



**2013**

# **Malaria Medicines Landscape**

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## Abbreviations

<b>ACT</b>	artemisinin-based combination therapy	<b>FFCR</b>	Four-Firm Concentration Ratio
<b>AETD</b>	adult equivalent treatment dose	<b>FPP</b>	finished pharmaceutical product
<b>AL</b>	artemether-lumefantrine	<b>G6PD</b>	glucose-6-phosphate dehydrogenase
<b>AMFm</b>	Affordable Medicines Facility-malaria	<b>GFATM</b>	Global Fund to Fight AIDS, Tuberculosis and Malaria
<b>AMT</b>	artemisinin monotherapy	<b>GMAP</b>	Global Malaria Action Plan
<b>API</b>	active pharmaceutical ingredient	<b>GMP</b>	good manufacturing practice
<b>ASAQ</b>	artesunate-amodiaquine	<b>ha</b>	hectare
<b>ASMQ</b>	artesunate-mefloquine	<b>ICF</b>	Inner City Fund
<b>ASSP</b>	artesunate sulfadoxine-pyrimethamine	<b>IPTp</b>	intermittent preventive treatment for pregnant women
<b>AQSP</b>	amodiaquine+sulfadoxine-pyrimethamine	<b>INJAS</b>	injectable artesunate
<b>A2S2</b>	Assured Artemisinin Supply System	<b>INN</b>	non proprietary name
<b>BCG</b>	Boston Consulting Group	<b>IPTi</b>	intermittent preventive treatment for infants
<b>CAGR</b>	compound annual growth rate	<b>INJAS</b>	injectable artesunate
<b>CHAI</b>	Clinton Health Access Initiative	<b>IVQ</b>	parenteral quinine
<b>CQ</b>	chloroquine	<b>K</b>	thousand (USD)
<b>DFID</b>	United Kingdom Department for International Development	<b>kg</b>	kilogram
<b>DHA PQP</b>	dihydroartemisinin+piperazine	<b>LIC</b>	low-income country
<b>DNDi</b>	Drugs for Neglected Diseases Initiative	<b>LMIC</b>	lower-middle-income country
<b>DRC</b>	Democratic Republic of the Congo	<b>LSHTM</b>	London School of Hygiene & Tropical Medicine
<b>EC</b>	European Commission	<b>M</b>	million
<b>EMA</b>	European Medicine Agency	<b>mg</b>	milligram
<b>FDA</b>	Food and Drug Administration (United States)	<b>MIT-Zaragoza</b>	Fundacion Zaragoza Logistics Center
<b>FDC</b>	fixed-dose combination	<b>ml</b>	millilitre
		<b>MMV</b>	Medicines for Malaria Venture

<b>nAT</b>	non-artemisinin therapy	<b>SRA</b>	stringent regulatory authority
<b>NFM</b>	new funding model	<b>SMC</b>	seasonal malaria chemoprevention
<b>NMCP</b>	national malaria control programme	<b>SP</b>	sulfadoxine-pyrimethamine
<b>nQAACT</b>	non-prequalified ACT	<b>SSA</b>	semi-synthetic artemisinin
<b><i>P. falciparum</i></b>	<i>Plasmodium falciparum</i>	<b>UNICEF</b>	United Nations Children’s Fund
<b><i>P. vivax</i></b>	<i>Plasmodium vivax</i>	<b>US</b>	United States
<b>PQR</b>	Price and Quality Reporting	<b>USA</b>	United States of America
<b>PMI</b>	United States President’s Malaria Initiative	<b>USD</b>	United States dollar
<b>PQP</b>	WHO Prequalification Programme	<b>WHA</b>	World Health Assembly
<b>PyA</b>	pyronaridine artesunate	<b>WHO</b>	World Health Organization
<b>QAACT</b>	quality-assured ACT	<b>WMR</b>	World Malaria Report
<b>QN</b>	quinine		
<b>R&amp;D</b>	research and development		
<b>RAS</b>	rectal artesunate		
<b>RBM</b>	Roll Back Malaria Partnership		
<b>RDT</b>	rapid diagnostic test		

### Executive summary

#### Introduction

This report 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 29% since the peak number of cases in 2000, and mortality rates have decreased by 45%, malaria remains a substantial global health problem. 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 2012 there were an estimated 207M cases of malaria across 99 countries. Africa has the highest burden, with 80% of total cases in 2012 and 90% of deaths. South-East Asia has the second-highest burden, with 13% of total cases in 2012. Malaria mortality primarily impacts children, with 77% of cases occurring in children under five years old. It is estimated that approximately 8M cases of uncomplicated malaria progress to severe malaria each year. 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 2012, 79 of the 88 malaria endemic countries had adopted ACTs as the first-line treatment. ACT delivery volumes have increased from 11M treatment courses in 2005 to 331M courses in 2012, largely due to scaled-up investments from international donors, increased procurement from public sector programs, and the Affordable Medicines Facility-malaria (AMFm). However, widespread access to ACTs remains an issue. Across 12 African countries, only 12% of all antimalarials given to febrile children are ACTs (range ~4–44%). In the public sector, less than 20% of antimalarials given to febrile children are ACTs, though in some countries it is >50%. In the “informal” private sector, this declines to less than 7%.

Given that a large proportion of malaria cases occurs in children under five years old, the availability of recommended antimalarials in formulations and dosage forms appropriate for use for children is a key consideration in evaluating access. WHO has identified flexible solid dosage forms as being most suitable for treating children under five years old in developing countries. 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. For tenders that ask for dispersible artemether-lumefantrine (AL) products, there are limited options available. Additionally, the overall pricing architecture of AMFm may constrain competitive price reductions, for example, prices are negotiated rather than reached through competitive tenders. With the availability of only two prequalified dispersible AL products, limited data from AMFm show that the availability of dispersible AL in registered pharmacies is low (11–14%), and is substantially lower than that of paediatric packs of solid AL tablets (42–48%).

WHO updated severe malaria treatment guidelines in 2011 recommending injectable artesunate (INJAS) over quinine (QN). However, uptake of this product has been low. In 2012, approximately 3.2M vials of INJAS were procured, representing approximately 750 000–1M treatments for severe malaria in children under five years old. This represents less than 15% of the total volume needed to treat global annual cases. Similarly, uptake of pre-referral treatment of severe malaria has been hindered by the absence of a WHO prequalified/stringent regulatory authority (SRA) rectal artesunate (RAS), which poses a significant threat to malaria mortality given that the risk of death from severe malaria is greatest in the first 24 hours.

## Technology landscape

### Currently available products

Medicines used in the treatment of uncomplicated malaria can be divided into three categories: ACTs, non-artemisinin therapies (nATs) and artemisinin monotherapies (AMTs).

#### nATs

Traditional therapies for treating malaria include chloroquine (CQ), QN, primaquine, sulfadoxine-pyrimethamine (SP). These have been available in markets for many years and are generally inexpensive, but emergence of resistance has reduced their efficacy in clinical settings. Thus, these therapies are no longer recommended as the first-line therapy for *Plasmodium falciparum*, though CQ is recommended as the first-line treatment of *Plasmodium vivax* in non-resistance settings where infections are still CQ-sensitive. In addition, SP is the recommended intermittent preventive treatment for pregnant women (IPTp) and intermittent preventive treatment for infants (IPTi).

#### AMT

The use of oral AMTs (e.g. artesunate, artemether, dihydroartemisinin) threatens the overall effectiveness of ACTs by fostering resistance. Despite WHO encouraging countries to prohibit oral AMTs, they continue to be available in some settings.

AMTs in injection form are still recommended for use in severe malaria, and intravenous artesunate (IVAS) is the recommended first-line treatment. QN tablets and QN injection are still used for uncomplicated malaria and for severe malaria in some markets as they are generally available at a lower price.

#### ACTs

WHO recommends that all endemic countries use ACTs as the first-line treatment of *P. falciparum*. There are currently five different combinations available and recommended in the WHO treatment guidelines:

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

ACTs are divided into those that are quality-assured ACTs (QAACs) and those that are not (nQAACs). Quality assurance, or prequalification, through the WHO Prequalification Programme (PQP) or by an



SRA is required before medicines can be purchased in the donor-funded market. There are 29 prequalified products from 8 manufacturers with varying combinations and formulations, including 23 ACTs. There also are 11 ACT products currently under assessment in the WHO PQP (Annex 1). nQAACTs have been found to have a 60% quality-control failure rate compared to less than 4% for QAACTs. nQAACTs also have been found to have a higher failure rate than nATs; for example, SP was found to have a 28% failure rate.

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. AL, DHA PQP, ASMQ and ASAQ are all available as FDCs. There are currently 18 FDC ACTs prequalified, including AL, ASAQ and ASMQ. In addition, there are prequalified co-blistered formulations of ASAQ and ASSP. There is an SRA-approved version of DHA PQP (not yet prequalified by WHO). Lastly, although not included in WHO treatment guidelines, there is a European Medicine Agency (EMA) Article 58 positive scientific opinion for pyronaridine artesunate (PyA) (with a corresponding cross-link to the WHO list of prequalified medicines).

WHO identifies flexible solid dosage forms as the most suitable form of medicine for children under five years old in developing countries, including for the treatment of malaria. Two products (Novartis and Ajanta) are prequalified for dispersible formulations of AL. In addition, ASAQ, although not flavour-masked, can be made soluble in water when administered to young children.

### **Pipeline products**

A strong research and development (R&D) pipeline of antimalarial medicines exists, including products to cure *P. vivax* hypnozoites (liver-stage infections), to offer a replacement for SP for IPTp, 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. Products in late-stage development that show high potential include:

- Artesunate I.R. (Registration): This is an RAS for pre-referral treatment of severe malaria. A product is currently under review by the United States Food and Drug Administration (FDA), however, the product assessment final outcome has not been communicated to date.
- Amodiaquine + sulfadoxine-pyrimethamine (AQSP, Registration): A co-blistered combination of AQSP for seasonal malaria chemoprevention (SMC) is currently under review by the WHO PQP. A dossier for infant packs is expected to be submitted to the WHO PQP in 2013 and efforts are being directed at developing dispersible and palatable tablets for SMC.
- Tafenoquine (Phase IIb/III): An 8-aminoquinoline, and the only pipeline molecule with published activity against *P. vivax* hypnozoites. It has a long half-life, which would reduce treatment from 14 days (as required with primaquine, the only medicine recommended today for liver-stage cure) to a single-dose cure. There are safety concerns for patients who carry the glucose-6-phosphate dehydrogenase (G6PD) deficiency—and depending on effective dosing requirements, G6PD screening may be recommended as a necessary step before drug administration. There is potential for co-formulation with an ACT.
- Azithromycin + CQ tablets (Phase IIb/III): Work is under way to develop an FDC tablet of this medicine as an alternative to SP for use as a chemoprevention drug for IPTp. It potentially offers the advantage of protecting against both SP and CQ-resistant parasites and helping reduce the burden of common sexually transmitted diseases during pregnancy.
- PyA dispersible for paediatric use (Phase IIb/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 will be 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.



- DHA PQP (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 2014–2015. DHA PQP 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 piperazine.
- OZ439 (Phase IIa): A fully synthetic peroxide that could provide an alternative to the currently available artemisinin derivatives. 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. It is currently in Phase II trials that will help determine an optimal partner drug 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.
- KAE609 (Phase IIa): KAE609 is a synthetic antimalarial molecule with a novel mechanism of action with the potential to inhibit *P. falciparum*. 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 has the potential to be part of a single-dose FDC cure.

## Market landscape

### *Funding, market size and market share of ACTs*

The future of the ACT market is dependent on long-term, multiyear funding commitments by donors. To date, international donor funding has been instrumental in supporting quality assurance and scaling up ACTs, and most of this funding has been directed towards the highest-burdened region, Africa. The donor community is responsible for purchasing the majority of ACTs and 31 % of malaria control funding has been invested in treatment. In particular, ACT purchases are concentrated among two donors—the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) and the United States President’s Malaria Initiative (PMI).

UNITAID strategic funding has been instrumental in supporting both improvements in the quality assurance of ACTs and their scale-up. By 2012, UNITAID initiatives had supported the delivery of 333M ACT treatment courses. AMFm, primarily supported by UNITAID in collaboration with international donors, has provided 151M ACT treatment deliveries between 2010 and 2011.

International donor funding has contributed to the rapid increase in volumes of ACTs procured in recent years, but volumes are forecasted to decline in 2013 and 2014. Deliveries of ACTs have increased dramatically in the past 10 years, from 11M treatment courses in 2005 to 331M treatment courses in 2012. The value of the donor-funded market saw a 96 % growth rate between 2008 and 2011. It is estimated that ACT deliveries will decline from a peak of 331M treatment courses in 2012 to 319–334M treatment courses in 2013. Estimates for 2014 deliveries are uncertain and will depend on the effect of the integration of AMFm into GFATM grants, the impact of the GFATM New Funding Model on overall procurement volumes, and the effect of the replenishment on grants and the timing of when funds will be available. Any future short-ages in funding will lead to a decrease in ACTs. Since there is no indication that the need for ACTs will decrease, the potential exists for shortfalls in ACT availability.

Three major delivery channels drive the overall market for ACTs and continue to determine access to quality medicines: (i) the public sector (not including AMFm public sector) delivering 183M courses in 2010, 126M courses in 2011 and 181M courses in 2012; (ii) the AMFm private sector, which delivered 106M courses in 2011 and around the same amount in 2012; and (iii) the premium private sector where ACT delivery estimates are difficult to obtain given the nature of this market. The degree to which deliveries are meeting true “need” is inconclusive due to limited data.

The overall demand for antimalarials (ACTs, nATs and AMTs) includes confirmed malaria cases and unconfirmed malaria cases due to limited diagnosis of febrile patients. The overall size of the private sector is estimated to account for 655M antimalarial treatment deliveries globally compared to the estimated 174M malaria cases in Africa in 2010. Improvements to the quality and use of rapid diagnostic tests (RDTs) alongside ACTs for febrile patients are needed to improve patient care, address the potential oversupply of antimalarial medicines and delay resistance.

The QAACT market is highly concentrated around two medicines. In 2012, 77% of ACTs delivered were AL (255M courses), and 22% were ASAQ (73M courses). Multiple prequalified products exist for both AL and ASAQ, and prequalification of ACTs has had a positive role in terms of diversification of supply in the donor-funded ACT market. There are currently eight manufacturers that produce prequalified medicines, and over time the market share has moved between these manufacturers, particularly towards an increased market share of generic medicines. Volumes procured through AMFm have contributed to the overall increase of generic products in this market; in 2011, 57% (116M) of the total number of generic ACTs procured in the donor-funded market was through AMFm.

Even though more generic companies have entered the ACT market, originator brands have maintained a strong presence. For example, Novartis had the greatest share of the AL market between 2008 (88%) and 2011–2012 (around 30%). However, by 2012, three generic manufacturers had obtained a significant proportion of the AL market: Ajanta Pharma (19%), Cipla Ltd (24%) and IPCA Laboratories Ltd (24%). Together, in 2012, they accounted for 67% of the AL market. Sanofi had a monopoly in the ASAQ market in 2012, likely because it had been the only FDC prequalified manufacturer since 2008. In November–December 2011, two more manufacturers received prequalification. Even though generic brands have entered the market, to date a corresponding decrease in price has not been observed. However, as generic companies have now captured a substantial proportion of the market, prices may begin to decrease in the future.

### ***Therapies at the facility level***

Despite efforts to scale up ACTs, nATs are still more commonly distributed in both public and private facilities in many endemic countries, and the market share of QAACTs is low. In non-AMFm countries, QAACTs are mostly distributed by the public sector (e.g. Democratic Republic of the Congo [DRC] 21%, Benin 49%, Zambia 66%), whereas in AMFm countries, it is a mix. The market share of oral AMTs distributed by both public and private facilities was less than 1% in three AMFm countries: Kenya, Madagascar and Uganda. But in Nigeria, the share of oral AMTs distributed by private facilities was still approximately 4.4%.

Furthermore, the high concentration of products and suppliers in the donor-funded market is reflected in the availability of QAACTs at country facilities, where recent data from ACTwatch show that outlet availability of QAACTs is concentrated by four brands: Coartem® (Novartis-AL); Lumartem® (Cipla-AL) and artemether-lumefantrine (IPCA Laboratories-AL); and Winthrop® (Sanofi-ASAQ).

### ***FDCs and co-blister ACTs***

There also has been a high uptake in the number of procured FDCs compared to co-blister ACTs. There are now 18 FDC ACTs prequalified compared to one in 2006, and in contrast to five co-blistered packs. In 2008, FDCs accounted for 54% of treatment courses procured in the donor-funded market and now account for around 98% of the products procured, equaling around 80% growth over five years.

### ***Retail ACT price***

The high retail price of ACTs compared to traditional nATs, especially in the private sector, remains a barrier to access. Access also may be dependent on supporting the sale of ACTs at an affordable retail price that does not require a subsidy. With the support of international donor funding, many endemic countries now are able to provide ACTs for free in public clinics and hospitals. However, outlet surveys show that in Benin and the DRC (non-AMFm countries) the median price of an ACT in public facilities in 2009–2010 and 2011 was US\$ 1.23 and US\$ 3.09, respectively. In private facilities, retail prices of QAACTs remain high, especially in non-AMFm countries (e.g. Benin US\$ 2.10 and Zambia US\$ 4.81), and are still found to be around 5–24 times more expensive than nATs.

### **Availability of ACTs**

Availability of QAACTs in private facilities is still low (38%) and is particularly low in non-AMFm countries (e.g. 20% in Zambia, <25% in Benin and <30% in DRC). Unlike private sector outlets, public channels in both AMFm and non-AMFm countries often have a large number of first-line ACT treatments available for use (e.g. 86% of public facilities stocked QAACTs across six African countries in 2011). While the availability of nQAACs appears to be low, the availability of nATs is still vast in both public and private facilities and across both AMFm and non-AMFm countries, despite a rapid emergence of resistance to these medicines. Progress, however, has been made towards minimizing the use and marketing of oral AMTs, and only private and public outlets in the DRC (40.5% and 10.2%, respectively) and Nigeria (35% and 16.8%, respectively) still had stock available at the time of the survey.

### **Paediatric ACTs and formulations for children under five years old**

Even though the ACT market is largely paediatric (68% of AL procured in 2012 was for children <35 kg), the uptake of child-friendly formulations for children under five years old has been low. The increase in child-pack procurement could be a result of the revisions made at the beginning of 2011 to the co-payment structure of AMFm to favour child-packs; however, this has not had an effect on ACTs for children under five years old. Dispersible tablet formulations of ACTs are preferred for infants and toddlers because of their easier mode of delivery, and are preferred over syrups due to their transportability and palatability. While achievements have been made by manufacturers to shift from distributing solid oral formulations towards dispersible, child-friendly formulations, in 2011 less than 10% dispersible AL was procured compared to solid oral AL packs. Prior to late 2012, dispersible Coartem® was the only prequalified product available and, therefore, Novartis has accounted for all dispersible sales in the donor market to date. As the only supplier, however, their dispersible formulation only accounted for 28% of the market share in 2011 compared to solid oral formulations, which accounted for the remaining market share. While solid oral AL still has a strong presence in the market, Novartis market share of their solid oral tablets has been replaced by their dispersible product over time, and by 2012 they were selling quite low volumes of the solid oral pack sizes for children under five years old (e.g. dispersible 6x1 and 6x2 tablets make up an estimated 94% of Novartis sales in this market). Now that Ajanta has achieved prequalification of a dispersible AL, the market landscape may change moving forward. The low uptake of dispersible AL in the donor market is seen to roll over into retail trends where limited data from AMFm show that their availability to patients in registered pharmacies is low (11–14%), and is lower than that of paediatric packs of solid tablets (42–48%).

ASAQ procurement has been more in favour of packs for children <35 kg since 2008, and hence before the AMFm revisions. This is thought to be caused by the fact that ASAQ comes in different strengths for different weight bands and so packs are procured along the lines of weight-based needs (i.e. there is less potential to stack child-packs ASAQ for an adult). FDC offers a simpler treatment delivery for children under five years old compared to co-blister, and since FDC has been prequalified, it has gained a significant proportion of the market compared to co-blister ASAQ (e.g. FDC ASAQ increased from 6M courses in 2009 to 12M in 2011 compared to co-blister 9M in 2009 and 2M in 2011). Co-blister ASAQ for children under five years old has not yet had any transactions reported for 2012. Sanofi has been the market leader for FDC ASAQ since 2009 because of its advantage of being the only prequalified manufacturer. IPCA received quality-assured approval to manufacturer FDC ASAQ in mid-2012 thus the market may become more competitive.

In general, ASAQ for children under five years old is cheaper per treatment course compared to AL for the same age group (e.g. packs tailored for toddlers in 2011, FDC ASAQ median price was US\$ 0.4 per unit versus solid oral AL US\$ 0.8 per unit and dispersible AL US\$ 0.8 per unit).

### **Severe malaria**

Uptake of INJAS has been low, and further monitoring of the INJAS market is needed to enhance scale-up and to reduce the treatment course price so the market can adopt INJAS over traditional injectable therapies such as QN. There is currently only one WHO prequalified INJAS product available (Guilin Pharmaceuticals) that is potentially impacting on the shortfalls in this market. In 2012, quantities procured were less than 15% of the total needed to treat global annual cases. Approximately 3.2M vials (roughly 750 000–1M treatments for children under five years old) were procured out of an estimated 48–50M vials needed to treat global annual cases. Although to treat someone with a course of INJAS costs more than injectable QN, overall treatment costs are found to be equivalent when total treatment costs such as administration and management costs are considered. Reasons for low-level procurement include: the absence of catalytic financing incentives; a slow policy process causing delays to updating policy guidelines; unfamiliarity with the product; provider preference; a higher price over parenteral QN; and buyer concerns over a single-prequalified supplier.

Pre-referral RAS is recommended by WHO in cases where parental medication is not immediately available. An RAS is yet to be prequalified by WHO or an SRA, however, Médecins sans Frontières and PMI have assured an RAS manufactured by Mepha (now Acino) and have programmes running to distribute this medication. However, limited data stand in the way of carrying out a thorough market assessment at this point in time.

### ***P. vivax* and CQ**

In most areas where *P. vivax* is endemic, particularly South-East Asia, CQ is the recommended first-line antimalarial medicine. In 2012 there were an estimated 27M cases and 42 000 malaria deaths. The GFATM Price and Quality Reporting (PQR) transactional data show that South-East Asia consistently has been purchasing CQ through donor-funded procurement channels since 2009. However, in 2011, the value of transactions for CQ was greater in the WHO Region of the Americas, and in 2012 transactions for Pakistan alone were greater than that for South-East Asia Region. Currently, there is no estimate for the number of *P. vivax* cases occurring in regions where CQ is still recommended. This information, along with improved monitoring of the number of CQ treatments delivered compared to the number of *P. vivax* cases, is needed to better understand this market and the market shortcomings.

