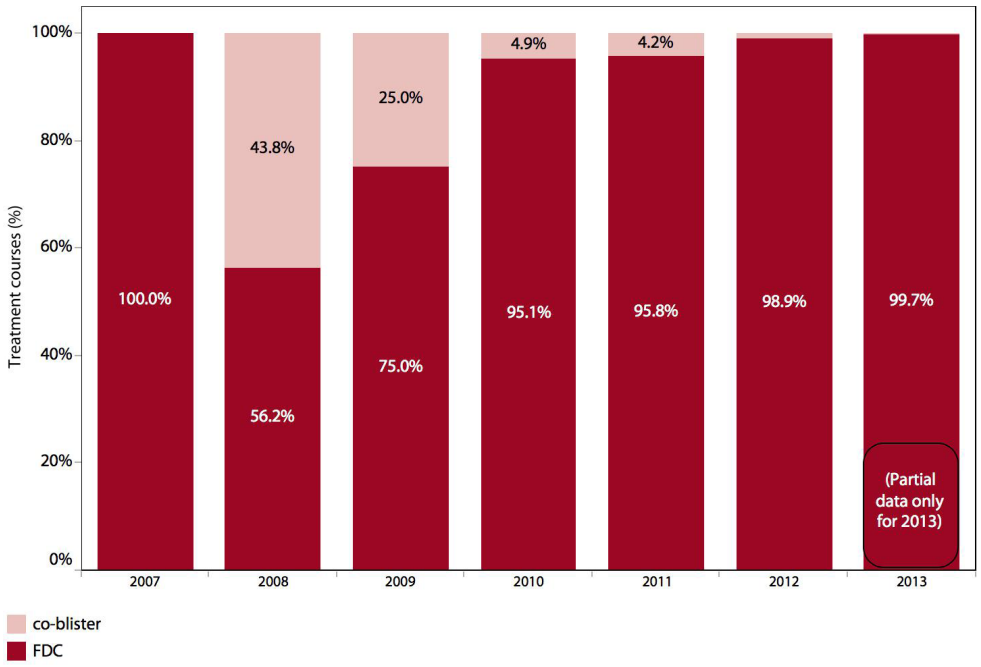
Even though these indices show that competition in the AL market technically is increasing, a corresponding trend has not been seen in decreasing pricing levels, where prices should be reducing to equilibrium levels. Instead, prices have aggregated around a certain price point. As more manufacturers are supplying prequalified ACTs, in general, there has been only a marginal difference in the procurement price of ACTs

between originator and generic products that are purchased through the Global Fund and AMFm (Section 5.4.3). Under AMFm, procurement prices were set through negotiations and not through competitive tenders *(67)*. Negotiating with manufacturers, AMFm set maximum prices, that is, the prices at or below which manufacturers participating in AMFm had to offer ACTs to first-line buyers *(67)*. To be included in AMFm, the manufacturer sale price had to be at or below the maximum price for a single full course of treatment, prior to application of the co-payment *(67)*. The maximum prices established were for each product formulation and pack size, across all suppliers, innovators and generics. This process potentially led to an aggregation around a certain price point. Although price competition was anticipated across suppliers by buyers, this was not observed in practice until late in 2013 towards the end of the AMFm pilot. Even then, it was smaller than anticipated (see Section 5.4.3). Under the Global Fund P4i there is a new tender process where volumes for individual manufacturers are capped (40% for AL non-dispersible products; 75% for AL dispersible products; and 40% for ASAQ products) *(70)*. In contrast to the AMFm pilot approach, prices are now negotiated for each supplier and for each product formulation and pack-size. Both price levels and market share are likely to be impacted by this new procurement process.

5.3.2.6 FDC and co-blistered formulation of ACTs

FDCs now account for almost 100% of the products procured, equalling an approximate 80% growth over five years. Looking forward, with the P4i architecture, only FDCs will be eligible for procurement in the donor-funded market, causing the complete phasing out of co-blister ACTs in this market (Figure 19) of the products procured, equalling an approximate 80% growth over five years. Looking forward, with the P4i architecture, only FDCs will be eligible for procurement in the donor-funded market, causing the complete phasing out of co-blister ACTs in this market.

Figure 19. Percentage of treatment courses that were FDCs, 2007–2013



Note: Includes all ACTs available for procurement in the donor-funded market: AL; ASAQ/AS+AQ; ASMQ; DHA PPQ; and AS+SP.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

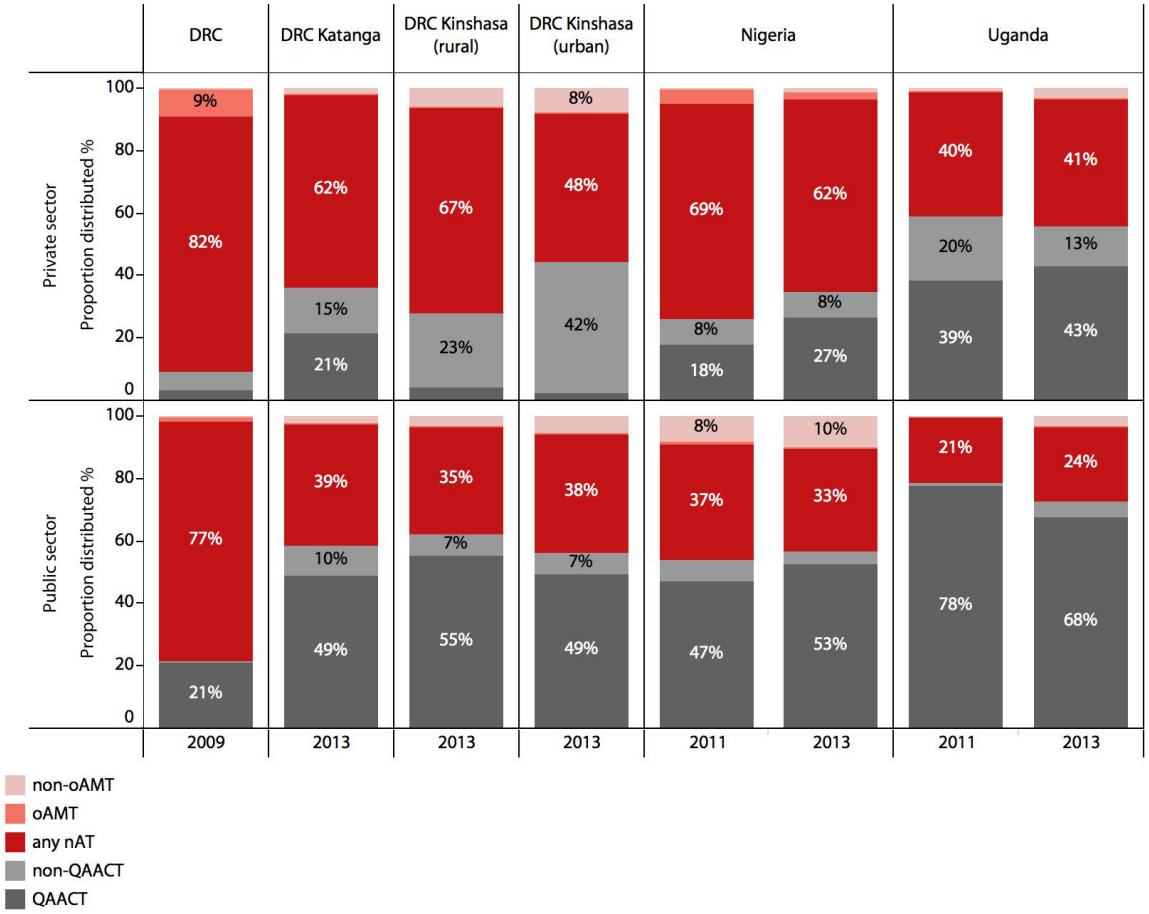
5.3.2.7 Market share of antimalarials distributed at the facility level

ACTs can be divided into two categories: (i) those that have been approved by the WHO PQP or by an SRA and are, therefore, eligible for procurement by international donors (QAACTs); and (ii) those that have not been approved and can only be procured outside donor programmes (e.g. by national governments, consumers and private retailers) (nQAACTs). Aggregated, quantitative data for nATs, AMTs and nQAACTs on the global market are limited. However, outlet surveys conducted by ACTwatch in 2009–2010, 2011 and 2013 offer some insights into market share trends at the facility level *(20)*.[19] ACTwatch outlet surveys show the relative market share of ACTs. Based on the number of AETDs in each unit, the total number of AETDs sold/distributed for each medicine is calculated. This measure shows the proportion of AETDs distributed to consumers for a given medicine or by a given outlet, relative to the total amount of AETDs sold/distributed. As the most recent surveys (2013) were conducted in the DRC (a non-AMFm country) and Nigeria and Uganda (AMFm countries), this section discusses trends from these three countries. For outlet data on other ACTwatch countries, refer to the first edition of the UNITAID *Malaria medicines landscape*.

While the proportion of ACTs distributed by sector has increased over time, nATs are still commonly distributed in both the public and private sector of countries that were surveyed in 2013 (Figure 20). In the private sector in all three countries, the volumes of QAACTs distributed increased since the last survey round (e.g. QAACT volumes increased from 18% in 2011 to 27% in 2013 in Nigeria). In Uganda, ACTs (both QAACTs and non-QAACTs) across both sectors accounted for more than half of all antimalarials distributed. In the public sector in Uganda, the proportion of QAACTs distributed declined since the previous survey round (78% in 2011 to 68% in 2013). Reasons for the decline are unclear, although it is noted that a fraction of the public sector antimalarial market share will continue to be accounted for by the use of SP for IPTp. Therefore, the market share for SP relative to QAACT in Uganda has likely been influenced by the rapid scale-up of QAACT used for presumptive treatment followed very recently by improved rational drug use with scale-up of malaria blood testing in the public sector.

19 ACTwatch is a multicountry research project of Population Services International (2008–2014) conducted in eight malaria endemic countries: Benin, DRC, Myanmar and Zambia (non-AMFm countries) and Cambodia, Madagascar, Nigeria and Uganda (AMFm countries). These surveys provided facility-level information on the availability, volume and price of antimalarial medicines, QAACTs, nQAACTs, nATs and AMTs across both public (including private not-for-profit outlets) and private sectors (including the "informal" private sector shops and hawkers).

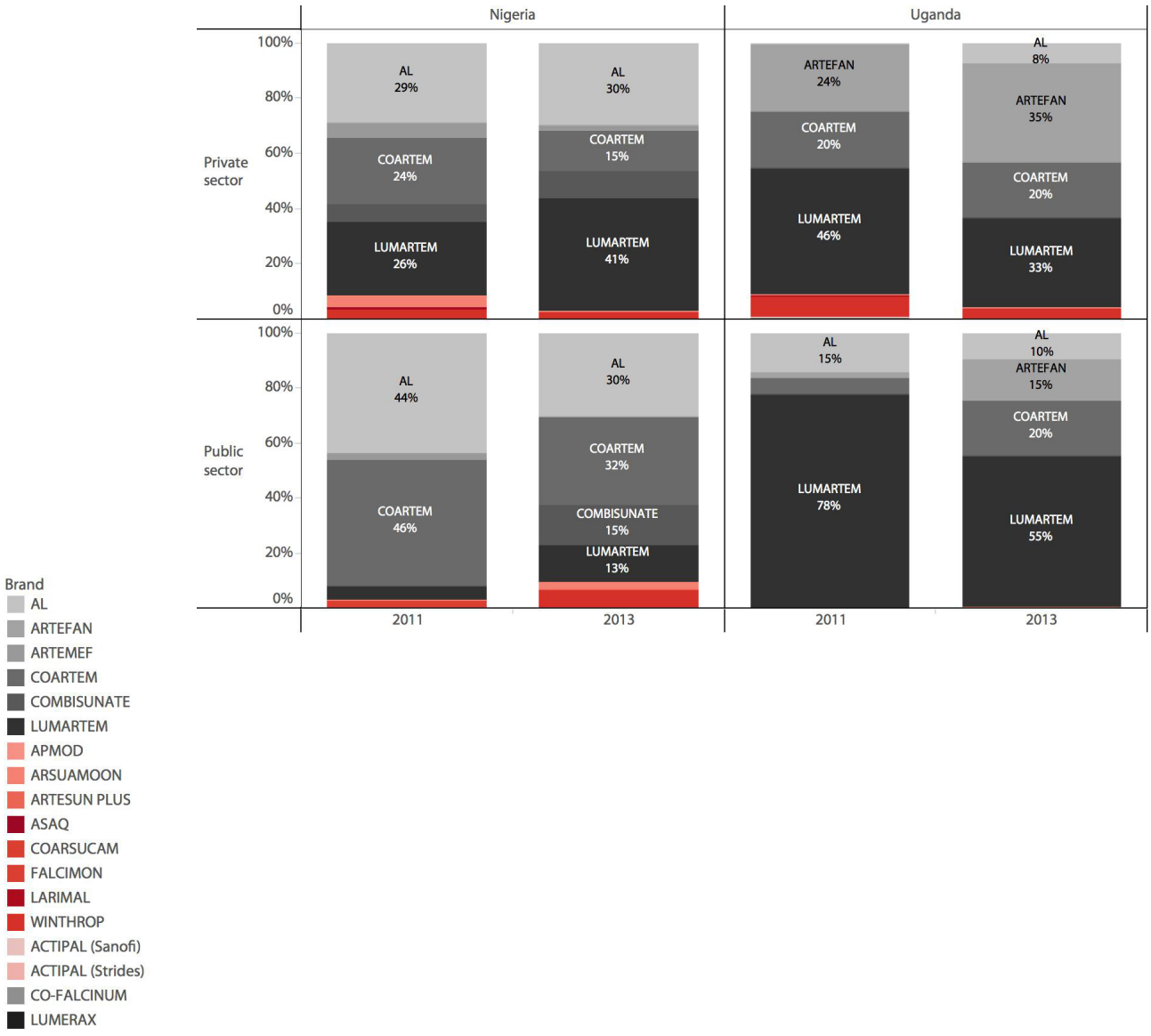
Figure 20. Market share of antimalarials distributed in the public and private sectors, over time (DRC, Nigeria and Uganda)



Notes: Graph includes non-oAMTs, which may be used for severe malaria. SP may be used for IPTp, therefore, nAT market share may include the distribution of SP for IPTp where this use is a part of the countries national policy. For these reasons, the proportions presented above are not necessarily 100% sale/distribution of QAACTs across outlet types.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

Recent data from ACTwatch show that the market concentration of QAACT manufacturers in the donor market carries over to the market share at the facility level. For example, in both Nigeria and Uganda, the market share of QAACTs between manufacturers has diluted over time (Figure 21). Specifically, in 2011, the market share of manufacturers in both the public and private sector of Nigeria and Uganda was highly concentrated by a few manufacturers (e.g. Coartem® [Novartis AL] that accounted for 46% of the market in the Nigerian public sector and AL [Ipca AL] that accounted for 44%). In 2013, the market share between manufacturers had spread over four brands: Coartem® = 32% (Novartis AL); Lumartem® = 13% (Cipla Ltd AL); AL 30% (Ipca AL); Combisunate® = 15% (Ajanta AL).

Figure 21. Market share of QAACT brands among all QAACTs sold/distributed within outlets in the past seven days, by sector (Nigeria and Uganda), 2011 and 2013



Note: Market share is the total market volume in QAACT AETDs for a given QAACT brand as a proportion of the total QAACT market volume in AETDs.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

5.3.3 Prices

5.3.3.1 ACT procurement prices in the donor-funded market

The following section focuses on the procurement price of ACTs purchased through the Global Fund and AMFm. Median prices that purchasing parties pay for one treatment course when procuring QAACTs in the donor market were calculated using transactional data from the PQR and AMFm. The retail price of ACTs, that is the price that ACTs are sold at private sector outlets, is discussed in Section 5.3.3.4.

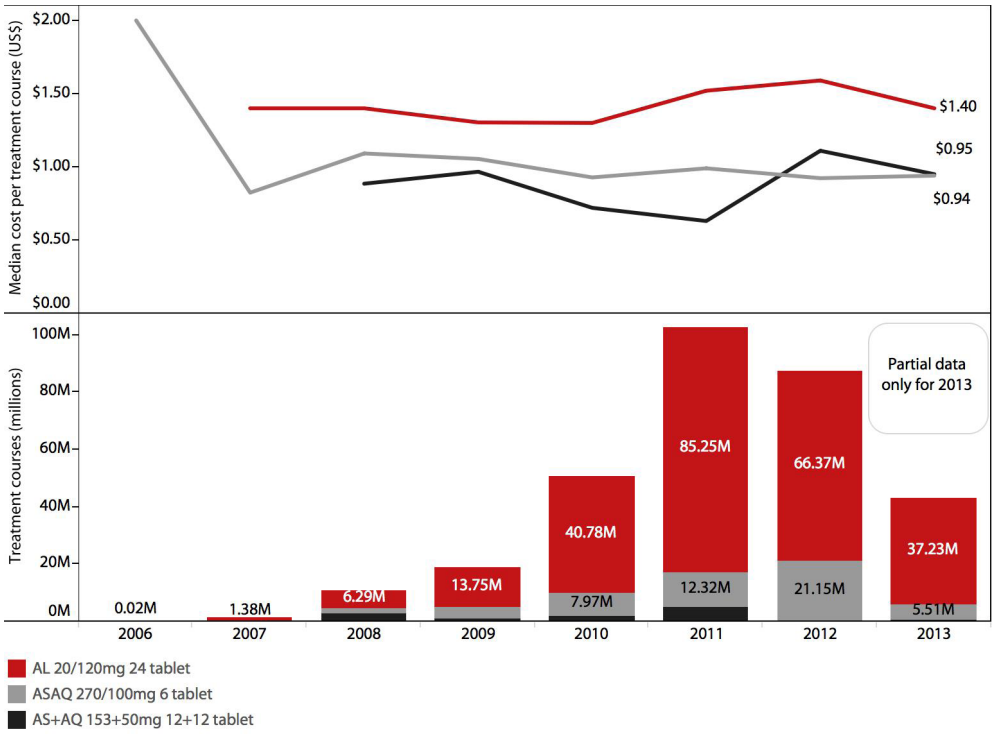
In light of the higher cost of ACTs relative to nATs, and in an effort to support scale-up efforts, some manufacturers have entered into partnerships with international organizations agreeing to provide ACTs at cost. For example, through the partnership of Sanofi and DND*i*, an agreement was reached to produce ASAQ at cost and without a patent *(81)*; and, in 2001, Novartis entered into an agreement with WHO to make Coartem® available at cost to ministries of health (i.e. the public sector) in developing nations *(82)*. This

agreement allowed WHO to generate global demand forecasts, while providing Novartis with a four-month lead time on all orders *(82)*.

Over the last six years, the median unit price of 6x4 AL slightly increased from US$ 1.40 (US$ 1.40–1.98) in 2007 to US$ 1.59 (US$ 0.01–2.33) in 2012 (Figure 22). In 2011, when the volumes of AL treatment courses procured in the donor-market peaked (85.2M), the median unit price was US$ 1.52 (US$ 1.52–2.33). The lowest median price of AL occurred in 2009, US$ 1.30 (US$ 1.09–44.68) per course. While Novartis was the sole prequalified manufacturer until December 2008, by the first half of 2009, Novartis, Ajanta and Cipla Ltd also had prequalified products available. The entry of competitors into this market may have attributed to the lower AL price observed in 2009. Although data available for 2013 are incomplete, the price of AL between 2012 and 2013 decreased from US$ 1.59 (US$ 0.01–2.33) in 2012 to US$ 1.40 (US$ 1.17–2.15).

The median price of 3x2 ASAQ has declined since first becoming prequalified in October 2008, from US$ 1.09 (US$ 0.69–1.09) in 2008 to US$ 0.92 (US$ 0.06–1.09) in 2012 (Figure 22). Until June 2012, Sanofi was the only prequalified manufacturer of ASAQ. The median price of AS + AQ has fluctuated since 2008 where the price in the donor-funded market started at US$ 0.9 (US$ 0.8–1.2), increased to US$ 1.0 (US$ 0.8–1.0) in 2009, declined to US$ 0.6 (US$ 0.6–0.8) in 2011 and peaked in 2012 with a median price of US$ 1.11 (US$ 1.11–1.11). The price of AS + AQ was approximately US$ 0.40 less than the ASAQ, however, it became US$ 0.20 more than ASAQ in 2012. This may have a corresponding relationship with the demand of AS + AQ decreasing because of new ASAQ manufacturers entering the market in 2012 (Ipca and Guilin). When comparing the median price of ASAQ to AL in 2012, the ASAQ price was US$ 0.7 lower (US$ 0.92 for ASAQ versus US$ 1.59 for AL). The most recent procurement transaction data from the PQR suggest that the price of AL has started to decrease (US$ 1.40 in 2013), however, the price of ASAQ remained relatively flat from 2012 (US$ 0.94 in 2013).

Figure 22. Median treatment course price of AL 6x4, ASAQ co-blister 12+12 and FDC 3x2 procured by international donors, 2006–2013



Notes: 24 tablet pack AL are adult-pack sizes, >35 kg and account for around 45% of all ACTs procured in this market. FDC ASAQ 6-tablet pack and co-blister 12+12 are adult-pack sizes and account for approximately <5% of this market.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.3.3.2 ACT procurement prices, comparison between the Global Fund and AMFm

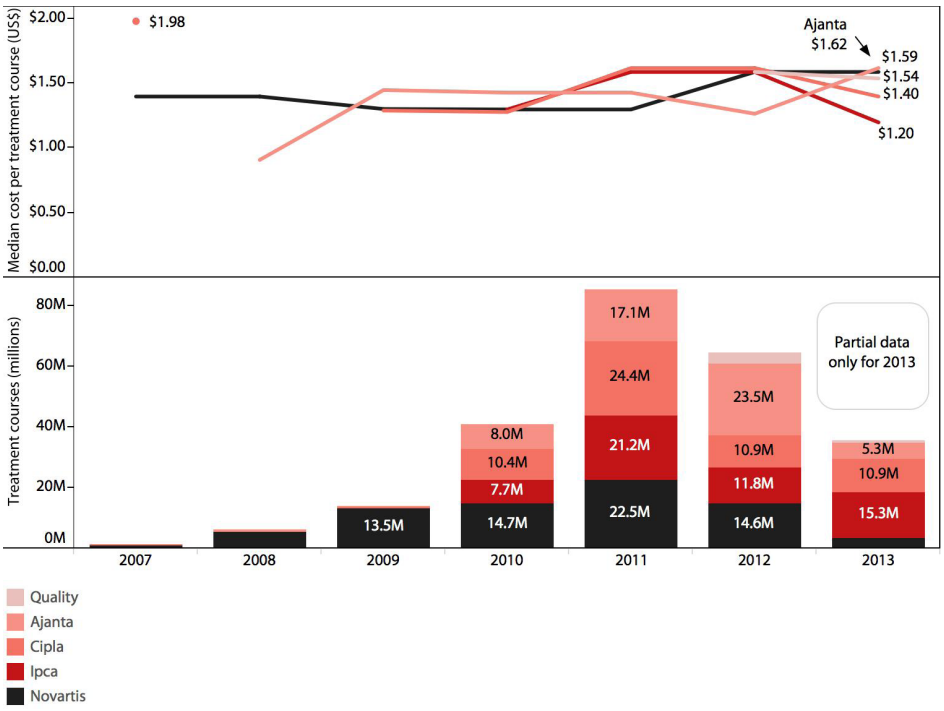
From the PQR dataset, price differences were also observed for both AL and ASAQ between AMFm (both public and private sector prices) and the Global Fund (public sector only). For both AL and ASAQ, the procurement price per treatment course has been lower than that of the AMFm price since the latter commenced.