### **Artemisinin**

Without long-term funding commitments for ACT purchases, which allow realistic production planning, it is very difficult to stabilize artemisinin prices. The upstream supply of artemisinin is based on a long and complex agricultural process (cycle from *Artemisia annua* crop to finished pharmaceutical product [FPP] is approximately 12–18 months), and involves many players. This long cycle limits market responsiveness to sudden changes in demand, and in the past has resulted in a volatile market with large price fluctuations (e.g. artemisinin selling price ranges: US\$ 1100/kg in 2005, down to US\$ <200/kg in 2007, and back up to US\$ 300/kg in 2009 when the AMFm master supply agreements were signed). Prices fell again in 2012, albeit from an artificially high price at the end of 2011/early 2012. Currently, falling prices and concerns regarding surpluses (i.e. in 2012, global production of artemisinin increased considerably; the supply for 2013 is estimated at 202 tonnes (possibly 262 tonnes) whereas the demand for 2013 treatment courses is estimated to be 319–334M, equivalent to 148–155 tonnes of artemisinin) have the potential to destabilize the market and reduce the level of commitment of both farmers, particularly by the relative attractiveness for farmers to plant other crops offering high prices, and artemisinin producers. This may result in a significant reduction in planting at the beginning of 2014.

Even though semi-synthetic artemisinin (SSA) has now been accepted by the WHO PQP for manufacturing APIs or FPPs, in light of the estimated production volumes of SSA and in the absence of an SSA market that can cover the global demand, there is still going to be a demand for agricultural artemisinin. 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 because of its significantly shorter lead time (three months) as compared with natural artemisinin. It is uncertain, however, whether it will be available in sufficient quantities to make up the foreseen gap, which may result in a shortage (production capacity is estimated at 35 tonnes for 2013 for Sanofi use, with a total production capacity of 50–60 tonnes in 2014). Concerns raised over its entry into the market include natural artemisinin producers regarding SSA as a risk to their market share, particularly with the recent uncertainty regarding the amount of funding available for ACTs, and unknown patent details that need to be closely monitored regarding the scope for widespread use by multiple manufacturers of this new API. A careful rollout of SSA will be required to ensure that it does not trigger agricultural suppliers to exit the market; maintaining and communicating up-to-date market intelligence on the demand for ACTs and artemisinin and on the market entry SSA are key mechanisms for stabilizing artemisinin prices.

### **Market shortcomings and their reasons**

Several shortcomings in the malaria medicine market, for ACTs and paediatric-specific medicines, and their reasons have been identified (Table 1, Table 2). These shortcomings represent potential areas for intervention to address the range of near-term and long-term challenges. 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 (Table 1) for ACTs as a whole also apply to paediatric pack sizes. In addition, Table 2 describes the market shortcomings specific to paediatric malaria medicines that have been identified.



**Table 1: Summary of market shortcomings for oral adult malaria medicines**

Category	Shortcoming	Reason
Availability	No alternative to primaquine for treating the liver stage of <i>P. vivax</i>	<ul style="list-style-type: none"> <li>■ Research is ongoing (e.g. tafenoquine) but products are not yet available</li> <li>■ 8-aminoquinolines are the only class of drugs known to have anti-hypnozoite activity and all suffer from safety issues, especially in G6PD-deficient patients</li> <li>■ Lack of incentives for manufacturers to invest in R&amp;D due to uncertainties around future demand, market size and return on investment</li> </ul>
	No single-dose ACTs to reduce current three-day dosing requirements	<ul style="list-style-type: none"> <li>■ Two candidates for a single-dose cure for uncomplicated <i>P. falciparum</i> malaria are under development but earliest availability is 2018</li> <li>■ Lack of incentives for manufacturers to invest in R&amp;D due to uncertainties around future demand, market size and return on investment</li> </ul>
Affordability	High ACT retail prices in non-AMFm countries (e.g. US\$ 4.81 in Zambia and US\$ 2.10 in Benin), with a high price differential between ACTs and nATs (ACTs are around 5–24 times more expensive than nATs)	<ul style="list-style-type: none"> <li>■ High ACT manufacturing costs, including expensive and variable raw material prices (artemisinin prices have ranged from US\$ 170–1100/kg).</li> <li>■ Despite an increase in the number of prequalified ACT suppliers in recent years, market share is still highly concentrated by a few manufacturers</li> <li>■ Future integration of AMFm into GFATM grant mechanisms suggests little scope for expansion of private sector subsidies</li> </ul>
	Limited price reductions over time of ACTs procured through the GFATM and AMFm	<ul style="list-style-type: none"> <li>■ Pricing architecture of key procurement channels</li> <li>■ Reliance on the assumption that increased market competition will stimulate competitive pricing</li> </ul>
Quality	Low market share and availability of QAACTs, particularly in the private sector of non-AMFm countries (e.g. market share of QAACTs: 3.1% in DRC, 6.3% in Zambia and 16.7% in Benin; proportion of private outlets with QAACTs in stock: <30% in Benin, DRC and Zambia)	<ul style="list-style-type: none"> <li>■ Low demand for QAACTs in the out-of-pocket market due to higher cost (see Affordability above)</li> <li>■ QAACT manufacturers have tight production capacity with low incentive for expansion due to uncertain future demand</li> <li>■ Lack of visibility on future orders and variability of raw materials prices</li> <li>■ Complexity and cost of prequalification process</li> <li>■ Weak and/or unharmonized regulatory standards in many endemic countries, which limit incentives for manufacturers to meet international drug quality standards</li> </ul>
	High quality-control failure rates among non-prequalified ACTs (60% quality control versus <4% for prequalified ACTs) and non-artemisinin treatments (e.g. 28% quality-control failure rate for SP)	<ul style="list-style-type: none"> <li>■ Existence of counterfeit drugs that form the basis for a profitable business, which benefits from insufficient local quality control and awareness</li> <li>■ Regulatory loopholes allow significant market penetration by substandard or non-proven therapies</li> <li>■ Technologies for on-the-spot quality control not widely used</li> </ul>

<sup>1</sup> Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). The public health sector includes government and non-profit facilities; the formal private sector includes private clinics and providers; the community sector is community health workers; the informal private sector includes pharmacies, shops and traditional providers. Figures represent the 10<sup>th</sup> and 90<sup>th</sup> percentiles.

<p>Acceptability/ adaptability</p>	<p>While ACTs are more widespread than in 2002–2006, their usage is still below that of non-recommended therapies (~4–44% among antimalarials given to febrile children)<sup>1</sup></p>	<ul style="list-style-type: none"> <li>■ Complex dosing regimen of ACTs compared to single-dose conventional therapies, which has been cited by patients and providers as a key acceptability barrier to ACTs (1)</li> <li>■ Non-availability of single-dose ACTs</li> <li>■ Limited palatable medicines for children, both for curative and preventive drug regimens</li> </ul>
<p>Delivery</p>	<p>Risk of supply shortages for artemisinin</p>	<ul style="list-style-type: none"> <li>■ The long, complex and multi-actor, upstream supply chain contributes to a volatile market and limits market responsiveness to sudden changes in demand</li> <li>■ SSA could help to stabilize the supply and price of artemisinin but ACTs made with SSA are yet to enter the market; market entry of SSA also could have a destabilizing effect on the market if shortages arise from growers and extractors of plant-based artemisinin exit the market</li> </ul>
	<p>Public sector stockouts of prequalified ACTs</p>	<ul style="list-style-type: none"> <li>■ Public sector supply is challenged by tight QAACT production capacity</li> <li>■ Delays in funding disbursements</li> <li>■ Demand uncertainty/unpredictability and diversion from public subsidized sector to private for-profit sector</li> <li>■ Suboptimal in-country planning and supply management and forecasting as well as uncertainty on the effect of diagnostics on treatment demand</li> </ul>
	<p>Low availability of ACTs in private sector facilities, particularly outside AMFm Phase I countries (e.g. 20% in Zambia; &lt;25% in Benin; &lt;30% in DRC)</p>	<ul style="list-style-type: none"> <li>■ Low private sector demand for ACTs is largely due to high ACT prices compared to non-artemisinin treatments (e.g. ACTs are 5–24 times more expensive than SP and CQ)</li> <li>■ Complex dosing regimen of ACTs and non-availability of single-dose ACTs, also may contribute to low demand</li> <li>■ 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</li> </ul>
	<p>Large rates of overtreatment with all antimalarials, including ACTs, particularly in the private sector (in 2010, it is estimated that 655M treatments were delivered through the private sector in Africa alone) (2)</p>	<ul style="list-style-type: none"> <li>■ Historical practice of presumptive treatment of fever with antimalarials</li> <li>■ Low uptake of quality, point-of-care diagnostic tools for malaria (RDTs), particularly in the private sector where presumptive dispensing prevails alongside low ACT availability</li> </ul>
	<p>Unpredictable future demand</p>	<ul style="list-style-type: none"> <li>■ 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</li> </ul>

**Table 2: Summary of market shortcomings for paediatric malaria medicines**

Category	Shortcoming	Reason
Availability	No RAS product has been WHO prequalified or approved by an SRA, despite being recommended by WHO for the pre-referral treatment of severe malaria	<ul style="list-style-type: none"> <li>■ One RAS product is currently under review by an SRA but has not yet been approved</li> <li>■ Lack of information on the size of the market for the pre-referral treatment of severe malaria</li> </ul>
Acceptability/adaptability	Low uptake of child-friendly ACT formulations for children under five years old (12% of the total donor-funded market for AL in 2011)	<ul style="list-style-type: none"> <li>■ Only one prequalified manufacturer of dispersible tablets until December 2012 (Novartis, and now Ajanta)</li> <li>■ Variable demand for dispersible tablets by different providers and caregivers</li> <li>■ Multiple non-prequalified paediatric formulations (e.g. suspensions) are available in local markets</li> </ul>
Delivery	Low uptake of INJAS for severe malaria	<ul style="list-style-type: none"> <li>■ Inadequate advocacy, education and training, leading to poor acceptance by patients and providers</li> <li>■ High treatment prices (three times more than injectable QN) due to low volumes and lack of competition</li> <li>■ Only one prequalified product (Guilin Pharmaceuticals), buyer concerns over single-prequalified supplier; if the single supplier cannot meet the demand, then there is potential for stockouts</li> <li>■ Commercial interests around injectable QN, which is often procured from local manufacturers</li> </ul>

### Opportunities and market interventions

Several opportunities exist for market-based interventions to address the market shortcomings described above. The opportunities described below represent a range of market-based interventions in malaria medicines markets that could be undertaken by different global health actors and stakeholders, including UNITAID. 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. Artemisinin Conference, Malaria Market Forum, Roll Back Malaria Partnership (RBM) Procurement and Supply Management Working Group meetings) and more exploratory interventions that require additional discussion and vetting.

Overall, longer-term funding commitments are critical mechanisms to stabilize the ACT market as well as the upstream market for raw materials such as artemisinin. Such commitments would 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 to understand the extent to which “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. In addition to this overarching opportunity, the following are specific opportunities that aim to address one or more of the market shortcomings identified in this landscape:

- Ensure rational and appropriate use of ACTs and improve access to appropriate diagnostics testing and treatment, i.e. getting the RDT/ACT ratio right.  
*Market shortcoming addressed: Delivery*
- Support the sale of quality-assured ACTs at an affordable retail price that does not require a subsidy.  
*Market shortcomings addressed: Affordability, Quality, Delivery*
- Facilitate market entry and scale-up of important, cost-effective products.  
*Market shortcoming addressed: Availability*



- Support the production of global ACT and RDT demand forecasts that project the need of ACTs and RDTs in relation to each other, the disease burden and funding available.  
*Market shortcoming addressed: Delivery*
- Stabilize artemisinin prices and supply through the collection and dissemination of information on supply and demand, and evaluate the need for additional targeted interventions.  
*Market shortcomings addressed: Affordability, Delivery*
- Encourage the uptake of IVAS to improve severe malaria outcomes.  
*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 five 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*

Acting strategically through market-based interventions to address these issues would lead to improved access to malaria medicines for people in need worldwide.

### 1. Introduction

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). 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 Malaria Vector Control Technology and Market Landscape complement this report.

This landscape analysis is designed to identify opportunities for market interventions that could have considerable public health and market impact. It also is designed to serve other stakeholders and the broader global health community interested in understanding the market for malaria medicines. As such, the Landscape is made available on the UNITAID website.

Studying the malaria medicines market is a timely exercise. The use of ACTs for malaria has rapidly expanded in recent years following the recommendations in medicines made in the World Health Organization (WHO) treatment guidelines in 2006. Since then, increased donor funding and the implementation of the Affordable Medicines Facility-malaria (AMFm) have spurred both public and private sector scale-up of ACTs. Going forward, lack of certainty around funds available to sustain the gains made in scaling up ACTs threatens to destabilize this market and makes it important to monitor market dynamics and trends.

Information in this report was collected in a variety of ways, including desk research, literature reviews, data analyses and through expert consultation. Although the information available on the malaria ACT market is increasing, very little aggregate data are available. As a result, the discussion in this report is based largely on limited data sets supplemented by key informant interviews. Given the limitations around data aggregation, it is important to note that individual country experiences may vary from the global trends presented. Robust quantitative data are limited for certain parts of the global market including data on non-artemisinin therapies (nATs), markets outside of AMFm countries and data from the private sector.

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 and case management, current treatment recommendations and the role of ACTs in malaria as well as trends in disease epidemiology and malaria case management. These sections also summarize current levels of access and concerns for malaria medicines in changing settings and in light of evolving donor policies and funding availability.

**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:** The medicines market landscape provides a historical overview of the ACT market, outlining the challenges faced at the time that WHO recommended ACTs, and describing market interventions that have been introduced to meet the existing market challenges. This section also analyses the current ACT market, including the market size and market share of ACTs over time. It looks at the availability of medicines and at international quality-assured procurement practices. The data have been gathered from ACT-watch household and outlet surveys, the Global Fund to Fight Aids (GFATM), the Tuberculosis and Malaria Price and Quality Reporting transactional database and from AMFm. Trends in the paediatric and severe malaria markets also are reviewed, and a high-level overview of the current market of chloroquine (CQ) is provided. Unless otherwise stated, reference to ACTs throughout this section refers to prequalified ACTs.

**Section 6:** This section identifies market shortcomings and their reasons. Findings from the market landscape are presented and explained in terms of the existing barriers impeding access to malaria medicines. It also describes these market shortcomings and explores the ways they represent potential areas for intervention to address the challenges that exist in the near and long term. The shortcomings are aligned with what is described as UNITAID's objectives (refer to UNITAID's strategy for further details) and arranged by these 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. Active interventions are ongoing projects and initiatives. Exploratory interventions are initiatives that have been identified by stakeholders and are pending vetting.

**Section 8:** Conclusion

A set of annexes provide further detail on specific topics to supplement the landscape.

## 2. Methods

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.

The landscape is focused on, but not limited to, WHO recommended first-line treatment of uncomplicated *Plasmodium falciparum* malaria, ACTs (3). Both the medicine technology landscape and the medicine market landscape are covered in this report.

### Medicine 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 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 (36), Google searches and product development partnership websites, such as the Medicines for Malaria Venture (MMV), 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. Conversations 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 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-malarial\*, treat\*, med\*, 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 cross-check 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						
Artemisinin*	OR	Treat*	OR	Med*	AND	Econ*
Anti-malarial*	AND	Treat*	OR	Med*	AND	ACT*
Anti-malarial*	AND	Treat*	OR	Med*	AND	Market
Anti-malarial*	AND	Treat*	OR	Med*	AND	Supply
Anti-malarial*	AND	Treat*	OR	Med*	AND	Demand
Anti-malarial*	AND	Treat*	OR	Med*	AND	Drug costs
Anti-malarial*	AND	Treat*	OR	Med*	AND	Price
Anti-malarial*	AND	Treat*	OR	Med*	AND	Share
Anti-malarial*	AND	Treat*	OR	Med*	AND	Quality

### Selection criteria

As a comprehensive literature review was completed by UNITAID in preparation for the 2012 Malaria Market Forum, and as global malaria policies have changed significantly within the last decade, the search was limited to English-language literature published between 2010 and 2013. The retrieved research studies that reported on key market indicators such as price, market share, product availability and quality were selected for use. Consumer demand-side issues such as willingness-to-pay also were excluded, but were considered as supplementary information for insight into the broader market issues associated with commodity availability. Preference was given to studies that reported data from more than one country, although some single-country studies were included for potential lesson learning and opportunity scoping.

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 medicine landscape returned 76 relevant articles between 2010 and 2013. The search retrieved 46 multicountry and 30 single-country publications for malaria medicine. After the selection criteria were employed, 34 publications were found to present comprehensive findings on the overall malaria medicine market (Table 4). Twenty-three articles were found to be current and included to expand on the results from the UNITAID 2012 literature review. By topic area, the breakdown of the 23 studies shows: 16 related to AMFm and two on the market characteristics of active pharmaceutical ingredients (APIs). One article was found for each of the following market dynamics including the private sector; paediatric formulation; quality; supply and demand; and treatment and policy guidelines.

**Table 4: Breakdown of results by topic area, 2010–2013**

Topic area breakdown	2013	2012	2011	2010	Total
AMFm	1	15	1	2	19
API	1	1		1	3
Private sector		1	1		2
Paediatric formulation		1	1		2
Quality		1			1
Supply and demand (and price)		1	1	2	4
Treatment and policy guidelines		1	1	1	3
Total	2	21	5	6	34

## 2.2 Data collection and analysis

Data presented in this landscape were retrieved from the following sources: a collection of published reports publicly available on the Internet; ACTwatch reports and presentations; and GFATM 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 (RBM). 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), the Demand Forecast for Artemisinin-based Combination Therapies, and the Inner City Fund (ICF) 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 of Population Services International, initiated in 2008 and between 2008 and 2012), conducted in seven malaria endemic countries: Benin, Cambodia, Democratic Republic of the Congo (DRC), Madagascar, Nigeria, Uganda and Zambia (4). Aggregated, quantitative data on nATs, artemisinin monotherapies (AMTs) and non-prequalified ACTs (nQAACTs) global markets are limited, however, household and outlet surveys conducted by ACTwatch between 2009/2010 and 2011 provide insights into these markets at the country level. Household surveys at the household level determine treatment-seeking behaviour and treatment usage. Outlet surveys provide facility-level information on the availability, volume and price of antimalarial medicines, quality-assured ACTs (QAACTs), nQAACTs, nATs and AMTs, across both public (including private not-for-profit outlets) and private sectors (including “formal” outlets such as registered pharmacies and for-profit health facilities and “informal” outlets such as shops and hawkers).

Outlet data were extracted from individual country reports from the 2011 country surveys that are provided on the ACTwatch website. Individual charts and tables were pulled from each report and then amalgamated, but not aggregated, to form one single chart. This was applied to charts showing the market share (Tables A10 and B1 in-country reports), availability (Tables A1 and B3 in-country reports) and price (Table A4/A5 in-country reports) of ACTs and other antimalarials available at the facility level and across both sectors. Where information was extracted on price, the reports that presented figures using OANDA 2010 US\$ exchange rates were updated with OANDA 2011 exchange rates. In analyses of prices over time (Fig-

ure 24, Figure 40), prices were standardized to 2010 using the consumer price indexes of each country to adjust for inflation/deflation.

Furthermore, ACTwatch provided UNITAID with data on QAACT brand market share for Benin, Madagascar, Nigeria, Uganda and Zambia from surveys in 2011. The data from Madagascar, Nigeria and Uganda were used in the end line AMFm evaluation. The QAACT products found in each country were listed by brand name and manufacturer. Information was presented in the following categories: total unweighted adult equivalent treatment doses (AETDs); weighted AETDs; relative QAACT market share by brand (among all outlets); and relative QAACT market share by brand (within outlet category). Many individual products had zero volumes as they were not found in a given country. These data were then presented in charts used in the market landscape. The country level data were not aggregated to show the overall market share by sector to avoid losing nuances across manufacturer distributions in countries with smaller populations.

### **GFATM Price and Quality Reporting (PQR) transactional database and AMFm**

Analyses of datasets from the GFATM PQR transactional database, the ACT Scale-Up Initiative and the 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 (5). Data were disaggregated to reveal market indicators, for example, procurement of ACT originator brands to generic brands; procurement of ACTs by the GFATM versus AMFm; fixed-dose combination (FDC) formulations versus co-blistered formulations; dispersible formulations versus child-friendly tablets; procurement by ACT (e.g. artemether-lumefantrine [AL] compared to artesunate-amodiaquine [ASAQ]); and median price assessments. Median prices were used over weighted average prices to reduce the effect of extreme values, or outliers, and the 10<sup>th</sup> and 90<sup>th</sup> quantiles range was obtained where the lowest and highest points were discarded. Except where noted, analyses reflect transactions from 2008 to 2012. Data from 2012 may not be complete due to time lags with reporting and because manufacturing surveys from 2012 have not yet been published, so it is not possible to determine the percentage of the overall market represented. However, the dataset includes over 162M treatment courses in 2012, so what is currently available from this year has been included to provide insight into how trends may evolve moving forward.

In order to analyse data retrieved from AMFm, GFATM and ACT Scale-Up, a master dataset was created in Microsoft Excel compiling the records from each individual set. AMFm and the PQR transactional datasets were first downloaded from the [www.globalfund.org](http://www.globalfund.org) on 25 March 2013. AMFm data were obtained from the report library and the PQR dataset was obtained from the PQR dashboard under the product category “anti-malarial medicines”. These sets were then cleaned by removing headers, footer and empty columns, and all cells were unmerged. Empty spaces from cells were all removed from columns where necessary using key commands such as ctrl g; Alt s; k; enter; = ;ctrl enter. Date formats were changed using Text to Columns in the datasets so that they were consistently formatted across sets. The data from the ACT Scale-Up report delivered by the United Nations Children’s Fund (UNICEF) at the end of the project were then added to the working file.

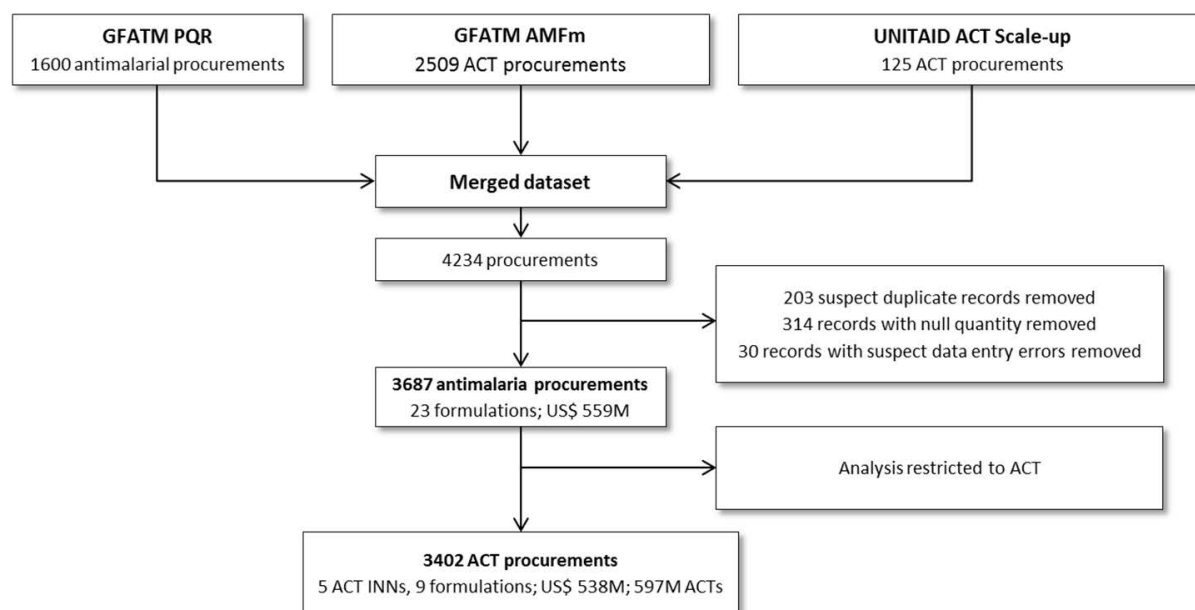
A master list of products, countries and suppliers was created and these were mapped by common definitions and nomenclature. Using VLOOKUPS, PQR INN (non proprietary name), Strength, PackSize and NumberSUoM were mapped to a list of number of treatments in each packs type (used to calculate the number of ACT treatments ordered). A merged dataset using formulas was created and data were standardized for packs and number of treatments per packs. Duplicates across datasets were screened and reviewed through a side-by-side comparison. Datasets were adapted, removing some data where it was obvious that duplication between datasets was occurring. Transactions viewed as high risk of duplicates were flagged, and a field to flag duplicates in the Merged Dataset was created (“X” = high-risk duplicate). Analysis of data points was carried out using pivot tables and filtering results with an X in the duplicate field.



## Results

A total of 4234 records (Figure 1) were retrieved across all three datasets. Then, 13 countries were identified with treatment courses reported by multiple datasets (i.e. Nigeria had transactions in PQR and public sector AMFm in the same year). A total of 203 records equalling 61M ACT treatment courses were flagged due to high-risk duplicates; 314 records were removed from the dataset because PQR listed them as “pending verification” and they contained null product quantities. A further 30 records were removed because of suspect errors/queries in original data entry (e.g. AMFm record for Niger 2012: 6x2 dispersible AL reported US\$ 84.00 per unit).

**Figure 1: Flow chart illustrating the merging of data sources and removal of duplicate records**



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 GFATM PQR and through the AMFm, plus volume deliveries through the President’s Malaria Initiative (PMI) that were retrieved from 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 GFATM PQR records and the AMFm dataset represents approximately 49% of the donor market in 2009, 73% in 2010, 86% in 2011 and 62% in 2012 (Table 5).



**Table 5: Estimated coverage of datasets collated for market share analysis**

Year	GFATM and AMFm	PMIa	WMR (total donor market)b	Estimated coverage of GFATM/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%
Total	572 435 584			

Sources: a [http://pmi.gov/resources/reports/pmi\\_annual\\_report13.pdf](http://pmi.gov/resources/reports/pmi_annual_report13.pdf); b Public and private sector ACT purchases extracted from the WMR 2010 and the WMR 2011.

### 2.3 Key informant consultation

Finally, discussions with key informants took place to ensure broad stakeholder engagement in preparation of the landscape. Representatives from organizations such as WHO, MMV, the Clinton Health Access Initiative (CHAI) and the Bill & Melinda Gates Foundation were consulted to discuss potential opportunities for market-based approaches to improve access to malaria medicines. Other experts in the field were consulted to give insight on possible publications that could be used and for a deeper understanding of the current environment of antimalarial treatments.

### 3. Public health problem

#### Key public health problem messages:

- More than 207M cases of malaria occurred in 99 countries in 2012.
- In 2012, 77% of malaria deaths were in children under five years .
- Sub-Saharan Africa accounted for 90% of malaria deaths worldwide in 2012.
- 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.

Malaria is a preventable and highly treatable parasitic disease (6). It is transmitted when a female *Anopheles* mosquito infected with the *Plasmodium* bites a person (7). There are five types of malaria *Plasmodium* that can cause disease in humans with variable prevalence based on geographic area (7).

<i>Plasmodium falciparum</i> ( <i>P. falciparum</i> )	<i>Plasmodium vivax</i> ( <i>P. vivax</i> )	<i>Plasmodium ovale</i> ( <i>P. ovale</i> )	<i>Plasmodium malariae</i> ( <i>P. malariae</i> )	<i>Plasmodium knowlesi</i> ( <i>P. knowlesi</i> )
<ul style="list-style-type: none"> <li>•Responsible for most malaria cases, especially in the African Region</li> <li>•Infection may develop suddenly and produce several life-threatening complications</li> </ul>	<ul style="list-style-type: none"> <li>•Has the largest geographic spread and is responsible for much of the malaria disease burden outside of Africa, especially throughout Asia and South America</li> <li>•Less severe symptoms than <i>P. falciparum</i> but the patient can suffer from relapses for up to three years</li> </ul>	<ul style="list-style-type: none"> <li>•Very rare and generally occurs in West Africa; similar to <i>P.vivax</i>, the patient can suffer from relapses</li> </ul>	<ul style="list-style-type: none"> <li>•Very rare, and has been wiped out from temperate climates, but still is present in Africa</li> </ul>	<ul style="list-style-type: none"> <li>•Usually only infects certain monkey species in South-East Asia but has recently been shown to cause severe infections in humans</li> </ul>

In 2005, the World Health Assembly set a goal to reduce the number of malaria cases and deaths by 75% by 2015 (8). Strategies implemented for malaria control and case management, as outlined in the RBM Global Malaria Action Plan (GMAP), and the targets set by the Millennium Development Goals, are leading to a reduction in the number of malaria cases and malaria deaths (9), (10). Approximately 207M malaria

cases occurred in 2012 (lower estimate 135M, upper estimate 287M) in the 99 countries with ongoing transmission (11). This represents a 29% decrease in malaria case incidence per 1000 persons at risk of malaria between 2000 and 2012 (11). In 2012, there were 627 000 deaths (range 473 000–789 000) from malaria indicating a 45% decrease in mortality rates since 2000 (11). Of these deaths, 77% (approximately 482 000) occurred in children under five years old (11). Further to this, severe malaria is a major cause of adult and childhood death where an estimated 8M cases of uncomplicated malaria progress to severe malaria each year (12). If severe malaria is left untreated, it leads to nearly 100% mortality (13). There is substantial variability in malaria disease burden across countries. While a some countries have reported an increase in the number of malaria cases in recent years, many countries are on track to meet or exceed the 2015 target of reducing reported malaria case incidence rates by 75% from 2000 levels; a few countries are already certified as malaria free (11) (6). However, 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.

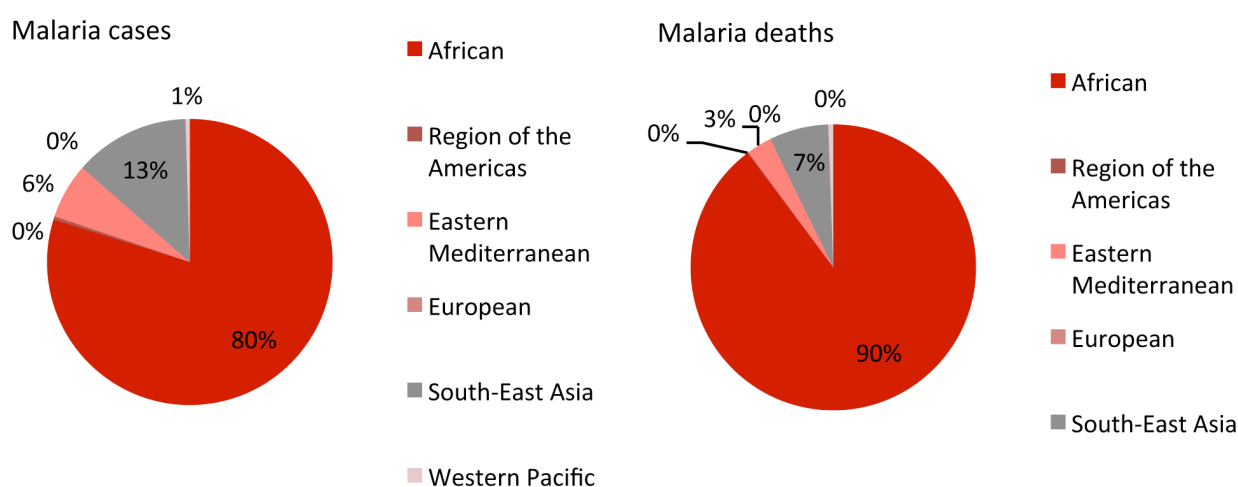
### Sub-Saharan Africa

The global malaria burden is highest in sub-Saharan Africa, which accounts for 80% of cases and 90% of worldwide deaths (Figure 2). In this region, the DRC and Nigeria together account for more than 40% of the global total of estimated malaria deaths (11) (6). *P. falciparum* was identified as the infecting organism in 99% of estimated cases. Children under five years old bear a significant burden of malaria morbidity and mortality in the African Region, accounting for 82% of estimated malaria deaths (11). In addition, children in sub-Saharan Africa are significantly burdened by severe malaria, which is often the main reason for paediatric hospital admission (14).

### South-East Asia

The South-East Asia Region has the second highest number of estimated cases and deaths after the African Region. This region had an estimated 27M cases and 42 000 deaths in 2012 (11). *P. falciparum* was identified in only 47% of cases, indicating this region has a higher burden of other forms of malaria parasites, particularly *Plasmodium vivax* (11). Mortality in children under five years old accounted for only 26% of all malaria-related deaths in this region (11). This correlates with the South-East Asia Region having less stable malaria transmission than the African Region, resulting in decreased immunity in older children and adult populations and, therefore, increased mortality in these cohorts. Severe malaria and the risk of death affect the broader population and not just young children.

**Figure 2: Malaria cases (estimated) by WHO region, 2012; malaria deaths (estimated) by WHO region, 2012.**



Source: WMR 2013.

### Country burden by World Bank income level<sup>1</sup>

Lower-middle-income countries (LMICs) and low-income countries (LICs)<sup>2</sup> have the highest malaria disease burden, together accounting for more than 97% of estimated malaria cases (44% and 53%, respectively) in 2010. They also account for more than 97% of deaths from malaria. LICs have a slightly higher percentage of deaths (47%) than cases, while LMICs have a slightly lower percentage of deaths (50%) than cases. Upper-middle-income economies account for slightly more than 2% of cases and only 2% of deaths, while high-income economies account for only 0.1% of estimated malaria cases and 0.08% of malaria deaths.

### 3.1 Global malaria guidelines and policy recommendations for treatment

In the first WHO treatment guidelines for malaria in 2006 and the updated guidelines in 2010 (Figure 3), recommended treatments for malaria are specific to the type of *Plasmodium* and the level of endemic and drug resistance in the region (3), (13). In addition to the updated guidelines of 2010, a further update was made in 2011 to reflect new guidance of the use of INJAS. A revised version of the guidelines is anticipated in the first half of 2014.

#### ACTs

WHO recommends ACTs as the first-line treatment of uncomplicated *P. falciparum* malaria (3). These combine an artemisinin derivative with another antimalarial class of medicine. Due to the threat of resistance to monotherapies, the choice of ACT should be country and region appropriate and based on the level of resistance to the partner medication, not the artemisinin base. Preferable formulations are FDCs and dispersible formulations for children, although co-blistered products still exist. Agents that have only ever been available as an FDC coupled with an artemisinin base, such as lumefantrine and piperaquine, generally have a lower level of resistance. ACTs also are recommended by WHO as the first-line treatment of acute blood-stage *P. vivax* infections in areas that are no longer CQ-sensitive because of resistance. The exception for using an ACT to treat *P. vivax* is using any artemisinin derivative combined with sulfadoxine-pyrimethamine (SP) because SP is ineffective due to resistance to pyrimethamine. ACTs are still known to be effective for pregnant women in the second and third trimesters of pregnancy.

#### CQ

In most areas where *P. vivax* is endemic, CQ is the recommended first-line antimalarial medicine (13). Due to resistance development, it is no longer recommended for *P. falciparum*. CQ is recommended to treat both *Plasmodium ovale* and *Plasmodium malariae*.

#### Primaquine

Primaquine is recommended after treatment with CQ or an ACT to clear the dormant liver stages and to prevent relapse for both *P. vivax* and *P. ovale*, particularly in the South-East Asia Region (13). Additionally, primaquine, due to its gametocytocidal properties, potentially has a major role in reducing malaria transmission in efforts to control *P. falciparum* as a single dose added alongside ACTs (15). Previously, there have been concerns associated with the use of primaquine in high transmission areas such as sub-Saharan Africa, because of the relationship between patients who are glucose-6-phosphate dehydrogenase (G6PD)-deficient and the risk of severe adverse events (13). However, in October 2012, WHO conducted a review of the evidence on the safety and effectiveness of primaquine as a single dose added alongside ACTs because of its gametocytocidal properties in the treatment of *P. falciparum*. The review indicated that in conjunction with ACT treatment, a single 0.25 mg base/kg dose is effective in blocking transmission and

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<sup>1</sup> 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.

<sup>2</sup> 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 to US\$ 4035; upper-middle-income economies US\$ 4036 to US\$ 12 475; and high-income economies ≥US\$ 12 476. Country-level classification is updated yearly as new economic indicator data become available.

is unlikely to cause serious toxicity in subjects with any of the G6PD variants in contrast to the previously recommended dose of 0.75 mg base/kg (15). The review also indicated the limited settings recommended for the use of primaquine. Based on the review of the WHO Evidence Review Group, the Malaria Policy Advisory Committee recommends that:

- In: (i) areas threatened by artemisinin resistance where single-dose primaquine as a gametocytocide for *P. falciparum* malaria is not being implemented; and (ii) pre-elimination and elimination areas that have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria:
  - ◆ a single 0.25 mg base/kg primaquine dose should be given to all patients with parasitologically confirmed *P. falciparum* malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants < 1 year old.

#### **Quinine (QN)**

QN is recommended to treat *P. falciparum* in pregnant women during their first trimester (13).

#### **Intravenous artesunate (IVAS)**

IVAS is the first choice of treatment of severe malaria in both adults and children (13). If intravenous access cannot be achieved, artesunate should be given via intramuscular injection (13). Intravenous artemether and QN are acceptable alternatives if artesunate is unavailable.

#### **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 (World Health Organization, 2010). Currently, RAS has not been approved by a stringent regulatory authority (SRA) or by the WHO PQP, but one component of the MMV UNITAID-supported severe malaria project is to secure prequalification of RAS by at least one manufacturer.

#### **Chemoprevention antimalaria agents**

In addition to antimalaria agents recommended by WHO for postinfection treatment, WHO recommends three strategies for the use of antimalarial medicines for the prevention of malaria: SP for intermittent preventative treatment for pregnant women (IPTp) and intermittent preventative treatment for infants (IPTi) (16), and amodiaquine + sulfadoxine-pyrimethamine (AQSP) for seasonal malaria chemoprevention (SMC) (17).

#### **SP**

SP for IPTp and IPTi is a strategy recommended by WHO since 2004, with the most recent amendments to the guidelines in 2012 (16), (18). IPTp-SP is recommended for all pregnant women at each scheduled antenatal care visit. WHO recommends a schedule of four antenatal care visits. 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 (16), (19). IPTi-SP is the administration of a full therapeutic course of SP. It has been recommended by WHO since 2011 and also is recommended to be geographically limited to countries in sub-Saharan Africa with a moderate-to-high malaria transmission (20).

#### **AQSP**

In 2012, WHO recommended AQSP for SMC in areas of highly seasonal malaria transmission across the Sahel subregion of Africa and where AQSP remains > 90% effective (17), (21). It is recommended for monthly use for children under five years old for up to four months during the transmission season (17).

**Figure 3: Summary of WHO treatment guidelines for malaria**

	Post-infection treatment							Chemopreventive treatment	
	Uncomplicated <i>P. falciparum</i>		Uncomplicated others			Severe <sup>f</sup>	pre-referral	IPTp/IPTi	SMC
	Pregnant women	Other	<i>P. vivax</i>	<i>P. Ovale/ P. Mal.</i>	Mix <sup>e</sup>	All	All	All	All
High-transmission	T1: QN+ Clin <sup>a</sup> T2-T3 : ACT <sup>b</sup>	ACT ACT+PQ <sup>c</sup> (PQ booster)	CQ+PQ if resistant AQ+PQ or ACT <sup>d</sup>	CQ (+PQ for Ovale)	ACT	INJAS <sup>g</sup>	RAS	SP	AQSP
Low-transmission without epidemic				CQ (+PQ for Ovale)		AS			
Epidemic period			CQ+ PQ			AM <sup>h</sup> or AS			

T = treatment; QN = quinine; Clin = clindamycin; ACT = artemisinin-based combination therapy; CQ = chloroquine; AQ = amodiaquine; PQ = primaquine; AS = artesunate; AM = artemether; INJAS = injectable artesunate

<sup>a</sup> Or ACTs where QN+clindamycin are not available.

<sup>b</sup> If effective – alternatives are AS+clindamycin or QN+clindamycin.

<sup>c</sup> Except artesunate sulfadoxine-pyrimethamine (ASSP) for *P. vivax*.

<sup>d</sup> Including *P. falciparum* or not.

<sup>e</sup> Mainly *P. falciparum*, very few cases of severe *P. vivax* treated like severe *P. falciparum*.

<sup>f</sup> 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.

<sup>g</sup> Intramuscular artemether.

<sup>h</sup> Single-dose 0.25 mg base/kg.

Sources: Image adapted from the BCG medicines market landscape (unpublished). Information derived from the WHO guidelines for the treatment of malaria 2006 and WHO guidelines for the treatment of malaria (second edition) 2010.

### 3.2 Commodity access issues in treatment

#### Key commodity access issues in treatment messages:

- Across 12 African countries, approximately 12% of antimalarials given to febrile children are ACTs, with a wide range observed across countries (~4–44%).<sup>2</sup>
- In the public sector, less than 20% of antimalarials given to febrile children are ACTs, though in some countries it is >50%.<sup>3</sup>
- In the “informal” private sector (pharmacies, shops, traditional providers), less than 7% of antimalarials given to febrile children are ACTs.<sup>4</sup>

Ensuring an adequate supply of recommended therapies and their correct formulations have a significant public health impact beyond the individuals who have access to effective treatment. They reduce the risk of emerging parasitic resistance as well as helping in the overall control and effort towards eventually

2 Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). World malaria report. Geneva: WHO; 2012.

3 Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). World malaria report. Geneva: WHO; 2012.

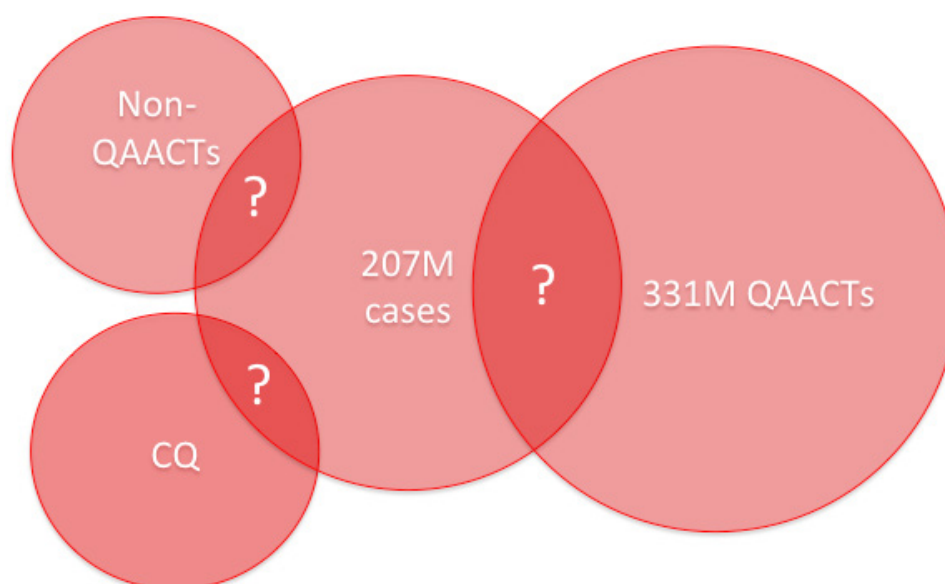
4 Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). World malaria report. Geneva: WHO; 2012.



eradicating the disease. Since the WHO 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 (11). The number of ACTs delivered by manufacturers also has increased substantially, from 11M in 2005 to 76M in 2006, 278M in 2011 and reaching 331M in 2012 (11) (6). This increase is due largely to scaled-up investments from international donors, with an increase in 2011 due largely to 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. While increased deliveries in 2012, primarily came from public sector procurement (11).