The GAFTM P4i programme issued the first tender to supply ACTs for 2014 with final contracts providing volume visibility for a two year period *(83)*. Nine ACT manufacturers engaged with the Global Fund and tendered bids in the first tender process under the new procurement structure *(83)*. After an evaluation that involved two elements: (i) commercial – considering base price and discounts offered; and (ii) technical – considering value propositions, quality and deliver performance, level of innovation and support to RSM, bidders were selected to supply the donor-funded market *(83)*. Individual product allocations were capped and two-year contracts have been signed and volumes committed. Overall, the Global Fund suggest that this process will deliver approximately 32% savings (US$ 102M over two years) *(83)*. As cost savings have been forecasted by the Global Fund, it is likely that there will be a corresponding trend in the median selling prices of ACTs in 2015.

5.3.3.3 ACT procurement prices, variation by individual manufacturer

Data from the Global Fund and AMFm indicate that the median unit price of adult-pack AL varies by individual manufacturer (Figure 23). To date, Ipca, Ajanta, Cipla Ltd and Novartis have been the four primary manufacturers of adult-pack AL. In 2008, when both Ajanta and Novartis received prequalification, the median price of Novartis' AL was US$ 1.40 (US$ 1.40–2.15) and Ajanta's median price was US$ 0.91 (US$ 0.91–0.91). Ajanta's AL product only became available for procurement in December 2009. Since that time and until 2012, Novartis sold adult-pack AL at around the same or at a lower median price than the two generic brands from Cipla Ltd and Ajanta: e.g. in 2009, the Novartis median unit price was US$ 1.30 (US$ 1.09–44.68) versus US$ 1.29 (US$ 1.29–1.29) and US$ 1.45 (US$ 1.45–1.45) for Cipla Ltd and Ajanta, respectively). In 2011, an increase in median price was observed for all three generic manufacturers with products available for donor-funded procurement (US$ 1.59, US$ 1.62 and US$ 1.43 for Ipca, Cipla Ltd and Ajanta, respectively), whereas the median price for AL manufactured by Novartis remained at US$ 1.30. Importantly, price trends for AL do not reflect the typical scenario whereby increasing competition results in lower prices, possibly due in part to the agreement between WHO and Novartis to sell Coartem® at cost. The volumes procured from each manufacturer in 2011 ranged from 17.1M (Ajanta) to 24.4M (Cipla Ltd). In 2012, Ajanta sold AL at a median price of US$ 1.27 (US$ 0.99–1.27) and also had the greatest volumes of treatment courses purchased (23.5M). Partial data available from the PQR for 2013 suggest that AL median prices have decreased as low as US$ 1.20 (US$ 1.17–1.64 from Ipca), and Ipca, Cipla Ltd and Quality median prices were all below the median price of Novartis' AL product.

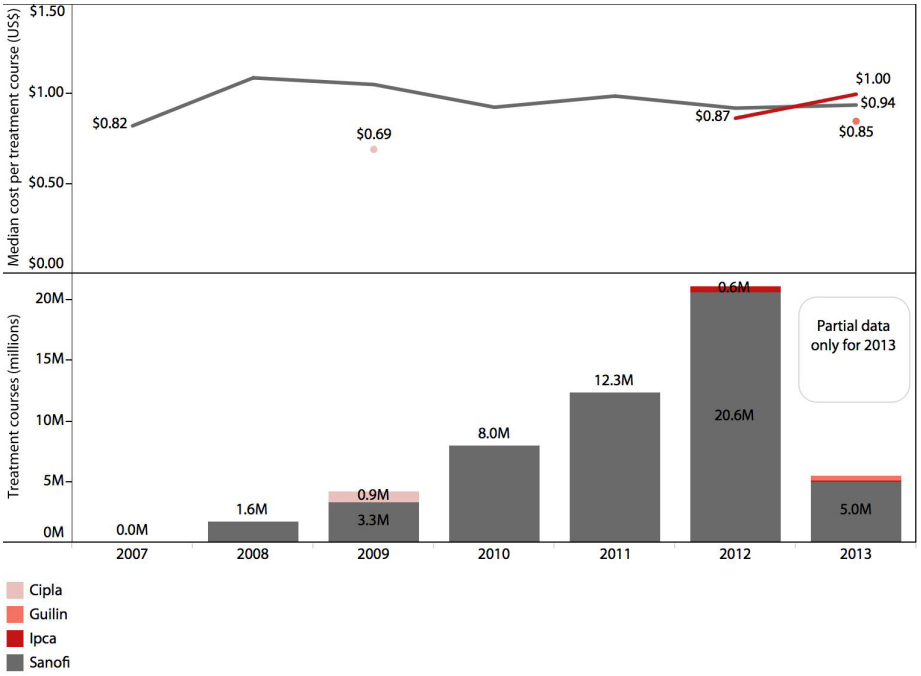
Figure 23. Median unit price, AL 6x4 treatment course, by manufacturer, procured by international donors, 2007–2013



Notes: 6X4 AL are adult-pack sizes, >35 kg and account for around 45% of all ACTs procured in this market.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Sanofi was the only prequalified manufacturer of ASAQ until June 2012. Before then, the median price of Sanofi adult-packs ASAQ had decreased from US$ 1.05 (US$ 0.94–1.18) in 2009 to US$ 0.92 (US$ 0.06–1.09) in 2012 (Figure 24). In 2012, when Sanofi had a spike in volumes procured compared to the previous year (12.3M versus 20.6M), the price that ASAQ adult-packs were purchased was also at the lowest point since entering the ASAQ donor-funded market. The median unit price of Ipca sales in 2012 was US$ 0.87 (US$ 0.86–0.89), that is, US$ 0.06 lower than Sanofi for that year. In 2012, a third ASAQ product manufactured by Guilin was prequalified for procurement in the donor market. Partial data indicate that Guilin's ASAQ product was purchased at a median price of US$ 0.85 (US$ 0.84–0.96 in 2013, which is US$ 0.15 lower than the median price of Ajanta's product in that same year (US$ 1.00).

Figure 24. Median unit price of ASAQ 3x2, by manufacturer, procured by international donors, 2007–2013



Notes: AS+AQ 12+12 is an adult-pack size and combined with ASAQ 3x2 accounts for approximately 5% of this market. Cipla Ltd FDC procurement volumes reported 2009 are unclear.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

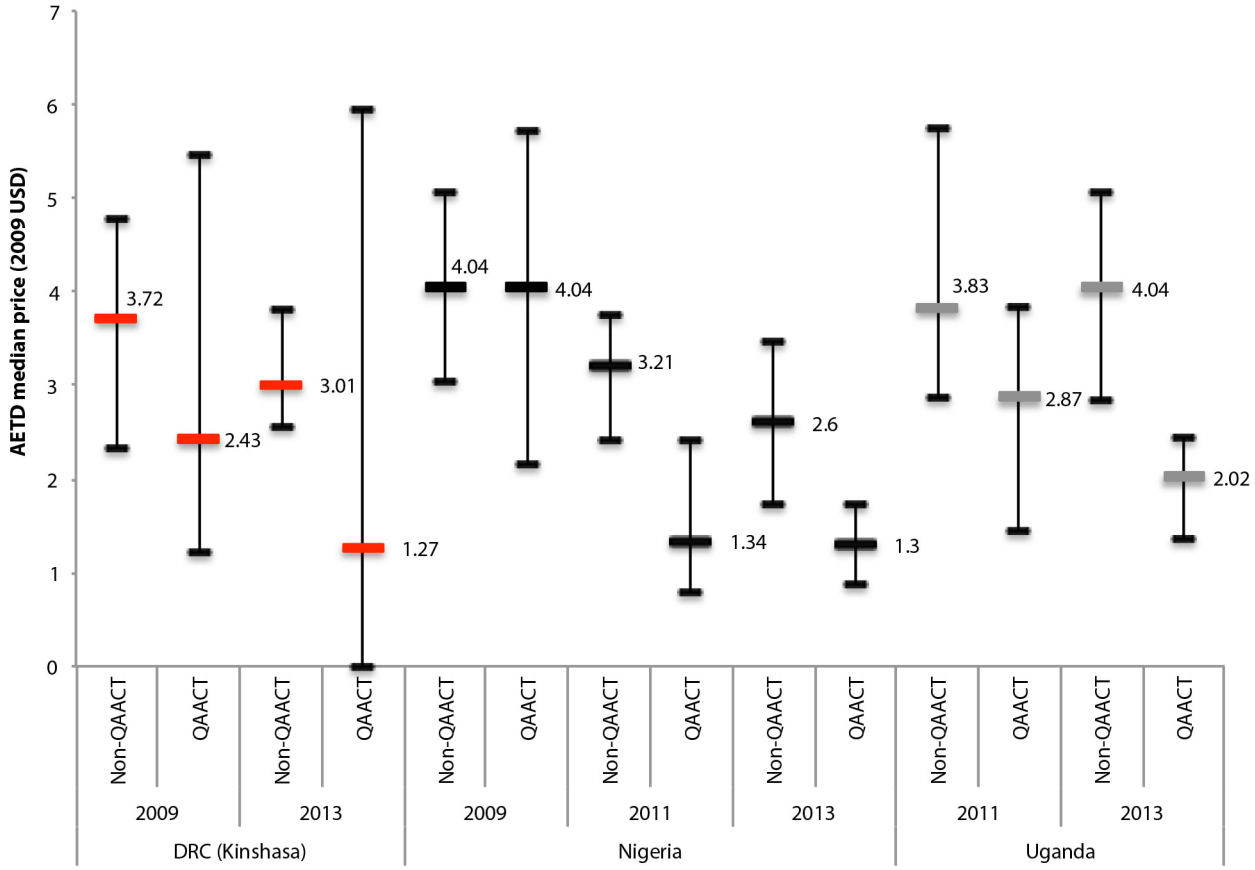
5.3.3.4 Median price of available QAACTs at private sector outlets

ACTwatch surveys can be used to show the median price of available AETD QAACTs.[20] Many endemic countries are able to provide medicines for free in the public sector *(3)*. For example, ACTwatch surveys between 2009 and 2012 reported that only in two countries, Benin[21] and the DRC, did patients have to pay for ACTs in the public sector *(84)*. In private facilities in the Kinshasa province of the DRC (non-AMFm), a decrease in the available median price of QAACTs was observed between survey rounds (Figure 25). However, it is important to note that there were low numbers of QAACTs audited in both survey rounds, reflecting limited availability. Wide ranges were also observed showing a high degree of variability of the price throughout the private sector. Scarcity of QAACTs may be influencing the wide price ranges in some circumstances. In relation to non-QAACTs, the median price of available QAACTs was lower than non-QAACTs in both survey rounds. As the DRC is a non-AMFm pilot country, reasons for lower prices may be attributed to nongovernmental organizations or government subsidy channels facilitating access to low-cost QAACT among a very limited number of private health facilities.

The median price of QAACTs in both Nigeria and Uganda has declined between survey rounds. The price of QAACTs has also remained lower than non-QAACTs in both countries since the first audit (Figure 25). Wide ranges were also observed in both Nigeria and Uganda in earlier round surveys. These ranges narrowed in the most recent survey rounds, and there was high availability of both QAACTs and non-QAACTs in both countries. Nigeria and Uganda both participated in the AMFm programme so the median price reported reflects a subsidized price and the downward price trend represents the effect of AMFm on prices in these countries. While decreases in the median price of QAACTs were observed, with the new Global Fund funding mechanism (see Section 5.1), looking forward it is uncertain how median price trends will be impacted.

20 The median price is typically reported for the private sector as a whole and among specific private sector outlet types. The number of medicines audited that are contributing to this price estimate is reported as well as the IQR, or the 25th and 75th percentiles. The median price and IQR are weighted using sampling weights. AETD is the total drug required to treat a 60 kg adult.
21 At the time of data collection in March/April 2011, patients had to pay; but, in October 2011, the government rolled out free treatment for children under 5 years old and pregnant women in Benin.

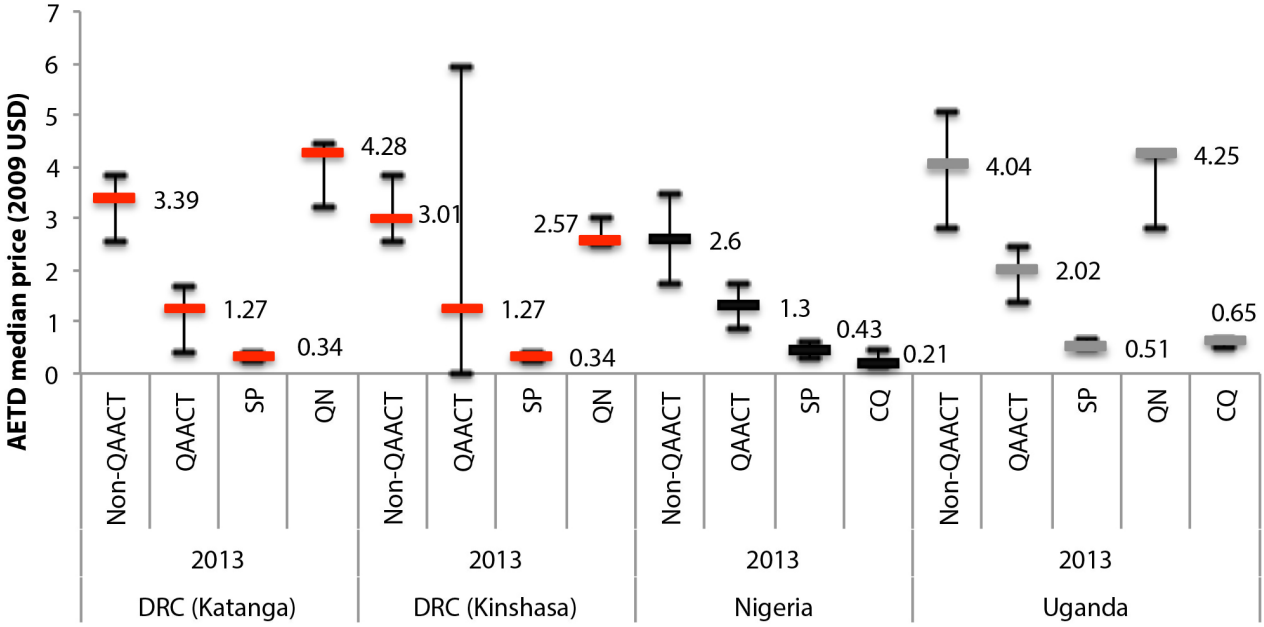
Figure 25. Price of QAACTs vs non-QAACTs AETD, among ACTs audited in the private, 2009–2013



Notes: Prices are standardized to the 2009 US$ using the consumer price indexes in each country to adjust for inflation/deflation. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs). In the DRC, in 2013, data were collected by province. Range represents the 25th and 75th IQR.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

Even though QAACT median prices have been decreasing over time, when compared to monotherapies (SP, CQ, QN) in the DRC Kinshasa/Katanga provinces, Nigeria and Uganda the price remains high (Figure 26). While the price of QN observed appears to be high when available, ACTwatch has noted through surveys that medicines such as QN are commonly sold/distributed at sub-therapeutic doses (i.e. less than a full AETD). For example, in the DRC, the blister pack for QN commonly distributed in the DRC contains only between 20% and 40% of an AETD. Therefore, the AETD is actually greater than what the consumer would typically pay for QN.

Figure 26. Price of QAACTs, non-QAACTs and non-oAMTs, AETD among outlets stocking at least one antimalarial at the time of survey in the private sector, 2013



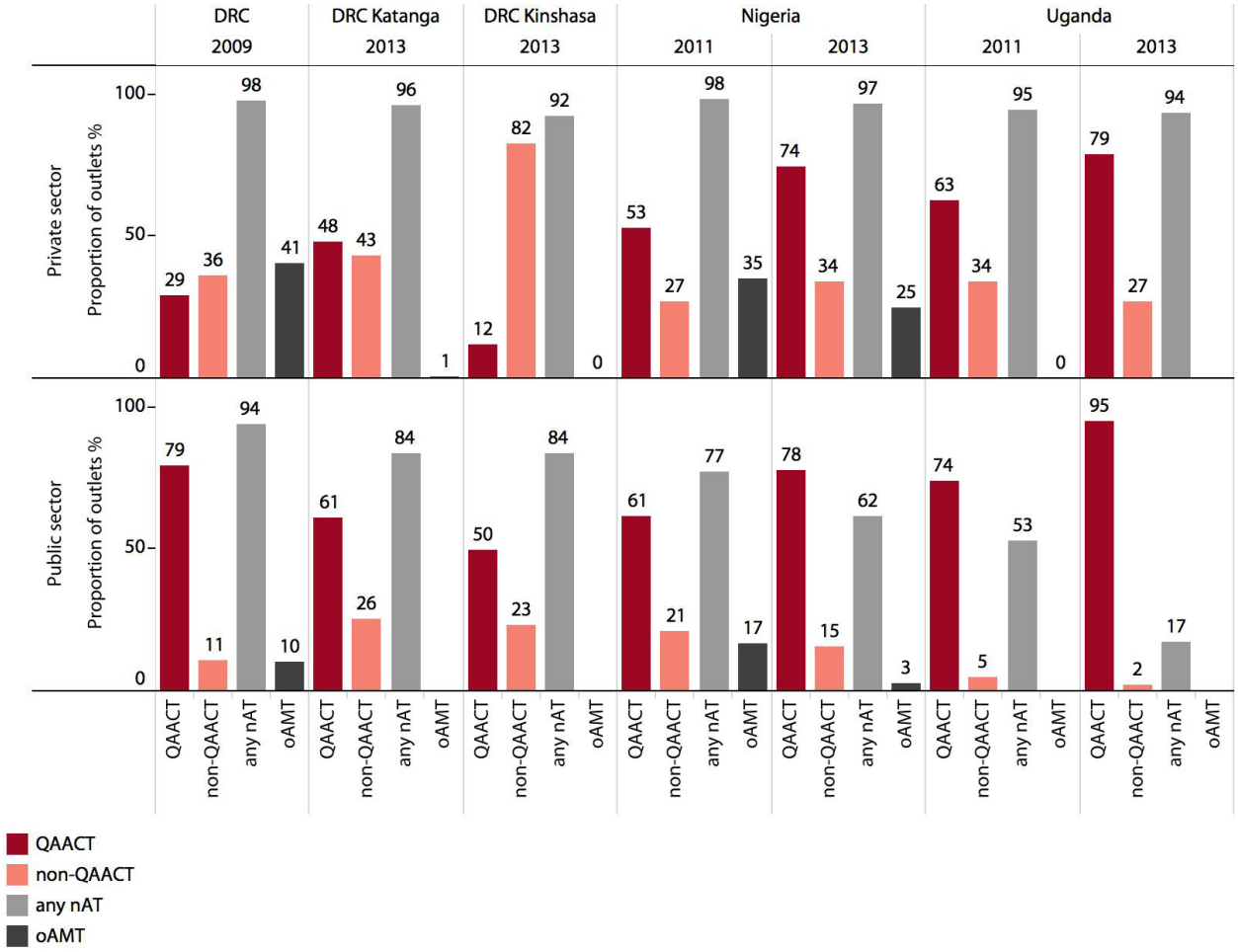
Notes: Prices are standardized to the 2009 US$ using the consumer price indexes in each country to adjust for inflation/deflation. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs). In the DRC, in 2013, data were collected by province. SP is also distributed for IPTp. Range represents the 25th and 75th IQR.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

5.3.3.5 Availability trends of quality-assured ACTs in private and public sector facilities

ACTwatch surveys also provide information on the availability of antimalarial medicines at the facility level.[22] Looking at a sample of ACTwatch countries with available surveys for 2013, the availability of QAACTs in both the public and private sector since the last survey round has increased (Figure 27). As an example, the availability of QAACTs in the Nigerian private sector increased from 53% to 74% between 2011 and 2013 survey rounds.

22 This only applies to the outlets that had antimalarials in stock on the day of the survey.

Figure 27. Availability of antimalarials, among outlets stocking at least one antimalarial at the time of survey, by sector



Notes: Public outlets include: public health facilities and private not-for-profit health facilities. Private outlets include: private for-profit health facilities, pharmacies, drug stores and general retailers. In the DRC, in 2013, data were collected by province.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

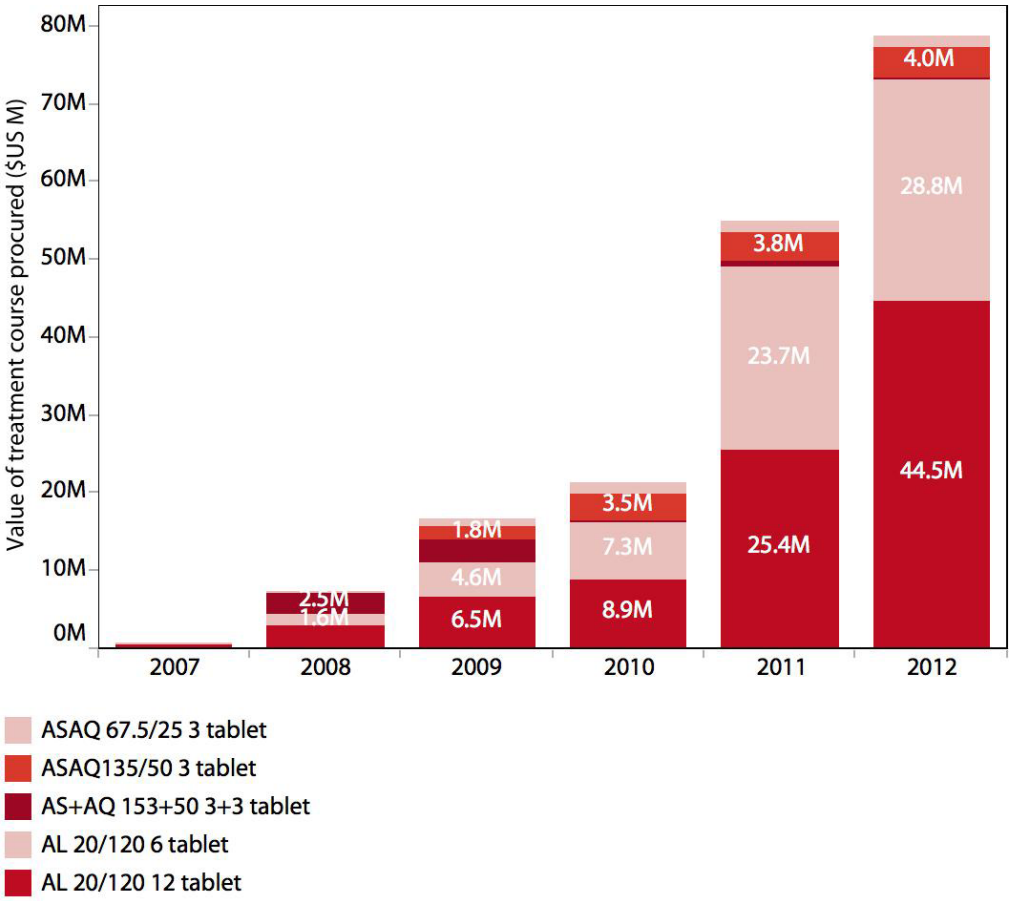
5.4 Paediatric ACTs

As children under 5 years old bear a significant proportion of the malaria disease burden (78%), it is important that appropriate and high-quality antimalarials are made available to ensure efficacy and widespread use *(2)*. This section examines child-packs of common ACTs in relation to adult-packs, and looks specifically at paediatric dosage forms such as dispersible tablets. Unless otherwise stated, reference to dispersible AL in this section includes only 6x1 and 6x2 AL pack types based on an average weight of 18 kg for children under 5 years old. There are also child-packs available for other ACTs; however, this section focuses on AL and ASAQ/AS + AQ given their large market share.