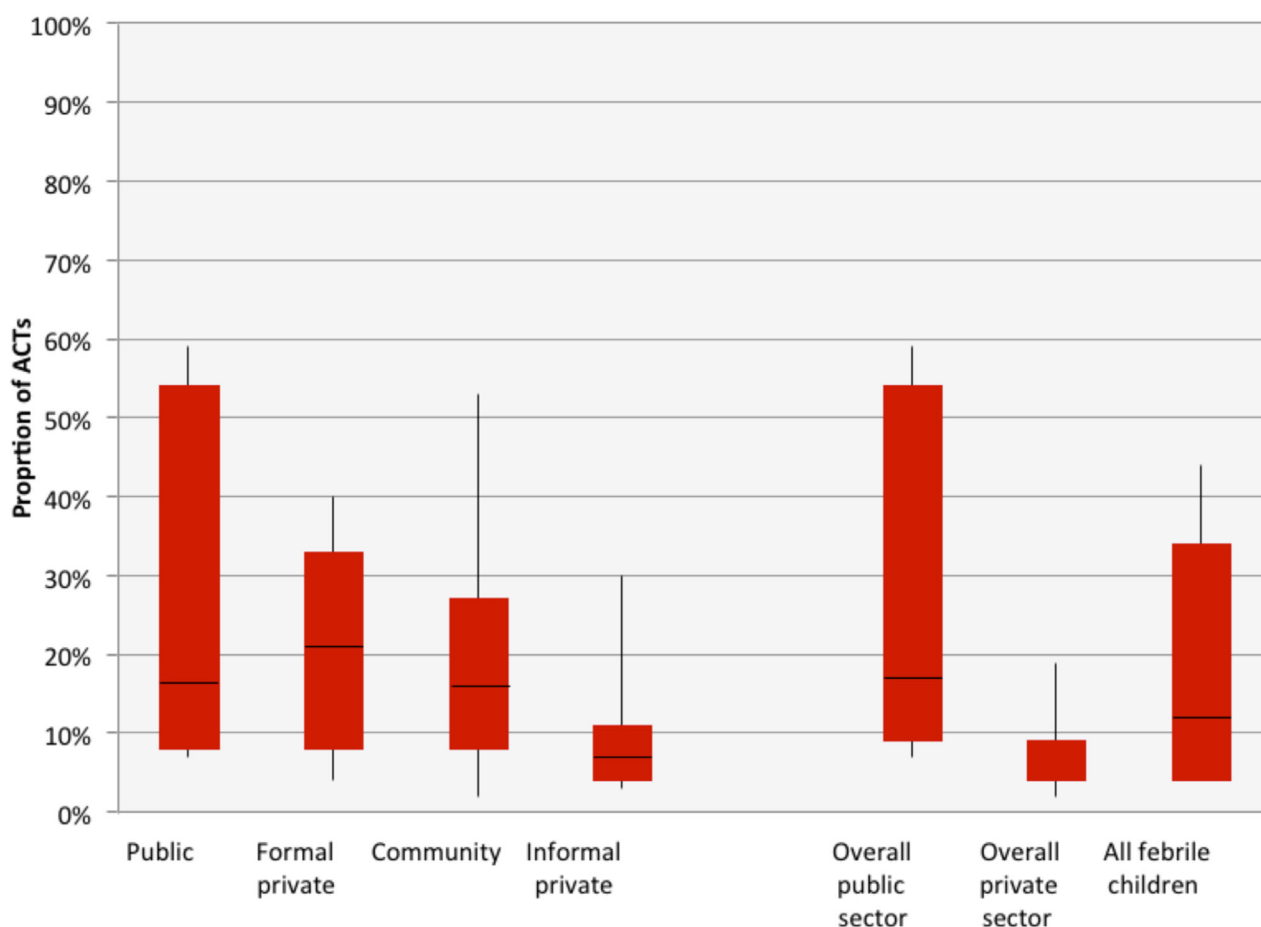
It is very difficult to estimate access to appropriate antimalarial treatment. There were around 331M QAACT treatments procured for approximately 207M cases of malaria in 2012 (Figure 4). However, due to presumptive treatment and lack of diagnostic testing, many fever cases are treated for malaria (22). For that reason, the overlap between people who actually have malaria and those who receive QAACTs is unknown. In addition, there are the issues of CQ, which is still recommended for *P. vivax*, and other ACTs (not WHO PQP or SRA approved) that may be of acceptable quality.

**Figure 4: Approximation of QAACT coverage compared to annual malaria cases, 2011**



Despite considerable progress in scaling up the use of ACTs in recent years, widespread access remains an issue. Household survey data from 12 African countries in 2010–2011 show that only about 12% of all antimalarials given to febrile children are ACTs, with a wide range observed across countries (~4–44%, 10<sup>th</sup>–90<sup>th</sup> percentile, respectively) (Figure 5) (6). In the public sector, less than 20% of antimalarials given to febrile children are ACTs, though in some countries it is greater than 50% (6). In the “informal” private sector (pharmacies, shops, traditional providers), ACTs comprise less than 7% of antimalarials given to febrile children (6). It should be noted that this indicator of access, derived from household survey data, is only a proxy given that not all febrile children will actually have malaria. 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 (23). Additional efforts are needed to address current gaps in access to ACTs in order to ensure high malaria cure rates, reduce transmission and control the spread of drug resistance.

**Figure 5: Proportion of ACTs among antimalarial treatments given to febrile children, by health sector, selected countries with household surveys, 2010–2011**



Note: The top and bottom lines represent the 90th and 10th percentile, the box represents the limits of the 25th to 75th percentile or interquartile range, and the horizontal line through the box represents the median value.<sup>3</sup>

Source: WMR 2012.

### 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 (24).
- 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%) (25).

As children under five years old bear a significant proportion of the malaria disease burden (77%), it is important that effective antimalarials be available in formulations that facilitate their use for children (11). 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 five years old, including malaria (26).

<sup>3</sup> Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). Public health sector includes government and non-profit facilities; formal private sector includes private clinics and providers; community sector is community health workers; informal private sector includes pharmacies, shops and traditional providers. World malaria report. Geneva: WHO; 2012.



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 (24). Dispersible tablet formulations of ACTs, therefore, offer advantages for children in terms of palatability and dosing (24). For prequalified purchases of dispersible AL products, there are limited options available. Additionally, the overall pricing architecture of AMFm may constrain competitive price reductions; for example, prices are negotiated rather than reached through competitive tenders. Two WHO prequalified dispersible tablet formulations of the ACT AL are available; however, data indicate that uptake has been limited. Specifically, limited data from AMFm show that their availability in registered pharmacies is low (11–14%), and is lower than that of paediatric packs of solid tablets (42–48%) (24).

#### 3.2.2 Severe malaria treatments

##### **Key severe malaria treatments messages:**

- In 2012, approximately 3.2M vials of prequalified INJAS were procured, representing approximately 750 000–1M treatments for severe malaria in children under five years old. This represents less than 10% 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 (13).

Since 2011, when WHO recommended INJAS as the preferred treatment of severe malaria (13), uptake of INJAS has been limited. In 2012, quantities procured were less than 15% of the total needed to treat global annual cases. While other sources of INJAS were available to purchase, approximately 3.2M prequalified vials (roughly 750 000–1M treatments for children under five years old) were procured out of an estimated 48–50M vials that would be needed to treat global annual cases (27). Reasons for low-level procurement of INJAS include unfamiliarity with the product, a higher price over parenteral QN and buyer concerns about a single-prequalified supplier.

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 (13). However, the lack of a WHO prequalified product or approval by an SRA has limited access and hampered widespread use of this product.

## 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. IVAS for severe malaria and the ACT dihydroartemisinin+piperazine (DHA PQP) that offers once-a-day dosing), 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. These include a medicine addressing *P. vivax* hypnozoites, a potential replacement for SP for IPTp, a single-dose treatment of malaria and paediatric formulations.

### 4.1 Overview of current products on the market

Medicines used in the treatment of uncomplicated malaria can be divided into three categories: ACTs; AMTs; and 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* (3). 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 and supporting the introduction, use and maintenance of use 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) (13).

**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 (ASAQ)	2–10 mg/kg/day 7.5–15 mg/kg/day	Daily for three days
Artesunate+mefloquine (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 (ASSP) <sup>a</sup>	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+piperazine (DHA PQP)	4 mg/kg/day (2–10 mg/kg/day) 18 mg/kg/day (16–26 mg/kg/day)	Daily for three days

<sup>a</sup> In areas that are still SP-sensitive.

For an ACT to be eligible for purchase in the donor-funded market, it needs to be included in the WHO treatment guidelines (5). It also needs to be quality assured through either the WHO PQP or approval from an SRA, such as the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA), to become prequalified for purchase in the donor-funded market (5). Therefore, ACTs are often divided into those that are quality assured through one of the abovementioned mechanisms (QAACTs), and those that are not (nQAACTs). There are many nQAACTs that may be purchased directly by endemic countries or other market participants (typically wholesalers) under local good manufacturing practice (GMP) conditions, but are not prequalified. For example, in Tanzania, 12 manufacturers are registered to market ACTs, but only four were prequalified (28). Even though some products are GMP certified, 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 (29).

To date, WHO has prequalified 29 malaria products from 8 manufacturers with varying combinations and formulations, of which 23 are ACTs<sup>4</sup> (Annex 1) (30). There are a further 11 ACT products currently under assessment by the WHOPQP (Annex 2) (31). Most recently, WHO recommended DHA PQP as an ACT option for the first-line treatment of uncomplicated *P. falciparum* and *P. vivax* malaria worldwide as sufficient evidence on safety and efficacy became available. WHO prequalification recognizes the EMA Article 58 process thus, in 2012, the list of prequalified medicines was updated to include the Article 58 positive scientific opinion regarding Pyramax (pyronaridine artesunate—PyA.) While PyA is not yet in the WHO treatment guidelines, separately, WHO did call for its use as a potential tool in containing artemisinin resistance in Cambodia (32). In 2012, DHA PQP was granted marketing authorization from EMA, thus the European Commission (EC) granted marketing authorization of the product. This medicine offers an advantage over AL with its once-a-day dosing. A child-friendly granule formulation has been developed and is currently in Phase III trials (27).

Additionally, since 2006, WHO has recommended that wherever possible, FDC tablets should be used to treat malaria. FDCs offer several major benefits, including increased individual compliance to the full treat-

<sup>4</sup> Since the preparation of this landscape, an additional ACT, AL tablets 20 mg+120 mg, manufactured by Strides Arcolab Limited, achieved WHO prequalification on 24 June 2013.

ment course, reduced pill burden, delayed development of parasite resistance (for example, AL and DHA PQP 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 18 FDC ACTs prequalified by WHO, including AL, ASAQ and artesunate-mefloquine (ASMQ), and also DHA PQ approved by EMA (30). There also are a number of ACTs that have not been co-formulated into FDCs, including co-blistered formulations of ASAQ, artesunate sulfadoxine-pyrimethamine (ASSP) and ASMQ. Like FDCs, there are many co-blistered ACTs that are quality assured and many that are not.

WHO has identified flexible solid dosage forms as being the most suitable form of medicine for children under five years old in developing countries, including the treatment of malaria (26). There are now two prequalified products available from different manufacturers for dispersible formulations of AL (30). In addition, the prequalified FDC version of ASAQ is soluble in water (but not flavour-masked). As children bear a significant burden of malaria morbidity and mortality, and palatability and ease of administration are challenges in access to malaria medicine (24), child-friendly formulations are an important technology in the overall antimalarial landscape. Additional child-friendly formulations are under development; these are described in the following section.

### AMTs

The use of oral AMTs (for example, artesunate, artemether and dihydroartemisinin) threatens the long-term usefulness of ACTs by fostering resistance. An additional concern is that resistance can develop over a short period of time (6). If *P. falciparum* develops resistance to the artemisinin derivatives, then there will be no alternative effective compounds to treat malaria over the next 10 years that will have a significant impact on the population control of malaria (13). For these reasons, in 2006, WHO changed their guidelines to ACTs. WHO also has encouraged countries to prohibit the marketing of oral AMTs, (6) and there have been concerted efforts implemented to discourage or ban their use as a monotherapy such as the global plan for artemisinin resistance containment. Despite these efforts, oral AMTs continue to be available, and there are some endemic countries still allowing them to be marketed (33). In 2008, for example, 37 pharmaceutical companies were producing monotherapies and they were marketed in 29 countries (34). For malaria to progress from control to elimination and to eventual eradication, it is critical to maintain the effectiveness of artemisinin as the first-line treatment and that investments are scaled up further to support efforts.

In contrast to solid, oral AMTs, AMTs in injection form remain the WHO-recommended first-line treatment of patients with severe malaria (13). In 2010, IVAS, developed by Guilin Pharmaceuticals, was prequalified by WHO with the help of MMV (35). A goal of UNITAID and MMV is to encourage more manufacturers to supply IVAS, and recently there seems that there is hope of more IVAS suppliers entering the market in the coming years.

### nATs

Traditional therapies for treating malaria include the use of CQ, QN and SP for *P. falciparum*, and primaquine for *P. vivax*. These have been available in both the public and private markets of most endemic countries for many years. In the private sector specifically, nAMTs are generally inexpensive and, therefore, readily available and affordable compared to ACTs (2). However, there has been a rapid emergence of resistance to these medicines, reducing their efficacy in clinical settings (36). As a result, these therapies are no longer recommended as the first-line therapy for *P. falciparum* (13). However, some nATs are recommended as the first-line treatment of uncomplicated *P. vivax*; for example, CQ + primaquine is recommended for *P. vivax* in non-resistance settings where infections are still CQ-sensitive (13). 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 (13).

## 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 are needed that address the current limitations of ACTs, including (37):

- artemisinin supply insecurity influencing wide variations in price and availability;
- 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, mefloquine, piperaquine and SP;
- lack of child appropriate treatment courses and poor palatability of currently available paediatric formulations;
- relatively short shelf-life of currently available medications (three years).

Additional needs in malaria treatment include:

- quality RAS formulation for pre-referral treatment in cases of severe malaria when patients may experience over six hours of delay before parenteral treatment can begin;
- substitute for artemisinin as a result of emerging resistance;
- alternatives to primaquine for treatment and relapse prevention of *P. vivax* malaria given the substantial compliance (requires a 14-day treatment course) and safety issues associated with primaquine (15);
- alternatives to SP for use for IPTp and IPTi considering the growing resistance to SP;
- for effective rollout of the WHO SMC strategy for malaria prevention, suitable medications with characteristics including a long half-life, appropriate formulations and reasonable palatability;
- medicines that can block the transmission of malaria through activity against the gamocytes for disease elimination programmes; it has been proposed that an ideal medicine for elimination needs to combine transmission-blocking and anti-hypnozoite activity (ACT + primaquine) (38).

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 (39). 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 two 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 (39). 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 two years old.

Global funding for all malaria R&D in 2011 was US\$ 558.8M, accounting for around 18% of the total global R&D (40). Funding for overall malaria R&D comes from a variety of sources, with the top 12 funders accounting for 91.7% of all malaria R&D funding in 2011, and the top five funding organizations (the Bill & Melinda Gates Foundation, the United States National Institutes of Health, pharmaceutical industry, the Wellcome Trust, and the EC) accounting for three-quarters (75.6%) of total funding. Drug development for malaria accounted for more than one third of total funding (US\$ 204.7M, 36.6%) (40). 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 (35). The majority of the molecules and products in the current global malaria medicine R&D portfolio are being developed with support from MMV.

The global malaria medicine pipeline is more extensive than it has ever been (Figure 6). Products currently in registration include an RAS formulation for pre-referral treatment of severe malaria (41). These medicines are listed in further detail below.

### ■ Artesunate I.R. (Registration)

A rectally administered artemisinin derivative 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 (13). A product is currently under review by the FDA, however, the product assessment final outcome has not been communicated to date. MMV is working with TDR, the Special Programme for Research and Training in Tropical Diseases, and pharmaceutical partners to establish a solution for the review by the WHO PQP or an SRA (41).

### ■ AQSP (Launched, Under review by WHO-PQ)

A co-blistered combination of AQSP for SMC is currently under review by the WHO PQP (31). MMV is working with the manufacturer and Médecins Sans Frontières to develop user-friendly packaging to ensure proper patient use and patient cards to help ensure correct dispensing by community health-care workers (41). The tablets that are manufactured at present are not suitable for use in infants as they would require tablets to be individually cut. However, a dossier for an infant pack was submitted to the WHO PQP in 2013 (42). In addition, MMV is working with the same manufacturer to develop dispersible and palatable tablets for SMC (42).

A variety of products in Phases II and III represent ACTs, endoperoxides, synthetic endoperoxides, aminoquinolines, antibiotics and natural products (41), (37). Several of these products show high potential for public health and market impact including:

### ■ Tafenoquine (Phase IIb/III)

This 8-amiloquinoline is the only molecule in the pipeline with published activity against *P. vivax* hypnozoites (41). In contrast to piperazine, this medicine has a long half-life that would reduce treatment from 14 days (as required with Primaquine, the only medicine recommended today for liver-stage cure) to a single-dose cure, thus enhancing treatment compliance (41). As with primaquine, there are safety concerns for patients who carry the G6PD deficiency—and, depending on effective dosing requirements, G6PD screening may be recommended as a necessary step before drug administration (41). Tafenoquine could significantly improve the treatment of *P. vivax* malaria, especially if it could be co-formulated with an ACT or single new chemical entity with potent activity against *P. vivax* blood stages (43), (37). The launch of this product is not expected until 2017 (42).

### ■ Azithromycin + CQ tablets (Phase IIb/III)

MMV is working with Pfizer and LSHTM to develop an FDC tablet of this medicine to replace SP for IPTp (41). Upon successful completion of its Phase III programme, expected in 2014, the drug dossier will be submitted for regulatory review. It potentially offers the advantage of protecting against



both SP- and CQ-resistant parasites and helping reduce the burden of common sexually transmitted diseases during pregnancy (41).

### ■ PyA dispersible for paediatric use (Phase IIb/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 will be 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 (41).

### ■ DHA PQP 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 2014–2015. DHA PQP 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 piperaquine (41).

### ■ OZ439 (Phase IIa)

This product is a fully synthetic peroxide under development by MMV that could provide an alternative to the currently available artemisinin derivatives (41). 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. It is currently in Phase II trials that will help determine an optimal partner drug 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 (42).

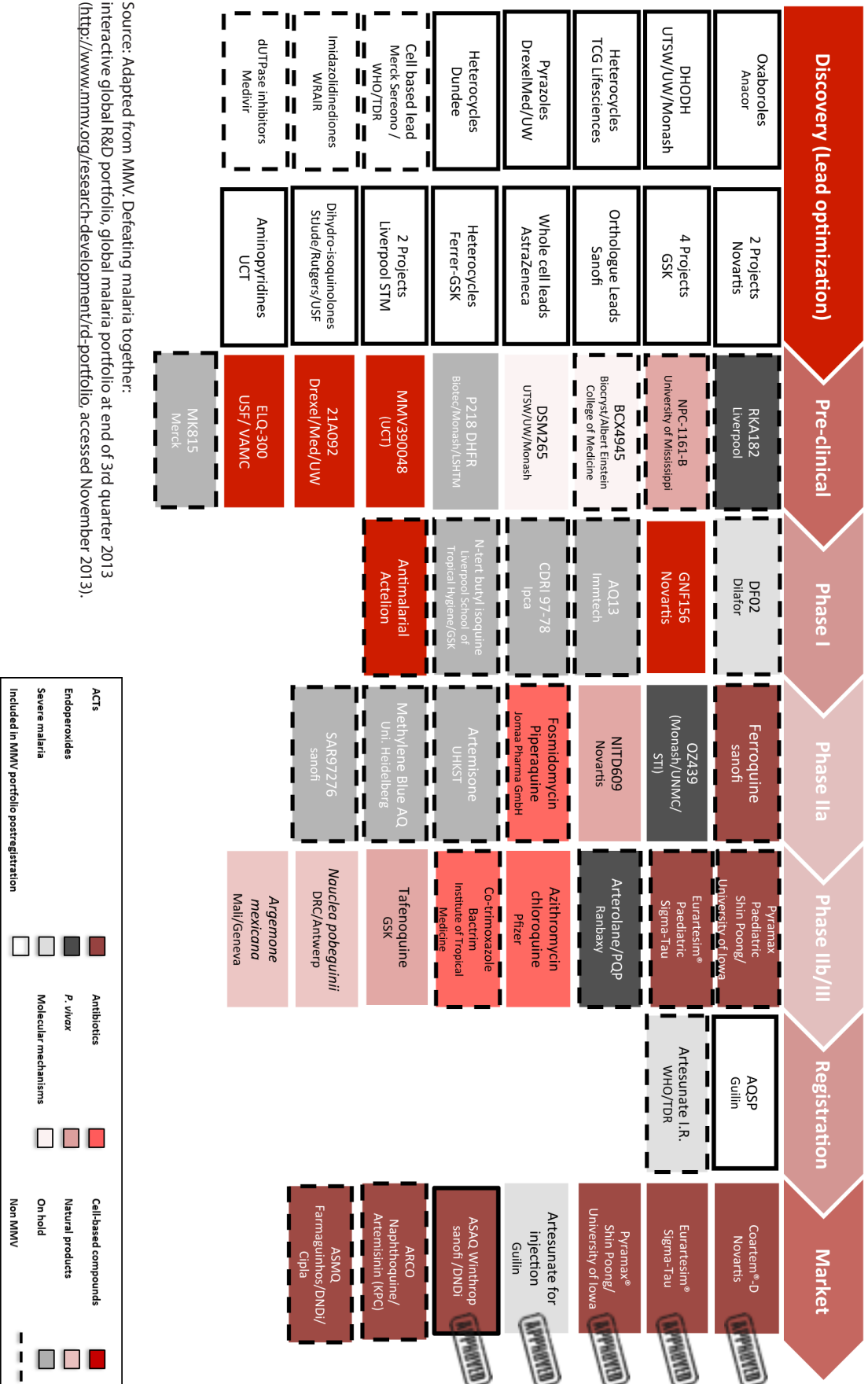
### ■ KAE609 (Phase IIa)

KAE609 is a synthetic antimalarial molecule with a novel mechanism of action with the potential to inhibit *P. falciparum*. 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 has the potential to be part of a single-dose FDC cure (41). 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 (41).

There are also numerous new chemical entities currently in the transition and development pipeline, which is necessary for addressing parasite resistance to all existing malaria classes (37). Of the 15 products in Pre-clinical and Phase I stages of development, 5 are currently on hold (41). Furthermore, one of these compounds is coupled with an existing antimalarial and two from a class of antimalarials already commonly used (CQ) (41). Only two have potential for transmission blocking (ELQ-300 and MMV390048), and one has clear anti-hypnozoite activity (GNF156) (41).



Figure 6: Global malaria medicines pipeline



Source: Adapted from MMV. Defeating malaria together: interactive global R&D portfolio, global malaria portfolio at end of 3rd quarter 2013 (<http://www.mmv.org/research-development/rd-portfolio>, accessed November 2013).

## 5. Medicine market landscape

### Key malaria market landscape messages:

- Donor funding, including funding from UNITAID, has been instrumental in supporting the scale-up of quality-assured ACTs.
- The private sector is still a channel where many people access malaria treatment, yet ACT penetration into the private sector is still low outside AMFm.
- Market stability for ACTs, as well as the artemisinin raw ingredient, could be improved by multiyear funding commitments by donors that would strengthen the accuracy of demand forecasts and improve production planning.

ACTs are considered the most effective treatment of the majority of malaria cases worldwide (33). As such, they are recommended by WHO as the first-line treatment of uncomplicated *P. falciparum* (3). They are also currently the best available treatment to safeguard against the potential threat of parasite resistance to artemisinin (33). Understanding the characteristics of the current market for ACTs as well as trends for the future is, therefore, an important activity towards ensuring that healthy market conditions exist that enable access to ACTs for those who need them. The first section of the market landscape begins with a brief historical overview of the ACT market that describes the evolution of the ACT market during the past decade. An analysis of the current ACT market is then presented, including key market indicators such as market size, market share/competition and price levels. Children under five years old bear a significant proportion of the malaria disease burden (77%), and the high risk of mortality associated with severe malaria if treatment is not readily available (11). The final section investigates trends in paediatric ACT and severe malaria markets and the current market of CQ for treating *P. vivax* (6). Unless otherwise stated, reference to ACTs throughout this section refers to prequalified 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. In 2005, 11M ACTs were delivered through the public sector, compared to an estimated 244M cases of malaria. At that time, malaria was generally treated using “traditional therapies” such as CQ, QN, SP, etc. These have been available in the markets of most endemic countries for many years, are generally inexpensive and, therefore, readily available and affordable. In 2006, WHO published their first malaria treatment guidelines, which recommended ACTs as the first-line therapy for uncomplicated *P. falciparum* malaria. However, the nascent ACT market encountered several challenges, or *market shortcomings*, that needed to be addressed in order to scale up access to ACTs.

First, prior to the publication of the WHO treatment guidelines, the number of *quality-assured* products available to procurers was limited. Quality assured refers to those that have been approved through the

WHO PQP or by an SRA. A product needs to be quality assured through one of these channels before it is eligible for purchase with international donor funding. Specifically, in 2005 there was only one WHO prequalified product on the market (AL, Coartem®, manufactured by Novartis) (30). In 2005, Coartem® accounted for 100% of ACTs delivered by the donor-funded market in the public sector (6). While a prequalified ACT was available, its affordability was also a barrier to adoption and widespread use. Specifically, the cost of ACTs was 10–40 times higher than that of older first-line treatments such as QN and SP (44). This price differential was particularly problematic because a large proportion of antimalarial treatments is purchased by patients in endemic countries through private vendors (44). In addition, the higher cost of ACTs limited the number of treatment courses that could be supported with international funding. External financial support for malaria control was less than US\$ 100M in 2000 and increased to US\$ 393M in 2005, dramatically lower than the over US\$ 1.5 billion/year from 2009 onwards (45). The cost of ACTs hindered their uptake in the public sector and across private channels, limiting the *delivery* of ACTs throughout both sectors. Another key delivery issue was ensuring a sufficient supply of the artemisinin raw ingredient needed to produce the APIs used in ACTs. Artemisinin is derived from the plant *Artemisia annua* and is subject to a long and complex agricultural supply chain that cannot respond rapidly to sudden changes in demand (44). Ensuring a consistent and stable supply of artemisinin is, therefore, an important prerequisite to any scale-up efforts. An overview of the artemisinin market is provided in Section 5.8.

Artemisinin was found to have a very rapid action against *P. falciparum*, with the vast majority of acute patients treated showing significant improvement within one to three days of receiving treatment. However, use of artemisinin on its own (not in combination with other antimalarial medicine) raises the risk of parasites developing resistance (33). Using the more expensive combination therapies to avoid resistance has a positive externality to the society as a whole, but it is the purchaser who bears the costs (in higher prices for ACTs as compared to other antimalarial medicines) for these positive externalities.

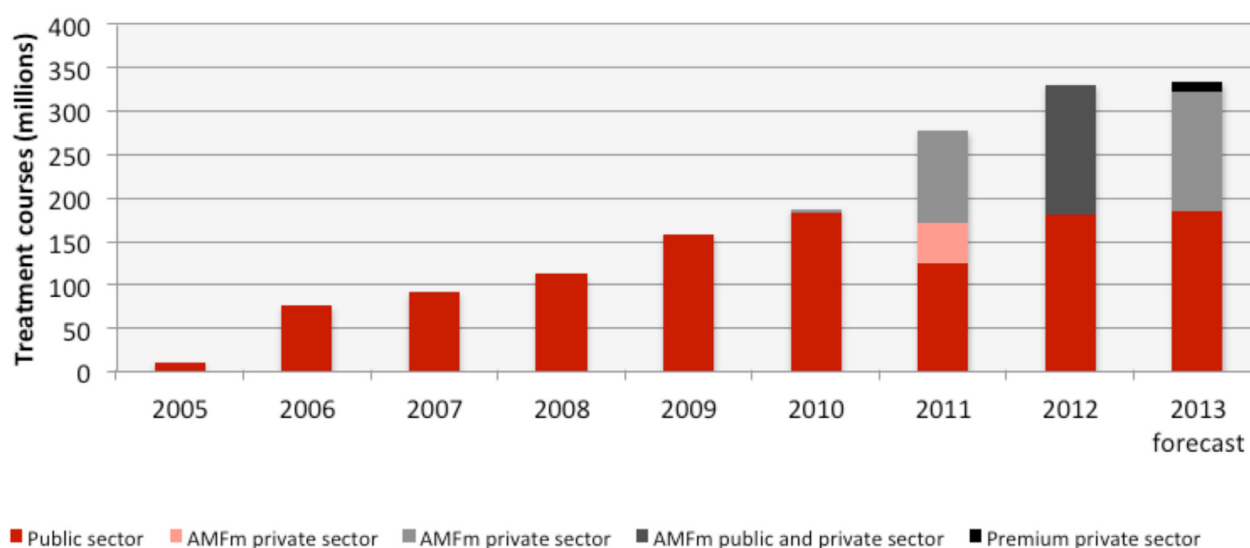
A further market challenge was the *acceptability* and *adaptability* of ACTs, namely the lack of availability of suitable formulations such as FDCs. FDCs were only available for AL, and other ACTs such as ASAQ, ASSP and ASMQ were only available in co-blistered packs (46). FDCs are preferred to co-blistered ACTs because of the benefits they offer with patient compliance and delayed development of parasite resistance. In addition, formulations suitable for use in young children, such as dispersible tablets, were not available (30). Finally, the more complex dosing regimen of ACTs compared to traditional therapies such as CQ and SP made ACTs more susceptible to compliance issues. For instance, AL is taken twice a day for three days as compared with SP, which is a single dose taken for one day (47).

### 5.2 Evolution of ACTs in the last decade

Since 2006, considerable efforts have been made to scale up access to ACTs and to respond to the market shortcomings detailed above. Through substantial international efforts to scale up ACTs, the volume of procured quality-assured ACTs has increased rapidly over time, from 11M treatment courses in 2005 to 76M in 2006, 278M treatment courses in 2011 and reaching 331M in 2012 (Figure 7).<sup>5</sup> It is estimated that ACT deliveries will decline from a peak of 331M treatment courses in 2012 (World Malaria Report, 2013), to 319–334M treatment courses in 2013 (Demand Forecast for Artemisinin-based Combination Therapies (ACTs) in 2013-2014. Q2-2013 Update (unpublished draft), 2013). In parallel to international efforts, national policy adoption by endemic countries also has increased whereby the end of 2011, 79 of the 88 countries with endemic *P. falciparum* had adopted national treatment policies listing ACTs as the first-line treatment (3).

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5 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 7: ACT deliveries, by health sector and initiative status, 2005–2012, and forecast 2013**

Note: Breakdown of figures to disaggregate AMFm public sector and AMFm private sector deliveries for 2012 was not available at the time of publication but will be included in the next update.

Sources: WMR 2013<sup>6</sup> and Demand forecast for artemisinin-based combination therapies (ACTs) in 2013–2014, Q2-2013 update (unpublished draft). Estimates for 2013 represent upper limit of the range forecasted.

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

### **International donor funding**

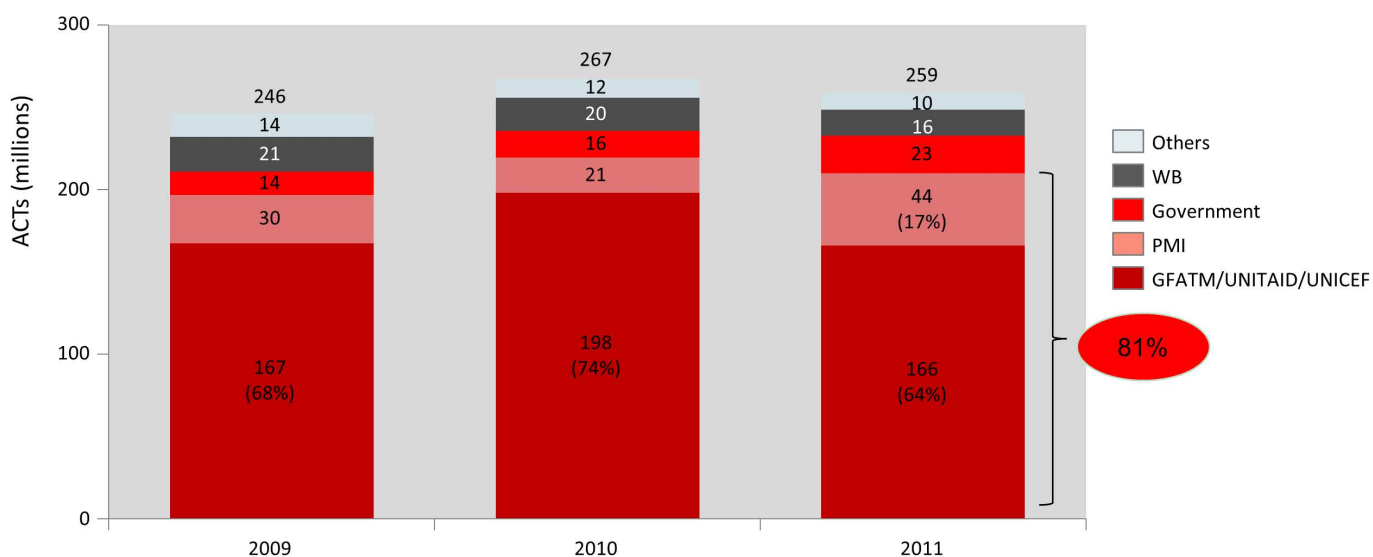
External expenditure on malaria control has expanded over the past 10 years, with international disbursements rising steeply from less than US\$ 100M in 2000 to US\$ 1.94 billion in 2012 and an estimated US\$ 1.97 billion in 2013 (11). The GFATM has been the biggest source of malaria control funding, accounting for approximately half of disbursed funds in 2008, approximately 40% in 2011 and 50% in 2013 (11). International disbursements have slowed in recent years where funding has increased at around 4% per year from 2009–2013 compared to an increase average of 43% per year between 2005–2009 (11). While GFATM disbursements likely will be reduced with its New Funding Model (NFM) that will provide funding for the years 2014–2016, these reductions are predicted to be offset by disbursements from the United Kingdom Department for International Development (DFID), PMI and increased funding from the Canadian International Development Agency (11). Pending GFATM decisions on Phase II renewals, NFM early applicants and NFM interim applicants likely will have an impact on future procurement, but to what extent is still unclear (11).

Most malaria donor funding has gone to sub-Saharan Africa and mainly has been allocated towards malaria prevention (42%) and treatment (31%) (45). The donor community is responsible for purchasing the majority of ACTs in Africa (Figure 8), 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

<sup>6</sup> 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.

GFATM and PMI. A large number of countries rely on GFATM financing for procuring ACTs and public sector procurement using GFATM grants contributes to more than one third of the global ACT market (49).

**Figure 8: Number of ACTs procured in Africa per funding entity**



WB = World Bank

Sources: Image adapted from the BCG medicines market landscape (unpublished). ACT RDT scale-up assessment. MMV RBM report, October 2009.

### 5.3 UNITAID and scaling up ACTs

UNITAID strategic funding towards specific interventions, together with constructive engagement with the international community, has been instrumental in supporting the scale-up of quality-assured ACTs. By 2012, over 315M ACT treatment courses had been delivered through UNITAID support (50).

#### Inclusion of ACTs in the WHO PQP

Strengthening the prequalification of antimalarial medicines has been an important instrument in enabling national governments and the donor community to purchase high-quality medicines that both effectively treat malaria and prevent the emergence of resistance. To date, WHO has prequalified 29 products from 8 manufacturers with various combinations and formulations; 23 of these are prequalified ACTs, which is a marked increase from one prequalified ACT (AL, Novartis) in 2005 (30). There are a further 11 ACT products currently under assessment by the WHOPQP (31). UNITAID has been an active supporter of the WHO PQP, allocating US\$ 47M to the programme from 2008 to 2012 (51).

#### Public sector ACT scale-up initiatives

Working closely with the GFATM and United Nations Children’s Fund (UNICEF), UNITAID has invested in the scale-up of ACTs through strategic market-based projects. ACT Scale-Up was a project aimed at decreasing delivery lead times and preventing ACT stockouts, increasing the number of quality manufacturers and products, and achieving a continuous supply of ACTs. UNITAID committed US\$ 78.9M from 2006 to 2011 for purchase and scale-up of ACTs. By December 2011, 34.5M treatment courses had been delivered through ACT Scale-Up.

UNITAID also provided support to the GFATM Round 6, Phase 1 project that was specifically aimed at financing ACT purchases. UNITAID committed US\$ 21.5M towards ACT deliveries through this project between 2007 and 2010. UNITAID support to this project facilitated the delivery of 2.8M treatment courses in 13 countries by the end of 2011 (51).

### **AMFm**

AMFm is 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 (23). It 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 GFATM, AMFm was launched as a pilot in eight countries in 2010. AMFm has three components: facilitating price reductions through negotiations with ACT manufacturers; implementing a buyer subsidy “co-payment” at the top of the global supply chain; and supporting interventions that promote appropriate use of ACTs (23). Only WHO prequalified or SRA-approved ACTs are eligible for procurement through this programme. The GFATM negotiates with quality-assured manufacturers to reduce the price of ACTs and has set a requirement with manufacturers that sales prices must be the same for both public and private first-line buyers (52). 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 sectors in 2012 (11). Through AMFm innovative price subsidy co-payment, ACTs have been made available in the private sector at a lower price in the following eight endemic countries: Cambodia; Ghana; Kenya; Madagascar; Niger; Nigeria; Tanzania; and Uganda. Through the AMFm negotiations with manufacturers, private importers now pay up to 80% less than they did in 2008–2009, and through the supporting interventions component, ACT awareness and use has increased. In particular, programmes where the subsidy worked alongside supporting interventions have been effective in rapidly improving availability (52).

Funding for AMFm has been directed to two arms of the programme. Approximately US\$ 336M has been contributed to a co-payment fund (52). UNITAID is the primary funder of this fund, contributing US\$ 180M to the programme between 2006 and 2011 (51). This fund also is financed by Canada, the United Kingdom and the Bill & Melinda Gates Foundation. Funds have been accrued to the amount of US\$ 127M from existing GFATM malaria grants directed at support interventions at the local level in AMFm pilot countries. This funding has subsidized over 300M treatment courses, and UNITAID investment between 2010 and December 2011 had contributed to the delivery of 151.8M ACT treatment courses (52), (51).

In November 2012, the GFATM Board decided to integrate AMFm into core GFATM grant management and financial processes following an orderly transition period in 2013 (53). This means that as of 2014 AMFm will be included in the GFATM indicative funding, rather than as a supplement to grants. Funding for the transition of AMFm will come from UNITAID and DFID (52), however, an approach for 2014 still needs to be defined. Future grants from the next replenishment are not likely to be available until the end of 2014, which could impact the future demand of ACTs. The GFATM is expected to provide more information about its updated Procurement and Supply Management plans and how the underlying mechanism will change going forward. The longer-term impact this will have on private sector availability and price and, therefore, ACT access, is still to be determined and needs to be closely monitored to identify opportunities to improve market dynamics by assuring supply.

### **A2S2**

A2S2 was launched in mid-2009 as a mechanism to support the global production of sufficient artemisia/artemisinin to meet the expanded need for ACTs, specifically following the introduction of AMFm and increased GFATM supplies (54). A2S2 provides market intelligence on the artemisinin supply to improve stability in the market. UNITAID, the programme funder, has committed US\$ 9.2M to A2S2 (51). Since inception of the project, 36 metric tonnes of the plant artemisinin (15% of global demand) have been secured by brokering contracts between growers and extractors to produce ACTs (54).



### Artemisinin and ACT Demand and Supply Forecasting

Funded and coordinated by UNTAID, the Artemisinin and ACT Demand and Supply Forecasting project brings together forecasters originally working under the RBM umbrella in an effort to produce a single ACT forecast that can be used by the malaria community (48). Quarterly demand forecasts are coordinated by UNTAID to inform policy-makers and market participants. These ACT forecasts are produced by the ACT forecasting consortium, which includes the Boston Consulting Group (BCG) and its partners—CHAI and the Fundacion Zaragoza Logistics Center (MIT-Zaragoza). The consortium is overseen by a steering committee that includes representatives from AMFm, GFATM, MMV, RBM, UNTAID and WHO. UNTAID has invested around US\$ 1M to this project over four years (51).

## 5.4 Current ACT market

### 5.4.1 Market size

Three major delivery channels determine the overall market size for ACTs: the public sector (including the AMFm public sector procurers); the AMFm private sector; and, to a lesser extent, the premium private sector (unsubsidized not engaged with AMFm). Prior to AMFm, ACT volume delivery data were largely limited to the public sector. Reference to ACTs throughout this section refers to prequalified ACTs unless otherwise stated.

#### 5.4.1.1 Market size by volume

##### 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 187M treatment courses in 2010 (Figure 7). Public sector ACT volumes decreased from 187M treatment courses in 2010 to 172M in 2011, with 27% of 2011 volumes delivered by the AMFm public sector (46M) (World Malaria Report, 2012). Despite the decrease in public sector deliveries in 2011, overall delivery volumes increased due to the deliveries made through the AMFm private sector. Between 2011–2012 public sector deliveries increased by around 50% (approximately 181M treatment courses were procured by the public sector), whereas during that time the AMFm public sector volumes decreased (World Malaria Report, 2013).<sup>7</sup>

##### Market size of the donor-funded private sector

It is estimated that 40% of malaria patients worldwide seek treatment in the private sector, making this an important source of treatment of malaria in many countries (55). The primary mechanism for donor intervention in the private sector antimalarial market is AMFm. Of the total number of ACT treatment courses delivered in 2011, approximately 40% (160M) were delivered by the AMFm private sector (Figure 7) (6). In 2012, volumes of procured ACTs delivered by the AMFm private sector were similar to the volume of treatment courses procured in 2011, however an estimate number of volume deliveries for 2012 is not available at this point in time, but will be included in the next landscape update. Engaging the private sector, however, remains problematic because of higher ACT prices that are often prohibitive compared to less effective monotherapies (2). While the AMFm private sector volumes (around 160M) represent a substantial proportion of ACTs delivered, they represent a small proportion of the total private sector market that was estimated to be 655M in Africa alone in 2010 (2). This is due to the fact that up until 2013, AMFm has only been a pilot in a small number of countries. Overall ACT penetration in the private sector remains limited, and has been inhibited by prices that are higher than monotherapies and are often unaffordable. These issues are discussed in more detail in Section 5.4.2 and Section 5.4.3.

##### Market size and comparison with need

National malaria control programmes (NMCPs) play a major role in the distribution of ACTs, and data collected from these programmes can provide estimates on how globally procured ACT volumes are meeting

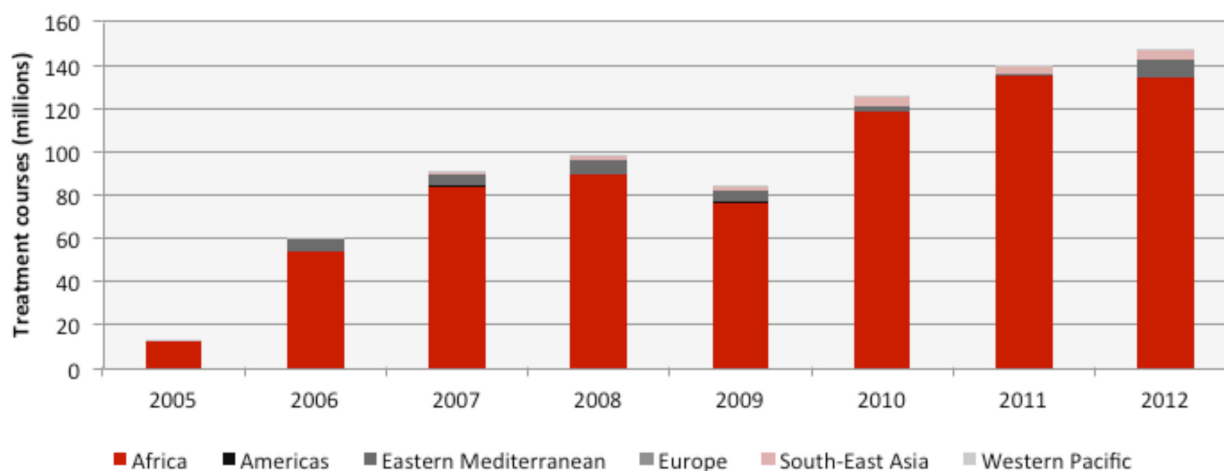
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<sup>7</sup> Breakdown of figures to disaggregate AMFm public sector and AMFm private sector deliveries for 2012 was not available at the time of publication but will be included in the next update.



the demand in the public sector. NMCPs distributed approximately 13M ACT treatment courses in 2005 and the African Region accounted for 95% of them (Figure 9) (11). The volumes that NMCPs distributed increased to 147M ACT treatment courses in 2012 (11). The African Region again accounted for the greatest number of ACTs distributed globally by NMCPs (134M). (11).

**Figure 9: Number of ACT treatment courses distributed by NMCPs, by WHO region, 2005–2012**



Source: WMR 2013.

### Delivery and demand in the overall private sector

The overall demand for 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 (2). One study estimates that in 2010, 655M antimalarial treatments were delivered through the private sector in Africa, compared to 174M estimated malaria cases (2). Together with a substantial public sector market, the total annual demand for antimalarials could possibly exceed one billion treatment courses (2).

### Forecasted market volume trends of donor-funded ACTs

For 2013 and 2014 actual delivery volumes are still to be determined. While in 2012 there was an increase in ACT treatment courses procured from 2011, (Figure 7), donor-funded ACT deliveries are expected to decrease in 2013, to approximately 319–334M treatment courses (48). The public channel remains the largest driver of orders for QAACTs in 2013, with projected orders for 170–186M treatments. In the donor-funded private channel (i.e. AMFm), approved orders are forecasted to reach at least 137M treatments in 2013 (48).

Looking ahead to 2014, there is significant uncertainty around procurement levels for QAACTs stemming from several factors:

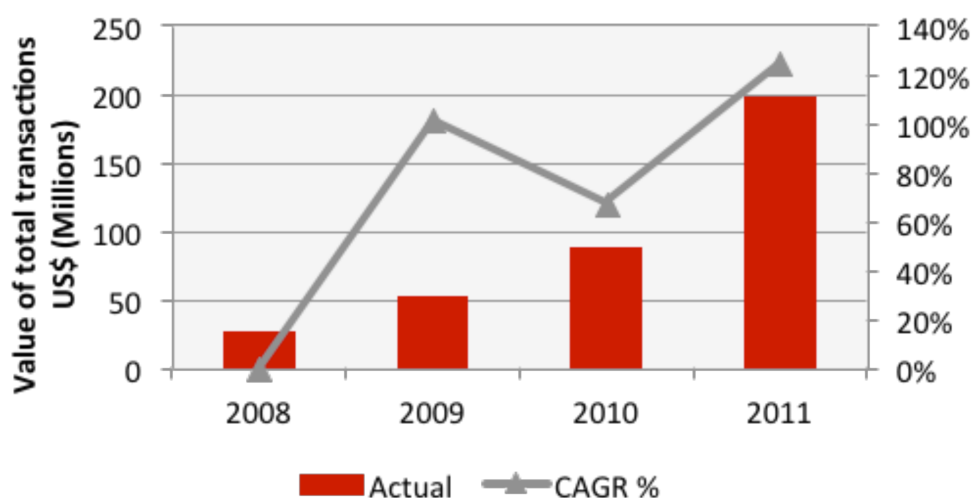
- the effect of AMFm being integrated into the GFATM *indicative funding* on private sector ACT procurement;
- the effect of the GFATM NFM on overall procurement volumes;
- the effect of the level of replenishment on future GFATM grants and the timing of when these funds will become available.