5.4.1 Market characteristics of donor-procured, child-pack ACT

Based on data from the Global Fund and AMFm as a proxy for the donor market, the market value for ACTs for children under 5 years old has increased from approximately US$ 17M in 2009 to US$ 21M in 2010 and US$ 54M in 2011 (Figure 28). In 2012, the value of donor-procurements for children under five reached $US79M.

Figure 28. Market value of AL and ASAQ/AS+AQ procured in the donor market for children under 5 years old, 2007–2012

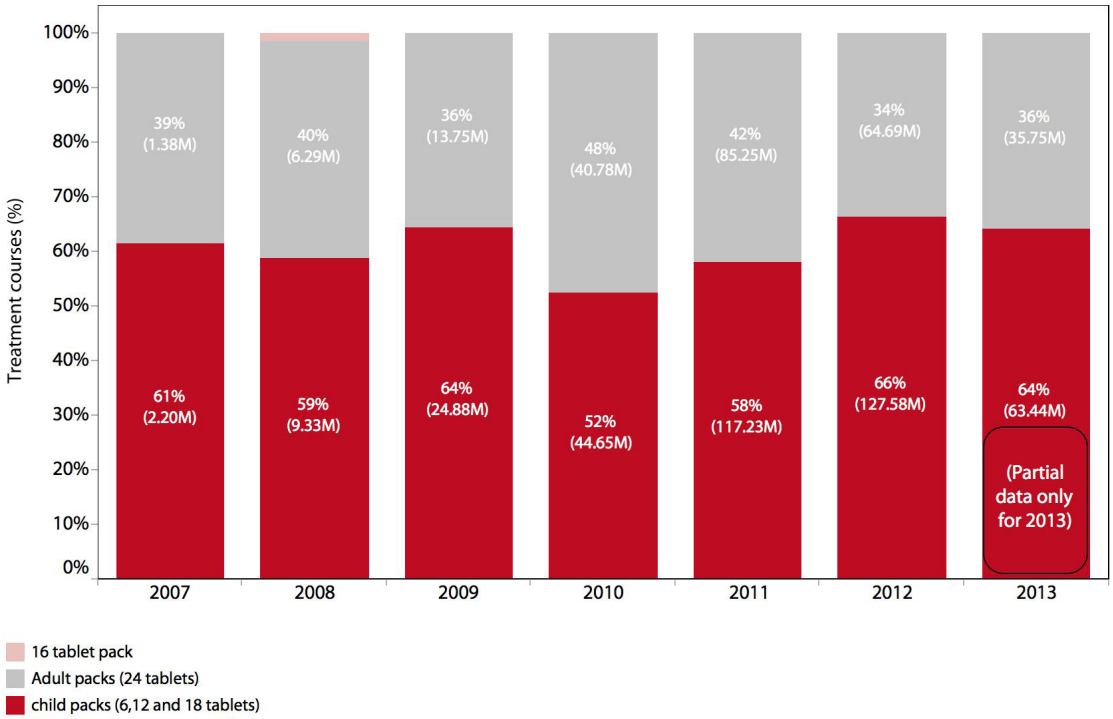


Notes: The chart only represents pack sizes tailored for children under 5 years old (average weight 18 kg). It represents 6x1 and 6x2 pack sizes; 6x3 and 6x4 pack sizes are available for procurement, but are not represented in this chart. Co-blister 3+3 pack sizes at 50/153 mg and FDC 3x1 pack sizes at 25/67.5 mg and 50/135 mg.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

The *World malaria report 2013* reported that between 2005 and 2012, the number of child-packs of AL delivered to the public and private sector has increased *(2)*. Since 2009, child-packs of AL have accounted for the greatest volumes of AL procured *(2)*. In 2012, 68% of all AL procured was for children (6x1 packs [31%], followed by 6x2 and 6x3 packs), compared to 32% for patients with a body weight of >35 kg (6x4 packs) *(2)*.

Incremental increases in proportion of AL child-packs also can be seen from the compiled Global Fund PQR and AMFm datasets between 2010 and 2013 (Figure 29). Of the total yearly AL volumes procured between 2008 and 2012, child-packs represent over 50% each year. In 2013, from the ACT transactions that have been reported, packs procured for body weight <35 kg accounted for 64% of AL treatments procured.

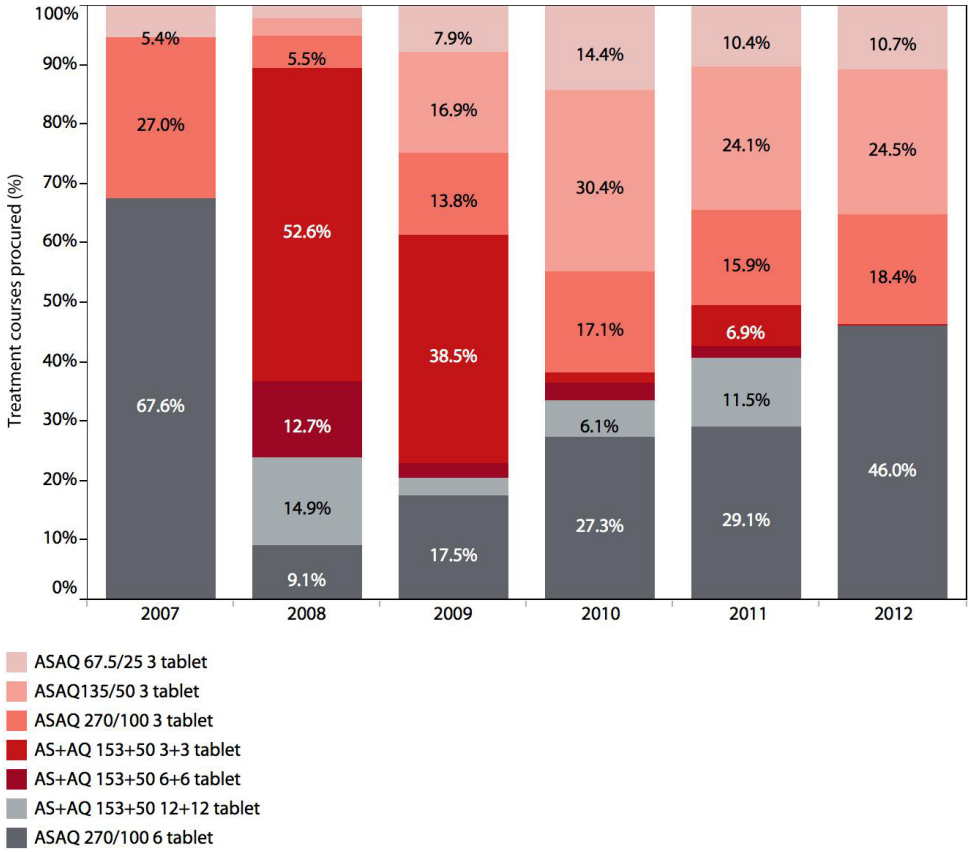
Figure 29. AL relative percentage of pack sizes procured in the donor market, 2007–2013



Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

The same dataset shows that for ASAQ/AS + AQ, the proportion of child-packs (co-blister 3 + 3 50/153 mg and FDC 3x1 50/135 mg and 25/67.5 mg) versus adult-packs of both FDC and co-blister has been more in favour of child-packs since 2008 (Figure 30). Child-pack ASAQ/AS + AQ procured in 2009 accounted for around 80% of the market share. Since that time, however, the proportion of child-pack ASAQ/AS + AQ declined to 66% in 2010, 59% in 2011 and 53% in 2012. Reasons for the decline in the proportion of child-pack ASAQ/AS + AQ are unclear.

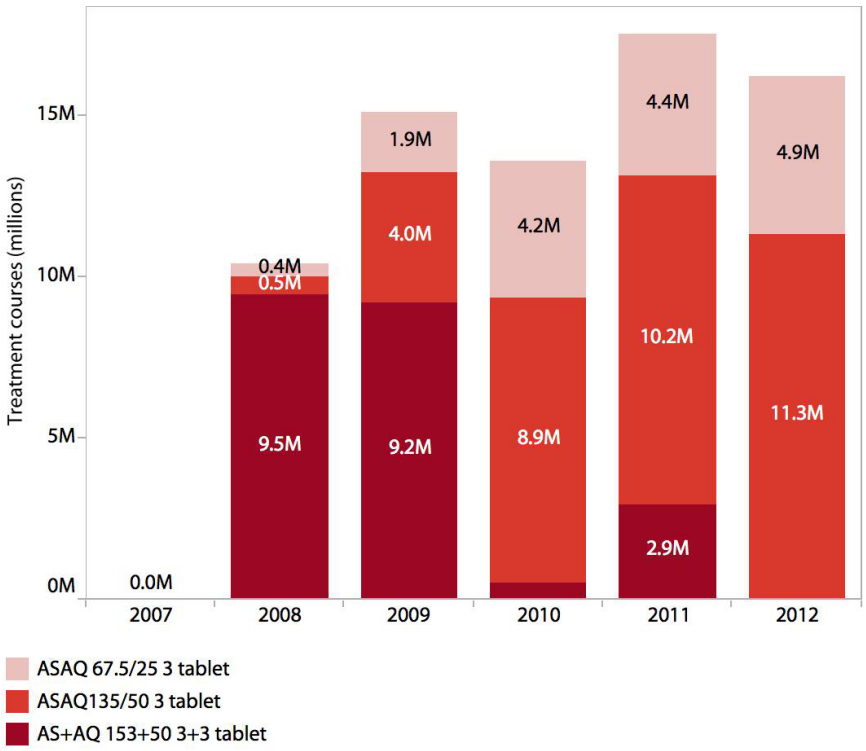
Figure 30. ASAQ and AS+AQ relative percentage of pack sizes procured in the donor market, 2007–2012



Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

In the donor market, ASAQ/AS + AQ packs procured for children under 5 years old increased from 10M treatment courses in 2008 to 15M in 2009, but since then have remained relatively flat. However, there has been a change in the product mix following the prequalification of Sanofi's ASAQ product in October 2008 (Figure 31). Volumes of ASAQ for children under 5 years old increased from 6M in 2009 to 14M in 2011 and 16M in 2012. In 2012, only 20 000 treatment courses of AS + AQ were procured showing that the market has almost completely ceased procuring co-blistered AS + AQ for children under 5 years old. A similar trend was observed in the procurement of adult-packs.

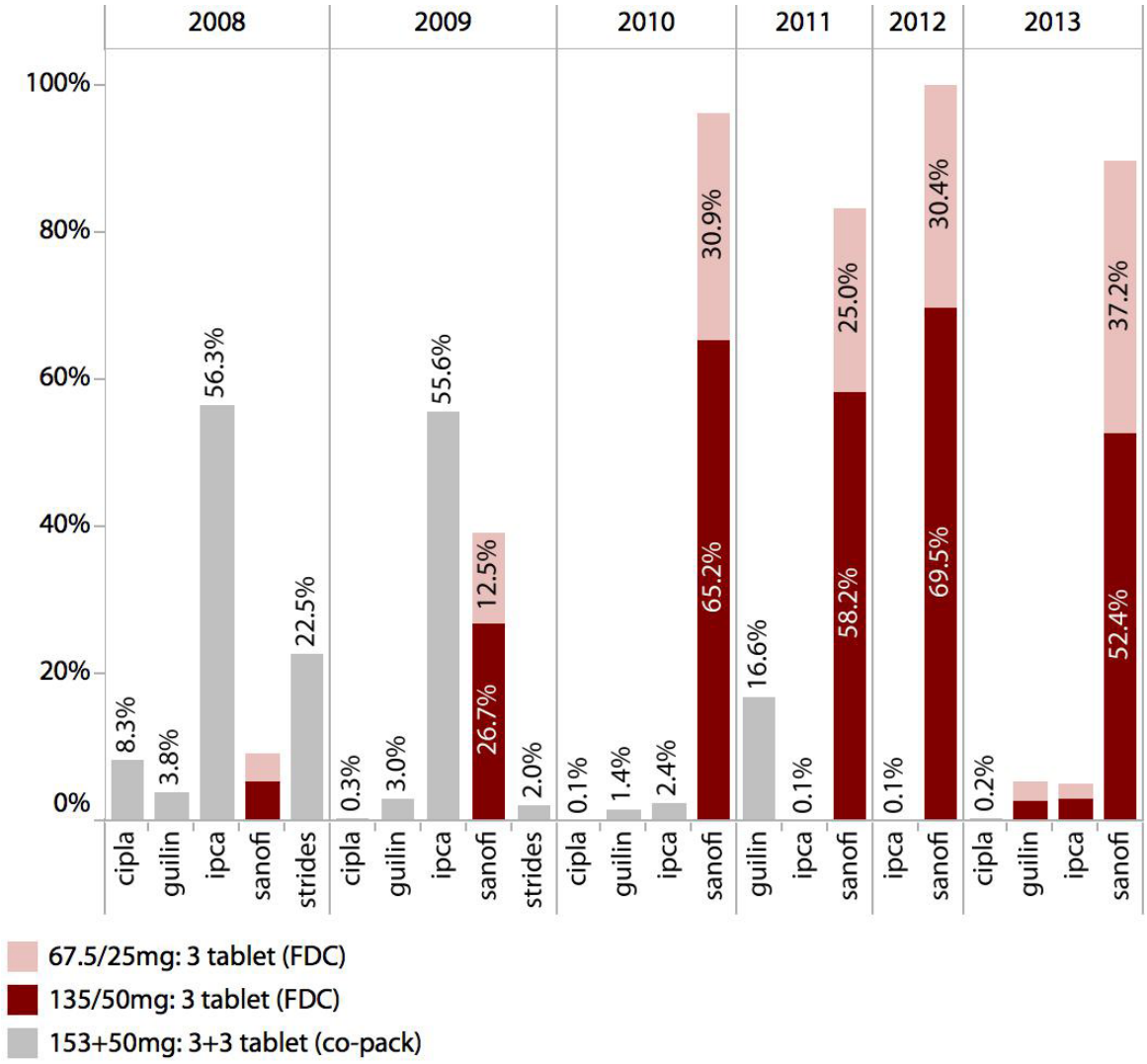
Figure 31. Volumes of ACT packs for children under 5 years old (ASAQ and AS+AQ) procured by international donors, 2007–2012



Note: The chart only represents pack sizes tailored for children under 5 years old (average weight 18 kg).
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Sanofi is the market leader of ASAQ and was the sole prequalified manufacturer until 2012. As a proportion of all ASAQ/AS + AQ available for children under 5 years old, the Sanofi market share for child-packs ASAQ has increased from 38% in 2009 to 99% in 2012 (Figure 32). Moreover, all products procured in this category were ASAQ in 2012. In 2012, Guilin and Ipca became prequalified to manufacture ASAQ. From the data that are currently available, both Guilin (5%) and Ipca (5%) products have been procured. At this point in time, these proportions appear fractional to Sanofi's procurement volumes (90%), however, the market may become less concentrated looking forward and this could possibly have a positive effect on price.

Figure 32. Proportion of AS+AQ and ASAQ packs for children under 5 years old procured by international donors, by manufacturer, 2008–2013



Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

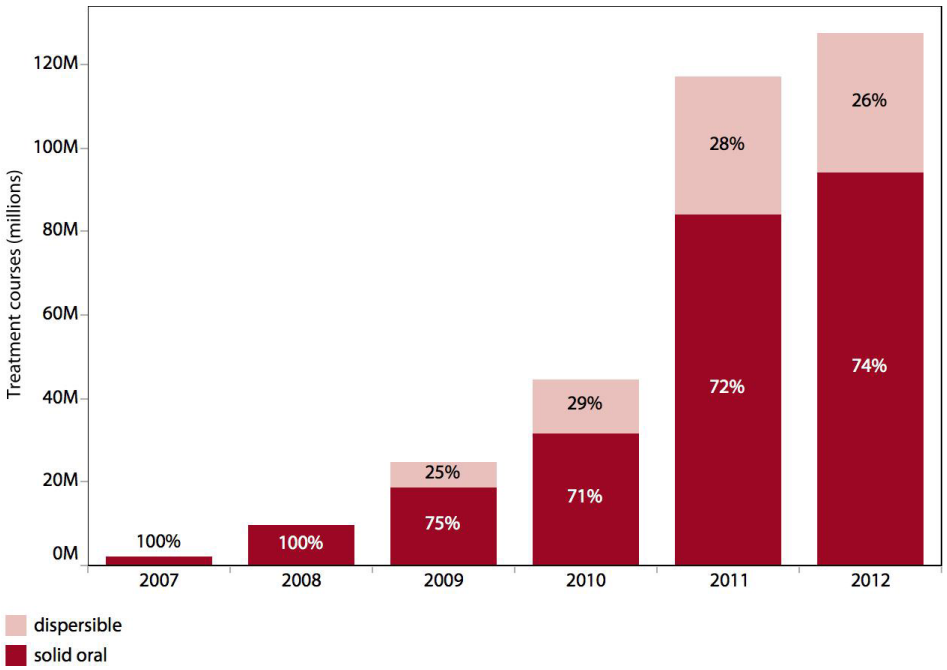
5.4.2 Characteristics of the market for dispersible AL

While dispersible AL is available for all pack sizes, this section focuses on pack sizes targeted at children under 5 years old (i.e. 6x1 and 6x2 packs).[23]

Data from the Global Fund and AMFm purchase transactions show that the procurement of dispersible AL has increased over time, but volumes remain low relative to equivalent pack sizes of solid oral formulations. Volumes of both solid orals and dispersibles have increased over time (from 31M in 2010 to 83M in 2011 and 94M in 2012 for solid orals; and from 12M in 2010 to 33M in 2011 for dispersibles) (Figure 33). Volumes of dispersible AL procured remained flat in 2011–2012, with 33M courses procured in 2012.

23 Pack sizes tailored for children under 5 years old are based on an average weight of 18 kg or less.

Figure 33. Volume of AL packs for children under 5 years old procured by international donors, 2007–2012, by dispersibility

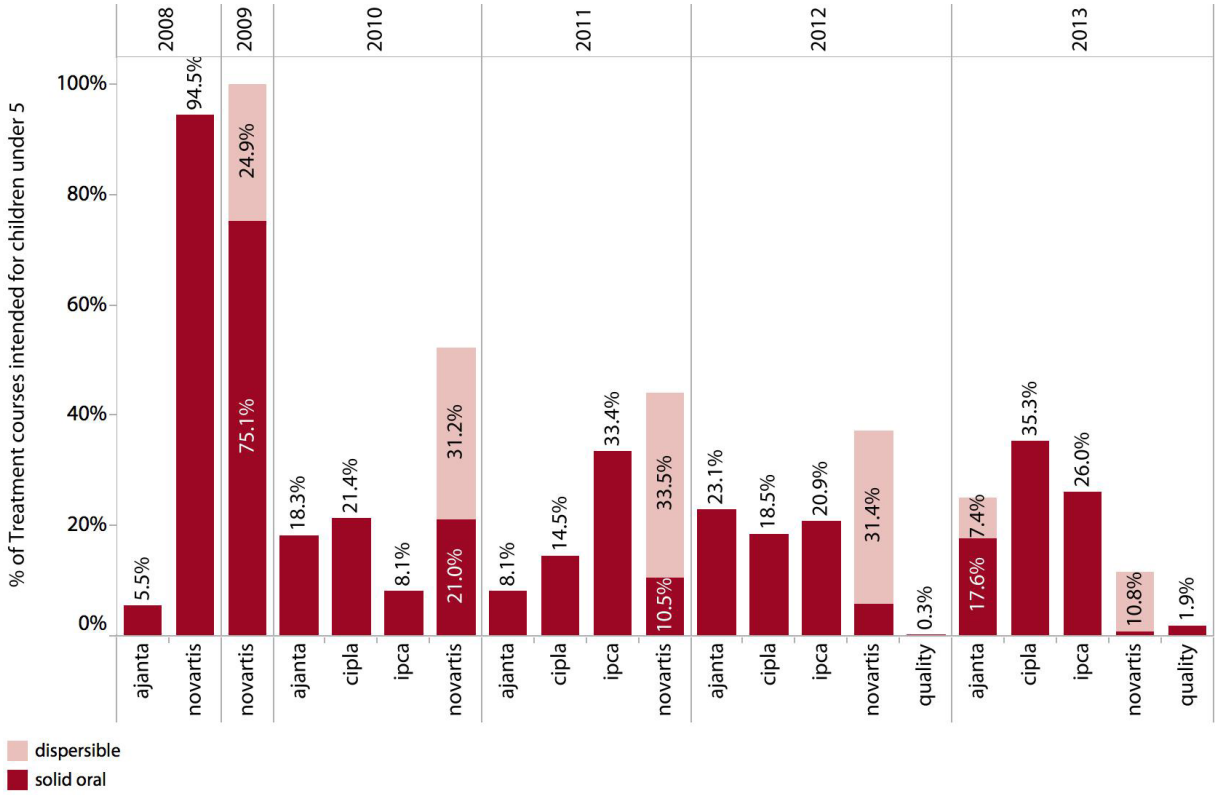


Notes: The chart only represents pack sizes tailored for children under 5 years old (average weight 18 kg). It represents 6x1 and 6x2 pack sizes; 6x3 and 6x4 pack sizes are available for procurement, but are not represented in this chart.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Until December 2012, only one prequalified dispersible AL tablet (Novartis Coartem®) was available for procurement. The Ajanta dispersible AL formulation became prequalified in December 2012, which will bring competition into this space *(5)*. Despite a Novartis monopoly on dispersibles, their total market share (dispersible and solid oral AL) has declined over time as more generic manufacturers of solid oral formulations have had products prequalified (Figure 34). In 2008, Novartis accounted for 95% of the AL child-packs in the donor-funded market and Ajanta accounted for 5%. In 2009, Novartis had the full share of the child-pack AL market. In 2012, Novartis still accounted for the greatest share of procured child-packs (37%), but the remaining share of this market was divided between Ajanta (23%), Cipla Ltd 18.5%) and Ipca (20%).

The market share of Novartis' paediatric products has been shifting to dispersibles over time. By 2012, Coartem® was selling low volumes of solid oral formulations (15%) in pack sizes for children. Ajanta introduced a second prequalified dispersible AL product into the market in December 2012. Although data for 2013 are incomplete, from the data currently available, Ajanta's dispersible product achieved 7% of the AL market share for children under 5 years old. However, with Ajanta and Novartis' products combined, dispersible AL only accounted for 17% of the market share.