### 5.4.1.2 Market size by value

#### Market value of donor-funded ACTs

While the total value of donor-funded ACTs is unknown, data from the GFATM 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 this data, the value of all ACTs (AL, ASAQ, ASMQ, ASSP 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 2011 of a total market value of more than US\$ 200M (Figure 10).<sup>8</sup> This represents a compound annual growth rate (CAGR) of 96% between 2008 and 2011.

**Figure 10: CAGR of the value of the prequalified ACT market, 2008–2011**



Notes: The figures represented are indicative of all ACTs and all pack-types procured via GFATM and AMFm from 2008 to 2012. This includes: AL, ASAQ, ASMQ, ASSP and DHA PPQ

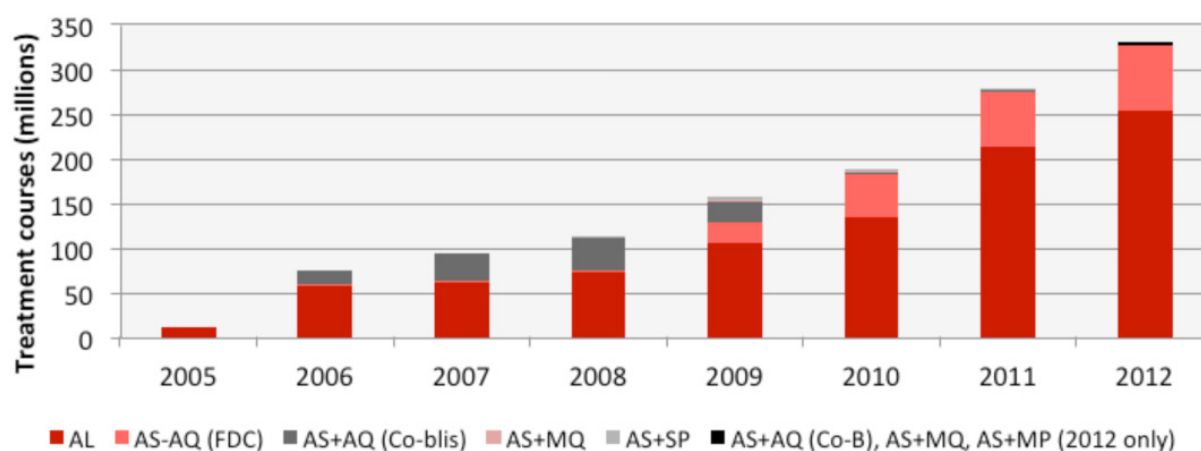
Sources: Calculated from transactions reported in GFATM PQR data and AMFm data.

### 5.4.2 Market share

#### 5.4.2.1 Donor-funded market share by product

The market share of ACT volumes procured in the donor-funded market is highly concentrated on two ACTs—AL and ASAQ—which accounted for 77% (255M treatments) and 22% (73M treatments) of ACTs delivered in 2012, respectively (Figure 11) (11). For this reason, analysis of the market share in the donor-funded market is focused on these two ACTs unless otherwise stated. Data analysed in this section have been obtained from the WMR 2013, which represents procurement trends and transactions of prequalified ACTs in the international donor market. Data also have been gathered from the PQR and AMFm databases in order to obtain additional product and brand-specific information such as market share of AL and ASAQ between manufacturers and average procurement prices. While this does not represent complete volumes procured by the international community (for example, PMI delivers substantial volumes of ACTs every year), it does represent a substantial proportion (86% in 2011) and can provide insights into overall trends. Refer to Section 2 for details on the estimated coverage of the donor-funded market represented in the following analyses.

<sup>8</sup> The value of the donor-funded ACT market has been estimated using the merged results from the GFATM PQR AMFm database.

**Figure 11: ACT deliveries to the public and private sector, 2005–2012**

AL = artemether-lumefantrine; AQ = amodiaquine; AS = artesunate; MQ = mefloquine; SP = sulfadoxine-pyrimethamine; Co-blis = co-blistered packs; FDC = fixed-dose combination

Source: WMR 2013.

#### 5.4.2.2 Donor-funded market share by product and manufacturer

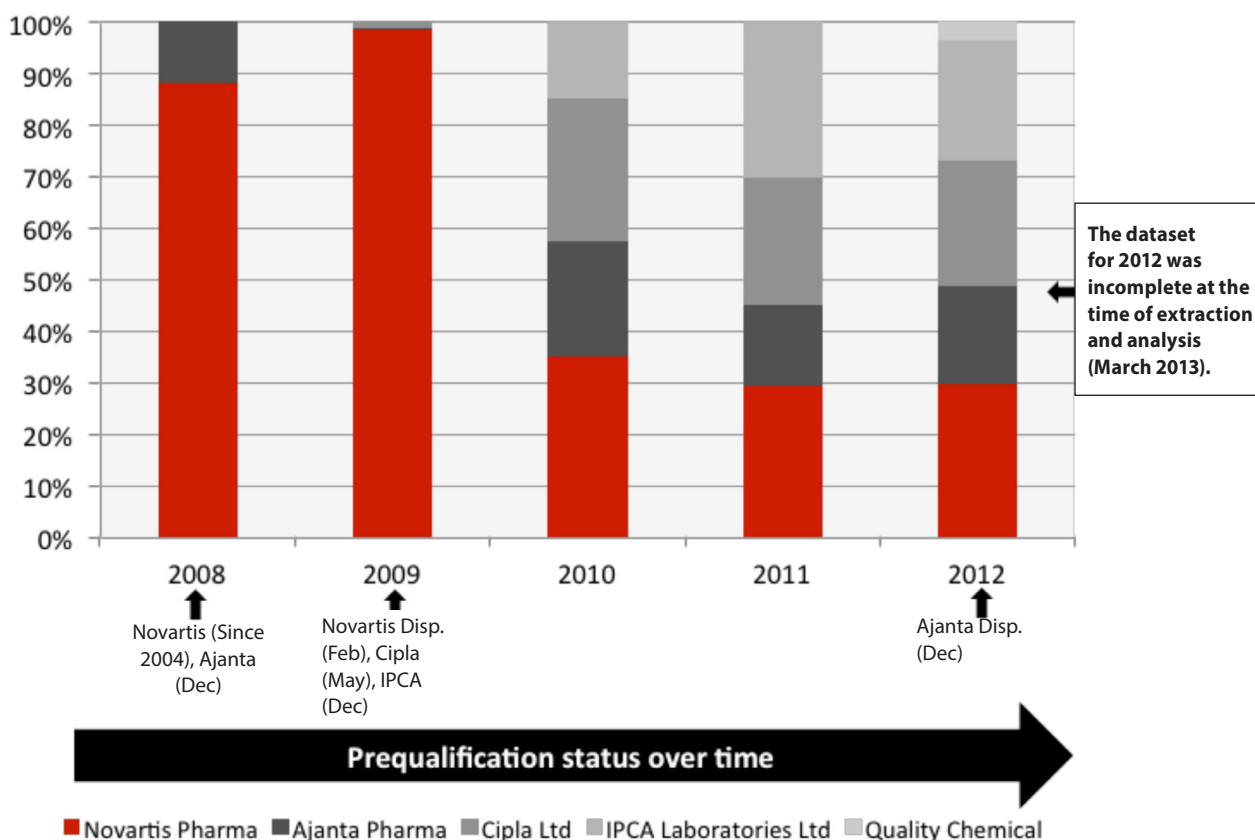
There are currently eight manufacturers that produce prequalified ACTs. Data from PQR and AMFm show that since 2008 the proportion of donor-funded procurement volumes purchased from generic manufacturers has been growing. In 2012, generic medicines accounted for 57% of total AL and ASAQ donor-funded procurement volumes.

As more manufacturers have received prequalification, there has been an increase in market entrants and the market share has changed, however, both AL and ASAQ markets are still highly concentrated by a few manufacturers.

In 2008, Novartis accounted for the greatest share of AL (88%) procured in the donor-funded market (Figure 12). Between 2008 and early 2009, only Novartis and Ajanta had AL products prequalified and, therefore, available for donor procurement.<sup>9</sup> By 2012, three generic manufacturers, Ajanta Pharma, Cipla Ltd and IPCA Laboratories, together had secured 67% of the AL market procured by international donors (or 19%, 24% and 24%, respectively), compared to 30% for Novartis.

<sup>9</sup> It is important to note that the Novartis child-friendly dispersible FDC became available for international purchasing in 2009. Until recently, Novartis has been the only manufacturer with a quality-assured dispersible formulation of AL. The relationship between child-friendly formulations and the ACT market is explored further in Section 5.6.

Figure 12: Market share by volume of AL by manufacturer, 2008–2012

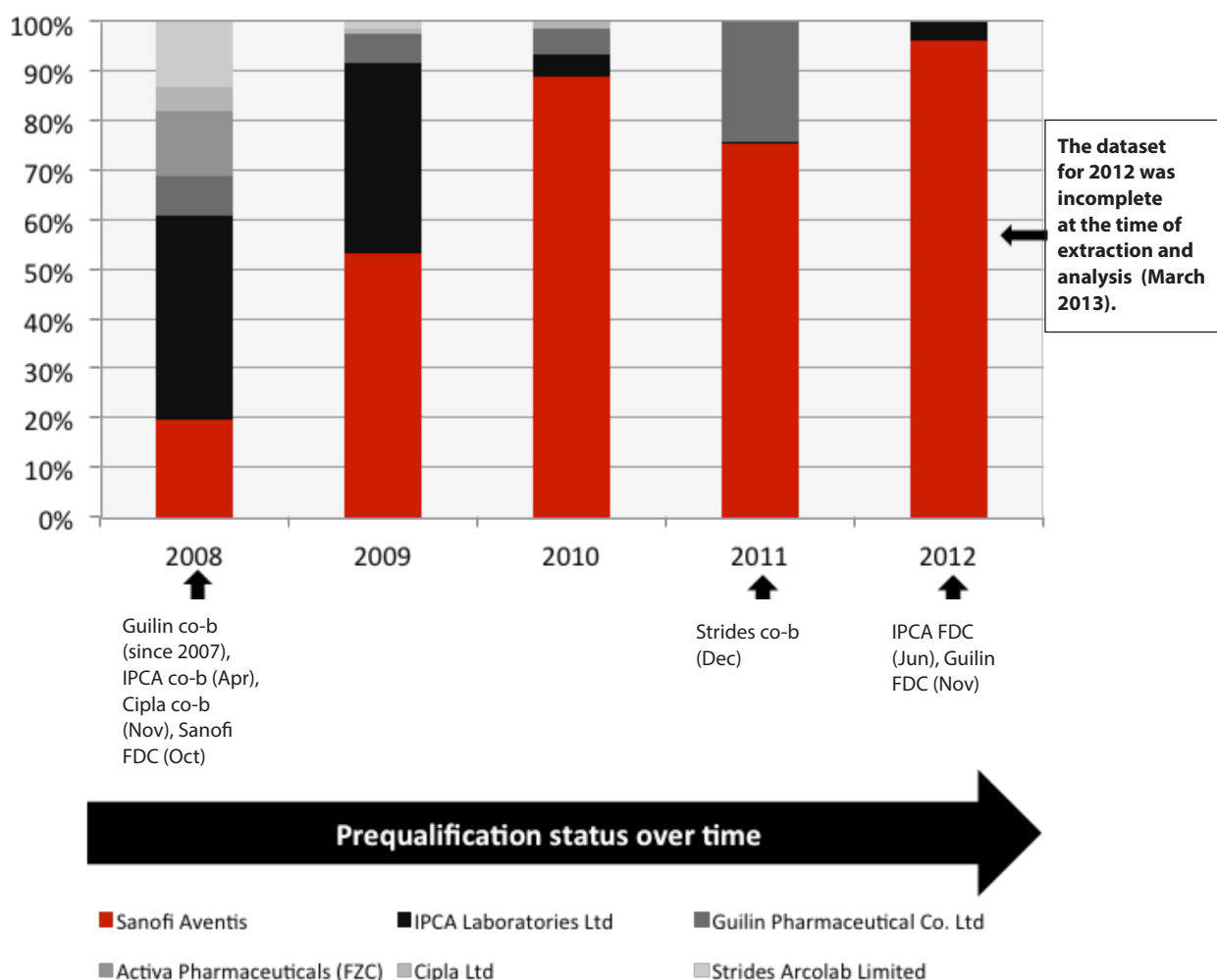


Disp = dispersible tablets

Sources: Calculated from transactions reported in GFATM 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, manufactured by Sanofi. In 2008, the Sanofi co-blistered product only accounted for 20% of total ASAQ treatment courses procured by international donors, while the IPCA Laboratories co-blistered product accounted for the greatest proportion (41%) (Figure 13). Following prequalification of the Sanofi FDC ASAQ in October 2008, its market share has grown substantially. In 2012, Sanofi accounted for approximately 96% of volumes procured, and only one other manufacturer, IPCA Laboratories, received purchases from donors. Between June and November 2012, six more FDC ASAQ have become prequalified from two manufacturers (IPCA and Guilin). This is likely to have an impact on the market of ASAQ suppliers in the future.

Figure 13: Market share by volume of ASAQ by manufacturer, 2008–2012

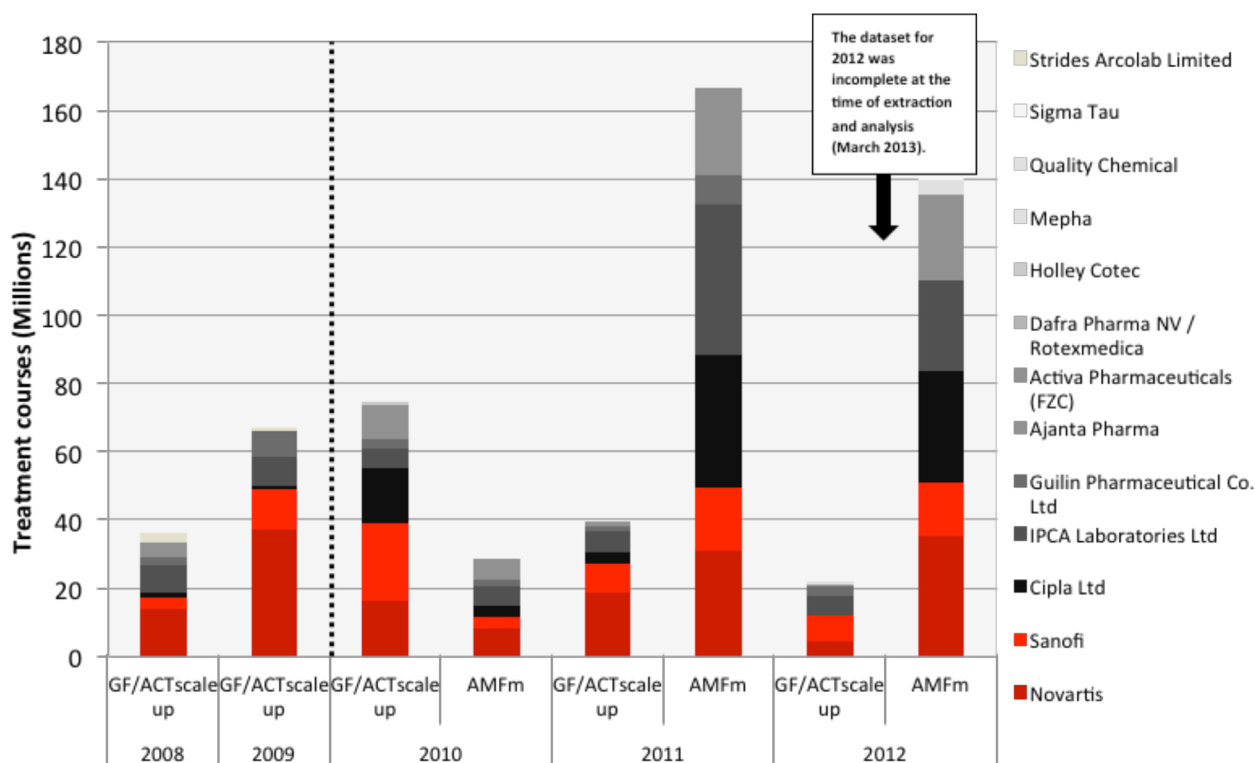


co-b = co-blistered, FDC = fixed-dose combination

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

#### 5.4.2.3 AMFm impact on global market share of ACT manufacturers

The availability of prequalified generic medicines, together with increased donor-funded procurement volumes, have resulted in an increase in the market share of generic companies. When looking at all ACTs (AL, ASAQ, ASMQ, ASSP, DHA + PPQ) procured through the GFATM and AMFm since 2008, total volumes of generic medicines procured have increased over time (Figure 14). In 2008, originator brands and generics represented 49% and 51% of the volumes procured through the GFATM, respectively. Over time, market share of generics has decreased: in 2010 and 2011, generics accounted for 47% and 30% of total volumes, respectively. Conversely, the proportion of generic medicines purchased through AMFm has been substantially greater than originator brands (e.g. 59% of total volumes in 2010 and 70% in 2011). Overall, in 2011, generics procured through AMFm accounted for 57% (116M) of the total number of ACTs (originator brands and generics) procured through the GFATM and AMFm.

**Figure 14: Market share of manufacturers procured by GFATM and AMFm, 2008–2012**

GF = GFATM

Notes: Includes all ACTs available for procurement in the donor-funded market: AL, ASAQ, ASMQ and ASSP. Originator medicines are in red and generic medicines are in grey.

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

#### 5.4.2.4 Concentration of competition

Efforts to bring more manufacturers into the quality-assured ACT market have increased competition in the donor market and seem to have diluted the concentration of manufacturers in the market. The Herfindahl Index is a concept applied to measure the size of a company in relation to the overall size of the industry and, therefore, the level of competition between companies in that given industry. It can indicate whether an industry is highly competitive (below 0.01%), unconcentrated (below 15%), moderately concentrated (between 15–25%) or highly concentrated (above 25%). Using this index, the donor-funded ACT market over the last five years has had a moderate concentration of competition, ranging from 19–37%, and the number of competitors in the market has been increasing since 2009 (Table 7).

The Four-Firm Concentration Ratio (FFCR) is the percentage of the market share held by the four largest firms in an industry. It can be used to show the extent of control of the largest firms in the ACT market and illustrate the degree to which it is oligopolistic. The FFCR depicts whether an industry has no concentration (0%, i.e. the four largest firms in an industry do not have any significant market share) to total concentration (100%, i.e. there is a monopoly in the industry). The FFCR is divided into the following concentration levels: low (0–50% ranging from perfect competition to oligopoly); medium (50–80% indicating a likely oligopoly in the industry); and high (80–100% ranging from oligopoly to monopoly). When analysing the top four firms that accounted for the greatest volumes of procured ACTs combined in the donor market, the figures in Table 7 show that competition over the last five years in the ACT market ranges from an oligopoly to a monopoly (78–98% range). In 2009, Novartis had a near monopoly in the market that was probably a result of the dominant market share of AL at that time. Over time, however, their lead has declined. The four firms that had a predominate share of the ACT market between 2008 and 2009 were: Guilin Pharmaceutical Co. Ltd; IPCA Laboratories Ltd; Novartis Pharma; and Sanofi. By 2012,

the top four firms in the ACT market were: Ajanta Pharma; Cipla Ltd; IPCA Laboratories Ltd; and Novartis. This trend is aligned with AL having the largest market share of the donor market.

**Table 7: Competition dispersion of the ACT market, 2008–2012**

Year	Herfindahl Index <sup>a</sup>	FFCR <sup>b,c</sup>
2008	24%	78%
2009	37%	98%
2010	20%	84%
2011	20%	82%
2012	19%	81%

Note: Includes all ACTs available for procurement in the donor-funded market: AL, ASAQ, ASMQ and ASSP.

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 Pharmaceutical Co. Ltd, IPCA Laboratories Ltd, Novartis Pharma, Sanofi.

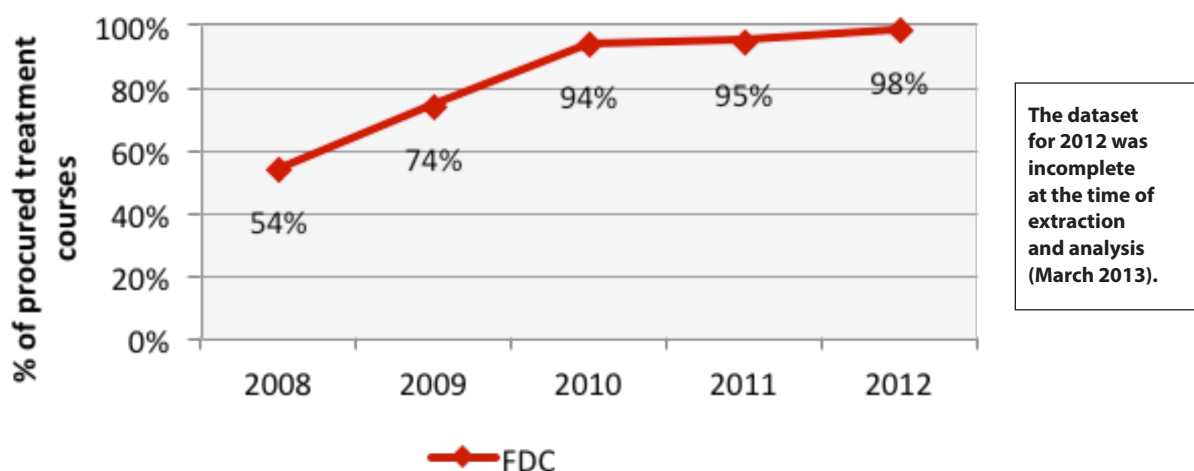
Sources: Calculated from transactions reported in GFATM PQR data and AMFm data.

Even though these indices show that competition technically is increasing, a corresponding trend has not been seen in decreasing pricing levels, where ACT 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 GFATM and AMFm (Section 5.4.3). Through AMFm, procurement prices were set through negotiations and not through a competitive tender (52). To negotiate with manufacturers, AMFm set maximum prices, that is, the prices at or below which manufacturers participating in AMFm must offer ACTs to first-line buyers (53). To be included in AMFm, the manufacturer sale price must be at or below the maximum price for a single full course of treatment, prior to application of the co-payment (52). This process potentially led to an aggregation around a certain price point. However, it is important to note that the most recent procurement transaction data from PQR are showing that prices are beginning to decrease and this will be investigated further in the updated landscape in 2014 (56).

#### 5.4.2.5 Fixed-dose combination and co-blistered formulation of ACTs

FDCs are recommended as the preferred ACT formulation wherever possible. FDCs improve patient compliance because of their simpler dosing regimen, making completion of an entire treatment course less burdensome. Considerable progress has been made in improving the accessibility of FDCs, especially as more prequalified FDCs have become available. Compared to 2006, when only one FDC ACT was available, there are now 18 products approved for procurement in the donor-funded market, in contrast to five ACT co-blistered packs (30). In 2008, FDCs accounted for 54% of the treatment courses procured in the donor-funded market (Figure 15). Now, they account for around 98% of the products procured, equaling an approximate 80% growth over five years.