Figure 34. Proportion of dispersible and solid oral AL packs for children under 5 years old procured by international donors, by manufacturer, 2008–2013



Notes: The chart only represents pack sizes tailored for children under 5 years old (average weight 18 kg). It represents 6x1 and 6x2 pack sizes; 6x3 and 6x4 pack sizes are available for procurement, but are not represented in this chart.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

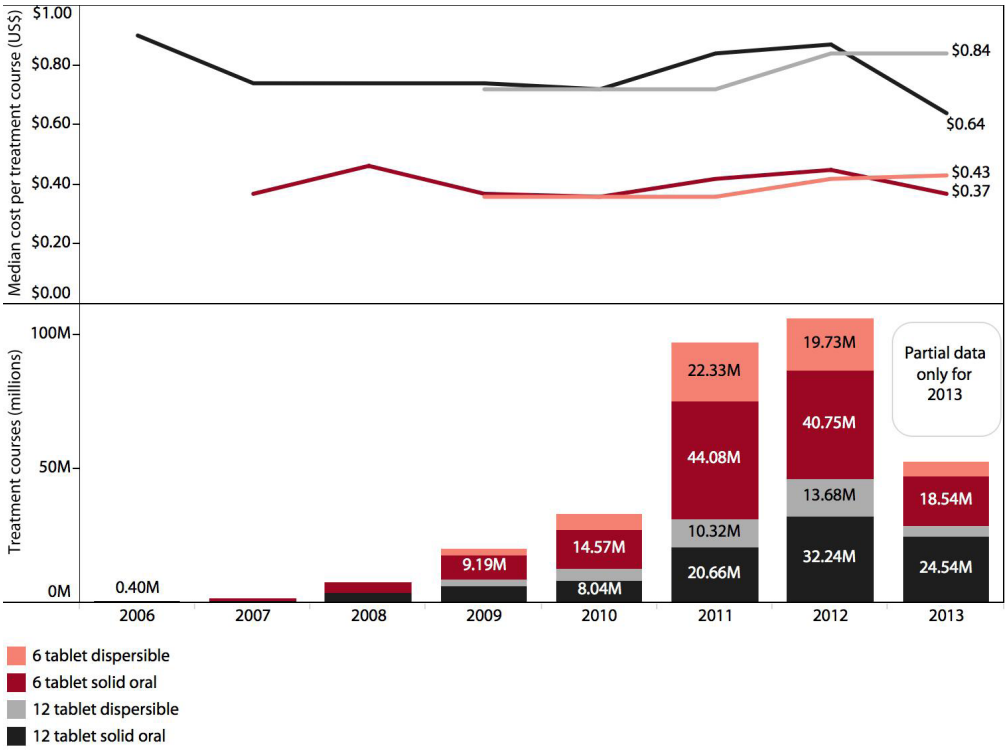
5.4.3 Procurement prices of ACTs for children under 5 years old in the donor-funded market

5.4.3.1 Dispersible and solid oral AL procurement prices for children under 5 years old in the donor-funded market

Since 2009, dispersible 6x1 AL was procured at a constant median unit price of US$ 0.36 from 2009 to 2011. In 2012, the median selling price of dispersible 6x1 AL increased to US$ 0.42 (Figure 35). Solid oral 6x1 AL (all brands) had the same median price as the equivalent dispersible until 2011 when the price increased to US$ 0.42 (US$ 0.01–0.64) in 2011 and US$ 0.45 (US$ 0.32–0.62) in 2012. Therefore, both dispersible and solid oral 6x1 AL have been purchased at a similar median price except in 2011, when the dispersible formulation price was lower. In 2012, the dispersible AL price increased meeting a similar price to the solid oral formulation.

The median price data from the PQR show similar trends between the 6x1 and 6x2 AL formulations. Dispersible 6x2 AL median prices were constant between 2009 and 2011 at US$ 0.72 and increased to US$ 0.84 in 2012, the year when Cipla received prequalification. The median price of solid oral 6x2 AL (all brands) has increased from US$ 0.74 in 2009 to US$ 0.87 in 2012. Data available for 2013 procurement prices portray that the median price of solid oral 6x1 and 6x2 decreased again to lower prices than the dispersible formulations.

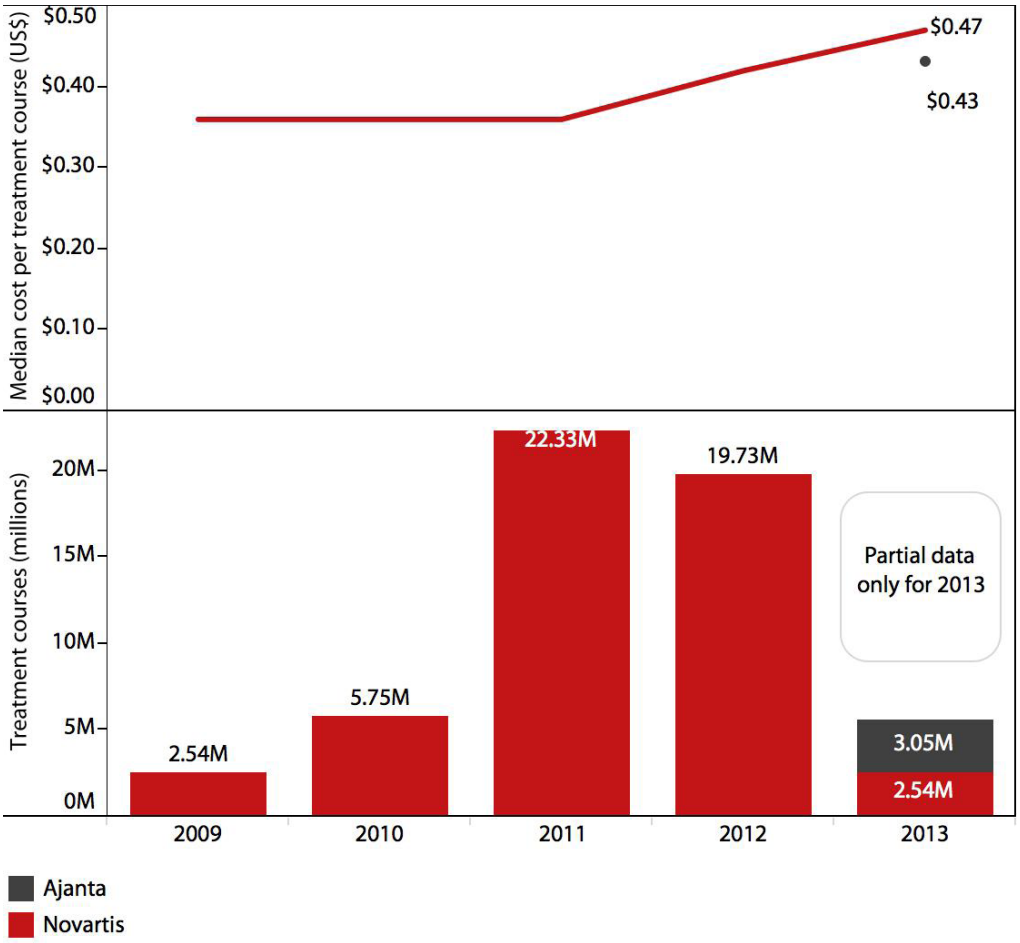
Figure 35. Median unit price of AL for children under 5 years old procured by international donors, dispersible and FDC, 2008–2013



Note: 6x1 and 6x2 AL packs are tailored for children weighing less than 18 kg.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Novartis was the only prequalified dispersible AL supplier until 2012. During this time, Novartis committed to providing both dispersible Coartem® and solid oral Coartem® at the same price thus the solid oral formulation is not preferred by procurers because of affordability issues *(85)*. In 2012, Ajanta received prequalification for a dispersible AL product. The incomplete data from 2013 available from the PQR and AMFm indicate that, for dispersible 6x1 AL, Ajanta entered the market with a median selling price of US$ 0.43 (US$ 0.40–0.55), equalling around US$ 0.05 lower than the median price of Novartis' AL product (Figure 36). Looking forward, as dispersible formulations are preferred for children, the price of dispersible AL between the two manufacturers will be important to monitor.

Figure 36. Median unit price and treatment courses procured of dispersible 6x1 AL for children under 5 years old, procured by international donors by manufacturer 2009–2013

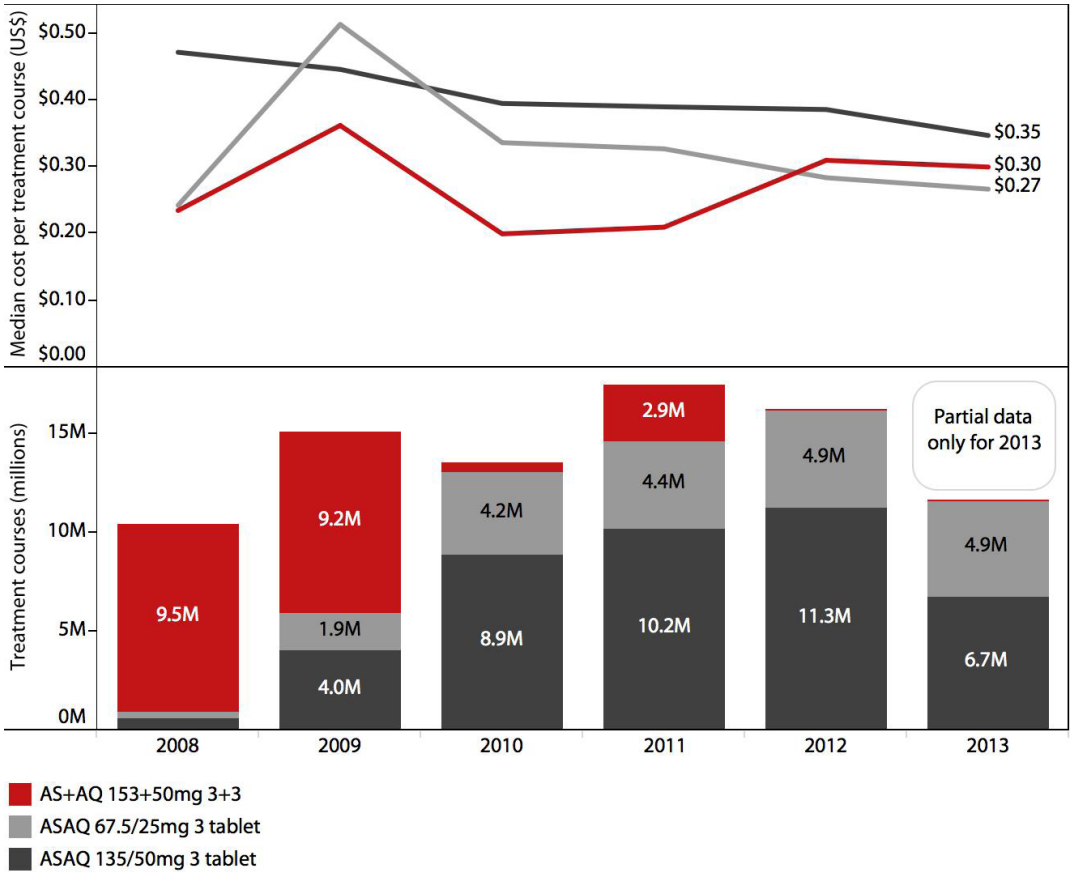


Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.4.3.2 Co-blister and FDC ASAQ procurement prices for children under 5 years old in the donor-funded market

Since 2009 when dispersible AL first became available, the median price of ASAQ and AS + AQ for children under 5 years old has decreased (Figure 37). The price of ASAQ for both infants and toddlers (135/50 mg packs) has continuously decreased since 2009. For example, ASAQ for toddlers declined from a median selling price of US$ 0.51 (US$ 0.35–0.55) in 2009 to US$ 0.28 (US$ 0.24–0.38) in 2013. The median price of AS + AQ (153mg + 50mg) formulations for this age category has fluctuated. In 2009, the median selling price was US$ 0.36 (US$ 0.20–2.40), US$ 0.20 (US$ 0.21–0.27) in 2010 and US$ 0.31 (US$ 0.31 – 0.31) in 2012. In 2012, ASAQ 67.5/25 mg packs were cheaper to purchase in the donor-funded market than AS + AQ for this age range, and data available for 2013 suggest a similar trend for 2013.

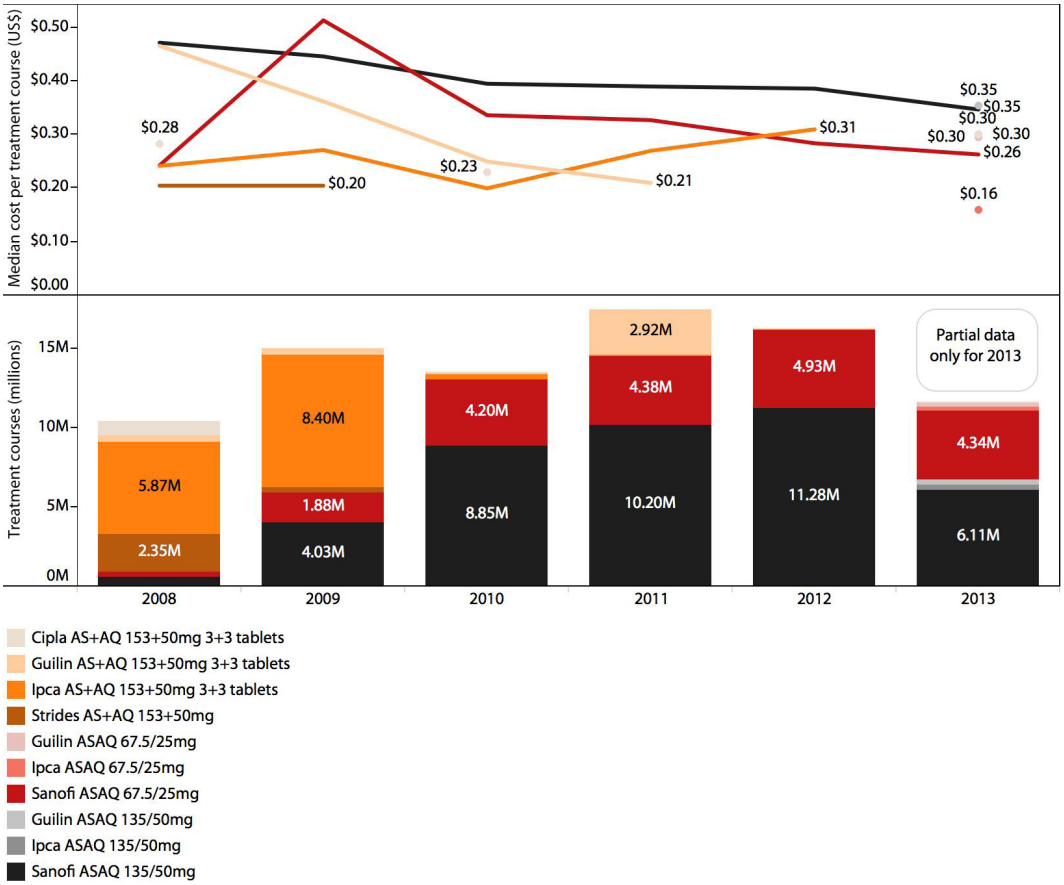
Figure 37. Median unit price of ASAQ and AS+AQ for children under 5 years old procured by international donors, 2008–2013



Note: AS+AQ 3+3 and ASAQ 67.5/25 mg, and ASAQ 135/50 mg packs are tailored for children weighing less than 18 kg.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

Overall, the median prices of ASAQ for children under 5 years of age procured in the donor-funded market have been decreasing since 2009 (Figure 38). Looking at Sanofi's price trends as the only supplier of ASAQ until 2012, the median price of Sanofi's ASAQ 135/50 mg packs suitable for children under 5 years old decreased from US$ 0.47 (US$ 0.46–0.49) in 2008 to US$ 0.39 (US$ 0.01–0.47) in 2012. There are potentially further reductions in the median price of this product (US$ 0.35, US$ 0.01–0.61) based on the 2013 data currently available. In 2012, two additional ASAQ manufacturers received prequalification. At this point in time, the available data for ASAQ 135/50 mg packs indicate that Guilin entered the market at US$ 0.35 and Ipca entered at the lowest median price of US$ 0.30 (US $0.16–0.39).

Figure 38. Median unit price and treatment volumes procured of ASAQ/AS+AQ (3 tabs and 3+3) by manufacturer, 2008–2013



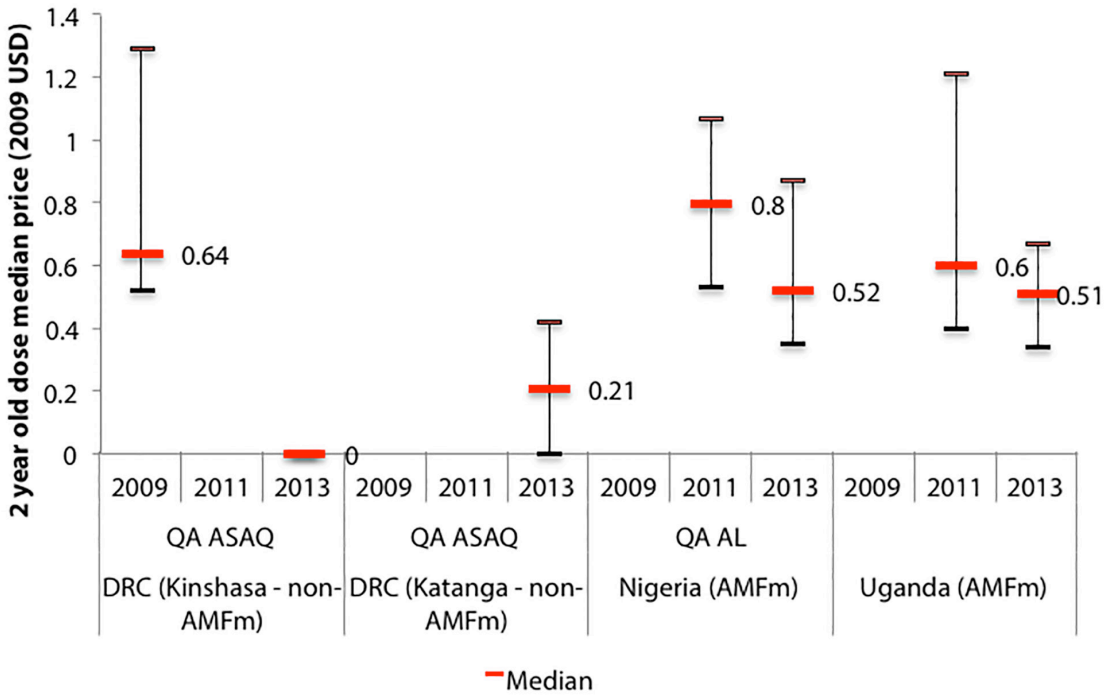
Note: AS+AQ 3+3 and ASAQ 67.5/25 mg, and ASAQ 135/50 mg packs are tailored for children weighing less than 18 kg.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.4.4 Retail availability and price of child-dose QAACTs

ACTwatch surveys from the DRC (Katanga and Kinshasa provinces), Nigeria and Uganda surveyed in 2009–2010, 2011 and 2013, provide estimates of the median price of quality-assured AL and quality-assured ASAQ in the private sector for children under 2 years old.[24] As with AETDs, the number of medicines available to audit on the day of the survey influences the prices reported below. For this reason, the following only reports on the most common treatment for each country (either quality-assured ASAQ or quality-assured AL). In the Kinshasa province of the DRC (non-AMFm), the median treatment price of quality-assured ASAQ was low (Figure 39), however, there is low availability of this medicine. The treatments that were available at the time of the audit may have been available through a local subsidy programme. In Nigeria, in 2013, an AMFm country, quality-assured AL was moderately available in retail outlets at a median price of US$ 0.52 (US$ 0.35–0.87). In Uganda, the median price of available quality-assured AL decreased between 2011 and 2013 from US$ 0.60 to US$ 0.51, respectively. Quality-assured AL was also highly available in private outlets at the time of the survey.

24 QAACT prices reported represent a mix of subsidized QAACTs (i.e. QAACTs with the AMFm logo), unsubsidized QAACTs and includes a number of different brands *(3. World Health Organization. World Malaria Report. Geneva: World Health Organization; 2013.*

Figure 39. Median patient price of quality-assured AL, quality-assured ASAQ and any QAACT tablets for children under 2 years old (10 kg) in the private sector, including the informal private sector



Notes: Prices are standardized to the 2009 US$ using the consumer price indexes in each country to adjust for inflation/deflation. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs). In the DRC, in 2013, data were collected by province. Range represents the 25th and 75th IQR.
Sources: ACTwatch outlet surveys 2009–2010, 2011 and 2013.

5.5 Severe malaria

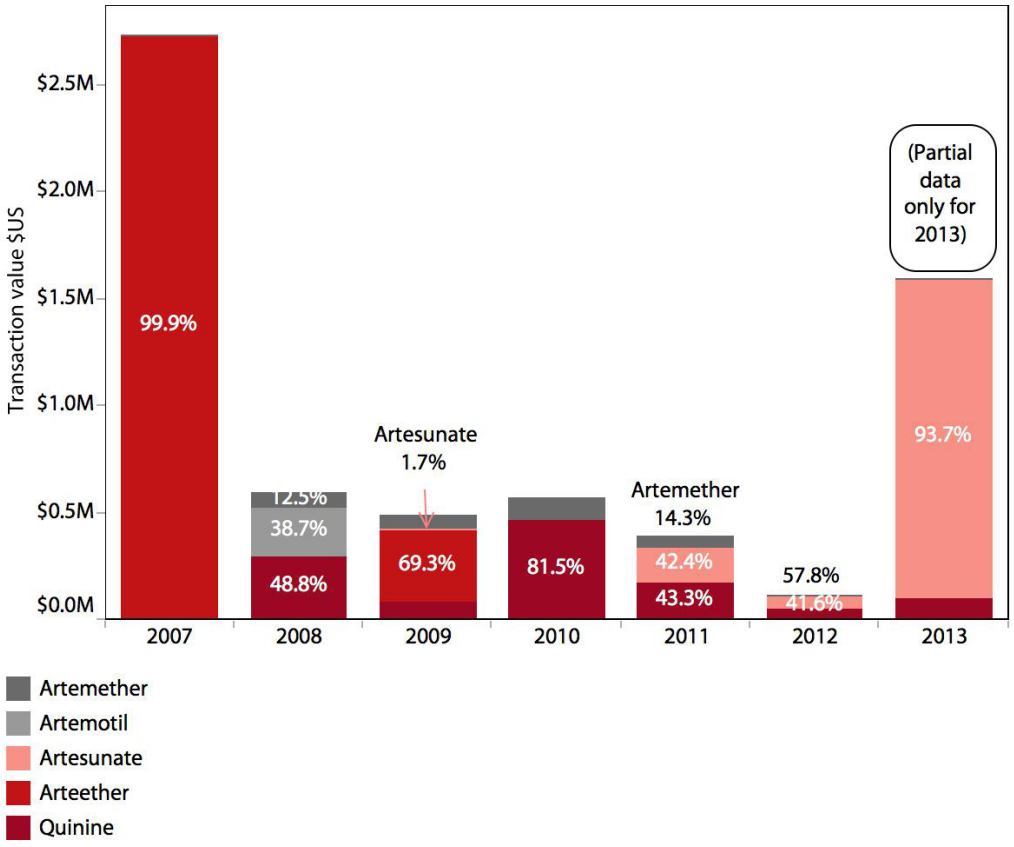
5.5.1 Injectable therapies for severe malaria market overview

There is currently only one WHO prequalified IVAS product available (Guilin). Until 2012, uptake of INJAS was low: quantities procured in 2012 were less than 25% of the total needed to treat global annual cases. Approximately 12M vials (roughly 1.5–2M treatments) for children under 5 years old were procured out of an estimated 48–50M vials that would be needed to treat global annual cases *(7)*. Reasons for low-level procurement of IVAS included a higher price over IVQ, the absence of catalytic financing incentives to purchase IVAS, unfamiliarity with the product and buyer concerns over a single prequalified supplier. It is important to note that although the average treatment course cost of INJAS is currently higher than IVQ (US$ 3.3 compared to US$ 1.3), overall costs are found to be equivalent when total costs are considered. In particular, when considering the cost of administering the two drugs and management of side-effects, artesunate is found to be cost effective *(86)*. In 2013, a significant shift in procurement volumes was observed (Figure 40). Figure 40 shows the value of transactions for injectable antimalarials in the donor-funded market over time.[25] While IVQ has historically accounted for the greatest value of injectables procured, the transaction value of IVAS looks to have increased, notably reaching US$ 1.5M compared to IVQ only and totalling around US$ 100K in 2013, suggesting an increase in uptake.

25 Countries generally procure IVQ with national funding. Even though volume information on these medicines is not obtainable from the database, given that the price of IVQ is around three times lower than IVAS at health facilities and assuming that the price difference at the facility level is reflective of the price margin between the two products for first-line buyers in the donor market, it can be inferred that more quantities of IVQ were procured by the international community in the donor-funded market in 2011 than IVAS.

UNITAID is also working to catalyse the market for INJAS by scaling up access in six high-burden countries. As there is currently only one supplier, the UNITAID project is also aiming to bring additional suppliers into the market in order to increase competition and reduce prices *(7)*.

Figure 40. Total value (US$) of PQR transactions for INJAS, artemether, artemotil and IVQ, 2007–2013



Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.5.2 RAS market overview

Given that the risk of death from severe malaria is greatest in the first 24 hours, access to pre-referral treatment is also important to "buy time" for patients who are in transit to a facility where they can receive intravenous treatment. In situations where parenteral medication is not possible and when the referral time is greater than six hours, WHO recommends the use of a single dose of RAS for pre-referral treatment *(6)*. However, the lack of a WHO prequalified product or approval by an SRA, has limited access and hampered widespread use of this product. UNITAID has supported an MMV project that is focused on an RAS product receiving prequalification in the near future.

Currently, there are two RAS products marketed by Cipla and Mepha (now Acino), and Mepha is currently the dominant market manufacturer. The Mepha product has been tested by Médecins sans Frontières and PMI; it has been widely used by Médecins sans Frontières in its country programmes since 2007.[26] In 2009 and 2010, PQR records indicate that Mepha's RAS suppositories also were procured through the Global Fund for Eritrea, Sierra Leone and the Sudan. Information from the UNICEF supply catalogue, where Mepha's RAS is available, indicates that suppositories are priced at US$ 5.06 for a box of six 200 mg, and US$ 1.92 for a box of six 50 mg. In addition to the Mepha product, Cipla has a 50 mg product that has

26 To assess and validate the quality of a medicinal product, Médecins sans Frontières and procurement agency pharmacists have developed a qualification procedure based on WHO recommendations. From the analysis of parameters linked with the production site to the product itself, the entire production chain is checked before being validated. No information is available on the PMI quality assurance process.

been used by Médecins sans Frontières in Sierra Leone, but it is not widely registered. There is a third RAS product, as mentioned in Section 4.2, which is currently in the registration phase.

5.6 Overview of the antimalarial market in the WHO South-East Asia Region and Western Pacific Region

Both the WHO South-East Asia Region and Western Pacific Region are particularly important in the supply of antimalarial medicines: six of the nine manufacturers that supply WHO prequalified medicines are based across both of these regions *(87)*. Five of these are based in India and the other in China. Furthermore, the vast majority of the natural artemisinin supply is grown in this region (primarily China and Viet Nam; the artemisinin market is described in Section 5.7).

Additionally, access to quality ACTs in both of these regions remains a problem even though there is substantial potential within these regions to expand quality ACT manufacturing. A key challenge will be to improve the quality of ACTs manufactured in this region to international standards without impacting the user price *(87)*.

5.6.1 Market size and share of malaria products procured for the WHO South-East Asia Region and Western Pacific Region

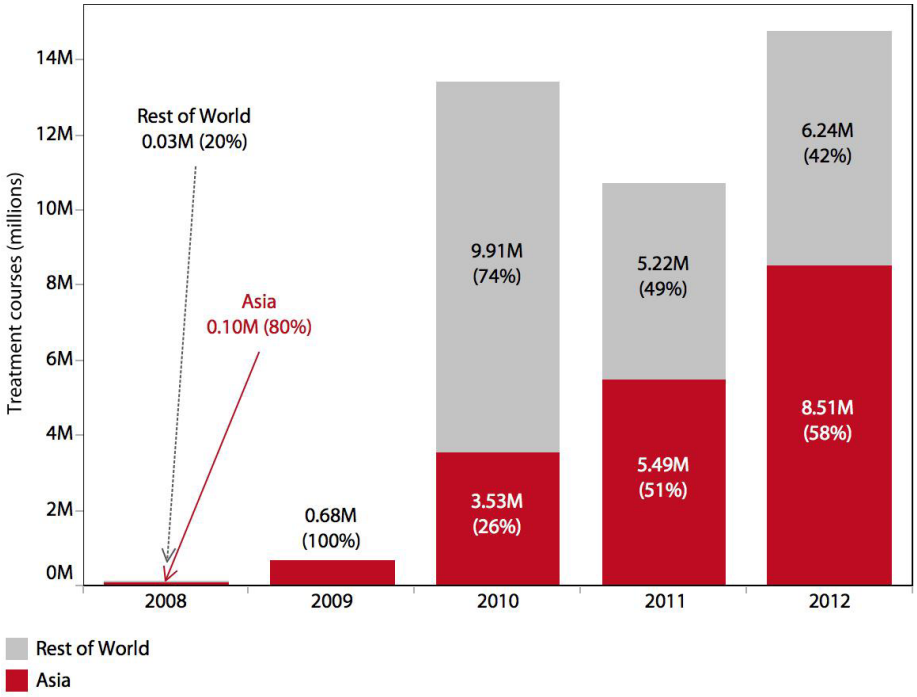
Assessing the size and share of the CQ, PQ and DHA PPQ market is limited to procurement data available from the PQR database. Global Fund PQR and AMFm datasets represented approximately 73% of the donor market in 2010, 86% in 2011, 62% in 2012 and 35% in 2013 (excluding PMI volumes) (Table **5**). However, the donor portion is a lower portion of the overall antimalarial market in these regions than in the WHO African Region.

CQ

Although treatment failure to CQ has been observed in 23 countries, CQ remains the currently recommended drug to treat *P. vivax* in most endemic areas where the drug is still effective *(6)*. In the South-East Asia Region and Western Pacific Region, CQ + PQ is the national policy to treat *P. vivax* in 14 out of 19 countries *(3)*.[27] CQ is also recommended to treat uncomplicated unconfirmed malaria in India, Nepal and the Republic of Korea, and it is recommended to treat both *P. ovale* and *P. malariae*. Figure 41 shows that the size of the CQ market in Asia has grown from 0.5M treatment courses procured in 2009 to over 8M in 2012. Except for 2010, CQ principally has been procured for the markets in the South-East Asia Region and Western Pacific Region.

27 Countries in these regions with non-CQ first-line policies to treat *P. vivax* include: Cambodia (DHA PPQ); Indonesia (ASAQ, DHA PPQ+PQ(14D)); Papua New Guinea (AL+PQ); Solomon Islands (AL+PQ(14D)); and Vanuatu (AL+PQ(14D)).

Figure 41. Total volumes (treatment courses) of PQR transactions for CQ, by WHO region, 2008–2012



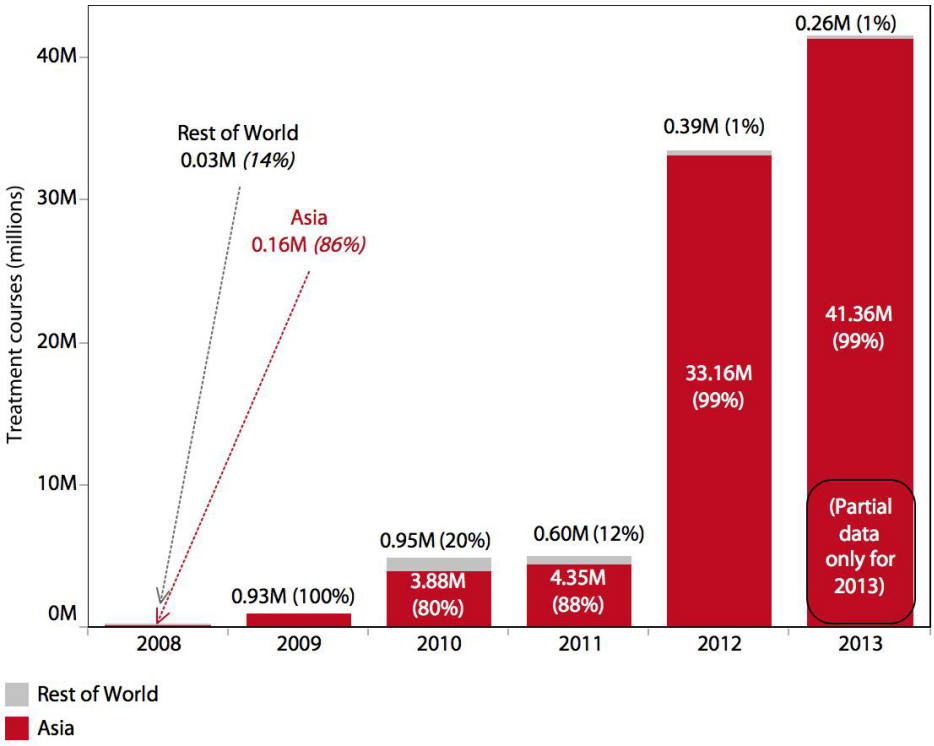
Note: Asia is defined by United Nations geographical regions and includes eastern, southern, western and central Asia and Oceania, which comprises the countries of the WHO South-East Asian Region and Western Pacific Region.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

While CQ is still sensitive to treat some cases of P. *vivax*, treatment failures to monotherapies, including CQ and SP, have been observed in both India and Pakistan, and other South-East Asian countries *(6)*. ACTs are now recommended for the treatment of CQ-resistant *P. vivax*, particularly where ACTs have been adopted as the first-line treatment of *P. falciparum (6)*. Currently, there is no estimate for the number of cases of *P. vivax* occurring in regions where CQ is still the recommended first-line treatment. With this information, it would be possible to calculate the rational volumes of CQ, and also the amount of CQ being used in regions where it is not recommended, including sub-Saharan Africa for *P. falciparum.* Therefore, improved monitoring of the number of CQ treatments delivered compared to the number of *P. vivax* cases is needed to better understand this market.

PQ

Procured PQ treatment volumes have increased significantly in recent times (Figure 42). In 2011, around 4M treatment courses were procured compared to 33M in 2012. While the 2013 data are incomplete, currently available data indicate that procured treatment courses of PQ increased to 41M in 2013. Additionally, as PQ procurement levels have decreased for Africa, volumes procured have increased in the South-East Asia Region and Western Pacific Region (88% in 2011, 99% in 2012, 99% in 2013). Increased volumes are likely attributed to an increase in uptake for *P. vivax* liver-stage clearance.

Figure 42. Total volumes (treatment courses) of PQR transactions for PQ, by WHO region, 2008–2013



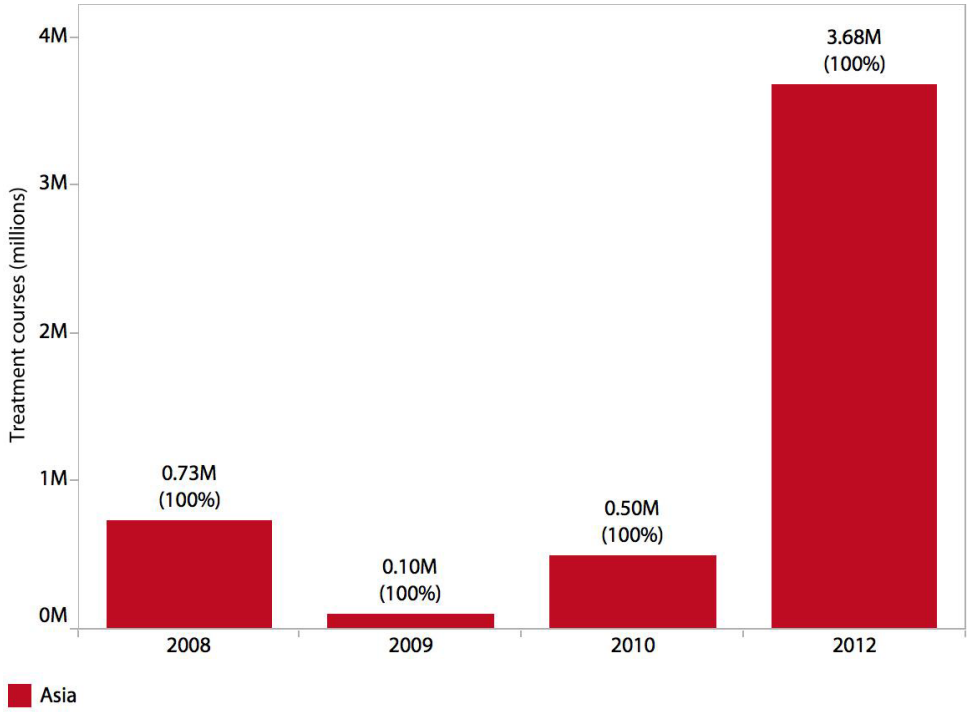
Note: Asia is defined by United Nations geographical regions and includes eastern, southern, western and central Asia and Oceania, which comprises the countries of the WHO South-East Asian Region and Western Pacific Region.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

DHA PPQ

DHA PPQ is a relatively new ACT that is primarily being used in Asia. Following EMA marketing approval in 2011, the volumes procured in the donor-funded market increased to 3.6M treatment courses in 2012 (Figure 43). While procured volumes of DHA PPQ have increased over time, there is only one supplier of prequalified DHA PPQ,[28] and the current EMA label of the only prequalified product in the donor-market advises an ECG is obtained before the last of the three daily doses (48),[29] Both of these factors are potentially impacting the uptake of this new drug in the market.

28 There are currently three DHA PPQ products under assessment by the WHO PQP.
29 A recent Cochrane review has found that DHA PQP was associated with more frequent prolongation of the QTc interval (low quality evidence), but no cardiac arrhythmias were reported *(47)*.

Figure 43. Total volumes (treatment courses) of PQR transactions for DHA PPQ, by WHO region, 2008–2012

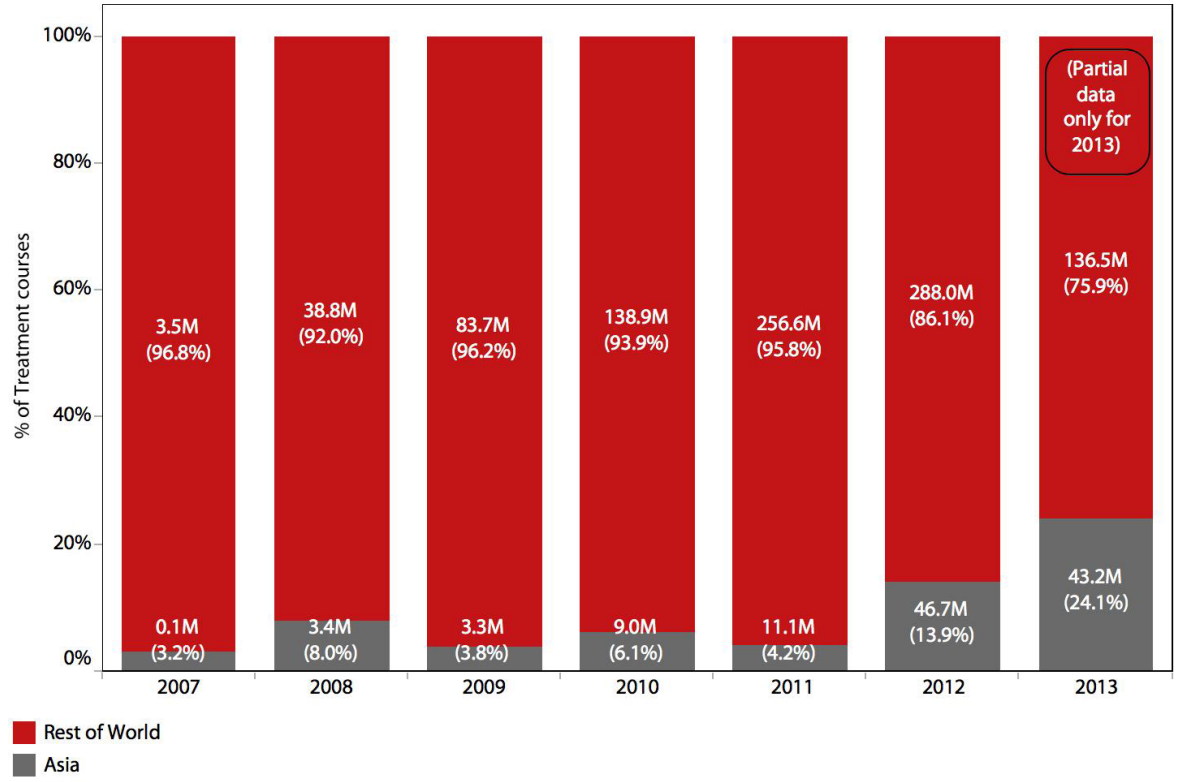


Note: Asia is defined by United Nations geographical regions and includes eastern, southern, western and central Asia and Oceania, which comprises the countries of the WHO South-East Asian Region and Western Pacific Region.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

5.6.2 Market share of ACTs and non-artemisinin monotherapies (oral therapies) procured in the donor-funded market for the WHO South-East Asia Region and Western Pacific Region

The size of the donor-funded market of all ACTs procured in the WHO South-East Asia Region and Western Pacific Region compared to the rest of the world has generally increased since 2009 (Figure 44). In 2009, 3.8% of ACT treatment courses were procured for the South-East Asia Region and in 2012 this increased to 13.9%. As the dataset for 2013 is incomplete, data that are currently available suggest that ACT treatment courses procured increased to approximately 24% of the donor-funded market.

Figure 44. Proportion of oral antimalarial treatment courses procured for Asia compared to the rest of the world (WHO regions), 2007–2013



Note: Asia is defined by United Nations geographical regions and includes eastern, southern, western and central Asia and Oceania, which comprises the countries of the WHO South-East Asia Region and Western Pacific Region.
Sources: Calculated from transactions reported in Global Fund PQR data and AMFm data.

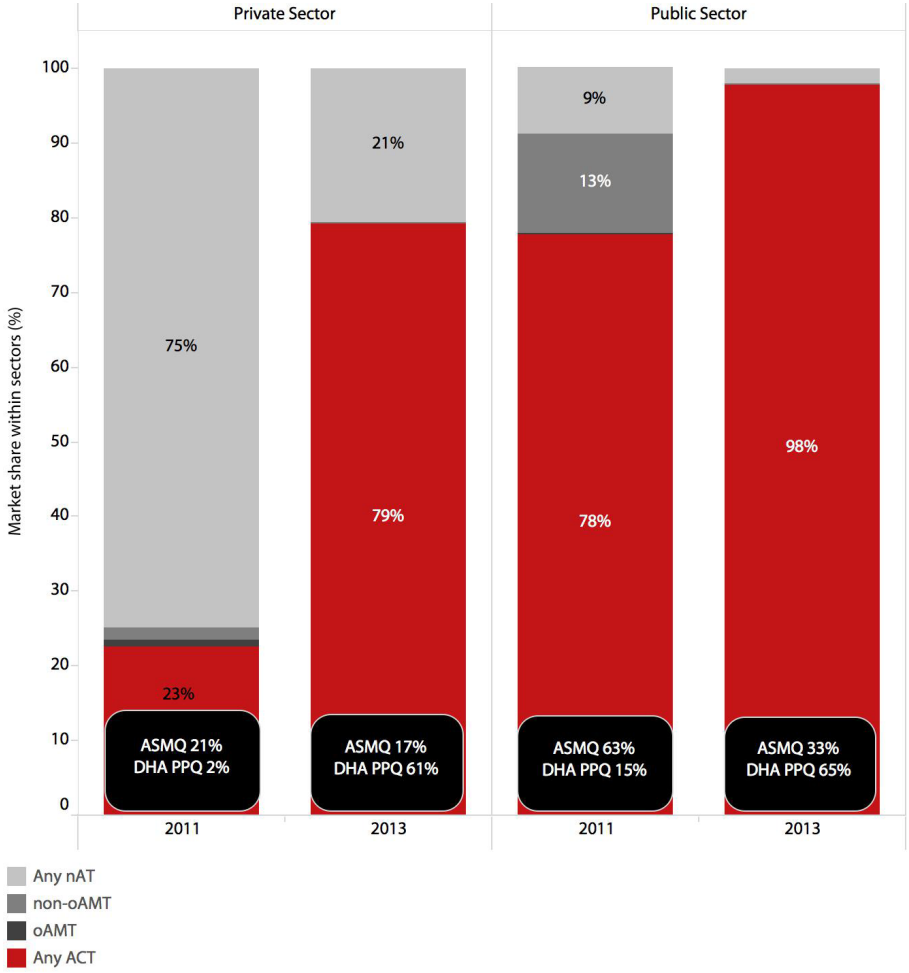
5.6.3 Market share of antimalarials distributed at the facility level in Cambodia and Myanmar

Around 80% of health care in the Asia Pacific (which includes the WHO South-East Asia Region and Western Pacific Region) is delivered through the private sector and manufacturers supplying cheap (often poor quality drugs) is favoured in this sector as care-seeker choice is often influenced by availability and price *(44)*. ACTwatch monitors the antimalarial market in Cambodia (AMFm country) and more recently in Myanmar (non-AMFm country). These countries are both situated in the Greater Mekong subregion where artemisinin drug resistance has now been detected, meaning strategies to improve the coverage of ACTs and appropriately manage the threat of artemisinin resistance are increasingly urgent *(33)*.

ACTwatch outlet surveys from Cambodia show the relative market share of ACTs. Based on the number of AETDs in each unit, the total number of AETDs sold/distributed for each medicine is calculated. This measure shows the proportion of AETDs distributed to consumers for a given medicine or by a given outlet, relative to the total amount of AETDs sold/distributed. In Cambodia, the market share of ACTs has increased in both the public and the private sector since 2011 (Figure 45). For example, the market share of ACTs in the private sector in 2011 was 23% and increased to 79% in 2013. In addition to this, the market share of DHA PPQ also increased from 2% in 2011 to 61% in 2013 in the private sector, while oAMTs (oral artemisinin monotherapy) have been entirely phased out. This reflects the change in Cambodia's first-line therapy from ASMQ to ASMQ or DHA PPQ in 2012, particularly for resistance containment areas. Prior to this, DHA PPQ was not yet widely available as it was only deployed largely through the public sector in artemisinin resistance zones *(88)*. Recently, Pyramax® (APSY) was registered for use in Cambodia thus increasing the range of ACTs available to patients *(50)*. This medicine is also registered for the treatment of both *P. falciparum* and *P. vivax* making it a useful tool in Cambodia where the parasites coexist. The

introduction of Pyramax® into the market in Cambodia is likely to impact the market share of ACTs in both sectors looking forward *(50)*.

Figure 45. Market share of antimalarials sold or distributed in the past week in Cambodia, within sector, 2011 and 2013



Any nAT, any non-artemisinin therapy; non-oAMT, any non-oral artemisinin monotherapy; oAMT, artemisinin monotherapy; any ACT, any artemisinin combination therapy including QAACTs and non-QAACTs

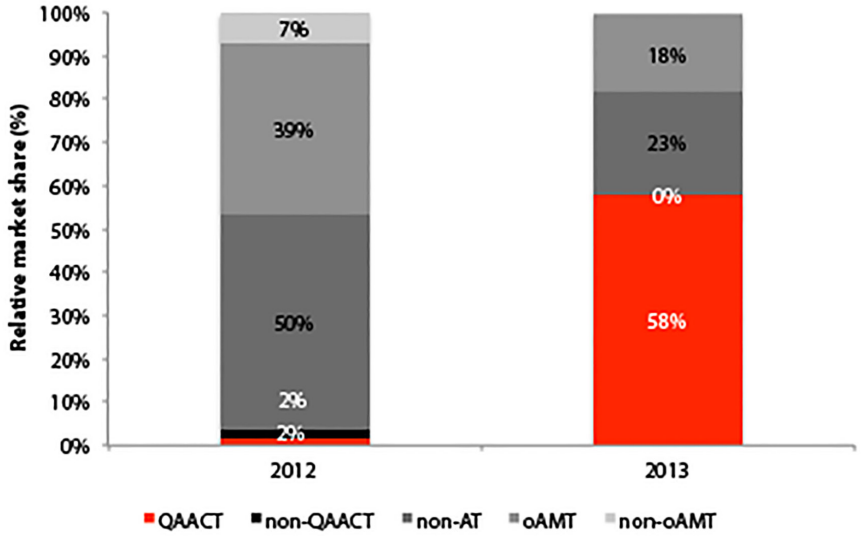
Notes: Image represents AETDs sold or distributed in the previous week by antimalarial type as a percentage of all AETDs sold/distributed within each sector. Private sector includes pharmacies, drug stored, general retailers and itinerant drug vendors. Public sector includes public health facilities and community health workers.