**Figure 15: Percentage of treatment courses that was FDCs, 2008–2012**

Note: Includes all ACTs available for procurement in the donor-funded market: AL, ASAQ, ASMQ and ASSP.

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

#### 5.4.2.6 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 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 between 2009/10 and 2011 offer some insights into market share trends at the facility level from three non-AMFm countries (Benin, DRC and Zambia) and four AMFm countries (Kenya, Madagascar, Nigeria and Uganda).<sup>10</sup>

Despite efforts to scale up ACTs, nATs are still the most commonly distributed antimalarials in both public and private facilities in many endemic countries, and the market share of QAACTs is still low. In non-AMFm countries, the public sector is still the dominant distributor of QAACTs (Figure 16). For example, in Zambia, Benin and DRC, QAACTs represent 66%, 49% and 21%, respectively, of total antimalarial volumes in the public sector, compared to 6%, 17% and 3%, respectively, in the private sector. It should be noted that while the proportion of caregivers seeking treatment in the private sector is substantial in Benin (50%) and DRC (75%), it is significantly lower in Zambia (28%) (22). In AMFm countries, QAACTs represent a higher proportion of total antimalarial volumes in the private sector, ranging from 18% in Nigeria to 61% in Kenya.

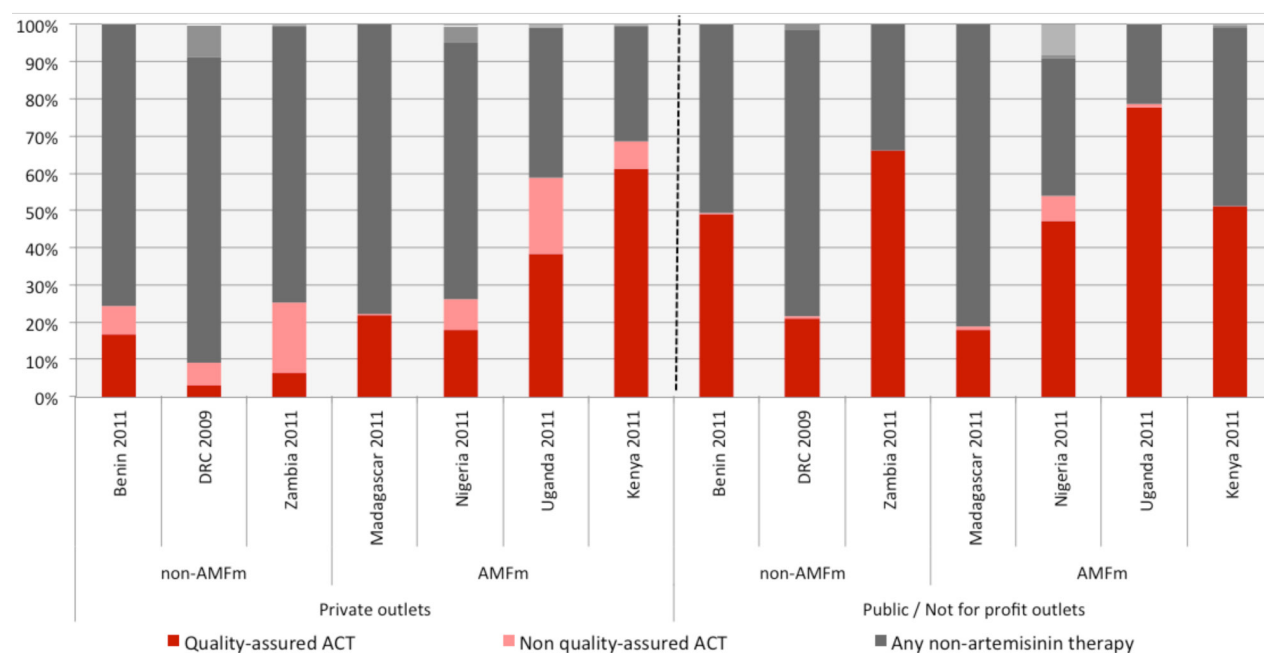
In private facilities outside of AMFm countries, nATs account for the largest proportion of antimalarial volumes distributed (e.g. 75% in Benin, 81% in DRC and 74% in Zambia). In AMFm countries, nATs dominated the proportion of volumes distributed in private outlets in Madagascar (78%) and Nigeria (69%), but in Kenya and Uganda, the proportion of nATs distributed in the private sector was low (31% and 40%, respectively). Out of the nATs distributed, SP accounted for the greatest proportion of volumes distributed in the public sector across seven countries (Benin, DRC, Kenya, Madagascar, Nigeria, Uganda, Zambia), and across five countries in the private sector (Benin, Kenya, Nigeria, Uganda, Zambia).

Crowding out oral AMTs is a core objective of AMFm (23). In AMFm countries, the market share for oral AMT was less than 1% across facilities in both sectors in Kenya, Madagascar and Uganda. In Nigeria,

<sup>10</sup> ACTwatch is a multicountry research project of Population Services International (2008–2012) conducted in seven malaria endemic countries: Benin, DRC 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).

however, the market share of oral AMTs distributed by private facilities was 4.4%. Also, according to the AMFm Independent Evaluation Report, oral AMT market share was somewhat higher at baseline and large and significant falls were observed in Nigeria (23). This likely could reflect a combination of the AMFm subsidy and complementary regulatory measures. In two non-AMFm countries, Benin and Zambia, the market share of AMTs was 0% in public facilities and less than 1% in private facilities. In the DRC, the share of oral AMTs distributed by private sector facilities was approximately 9%, and 1.6% for public facilities.

**Figure 16: Relative volumes of antimalarials distributed by sector, by drug type**



CQ = chloroquine; SP = sulfadoxine-pyrimethamine; QN = quinine; AQ = amodiaquine

Notes: Public/not-for-profit 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. Last survey round in the DRC was in 2009. Breakdown of nAT is representative of market share within that category.

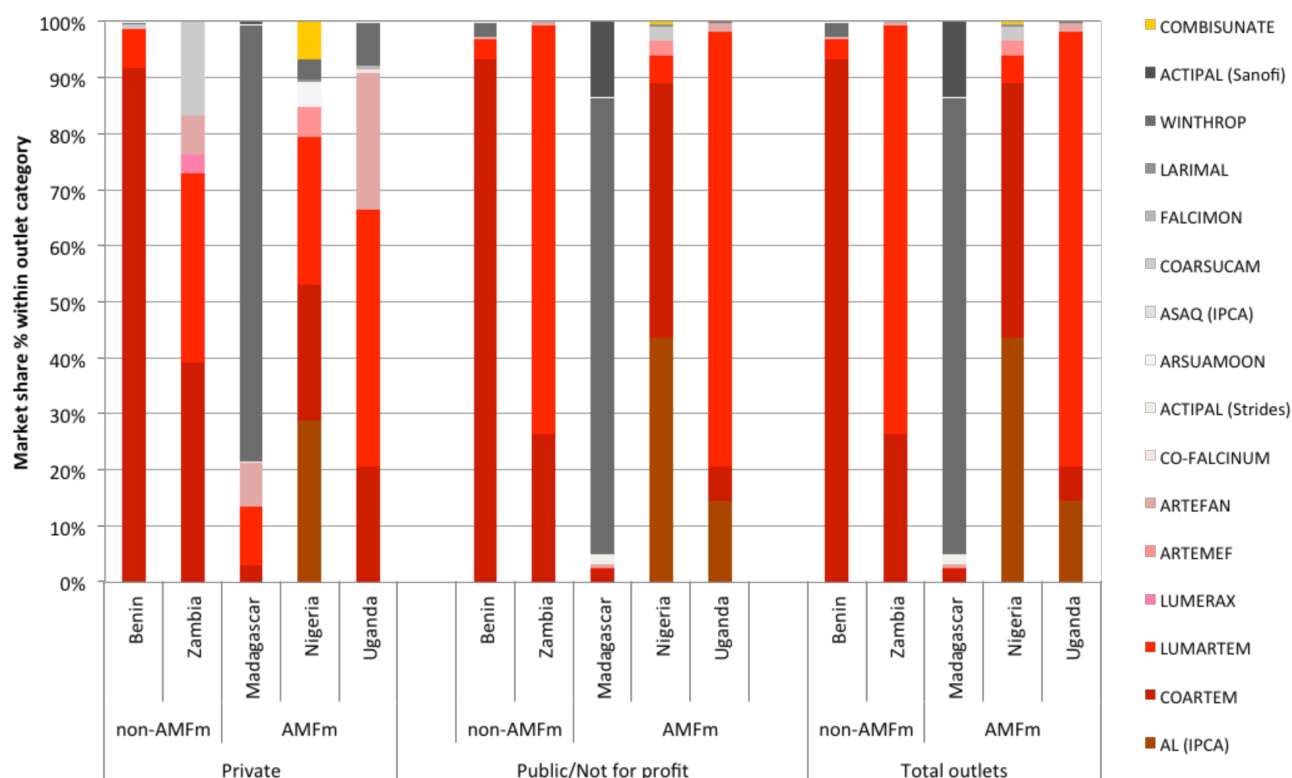
Sources: ACTwatch outlet surveys 2009/2010 and 2011.

#### 5.4.2.7 Market share of quality-assured ACTs distributed at the facility level by brand

Recent data from ACTwatch show that the market concentration of QAACT manufacturers in the donor market carries over to market share at the facility level. Specifically, the market share of QAACTs in country facilities<sup>11</sup> is highly concentrated by four products (Figure 17): Coartem® (Novartis-AL); Lumartem® (Cipla-AL); artemether-lumefantrine (IPCA Laboratories-AL); and Winthrop® (Sanofi-ASAQ). In Benin, 92% of QAACTs distributed by both the public and private facilities was Coartem®. Lumartem® accounted for the highest share of QAACT volumes distributed in Uganda (66%) and Zambia (72%) and, in Nigeria, AL produced by IPCA Laboratories accounted for 32% of the QAACT market share within both sectors, followed by Coartem® (28%) and Lumartem® (22%). In Madagascar, Winthrop® accounted for the greatest share of QAACTs distributed in both sectors (78%). This could possibly be attributed to the paediatric subsidy programme for ASAQ run by Population Services International. This programme has been operating in Madagascar since 2008 and medicine is distributed through community health workers and authorized retailers (23). Annex 3 provides further information on the relative market share of QAACT brands distributed between private and public outlets in 2011.

<sup>11</sup> Information available as 2011 for Benin, Madagascar, Nigeria, Uganda and Zambia.

**Figure 17: Relative market share of QAACT brands among all QAACTs sold/distributed within outlets in the past seven days, by sector, 2011**



Notes: Public/not-for-profit 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. Shades of red represent artemether-lumefantrine (AL) products, shades of grey represent artesunate-amodiaquine products and yellow (combisunate) represents artesunate sulfadoxine-pyrimethamine (ASSP).

Source: ACTwatch outlet surveys 2011.

### 5.4.3 Prices

#### 5.4.3.1 ACT procurement prices in the donor-funded market

The following section focuses on the procurement price of FDCs and co-blister adult-packs of ACTs purchased through the GFATM 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 PQR and AMFm. The retail price of ACTs, that is the price that ACTs are sold to patients, is discussed in Section 5.4.3.4.

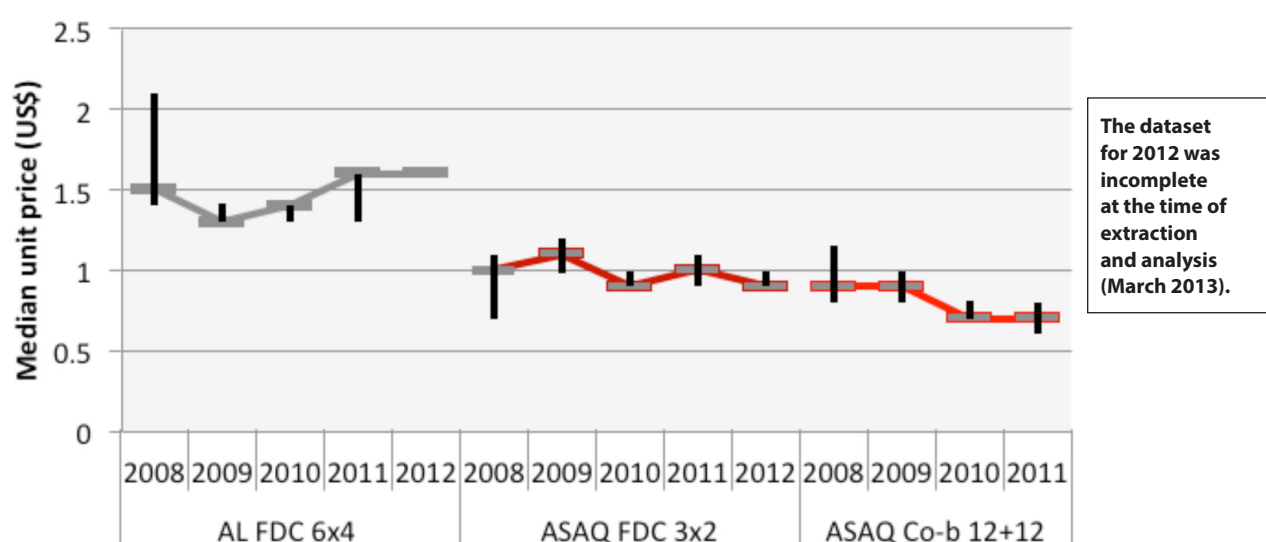
In light of the higher cost of ACTs relative to nATs, and in an effort to support scale-up efforts, some manufacturers have entered into partnerships with international organizations agreeing to provide ACTs at cost. For example, through the partnership of Sanofi and the Drugs for Neglected Diseases Initiative (DNDi), an agreement was reached to produce ASAQ at cost and without a patent (57); and, in 2001, Novartis entered into an agreement with WHO to make Coartem® available at cost to ministries of health in developing nations (49). This agreement allowed WHO to generate global demand forecasts, while providing Novartis with a four-month lead time on all orders (49).

Over the last five years, the median unit price of 6x4 AL slightly increased from US\$ 1.5 (US\$ 1.4–2.4) in 2008 to US\$ 1.6 in 2012 (Figure 18). The lowest median price of AL occurred in 2009, US\$ 1.3 (US\$ 1.3–1.4) 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.

The median price of FDC ASAQ has declined since first becoming prequalified in October 2008, from US\$ 1.0 (US\$ 0.7–1.1) in 2008 to US\$ 0.9 (US\$ 0.9–1.0) in 2012 (Figure 18). Until June 2012, Sanofi was the only prequalified manufacturer of FDC ASAQ. The median price of co-blister ASAQ also has declined since 2008 from US\$ 0.9 (US\$ 0.9–\$ 1.0) to US\$ 0.7 (US\$ 0.8–0.7) in 2011. Therefore, in 2011, the median price of co-blister adult-packs was US\$ 0.04 less than the equivalent FDC, however, as shown in Figure 11, the market share of co-blister ASAQ was minimal in that year. When comparing the median price of FDC ASAQ to AL in 2012, the ASAQ price was US\$ 0.7 lower (US\$ 0.9 for ASAQ versus US\$ 1.6 for AL).

It is important to note that the most recent procurement transaction data from PQR are showing that prices are beginning to decrease and this will be investigated further in the updated landscape in 2014 (56).

**Figure 18: Median treatment course price of AL 6x4, ASAQ co-blister 12+12 and FDC 3x2 procured by international donors, 2008–2012**



FDC = fixed-dose combination; Co-b = co-blister

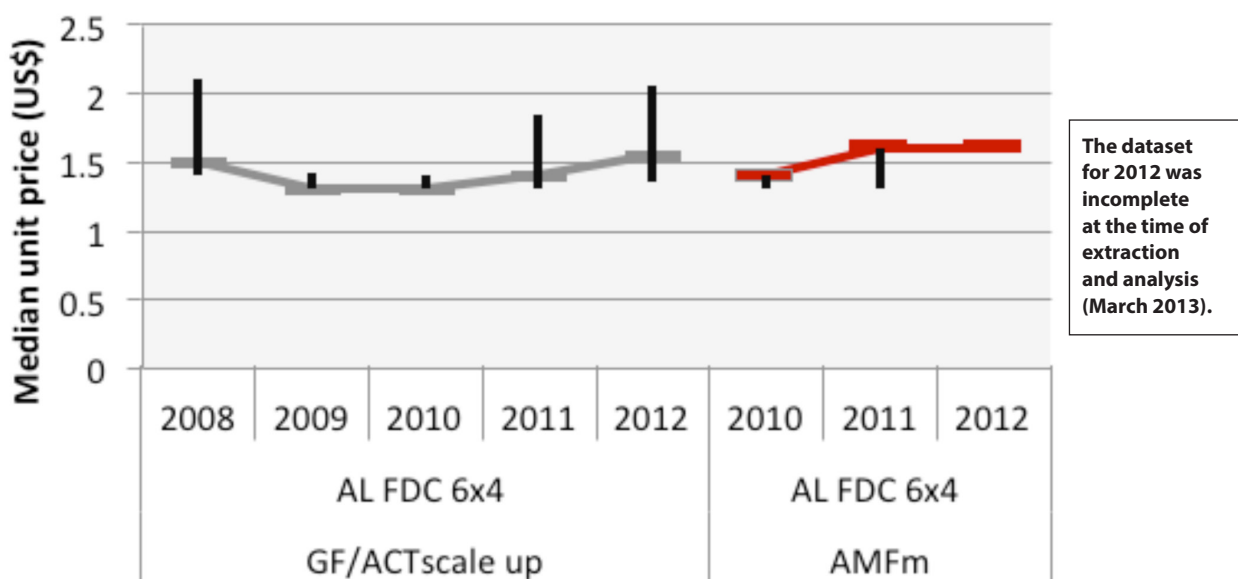
Notes: 6X4 FDC AL are adult-pack sizes, >35 kg, and account for around 50% of all ACTs procured in this market. FDC ASAQ 3x2 and co-b 12+12 are adult-pack sizes and account for approximately 38% of this market. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quantile. The horizontal line is the median value.

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

#### 5.4.3.2 ACT procurement prices, comparison between the GFATM and AMFm

The following prices represent AMFm *pre-subsidized* prices and reflect sales to both public and private channels, whereas the GFATM transactions are solely with the public sector. The median GFATM price of adult-pack AL has been lower than that of AMFm since Phase 1 commenced (Figure 19). The median GFATM price of adult-pack AL was US\$ 1.3 (US\$ 1.3–1.4) in 2010, US\$ 1.4 (US\$ 1.3–1.84) in 2011 and US\$ 1.55 (US\$ 1.35–2.05) in 2012. The median AMFm price of adult-pack AL was US\$ 1.4 when the programme started in 2010, and has increased to US\$ 1.6 in 2011 and 2012. Based on currently available data, by 2012, the difference between the procurement price of AL through the GFATM and AMFm was approximately US\$ 0.05.

**Figure 19: Median unit price of AL 6x4, AMFm and GFATM, 2008–2012**

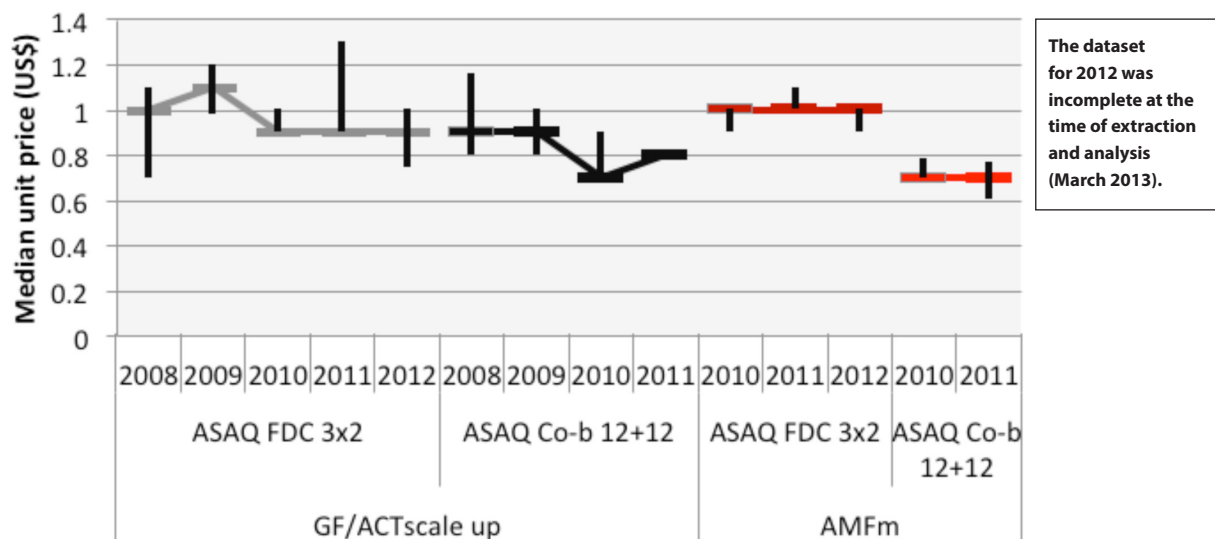


Notes: AMFm prices are pre-subsidized prices. 6X4 FDC AL are adult-pack sizes, >35 kg, and account for around 50% of all ACTs procured in this market. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quantile. The horizontal line is the median value.

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

The same trends seem to have occurred for FDC adult-packs of ASAQ, where the median GFATM price was US\$ 0.9 between 2010 and 2012, compared to US\$ 1.0 for AMFm during the same period (Figure 20).

**Figure 20: Median unit price of ASAQ FDC 3x2, co-blister 12+12, AMFm and GFATM, 2008–2012**



Notes: FDC = fixed-dose combination; Co-b = co-blistered. FDC ASAQ 3x2 and co-b 12+12 are adult-pack sizes and account for approximately 38% of this market. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quantile. The horizontal line is the median value.