Sources: Cambodia outlet surveys 2011 and 2013.

In 2012, Population Services International *(19)* was funded by UK Aid/DFID, the Bill & Melinda Gates Foundation, and Good Ventures to specifically implement the Artemisinin Monotherapy Replacement Project (AMTR) within the Myanmar Artemisinin Containment Project (MARC) areas of eastern Myanmar to rapidly displace availability and use of oAMTs. The AMTR project specifically targeted artemisinin resistance containment in Myanmar and aimed to rapidly replace oAMTs with QAACTs (the national first-line, AL) in the private sector, primarily through the implementation of a sustained price subsidy *(19)*. The AMTR project specifically targeted private sector outlet types with subsidized QAACT and medical detailing for pharmacies, itinerant drug vendors and general retailers to support correct provider behaviour *(19)*. ACTwatch-style outlet surveys were adopted as a monitoring and evaluation tool for the AMTR project to consider the market share, availability and price of malaria medicines in the context of the AMTR project *(88)*. The analysis below is restricted to data available from the AMTR project to show the impact of the project on ACTs in the designated areas.

Within one year of the AMTR project launch in 2012, the market share of QAACTs in the pure private sector of the MARC project areas increased (2% in 2012 to 58% in 2013) (Figure 46). At the same time, the market share of non-QAACTs, non-ATs, oAMTs and non-oAMTs decreased dramatically in this short time period.

Figure 46. Relative ratio of antimalarials sold in the pure private sector in the MARC area, 2012 and 2013

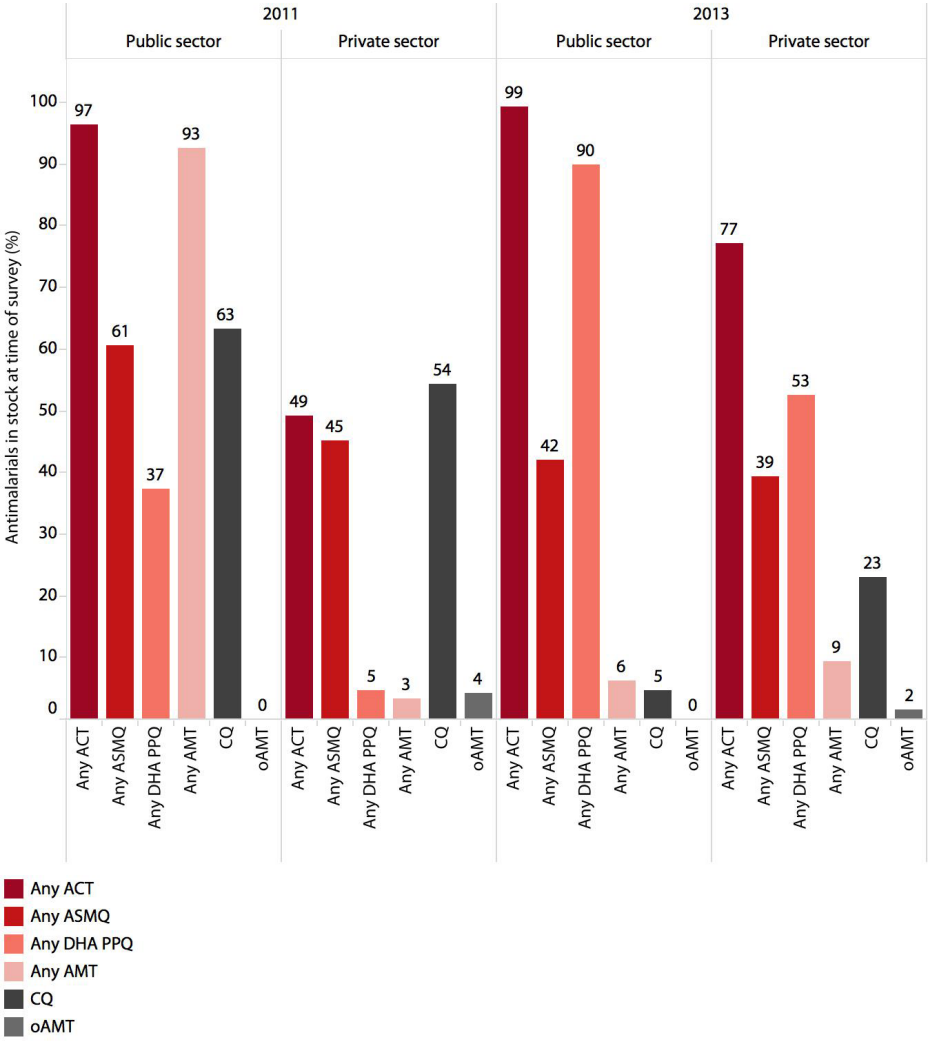


any oAMT, any oral artemisinin monotherapy; non-oAMT, any non-oral artemisinin monotherapy; any non-AT, any non-artemisinin therapy; non-QAACT, non-quality assured artemisinin combination therapy; QAACT, quality assured artemisinin combination therapy.
Notes: Image represents each antimalarial category as a proportion of the total volume of all antimalarials (AETDs) sold or distributed in the pure private sector in the past week. Pure private sector includes pharmacies, retailers and itinerant drug vendors.
Sources: ACTwatch Myanmar outlet surveys 2012 and 2013.

5.6.4 Trends in availability of antimalarials in private and public sector facilities in Cambodia and Myanmar

In the public sector in Cambodia, the availability of ACTs increased from 97% in 2011 to 99% in 2013 (Figure 47). Over this same time, there were reductions in the availability of the non-artemisinin mono-therapies like CQ (63% in 2011 to 5% in 2013). In the private sector, the availability of any ACT increased from 49% in 2011 to 77% in 2013. The availability of DHA PPQ increased from 5% in 2011 to 53% in 2013, representing an increase in uptake of the newly introduced first-line therapy in 2012.

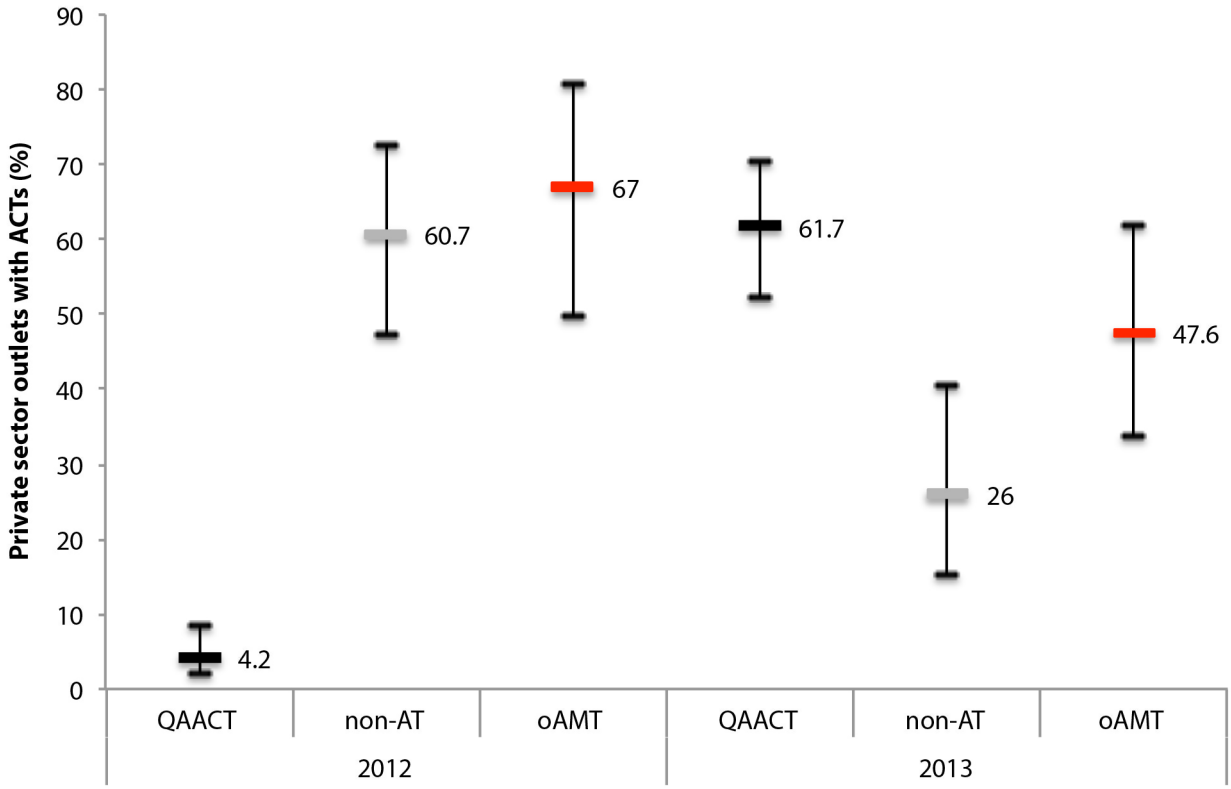
Figure 47. Availability of antimalarials in Cambodia among all outlets with antimalarials in stock on the day of survey, 2011 and 2013



Any ACT, any artemisinin combination therapy including QAACTs and non-QAACTs; any ASMQ, any artesunate+/mefloquine; any DHA PPQ, any dihydroartemisinin piperaquine; any AMT, any artemisinin monotherapy; CQ, chloroquine; oAMT, oral-artemisinin monotherapy.
Note: Image represents the proportion of outlets stocking the specified type of antimalarial, among outlets with at least one antimalarial at the time of the survey.
Sources: ACTwatch Cambodia outlet surveys 2011 and 2013.

In Myanmar MARC project areas, the availability of QAACTs in the pure private sector outlets surveyed as a part of the AMTR project also increased since its beginning in 2012 (Figure 48). Specifically, the availability of QAACTs increased from 4.2% in 2012 to 61.7% in 2013. In the pure private sector, median availability of non-ATs and oAMTs decreased between survey rounds.

Figure 48. Availability of ACTs in the Myanmar private sector, 2012 and 2013

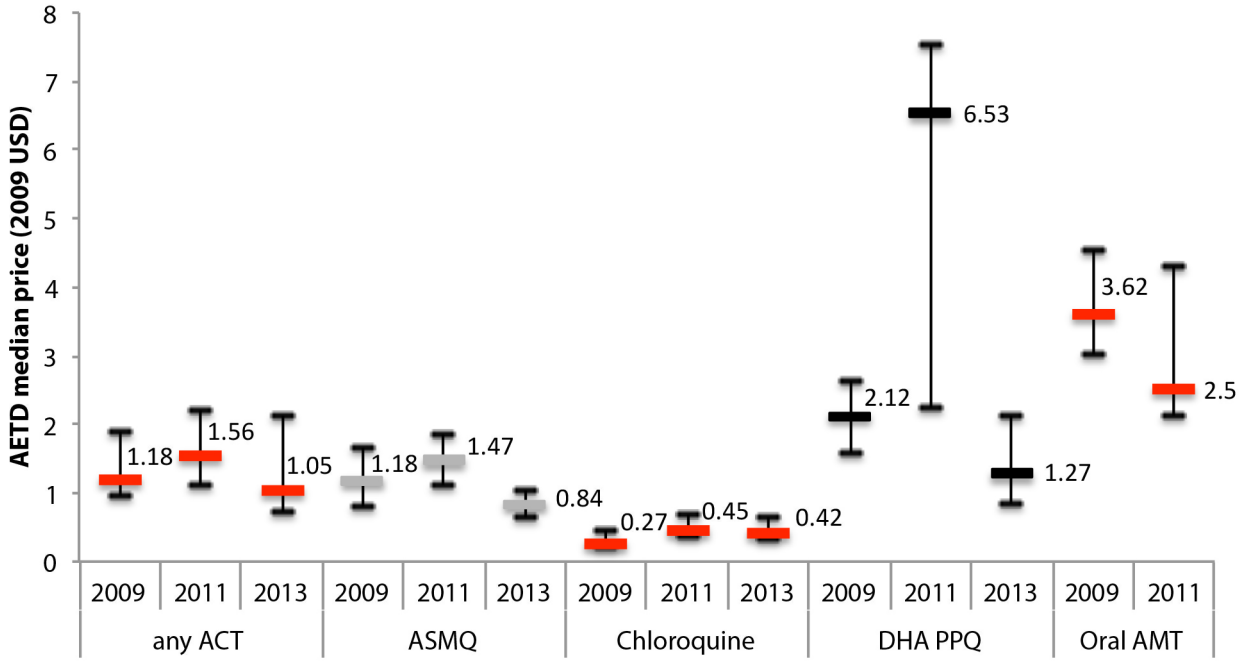


QAACT, quality assured artemisinin combination therapy; non-QAACT, non-quality assured artemisinin combination therapy; non-AT, non-artemisinin therapy.
Notes: Image reflects the proportion of outlets stocking the specified type of antimalarial, among outlets with at least one antimalarial at the time of the survey. Pure private sector includes pharmacies, retailers and itinerant drug vendors.
Sources: ACTwatch Myanmar outlet surveys 2012 and 2013.

5.6.5 Cambodia and Myanmar median price of available antimalarials in the private sector

Since 2009, the median patient price in Cambodia of any ACT has decreased from US$ 1.18 in 2009 to US$ 1.05 in 2013 (Figure 49). When looking at the median price of specific medicines available in Cambodia over time, it is important to highlight a general low availability of these products at the time of the survey. For example, the price of DHA PPQ increased from US$ 2.12 in 2009 to US$ 6.53 in 2011, but decreased to US$ 1.27 in 2013. In 2009 and 2011, less than 50 medicines were available to audit at the time of the survey, reflecting low availability. A reason for low availability was that the product was not widely available as it was only deployed in the public sector in artemisinin resistance containment zones. Similarly, ACT stock in general, including ASMQ, was relatively low during the 2011 survey thus impacting the price of products in that same year.

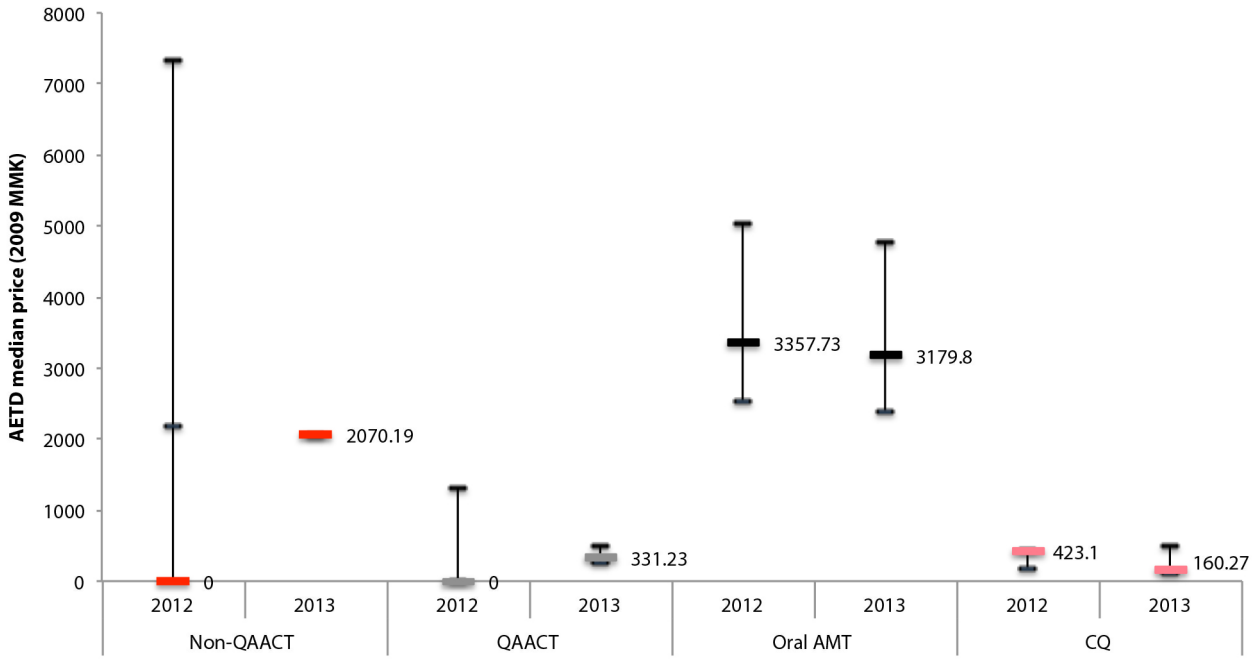
Figure 49. Median patient price of antimalarials (AETD) in the Cambodian private sector, 2009–2013



Any ACT, any artemisinin combination therapy including QAACTs and non-QAACTs; any ASMQ, any artesunate+/mefloquine; any DHA PPQ, any dihydroartemisinin piperaquine; any AMT, any artemisinin monotherapy; CQ, chloroquine; oAMT, oral-artemisinin monotherapy
Notes: Prices are standardized to the 2009 US$ using the consumer price indexes in Cambodia to adjust for inflation/deflation. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs).
Sources: ACTwatch Cambodia outlet surveys 2010, 2011 and 2013.

In the MARC area in Myanmar, where the project was specifically implemented to rapidly phase out oAMTs in 2012, the median price of QAACTs increased from Burmese Kyat (MMK) 0 in 2012 to MMK 331.23 in 2013, with a wide range observed in 2012 (Figure 50). However, there were only 38 QAACTs available at the time of the 2012 survey (compared to 407 in 2013). While the median price of oAMTs in the MARC area remained relatively flat (MMK 3357.35 in 2012 and MMK 3179.8 in 2013), the availability of the product at the time of the survey decreased.

Figure 50. Median patient price of antimalarials (AETD) in the pure private sector in the MARC area, 2012 and 2013



Notes: Prices are standardized to 2009 MMK using the consumer price indexes in Myanmar to adjust for inflation/deflation. Prices are reported in MMK to show a truer representation of the value of the currency.
Sources: ACTwatch Myanmar outlet surveys 2012 and 2013.

5.7 Artemisinin market overview

Artemisinin is the key starting material for the APIs used in ACTs, known as artemisinin derivatives. These derivatives (artemether, artesunate, DHA) can now be synthesized from artemisinin in one or two synthetic steps. Artemisinin, which is extracted from the plant *Artemisia annua*, is thus a starting material for the APIs.

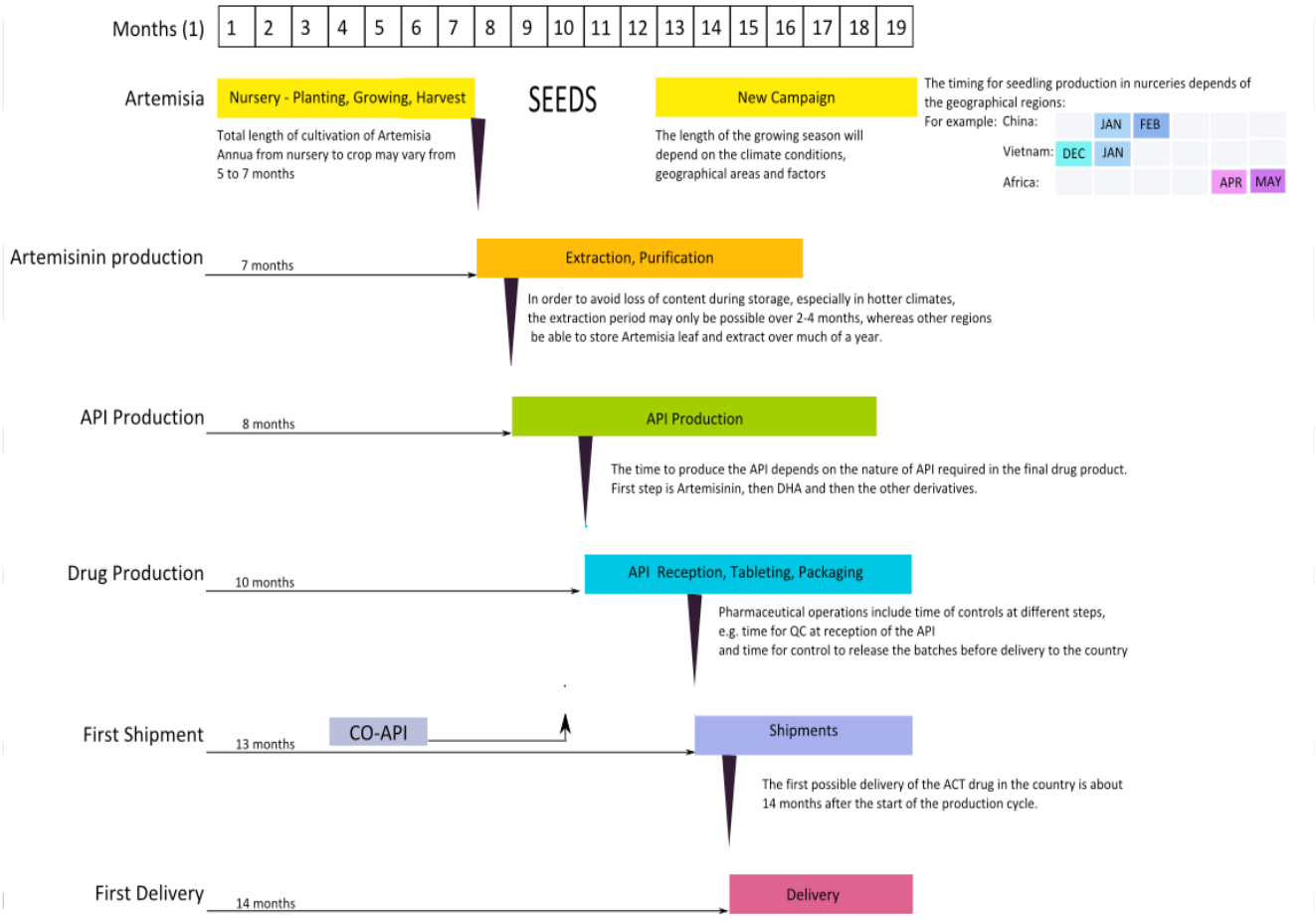
Plant leaves are the principal source of extracted artemisinin in commercial operations since they contain by far the most artemisinin by mass. The typical steps in the extraction process for natural materials includes: (i) determination of artemisinin content in dried leaves; (ii) isolation (raw material input) -> waste biomass; (iii) partial purification (crude extract input) -> side stream; and (iv) final purification (mainstream input) -> impurities.

Artemisinin quality varies according to agricultural conditions, the extraction steps and the purification conditions. Impurities may carry forward from the plant extracts or from synthetic process, or arise from the purification process or from degradation. Examination of a wide variety of artemisinin samples produced in various regions has shown a consistent presence of two impurities. The major impurity is 9-epi artemisinin and the minor impurity is artemisitene. Impurities in the starting materials may carry forward to impact the purity of the final API, and thus, into the final finished pharmaceutical preparation. Impurities can be tolerated in the starting material if the API manufacturing process efficiently removes them. However, redundant purification steps may reduce the yield of the final API and thus increase overall costs. Pesticide control, control of solvents and control of organic impurities are critical for artemisinin quality for use in ACTs *(46)*.

5.7.1 Artemisinin supply chain

The upstream supply of artemisinin is based on a long and complex agricultural process; the entire cycle from planting *A. annua* crops to final production of ACTs takes approximately 12–18 months (Figure 51). Upstream production begins with the planting and harvesting of *A. annua* by farmers. Artemisinin is then extracted and purified from the leaves of this plant. Extractors purchase dry leaves from farmers and related organizations, and use chemical processes to extract the artemisinin. Then, artemisinin is transformed into an API derivative of artemisinin (artesunate, arthemeter, etc.) and finally, the artemisinin derivative and a companion drug are co-formulated or co-packaged into an ACT.

Figure 51. Timeline for artemisinin and ACT production



(1) Start of planting season and length of cultivation phase vary according to geographical areas

Source: A2S2 website.

The supply chain of artemisinin involves many players, which contributes to its complexity. The cultivation of *A. annua* requires thousands of farmers, with an average area per farmer in Africa and China of approximately 0.2 hectares *(17)*. There are over 15 companies, mostly in China, that extract and purify artemisinin; a number of smaller companies extract artemisinin without purifying it. China represents 85–90% of annual (natural) artemisinin output. Six extractors, each with a capacity of over 20 tonnes per year, account for roughly 80% of output in China *(89)*.

Many API manufacturers and vertically integrated ACT manufacturers change their artemisinin source (artemisinin extractor) frequently. The reasons for changing this starting source material are volatility in prices and supply fluctuations. The time of year that *A. annua* is harvested also has a direct impact on the artemisinin content, and therefore the overall extracted artemisinin yield. These factors imply that the sourcing map for artemisinin to API manufacturer is dynamic *(46)*. Some ACT manufacturers purchase

artemisinin and then provide it to API manufacturers that convert it to artemisinin-based APIs based on conversion charges. To fill the artemisinin supply gaps, most manufacturers buy artemisinin "on-the-spot".

5.7.2 Artemisinin production costs

The agricultural production cost of artemisinin varies based on a number of factors, including seed type, plant yield, extraction methods and efficiency rates, conversion rates and preset contract terms between farmers and extractors. These elements have broad ranges; for example, the efficiency of selected extraction and purification technologies ranges from 55% to 80%, depending on technical specificities, solvents and other factors. In addition, a number of different higher-yielding seeds are in development, with some already in use in Madagascar, which may increase productivity. Table **11** displays an overview of the approximate artemisinin production costs for Africa, China and Viet Nam based on the 2011–2012 prices of leaves. It should be noted that prices are highly dependent on prices of leaves that vary a good bit each year depending on the demand and supply situation.

Table 11. Approximate artemisinin production costs for 2012

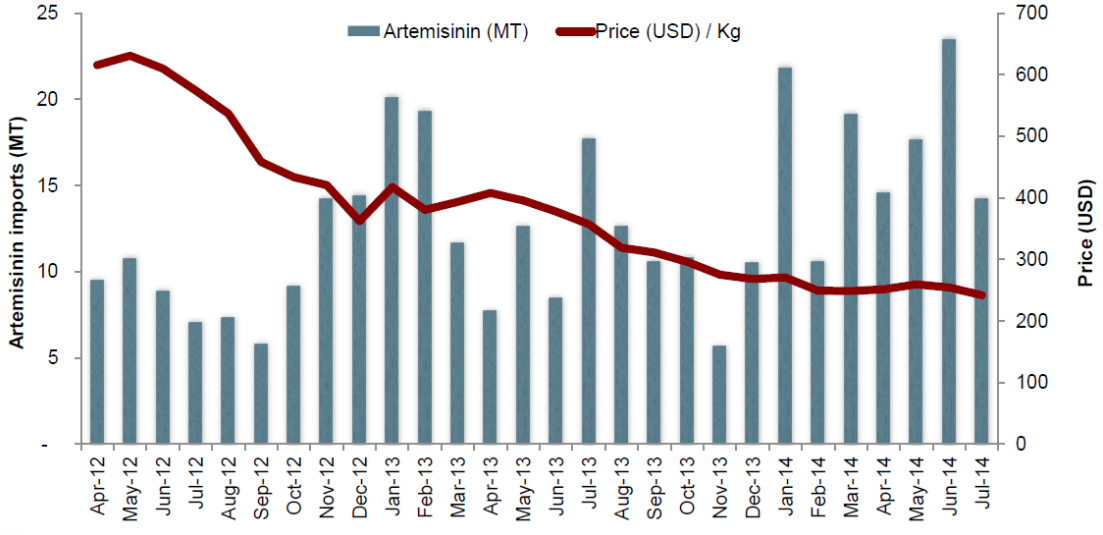
	China, 2012	Africa, 2012[a]	Viet Nam, 2012
Cost of cultivated leaves US$/tonne	1200–1600	1200–1400	900–1400
Cost of wild leaves US$/tonne	800–950	Not used	Not used
Artemisinin content of cultivated leaves	0.70%	1%	0.6–0.7%
Artemisinin content of wild leaves	0.55%	Not used	Not used
Processing costs (US$/tonne leaves)	950–1050	1350–1400	500–1000
Extraction/purification efficiency	75–80%	65%±5%	55%
Total cost/tonne leaves (US$)	2050–2400	2550–2800	1400–2400
Kg artemisinin/tonne leaves	5.1–5.4	6–7	3.3–3.9
Cost per kg artemisinin (US$/kg)	380–470	365–465	360–727

[a] Figures for East Africa and Madagascar are similar and for this reason are aggregated here.
Source: Assured Artemisinin Supply System (17).

5.7.3 Artemisinin prices

Average natural artemisinin prices are approximately US$ 350/kg *(46)*, however, they have been extremely volatile historically: at US$ 1100/kg in 2005 after WHO recommended the use of ACTs in 2002; down to < US$ 200/kg in 2007; and back up to US$ 300/kg in 2009 when the AMFm master supply agreements were signed. Supply shortages in 2011 placed sharp upward price pressures on the spot market, which reached US$ 1000/kg. Artemisinin prices fell in 2012, albeit from an artificially high level in the last quarter of 2011 and the beginning of 2012 *(90)*. Current reported spot market prices are around US$ 250/kg (Figure 52), which is less than the break-even point for artemisinin extractors. Low prices could impact the quantity of *A. annua* harvested in 2014 as well as future plantings. If market prices remain low in late-2014/early 2015, then *A. annua* cultivation is expected to decline further and some extractors may exit. Some farmers may also shift towards farming crops (e.g corn) that have offer greater market security and are potentially more profitable than growing *A. annua*. A significant decline in cultivation in 2015 could lead to an artemisinin shortage and/or high market prices in 2016–2017 *(91)*.

Figure 52. Volumes and prices of Indian artemisinin imports, April 2012–July 2014



Source: Yadav 2014 *(91)*.

5.7.4 Artemisinin supply forecasts

The global production of artemisinin increased considerably in 2012 as a result of increased *A. annua* plantings and good weather conditions during the growing season. Agricultural artemisinin supply for 2013 has been estimated at 238–264 tonnes *(89)*. Compared with total QAACTs delivered in 2013 (392M treatment courses *(2)*, equivalent to 182 tonnes of artemisinin), the 2013 supply suggests a surplus. The agricultural artemisinin supply for 2014, based on production in 2013, was similarly estimated at approximately 202–262 tonnes. However, artemisinin production in China may have been lower than originally estimated (approximately 100 tonnes instead of 170 tonnes) due to low artemisinin prices (below US$ 300/kg) and a lack of orders *(89)*.

Global artemisinin production in 2014, for 2015 supply, is estimated between 179 and 341 tonnes (Figure 53). This is 30–50% lower than in 2013, due to two main factors *(91)*:

- low market prices disincentivized farmers to cultivate and harvest *A. annua*;
- excessive rain may result in lower yield per hectare.

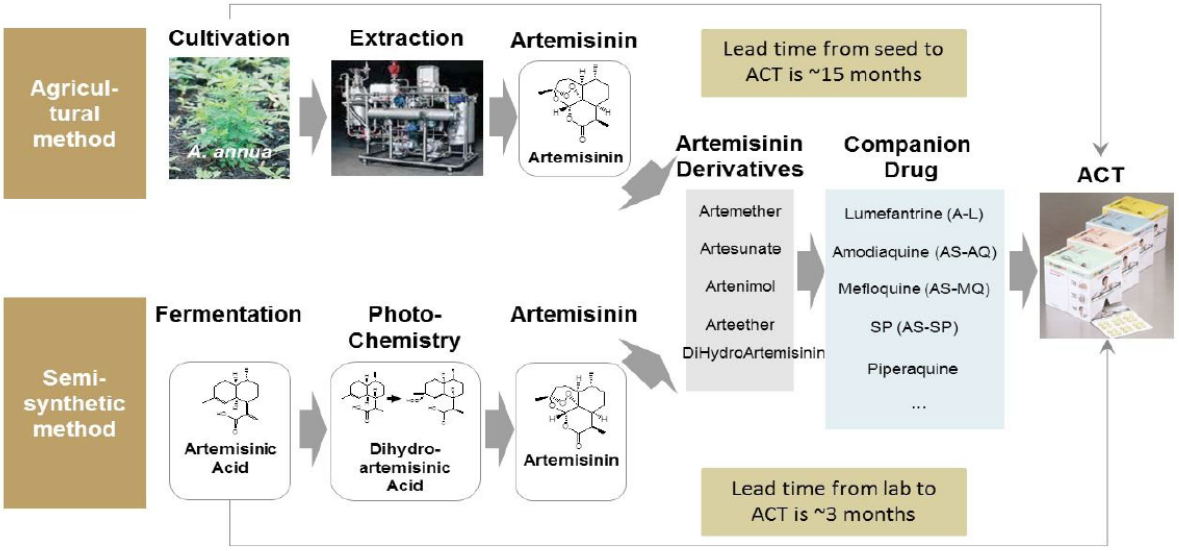
Aggregate of country production as collected by one extractor and presented at the eighth Artemisinin conference was 136 tonnes *(91)*.

In addition, some (small) extractors in Viet Nam and East Africa have temporarily stopped producing artemisinin *(91)*. One Viet Nam extractor, Cat Khan, has reported a decline in production from 21 tonnes in 2013 to 10 tonnes in 2014 *(95)*. Artemisinin production from China has also been reported to decline *(91)*. If market prices remain low in late-2014/early 2015, then *A. annua* cultivation is expected to decline further and some extractors may exit. A significant decline in cultivation in 2015 could lead to an artemisinin shortage and/or high market prices in 2016–2017 *(91)*.

Box 1: SSA

SSA uses biological and chemical processes to replicate the internal production of *A. annua* and offers an alternative source of artemisinin supply. The process, which was initially developed by the University of California Berkeley, Amyris Biosciences and the Institute for OneWorld Health, was subsequently licensed to Sanofi for commercial scale-up and production. A synthetic production route was developed at the University of California Berkeley with grant support from the Bill & Melinda Gates Foundation to produce artemisinic acid using microbial fermentation. Sanofi optimized this process at a commercial scale and developed additional steps including photo-oxidation and a step to convert the acid into artemisinin. Sanofi built a facility for the second process step in Italy and a manufacturing partner in Hungary is carrying out production of artemisinic acid using the first fermentation step *(46)*.

The aim of producing SSA is to provide a complementary source of non-seasonal, high-quality, affordable and short-lead time artemisinin and contribute to stabilizing the prices of ACTs *(92)*. A key advantage of SSA is the significantly shorter lead time (three months) as compared with natural artemisinin, which could help to smooth out the effects of demand volatility.



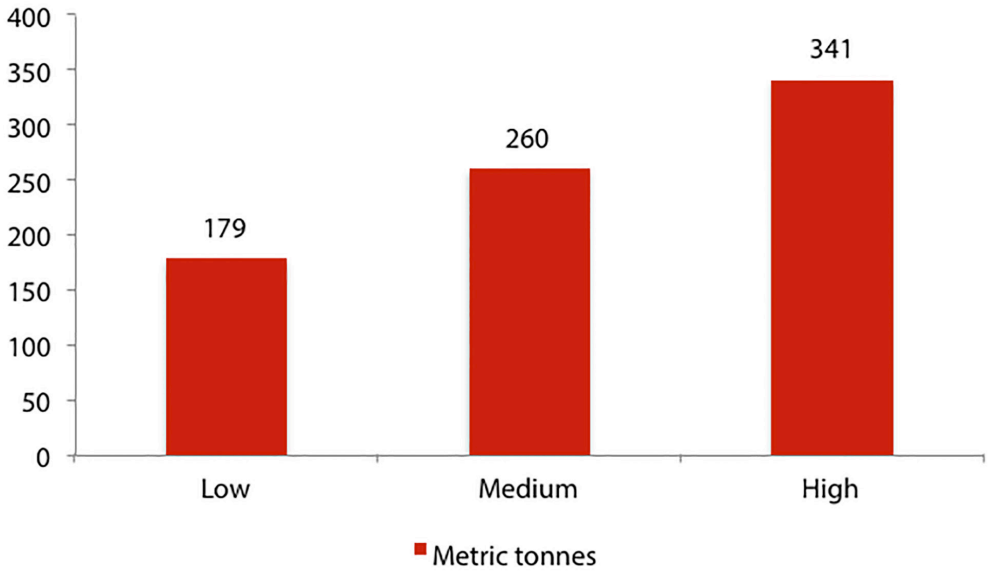
Source: MMV Artemisinin Conference 2010

SSA was accepted by the WHO PQP in May 2013 for use in the manufacture of APIs or finished pharmaceutical products (FPPs) *(93)*. The manufacturers of prequalified antimalarial FPPs that wish to use this new API source will need to submit a variation of their prequalified FPP to the WHO PQP. Similarly, manufacturers of prequalified artemisinin APIs (artesunate, artemether or dihydroartemisinin) that wish to use this new source of artemisinin will need to submit an amendment to the WHO PQP. Specifically, API manufacturers wishing to source non-plant-derived-artemisinin may request that the WHO PQP refers to the confidential sections of the SSA master file and only need include within their regulatory documents limited details regarding this material *(93)*. In addition to the stipulated requirements for change of starting material, the application for using synthetic artemisinin has to include a letter of access to the file provided by Sanofi. API manufacturers are then required to have a single harmonized set of specifications for artemisinin irrespective of source and a justification for these specifications *(46)*.

Total production capacity of SSA is approximately 60 tonnes per year, with at most 50% used for Sanofi's ACTs *(94)*. Sanofi currently has no plans to increase existing capacity. At the end of 2014, there was approximately 55 tonnes of SSA stock *(94)*. The current price estimate, based on a "no profit, no loss" model, is approximately US$ 400/kg at high capacity usage. The first delivery of ACTs produced with SSA to endemic countries occurred in 2014 *(94)*.

While SSA could help to secure the required levels of artemisinin to meet ACT requirements and smooth out the boom and bust cycles of natural artemisinin supply, concerns have been raised over its entry into the market. Specifically, with the recent uncertainty regarding the amount of funding available for ACTs, many natural artemisinin producers see SSA as a risk to their market share. At the same time, there is reluctance among many FPP manufacturers to source their artemisinin from Sanofi as they do not necessarily want to source from a competitor in the downstream market, unless there is a significant price advantage. Other ACT manufacturers, such as Guilin, Hisun, Ipca and Cipla, are carrying out preliminary experimentation with synthetic artemisinin production, that is, at least some steps of the process *(46)*.

Figure 53. Predicted agricultural artemisinin production, 2014



Note : Reflects all artemisinin, including artemisinin for non-QAACT uses.
Source: Yadav 2014 (91).

5.7.5 Market volatility

The supply of agricultural artemisinin has been volatile in the past decade due to a number of factors, resulting in price volatility and cycles of undersupply and oversupply. The long lead time for manufacturing artemisinin is a structural shortcoming in this market, which limits the ability to react to any changes in demand. Farmers make the decision to grow *A. annua* 12 months before harvest. They choose to grow it if they have reasonable expectations of selling the dried leaves at a better price after the harvest, as compared to other cash crops they can grow such as paddy rice. For the market, the use of synthetic artemisinin as a second source can help rectify some of this problem, as an additional source could mean a stable cost and steady supply, independent of the *A. annua* crop. Too many extractors purchasing from a small group of growers using multiple leaf collection agents also leads to information obfuscation and chaotic behaviour in the market *(46)*.

Currently, low prices have the potential to destabilize the market and reduce the level of commitment of both farmers and artemisinin producers. This may result in a significant reduction in planting in late 2014/early 2015. As it stands, it is not yet certain whether SSA will be available in sufficient quantities to make up this gap, which may result in a shortage.

6. Market shortcomings and their reasons

6.1 Market shortcomings for malaria medicines

Several shortcomings in the malaria medicines market remain largely the same as those that were identified and described in the first edition of the *Malaria medicines landscape* in 2013. These shortcomings, as well as their underlying reasons, are summarized in Table 12. For the most commonly used ACTs, adult and paediatric treatments consist largely of the same formulations sold as solid oral tablets in different pack sizes. The market shortcomings for ACTs as a whole, therefore, also apply to paediatric pack sizes. Section 6.2 describes the market shortcomings that have been identified as specific to paediatric malaria medicines.

Table 12. Summary of market shortcomings for antimalarial medicines

Category	Shortcoming	Reason
Availability	No alternative to PQ for treating the liver stage of *P. vivax*.	■ Research is ongoing (e.g. tafenoquine), but products are not yet available. ■ 8-aminoquinolines are the only class of drugs known to have anti-hypnozoite activity and all suffer from safety issues, especially G6PD-deficient patients. ■ Lack of incentives for manufacturers to invest in R&D due to uncertainties around future demand, market size and return on investment.
	No single-dose malaria medicines to reduce the current three-day dosing requirements of ACTs.	■ Two candidates for a single-dose cure for uncomplicated *P. falciparum* malaria are under development, but earliest availability is 2018. ■ Lack of incentives for manufacturers to invest in R&D due to uncertainties around future demand, market size and return on investment.
	Limited alternatives to SP for ITP.	■ The development of AZCQ ceased in late 2013. There are currently limited alternative therapy options in the pipeline specifically for use in IPTp (co-trimoxazole (Phase II) is a potential candidate for IPTp but there are concerns with daily administration and safety in HIV-positive populations when taken with SP. Piperaquine based combinations are currently being evaluated, as well as DHA PPQ for intermittent screening and treatment (ISTp)). ■ There are no drugs in development for use in IPTi, however, studies evaluating the efficacy of DHA PPQ have recently taken place.
Affordability	Varying ACT retail prices in countries where price subsidies have not been applied.	■ High ACT manufacturing costs, including expensive and variable raw material prices. ■ Despite an increase in the number of prequalified ACT suppliers in recent years, market share is still highly concentrated by a few manufacturers. ■ As private sector subsidies are no longer additional funding but instead are part of Global Fund country allocations, scope for expansion may be limited.
Quality	Although recently increasing, low private sector market share and availability of QAACTs, particularly of non-AMFm countries (which represent the majority of countries in sub-Saharan Africa and the Greater Mekong subregion).	■ Low demand for QAACTs in the out-of-pocket market due to higher cost (see Affordability above). ■ QAACT manufacturers have tight production capacity with low incentive for expansion due to uncertain future demand. ■ Lack of visibility on future orders and variability of raw materials prices. ■ Complexity and cost of prequalification process. ■ Weak and/or unharmonized regulatory standards in many endemic countries, which limit incentives for manufacturers to meet international drug quality standards. ■ Majority of QAACTs depend on agricultural artemisinin. The quality if the artemisinin extraction process greatly influences the API yield (i.e. the amount of impurities present in a yield), and has an overall effect on QAACT prices.
	High quality-control failure rates among non-prequalified ACTs.	■ Insufficient and weak local quality control, enforcement and low awareness. Weak regulatory systems that allow significant market penetration by substandard or non-proven therapies. ■ Technologies for on-the-spot quality control not widely used.
Acceptability/ adaptability	While ACTs are more widespread than in 2002–2006, their usage is still below that of non-recommended therapies.	■ Complex dosing regimen of ACTs compared to single-dose conventional therapies that are no longer recommended for use or are omitted from treatment guidelines in malaria endemic areas. Complex ACT dosing regimens has been cited by patients and providers as a key acceptability barrier to ACTs. ■ Limited palatable medicines for children, both for curative and preventive drug regimens.

Delivery	Risk of supply shortages and/or high market prices for artemisinin.	■ The long, complex and multi-actor upstream supply chain contributes to a volatile market and limits market responsiveness to sudden changes in demand. ■ SSA could help to stabilize the supply and price of artemisinin, but currently the 60 tonnes capacity is not being fully utilized. As demand for SSA increases, there may be supply risks associated with the fact that it is a single-source product with a defined production capacity. SSA could also have a destabilizing effect on the market if shortages arise from growers and extractors of plant-based artemisinin exiting the market.
	Long lead times to gain necessary regulatory approvals to bring new antimalarials to market.	■ Limited regulatory harmonization and capacity across countries and regions to register products. It should be noted that the East Africa Medicines Regulatory Harmonization Programme (EAC-MRH) *(15)*, which aims to harmonize medicines regulation systems and procedures in accordance with national and international policies and standards, is now operational and launched a request for proposals (RFP) for harmonized registration in December 2014. This represents an important step forward in streamlining the regulatory approvals process for medicines, including antimalarials.
	Limited diversification of first-line ACT treatments with continued dominance of AL and ASAQ.	■ While other prequalified ACTs are available, their use is limited due to a number of factors, including safety labels – e.g. the EMA label of DHA PPQ required ECG monitoring during treatment, higher costs and sole suppliers.
	Public sector stockouts of prequalified ACTs.	■ Delays in funding disbursements. ■ Demand uncertainty/unpredictability and episodic diversion from the public subsidized sector to the private for-profit sector. ■ Suboptimal in-country planning and supply management and forecasting as well as uncertainty on the effect of diagnostics on treatment demand (see below).
	Low availability of ACTs in private sector facilities, particularly outside AMFm countries.	■ Low private sector demand for ACTs, largely due to high ACT prices compared to non-artemisinin treatments. ■ Habitual purchasing behaviour; lack of awareness and education at the provider and consumer levels about the problems associated with the use of older (increasingly ineffective) antimalarial therapies.
	High rates of overtreatment with all antimalarials, including ACTs, particularly in the private sector.	■ Historical practice of presumptive treatment of fever with antimalarials. ■ Low uptake of quality, point-of-care diagnostic tools for malaria (e.g. RDTs), particularly in the private sector where presumptive dispensing prevails.
	Low uptake of INJAS for severe malaria until 2012, though an upward trend has been observed from 2013.	■ Inadequate advocacy, education and training, including poor communication around the superior efficacy, leading to poor acceptance by patients and providers. ■ High treatment prices (three times more than injectable QN) due in part to low volumes and lack of competition. ■ Only one prequalified product (Guilin), with buyer concerns over single-prequalified supplier (if the single supplier cannot meet the demand, then there is potential for stockouts). ■ Commercial interests around injectable QN, which is often procured from local manufacturers; behavioural issues around QN use.
	Unpredictable future demand.	■ Uncertainties around future funding, rate of scale-up of malaria RDTs and its impact, and the overall impact of prevention and control efforts on malaria epidemiology.

6.2 Market shortcomings for paediatric antimalarial medicines

The following market shortcomings have been identified (Table 13) paediatric malaria medicines:

Table 13. Summary of market shortcomings for paediatric malaria medicine

Category	Shortcoming	Reason
Availability	No RAS product has been WHO prequalified or approved by an SRA for the pre-referral treatment of severe malaria.	■ Work is under way to submit a dossier for RAS to the WHO PQP in 2015, but a decision is only expected in 2016. ■ Once an RAS product becomes available, there are likely to be market (e.g. single-source) and operational (e.g. community-based delivery) challenges to the scale-up of this product.
Availability	No taste-masked, dispersible AQ+SP tablets which would facilitate the administration of SMC; no alternative to AQ+SP for SMC which limits the use of this intervention to the Sahel region.	■ A prequalified, dispersible SMC regimen is not yet available. ■ Limited incentive for manufacturers to invest in R&D due to uncertainties around both future market size and return on investment for a low-margin product.
Quality	Limited supply of quality-assured SP and AQ, which has led to supply shortages of the AQ+SPSMC regimen, both in co-blister and bulk tablets, for the 2015 transmission season.	■ Rapid upsurge in demand for SP beyond supply-side forecasts ■ ASSP still prioritized in some countries though no longer promoted as treatment by WHO ■ The closing of a Chinese source of sulfadoxine API in 2014. ■ Parallel loss of Guilin API production capacity for both SP & AQ due to manufacturing site change combined with plant downtime needed to optimize process for SP to meet PQ standards. Late discovery of AQ API shortfall ■ Many generic versions of SP available, but with high quality control failure rates (28% across six sub-Saharan African countries).
Acceptability/ adaptability	Low uptake of child-friendly ACT formulations for children under 5 years old (26% of dispersible AL was procured in 2012).	■ Only one prequalified manufacturer of dispersible tablets until December 2012. ■ Although increased demand of dispersible AL has been reported (12M AL treatment courses were procured in the donor funded market in 2010 increasing to 33M in 2012), when compared to the demand of solid oral tablet for infants there is a variable demand for dispersible tablets by different providers and caregivers. ■ Multiple non-prequalified paediatric formulations (e.g. suspensions) of unknown quality are available in local markets.

7. Opportunities for market interventions

This section presents several opportunities for market-based interventions to address the market shortcomings described in Section 6. They include interventions that have been recently initiated, potential new interventions that have been identified through previous landscaping activities and have been discussed in various forums (e.g. the Artemisinin Conference, the Malaria Market Forum, the Roll Back Malaria Partnership Procurement and Supply Management Working Group meetings) and more exploratory interventions that require additional discussion and vetting. This section is not specific to interventions that fit within the UNITAID mandate and business model, but rather represents a range of market-based interventions that could be undertaken by different global health actors and stakeholders.

7.1 Potential opportunities

Overall, longer-term funding commitments are a critical mechanism to stabilize the ACT market as well as the upstream market for raw materials such as artemisinin. Given the long production cycle of plant-derived artemisinin and the tight production capacity of QAACT manufacturers, it is difficult for the artemisinin and ACT markets to respond to sudden changes in demand arising from expansions or constrictions in funding availability. While the demand for ACTs has been steadily increasing and is more predictable after the spikes that occurred with initial scale-up efforts as well as AMFm, longer-term funding commitments would still assist in stabilizing both markets through better matching of supply and demand, and would allow manufacturers and other actors to plan appropriately. It also would help to understand the extent to which the "need" for ACTs was being met, and allow donors, governments of malaria endemic countries and others to take mitigating steps as needed to ensure that access is being sustained. As part of the Global Fund's new initiative P4i, WHO prequalified ACT manufacturers now receive one-year visibility on allocated volumes. This offers greater demand certainty than under the previous system where ACT manufacturers only had visibility on demand when the Global Fund placed orders, a few months before expected delivery. However, as the allocated volume is only in the short term (one year), its impact on medium-term production planning is uncertain.

In addition to this overarching opportunity, the following are specific opportunities that aim to address one or more of the market shortcomings identified in Section 6.

- **Ensure rational and appropriate use of ACTs and improve access to appropriate diagnostics testing and treatment, i.e. getting the RDT/ACT ratio right**
  Supporting the scale-up of quality RDTs alongside the delivery of ACTs would improve treatment and referral/management of febrile illness and promote rational antimalarial drug consumption (i.e. use of ACTs for confirmed malaria cases only). While the quantity of procured RDTs is increasing (319M in 2013), the reported rate of RDT use in the public sector in sub-Saharan Africa was still around 60% in 2013 *(2)*. In the same region between 2006 and 2011, the number of RDTs distributed was less than half of the ACTs distributed *(2)*. In 2013, the number of RDTs provided exceeded the number of ACTs for the first time. Despite this increase, the ratio of diagnostic tests to ACTs should be ≥2 *(2)*. UNITAID has recently supported a project to catalyse the creation of a private sector market for malaria RDTs in five sub-Saharan African countries by: (i) promoting diagnosis among providers and consumers; (ii) regulating prices in the distribution chain and managing provider incentives; (iii) ensuring RDT quality; (iv) making RDTs accessible to private providers through a reliable supply chain; and (v) creating a conducive policy and regulatory environment. Additional interventions are needed to support the appropriate RDT to ACT ratio in different settings in the context of various levels of transmission and prevention scale-up, for example, including diagnostic testing in any future ACT scale-up or subsidy programme.
  Market shortcoming addressed: Delivery

- **Support the sale of QAACTs at an affordable retail price that does not require a subsidy**
  Despite efforts to tackle the high price of ACTs, alternative mechanisms need to be considered to make them more affordable and accessible. For example, in countries with social health insurance systems, the inclusion of ACTs as part of outpatient medicines benefits could be one mechanism to improve their affordability. Furthermore, reimbursement policies could be used as a lever to stimulate competition and lower prices (e.g. reimbursement rates based on a nationally approved reference price) as well as to promote the rational use of malaria medicines (e.g. reimbursement based on a positive diagnostic test; reimbursement for recommended treatments only).
  Market shortcomings addressed: Affordability, Quality, Delivery

- **Monitor the antimalarial R&D pipeline and facilitate market entry and scale-up of important cost-effective products**
  Section 4 of this report describes shortcomings in the current antimalarial technology landscape and identifies priorities for R&D. These include: a single-dose alternative to 14-day PQ for treating the liver stage of *P. vivax*; a single-dose ACT to reduce current three-day dosing requirements; and a prequalified RAS product for the pre-referral treatment of severe malaria. There are several products in the advanced stages of development that could address these needs and improve malaria treatment. Given the high likelihood for comorbidities in malaria endemic countries, particularly HIV, it will be important to ensure future products are appropriate for use in these populations. Opportunities, therefore, exist to speed up market entry by encouraging late-stage development, providing technical support to manufacturers regarding regulatory approval submissions, streamlining evidence review and policy/guideline modification, and preparing the market for uptake, including efforts to increase the supply capacity of manufacturers.
  Market shortcoming addressed: Availability

- **Encourage further research to develop new products for IPTp**
  The only immediate pipeline alternative to SP for IPTp (AZCQ) has ceased development. While co-trimoxazole is in Phase III clinical trials, there are concerns around the daily administration of this product and the risk of adverse effects when taken with SP in HIV-positive infected women *(64)*. Piperaquine based combinations are currently being evaluated, as well as DHA PPQ for intermittent screening and treatment (ISTp), but efficacy is still to be determined *(65)*. This means that as populations expand in areas where SP resistance exists, there is an urgent need for an alternative to SP for IPTp as resistance.
  Market shortcoming addressed: Availability

- **Support market approaches that strategically target scaling up medicines for radical cure of *P. vivax* malaria and the associated G6PD testing requirements**
  To date, the use of PQ for the radical cure of *P. vivax* has been limited by the lack of point-of-care tests to diagnose G6PD deficiency. As these tests have recently become available, opportunities exist to catalyse the market for both G6PD tests as well as radical cure treatment. Creation of the necessary infrastructure and quality management systems (including training and support) for G6PD testing would also facilitate the market entry of tafenoquine.
  Market shortcomings addressed: Availability, Delivery

- **Maintain and communicate up-to-date information on the future demand for ACTs**
  Maintaining and communicating up-to-date information on the future demand for ACTs, is a key mechanism for ensuring a consistent supply of both artemisinin and ACTs. In 2015, a new UNITAID-funded forecasting service will be launched, conducted by a consortium consisting of the Clinton Health Access Initiative, IMS Health and the Global Health Group, University of California San Francisco. Under the new project, RDT demand will be also be forecasted to monitor the impact that RDT demand is having on ACT demand. Furthermore, the forecasts will differentiate between the need of ACTs and RDTs in relation to the projected disease burden, the portion of the need that is funded by donors and the extent that the donor-funded ACT and RDT need will translate into sales and orders. The project will also estimate total artemisinin demand from all sources including WHO prequalified ACTs as well as non-SRA/non-WHO prequalified ACTs, injectables, syrups, artemisinin monotherapy, etc. Communications strategies will be put into place to ensure that forecast information is disseminated to all relevant stakeholders.
  Market shortcoming addressed: Delivery

- **Collect and disseminate information on artemisinin supply and demand, and evaluate the need for additional targeted interventions to stabilize artemisinin prices and supply**
  Ensuring appropriate supplies of artemisinin is critical to ensure ACT supply security as well as avoid long lead times and stockouts. An important supportive measure to reduce the volatility of the artemisinin market is the collection and communication of up-to-date market intelligence on the supply of, and demand for, artemisinin. This includes accurate forecasting of global demand for ACTs and other artemisinin-based products, and corresponding demand for artemisinin, both in the shorter and longer term. While the market for ACTs and artemisinin has expanded rapidly over the past decade, it has begun to level off in the past two years, potentially making demand more predictable in the short to medium term. Furthermore, the introduction of the Global Fund new funding model, which includes both a three-year funding cycle and procurement guarantees, should improve demand predictability for ACTs. However, it is unclear to what extent this will have a "trickle down" effect on the upstream supply chain for artemisinin. In addition, in the longer term changes resulting from shifting disease epidemiology, RDT scale-up and possible initiatives to treat asymptomatic carriers of malaria parasites as part of elimination efforts could all impact ACT and artemisinin demand. As such, continued monitoring of the artemisinin market is required with a view to evaluating what, if any, additional measures are needed to bring stability to this market.

  A careful and transparent rollout of SSA, with active information dissemination, is also required to allow different market actors to adapt to new dynamics that SSA brings to the artemisinin and ACT markets. While SSA has the potential to reduce price and supply volatility, currently the lack of manufacturers utilizing this source may be limiting the ability of SSA to mitigate supply volatility. In the short term, supply security could be improved by increasing the number of producers that are able to produce SSA-based ACTs.
  Market shortcomings addressed: Affordability, Delivery

- **Encourage the uptake of INJAS for the treatment of severe malaria**
  UNITAID has recently supported a project that will expand access to quality-assured INJAS by increasing public sector acceptance and use, encouraging market entry of a second supplier, generic manufacturers, and securing lower prices through negotiation and increased competition. The project, being undertaken by MMV, CHAI and the Malaria Consortium, will be implemented across six sub-Saharan African countries. PMI is also supporting the scale-up of INJAS in some endemic countries. At the same time, endemic countries are beginning to commit increased amounts of their Global Fund funding towards procuring INJAS *(61)*. This market should be closely monitored to assess whether there is a need for any further intervention.
  Market shortcomings addressed: Affordability, Delivery

- **Catalyse the market for artesunate suppositories for the pre-referral treatment of severe malaria**
  As part of the UNITAID project with MMV, CHAI and the Malaria Consortium to improve severe malaria outcomes, described above, market demand for pre-referral treatment of severe malaria (RAS) will be evaluated and the market entry of a WHO prequalified product will be supported. Following this, additional efforts may be needed to scale up the use of a prequalified product and encourage additional suppliers to enter this market, as well as potential operational support to enhance the delivery of RAS for pre-referral treatment.

  Given that rectally administered drugs may encounter acceptability issues in certain contexts, there may also be value in exploring other drug delivery/administration methods (e.g. mucosal) for pre-referral severe malaria treatment.
  Market shortcomings addressed: Quality, Delivery

- **Support a competitive market for child-friendly ACT formulations, especially for children under 5 years old**
  The market share of dispersible QAACTs for children under 5 years old is low compared to solid oral FDCs (28% versus 72%). Incentivizing a more competitive market for child-friendly formulations could include, for example, incentivizing the prequalification of additional dispersible AL products. This market would also benefit from the enactment of stronger regulatory/registration requirements in endemic countries to raise quality thresholds for better medicines for children. In addition, work is currently under way to develop two child-friendly formulations of recently approved ACTs (DHA PPQ and ASPY). Supporting their development and/or entry into the market would also increase options for the use of quality-assured, child-friendly ACTs for children under 5 years old. The bitter taste of some antimalarial medicines, such as AQ, makes the delivery of some currently available medicines for children difficult. Therefore, supporting the development of a taste-masked version of AQ would improve the acceptability of an antimalarial that is already prequalified. Taste masking AQ also could support the delivery of SMC.
  Market shortcoming addressed: Acceptability/adaptability

- **Support market intelligence on other antimalarial medicines**
  While ACTs are the recommended treatment of uncomplicated malaria in most circumstances, there is still a role for other antimalarial medicines. For example, CQ is still recommended in areas where *P. vivax* is endemic and not resistant to CQ, AQ + SP is recommended for SMC in the Sahel subregion, and SP is recommended for IPTp and IPTi *(36, 37)*. As such, a better understanding of the rational demand for CQ, SP and AQ and the corresponding target market size would be helpful in designing interventions to encourage more rational use of these medicines and limit their use in situations where they are not recommended.
  Market shortcoming addressed: Delivery

- **Support the scale-up of technologies to detect counterfeit and substandard medicines**
  Given the high rate of counterfeit and substandard antimalarials (42) measures to support better quality control of these products are warranted. Innovative quality-control technologies, such as hand-held tools to detect counterfeit products, should be further explored as a mechanism to promote greater market share of quality-assured products. Anti-counterfeit technologies to secure the supply chain or to validate product integrity at point of dispensing/point of sale also are emerging as technically and commercially viable offerings. As a first step, research should be undertaken to understand the technical, market and operational characteristics of these tools, including different mechanisms of deployment and enforcement of compliance with test results.
  Market shortcoming addressed: Quality

- **Explore whether targeted interventions are needed to scale up the use of newer, less widely used ACTs**
  Despite the availability of five different WHO-recommended ACTs, there is a heavy reliance on both AL and ASAQ especially in the public sector. Limited first-line quality assured ACT treatments pose a threat in terms of resistance and may be limiting competitive forces from occurring across different formulations. Further exploration is needed to determine whether interventions targeted at diversification of the ACT market across the currently recommended ACTs should be prioritized. This could include, for example, interventions to achieve greater scale for newer formulations.
  Market shortcoming addressed: Availability, Acceptability/adaptability

- **Support increased global production capacity of quality-assured AQ + SP for use in SMC, and actively coordinate among funders/implementers of SMC programs to ensure timely information on overall demand.**
  Several supply-side and demand-side challenges have limited the scale up of SMC programs to-date. On the supply-side, this has included a sole supplier with limited incentives for others to enter into a nascent market. Given that SMC drugs needs to reach countries in time for the transmission season, reliance on a sole supplier presents a particular risk to supply security. Currently, SMC programs are facing a challenging supply situation due to the reduced supply of prequalified sulfadoxine, which is limiting global production capacity for the AQ + SP regimen. On the demand side, key challenges to the scale-up of SMC include the costs and complexities of delivery which requires mass distribution during the rainy season when logistics are most difficult.

  In 2014, UNITAID committed US$67.4M for ACCESS-SMC, a project led by the Malaria Consortium. The project aims to create a well-structured market by implementing SMC at scale in seven countries in the Sahel and thereby address key supply-side and demand-side barriers to current scale-up efforts. Specifically, the project aims to create sustainable demand for SMC my demonstrating the feasibility and safety of implementation at scale and reduce total delivery costs. On the supply side, the project includes targeted efforts to increase global production of quality and acceptable (child-friendly) SMC products. Efforts in this area have focused specifically on API supply in light of recent shortages, and in 2014 a request for proposals was issued to manufacturers to produce AQ + SP co-blisters in an effort to diversity supply. However, in the light of the emergence of API supply restrictions, and questions around the degree of funding required by potential partners, the process was suspended; in the meantime, following discussions between MMV, UNITAID and Malaria Consortium, it was agreed that, rather than progressing a co-blistered tablet presentation, it would be preferable to focus on an additional child-friendly dispersible presentation. A follow-up RFI was accordingly issued recently. In addition to these activities, efforts to coordinate, share information, and establish mitigation measures to address the supply shortage have been underway among funding and implementing agencies such as UNITAID, WHO, UNICEF, Malaria Consortium, USAID/PMI, JSI, Medicines for Malaria Venture, RBM, PfSCM, and MSF.
  Market shortcoming addressed: Quality, Delivery

8. Appendices

Appendix 1. Prequalified medicines WHO list of prequalified medicinal products as of July 2014

Table created on 23 April 2014 and updated on 22 December 2014 from the website at http://apps.who.int/prequal/.

Manufacturer	INN	Strength	Formulation	Date of PQ
Ajanta Pharma Ltd	AL	Tablets 20 mg+120 mg	FDC	16-Dec-08
	AL	Dispersible tablets 20 mg + 120 mg	FDC	19-Dec-12
	AL	Tablets 67.5 mg + 25 mg	FDC	10-Jul-13
	AL	Tablets 270 mg + 100 mg	FDC	10-Jul-13
	AL	Tablets 135 mg + 50 mg	FDC	10-Jul-13
Artecef BV	Artemotil	Solution injection 50 mg/mL	Solution	1-Mar-06
	Artemotil	Solution injection 150 mg/mL	Solution	1-Mar-06
Cipla Ltd	AS+AQ	Tablets 153 mg (200 mg as hydrochloride) + tablets 50 mg	Co-blister	11-Nov-08
	AL	Tablets 20 mg + 120 mg	FDC	22-May-09
	ASAQ	Tablets 50 mg + 135 mg	FDC	8-Apr-14
	ASAQ	Tablets 25 mg + 67.5 mg	FDC	8-Apr-14
	ASAQ	Tablets 100 mg + 270 mg	FDC	8-Apr-14
DND*i*, Switzerland (Cipla Ltd is the supplier and is responsible for the product)	ASMQ	Tablets 25 mg + 50mg	FDC	12-Sep-12
	ASMQ	Tablets 100 mg + 200 mg	FDC	12-Sep-12
Guilin Pharmaceutical Co. Ltd	AQ	Film-coated tablets 150 mg	Tablet	30-Aug-07
	ASAQ	Tablets 67.5 mg + 25 mg	FDC	16-Nov-12
	ASAQ	Tablets 270 mg + 100 mg	FDC	16-Nov-12
	ASAQ	Tablets 135 mg + 50 mg	FDC	16-Nov-12
	AS+AQ	Tablets 150 mg + 50 mg	Co-blister	30-Aug-07
	AS	Tablets 50 mg	Tablet	21-Dec-05
	AS	Powder for Injection 60 mg	Powder	5-Nov-10
	AS+SP	Tablets + tablets 50 mg + [500 mg + 25 mg]	Co-blister	24-May-12
	AS+AQ	Tablets (co-blister) 150 mg + [25 mg + 500 mg]	Co-blister	20-Oct-14
	Artesunate	Powder for injection 30 mg	Powder	23-May-13
	Artesunate	Powder for injection 30 mg	Powder	23-May-13
Ipca Laboratories Ltd	ASAQ	Tablets 67.5 mg + 25 mg	FDC	1-Jun-12
	ASAQ	Tablets 270 mg + 100 mg	FDC	1-Jun-12
	ASAQ	Tablets 135 mg + 50 mg	FDC	1-Jun-12
	AS+AQ	Tablets 153 mg (200 mg as hydrochloride) + tablets 50 mg	Co-blister	23-Apr-08
	AL	Tablets 20 mg + 120 mg	FDC	15-Dec-09
Mylan Laboratories	AL	Tablets 40 mg + 240 mg	FDC	16-May-14
	AL	Tablets 40 mg + 240 mg	FDC	16-May-14
Macleods Pharmaceuticals Ltd	AL	Tablets 20 mg + 120 mg	FDC	21-Oct-13

Novartis Pharma	AL	Tablets 20 mg + 120 mg	FDC	26-Apr-04
	AL	Dispersible tablets 20 mg + 120 mg	FDC	27-Feb-09
Sanofi-Aventis Group	ASAQ	Tablets 67.5 mg + 25 mg	FDC	14-Oct-08
	ASAQ	Tablets 270 mg + 100 mg	FDC	14-Oct-08
	ASAQ	Tablets 135 mg + 50 mg	FDC	14-Oct-08
Shin Poong Pharmaceutical Co. Ltd	ASPY	Tablets 60 mg + 180 mg	FDC	EMEA article 58
Strides Arcolab Ltd	AS+AQ	Tablets (co-blistered) 153 mg + 50 mg	Co-blister	22-Dec-11
	AL	Tablets 20 mg + 120 mg	FDC	24-Jun-13

AL, artemether-lumefantrine; AQ, amodiaquine; AS, artesunate; MQ, mefloquine; SP, sulfadoxine-pyrimethamine

Appendix 2. Medicines under assessment for WHO prequalification

Table created on 23 April 2014 from the website at http://apps.who.int/prequal/.

INN	Product type	Strength	Assessment status
AL	Tablet	20 mg+120 mg	Assessment in progress: quality and efficacy/safety
AL	Tablet	20mg+120mg	Additional data to be provided by the manufacturer: quality and efficacy/safety
AL	Tablet	20 mg + 120 mg	Additional data to be provided by the manufacturer: quality Dossier part acceptable: efficacy/safety
AL	Tablet	20 mg + 120 mg	Assessment in progress: quality and efficacy/safety
AL	Tablet	20 mg + 120 mg	Assessment in progress: quality and efficacy/safety
AL	Tablet	80 mg + 480 mg	Assessment in progress: quality Additional data to be provided by the manufacturer: efficacy/safety
AL	Tablet	40 mg + 240 mg	Assessment in progress: quality Dossier part acceptable: efficacy/safety
ASAQ	Tablet	25 mg + 67.5 mg	Additional data to be provided by the manufacturer: quality Dossier part acceptable: efficacy/safety
ASAQ	Tablet	25 mg + 67.5 mg	Assessment in progress: quality Dossier part acceptable: efficacy/safety
ASAQ	Tablet	25 mg + 67.5 mg	Assessment in progress: quality Additional data to be provided by the manufacturer: efficacy/safety
ASAQ	Tablet	50 mg + 135 mg	Additional data to be provided by the manufacturer: quality Assessment in progress: efficacy/safety
ASAQ	Tablet	50 mg +135 mg	Assessment in progress: quality Additional data to be provided by the manufacturer: efficacy/safety
ASAQ	Tablet	50 mg + 135 mg	Assessment in progress: quality Dossier part acceptable: efficacy/safety
ASAQ	Tablet	100 mg + 270 mg	Assessment in progress: quality Additional data to be provided by the manufacturer: efficacy/safety
ASAQ	Tablet	100 mg + 270 mg	Assessment in progress: quality Additional data to be provided by the manufacturer: efficacy/safety
ASAQ	Tablet	100 mg + 270 mg	Additional data to be provided by the manufacturer: quality Dossier part acceptable: efficacy/safety
AS	Powder for injection	120 mg (vial)	Dossier part acceptable: quality and efficacy/safety

AS	Powder for injection	30 mg (vial)	Dossier part acceptable: quality and efficacy/safety
AQ+SP	Tablet	500 + 25 + 150 mg	Additional data to be provided by the manufacturer: quality Dossier part acceptable: efficacy/safety
AQ+SP	Tablet	250 mg + 12.5 mg + 75 mg	Assessment in progress: quality and efficacy/safety
DHA PPQ	Tablet	40 mg + 320 mg	Assessment in progress: quality and efficacy/safety
DHA PPQ	Tablet	20 mg + 360 mg	Additional data to be provided by the manufacturer: quality Assessment in progress: efficacy/safety
DHA PPQ	Tablet	20 mg + 160 mg	Additional data to be provided by the manufacturer: quality Assessment in progress: efficacy/safety
ASSP	Tablet	100 mg +5 mg + 500 mg	Additional data to be provided by the manufacturer: quality and efficacy/safety
Artemether	Oily injection	80 mg/mL	Additional data to be provided by the manufacturer: quality and efficacy/safety
Artemether	Oily injection	80 mg/mL	Additional data to be provided by the manufacturer: quality assessment in progress: efficacy/safety

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