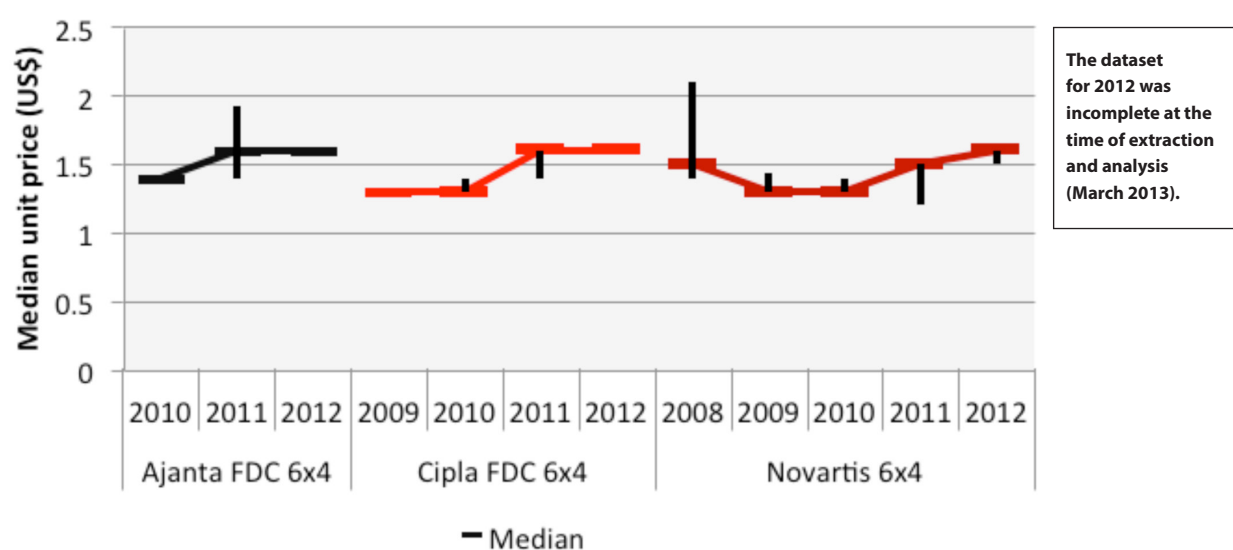
Sources: Calculated from transactions reported in GFATM PQR data and AMFm data.

**5.4.3.3 ACT procurement prices, variation by individual manufacturer**

Data from the GFATM and AMFm indicate that the median unit price adult-pack AL varies by individual manufacturer (Figure 21). To date, Ajanta, Cipla and Novartis have been the three primary manufacturers

of adult-pack AL. In 2009, when both Cipla and Novartis had prequalification, the median price of both brands was US\$ 1.3. Since that time, Novartis has sold adult-pack AL at either the same or at a lower median price than the two generic brands, Cipla and Ajanta (e.g., in 2010, the Novartis median unit price was US\$ 1.3 versus US\$ 1.3 and US\$ 1.4 for Cipla and Ajanta, respectively). An increase in the median unit price of US\$ 0.2 is observed in 2011 for all three manufacturers and, in 2012, price parity is observed at US\$ 1.6. 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.

**Figure 21: Median unit price, AL 6x4 treatment course, by manufacturer, procured by international donors, 2008–2012**

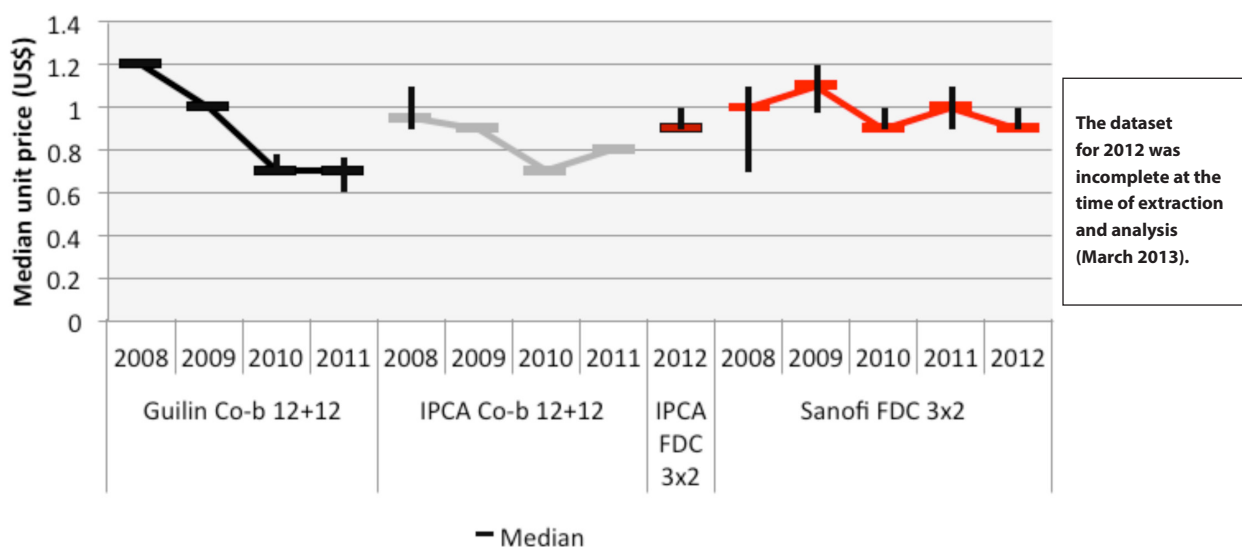


Notes: 6X4 FDC AL are adult-pack sizes, >35 kg, and account for around 50% of all ACTs procured in this market. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quantile. The horizontal line is the median value.

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

The procurement price of co-blister adult-packs ASAQ has decreased over time, despite reduced competition from companies (Activa Pharmaceuticals FZC and Cipla) exiting the market (Figure 22). Despite starting at a relatively high price in 2008 (Guilin, US\$ 1.2), co-blister ASAQ has generally been purchased at a lower median price compared to FDCs. When IPCA entered the market in 2008, they came in at a lower median price compared to Guilin (US\$ 0.9 versus US\$ 1.0) and, in the following year, both manufacturers had the same median selling price, which had decreased to US\$ 0.7. Even though the median price of the IPCA product increased to US\$ 0.8 in 2011, the Guilin product remained at the median unit price of US\$ 0.7. No co-blister ASAQ sales have been reported yet for 2012. Sanofi was the only prequalified manufacturer of FDC ASAQ until June 2012. Before then, the median price of Sanofi adult-packs FDC ASAQ had fluctuated between US\$ 1.1 (US\$ 0.7–1.1) in 2009 and US\$ 0.9 (US\$ 0.9–1.0) in 2012. The median unit price of IPCA sales in 2012 was US\$ 0.9 (US\$ 0.9–1.0), i.e. on par with Sanofi for that year.



**Figure 22: Median unit price of FDC and co-blister ASAQ, by manufacturer, procured by international donors, 2008–2012**

FDC = fixed-dose combination; Co-b = co-blistered

Notes: FDC ASAQ 3x2 and co-b 12+12 are adult-pack sizes and account for approximately 38% of this market. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quantile. The horizontal line is the median value.

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

#### 5.4.3.4 Patient price of available quality-assured ACTs

ACTwatch outlet surveys can be used to show the median price a patient pays for QAACTs for an AETD. It is important to note that in AMFm countries, prices of QAACTs represent a mix of subsidized QAACTs (i.e. QAACTs with the AMFm logo) and unsubsidized QAACTs (4).

International donor funding has made ACTs widely available in the public sector, and many endemic countries are able to provide ACTs to patients for free in public clinics and hospitals (4). Of the seven endemic countries monitored by ACTwatch between 2009 and 2012, there are only two countries (Benin<sup>12</sup> and DRC) where patients pay for ACTs in public sector facilities. The median price of all QAACTs in the public sector ranged from US\$ 1.26 (Benin) to US\$ 3.09 (DRC),<sup>13</sup> and the median price of first-line QAACTs ranged from US\$ 1.23 (Benin) to US\$ 0.54 (DRC).

In private facilities, retail prices of QAACTs remain high, especially in non-AMFm countries (e.g. Benin at US\$ 2.10 and Zambia at US\$ 4.81 Figure 23). In Benin and Zambia, price decreases were observed between survey rounds, which likely were due to changes in overall product mix rather than price reductions for individual products. For example, in Zambia, the drop in median QAACT price is driven by a changing product mix of AL brands available in the private sector (4). One trial using experimental data on household treatment-seeking behaviour in Kenya reported that the price of ACTs appears to have an inelastic impact on demand. The report suggests that ACT purchases are instead influenced by several factors, including the perceived urgency for treatment triggering a willingness to pay a higher price and the perceived health-risk level (58).

QAACTs were found to be around 5–24 times more expensive than nATs in the private sector (Figure 24), and they are significantly more expensive than the most popular antimalarials, SP and CQ, in each country (ACT versus nAT: Nigeria, US\$ 1.43 versus US\$ 0.45; Uganda, US\$ 1.69 versus US\$ 0.51; Benin, US\$ 2.10 versus US\$ 0.42; Zambia, US\$ 4.81 versus US\$ 0.48). In 2009, the median QAACT price in Madagascar was

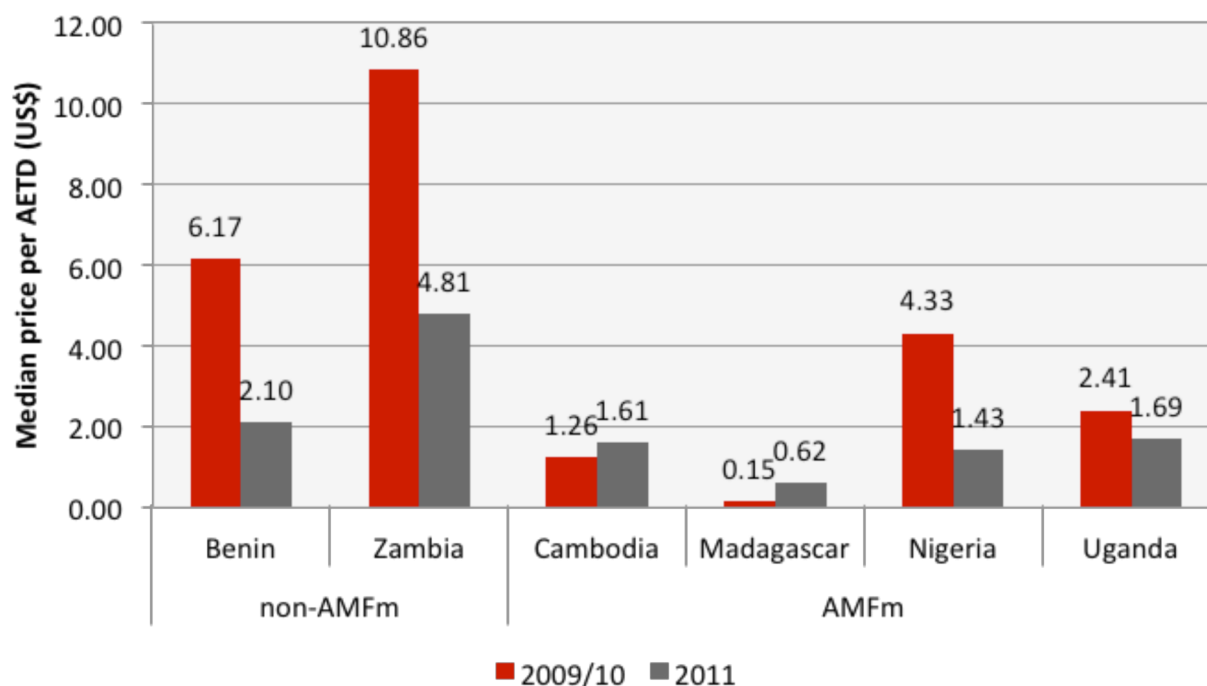
12 At the time of data collection in March/April 2011, patients had to pay; but in October 2011, the government rolled out free treatment for children under five years old and pregnant women in Benin.

13 OANDA average US\$ exchange rates for 2011: Benin, XOF 462.51; DRC, CDF 908.756.



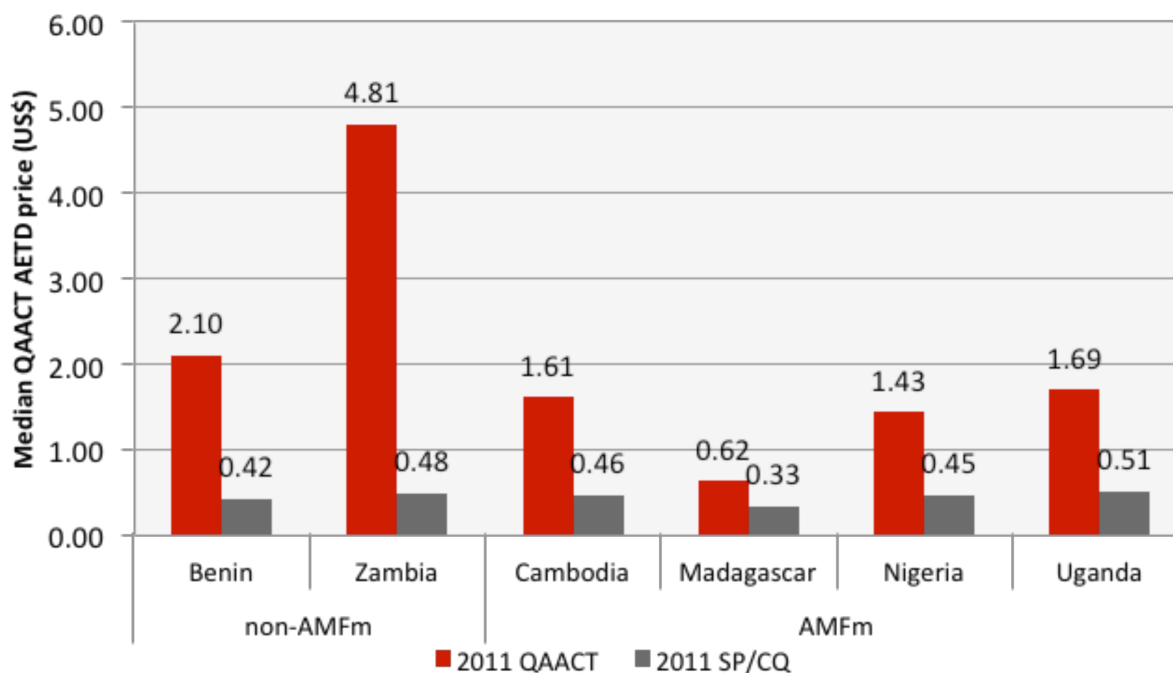
driven in part by the wide availability and low price of ACTs subsidized by Population Services International (ACTipal). However, in 2011, there was little ACTipal in the market and the price of other QAACTs (excluding ACTipal) dropped from a median US\$ 8.88 in 2009 to US\$ 0.68 in 2011 (2010 USD), showing the effect of AMFm on prices in this country.

**Figure 23: Median patient price of QAACT AETDs in the private sector, 2009/2010–2011**



Notes: Prices are standardized to 2010 using the consumer price indexes in each country to adjust for inflation/deflation. Cambodia is all ACTs. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs). Madagascar N=1057 (854 with the AMFm logo), Kenya N=1984 (1887 with the AMFm logo), Nigeria N=1894 (1637 with the AMFm logo), Uganda N=3291 (2832 with the AMFm logo).

Sources: ACTwatch outlet surveys 2009/2010 and 2011.

**Figure 24: Median patient price of QAACT AETDs and nATs (SP or CQ) in the private sector, 2011**

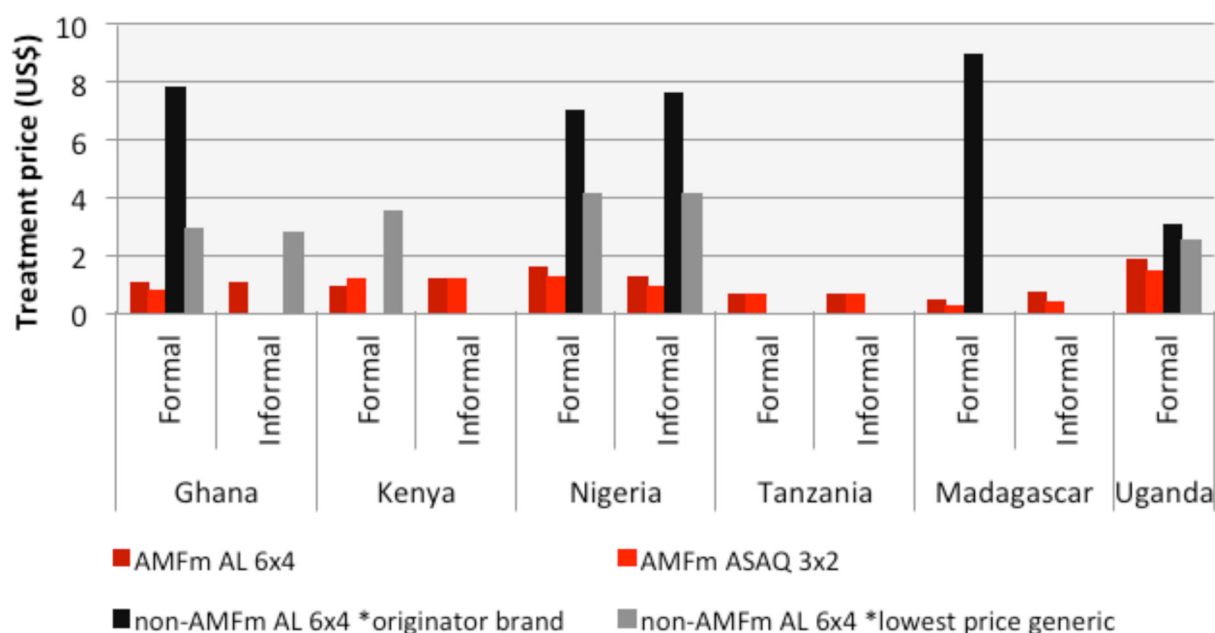
SP = sulfadoxine-pyrimethamine; CQ = chloroquine

Notes: Cambodia ACT category includes both prequalified and non-prequalified medicines. Prices for all AMFm countries represent all QAACTs collected, including QAACTs with the AMFm logo (i.e. subsidized ACTs). Madagascar N=1057 (854 with the AMFm logo), Kenya N=1984 (1887 with the AMFm logo), Nigeria N=1894 (1637 with the AMFm logo), Uganda N=3291 (2832 with the AMFm logo).

Sources: ACTwatch outlet surveys 2009/2010 and 2011.

In comparing the retail price of originator brand ACTs to generics, limited data from AMFm countries show that the median retail price of non-subsidized, originator brand AL was US\$ 7 or more in Ghana, Nigeria and Madagascar (Figure 25). Where both originator and generic versions of AL (non-subsidized) were found, the price of lowest-priced generics was significantly lower (e.g. originator brands were more than double the price of lowest-priced generics in Ghana).

**Figure 25: Median retail price of AL and ASAQ AETDs across all subsectors of AMFm countries, 2012**



AL = artemether-lumefantrine; ASAQ = artesunate-amodiaquine

Source: Health Action International. Retail prices of ACTs co-paid by AMFm and other antimalarial medicines: Ghana, Kenya, Madagascar, Nigeria, Tanzania and Uganda. Report of price tracking surveys. Survey date: September–October 2012.

#### 5.4.4 Availability at facilities

##### 5.4.4.1 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. This applies only to the outlets that had antimalarials in stock on the day of the survey. While there are often stockouts and supply issues at the local level, public facilities often have a large number of first-line ACT treatments available for use. Across six African countries in 2011,<sup>14</sup> approximately 84% of public and not-for-profit facilities had first-line QAActs in stock (Figure 26) (4). High public sector availability was observed in both AMFm and non-AMFm countries, for example, 88.8% in Benin, 79.1% in DRC and 93.6% in Zambia (non-AMFm countries), and 97.4% in Kenya, 91.9% in Madagascar and 73.9% in Uganda (AMFm countries).

In contrast, the availability of QAActs in the private sector, where 40% of people seek treatment, is still low (38%),<sup>15</sup> particularly outside of AMFm countries. For example, private sector availability in Zambia, Benin and the DRC was 20%, < 25% and < 30%, respectively. Madagascar, an AMFm country, had < 10% availability in the private sector. However, in Kenya (60.2%), Nigeria (52.9%) and Uganda (62.5%), more than half of the private outlets surveyed had QAActs in stock.

The availability of nQAActs in both non-AMFm and AMFm public outlets is generally low. The highest availability of nQAActs was observed in Nigeria (21.3%), followed by the DRC (10.8%). In private outlets in both AMFm and non-AMFm countries, the proportion of outlets stocking nQAActs was generally low

<sup>14</sup> Surveyed countries include Benin, Kenya, Madagascar, Nigeria, Uganda and Zambia. The DRC is not included in the figure presented as the last survey round available is 2009. In Cambodia in 2011, 95.1% of public/not-for-profit outlets surveyed had ACT treatments available at the time of the survey.

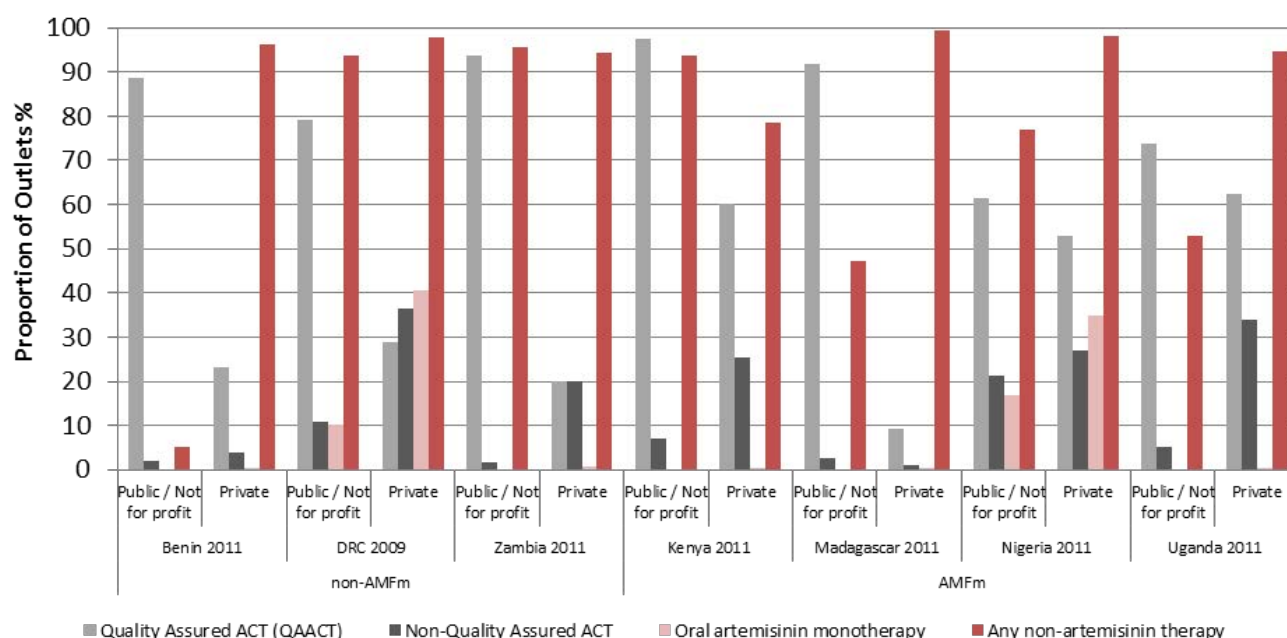
<sup>15</sup> ACTwatch 2011 outlet surveys from six African countries (Benin, Kenya, Madagascar, Nigeria, Uganda and Zambia). The DRC is not included in the figure presented as the last survey round available is 2009. In Cambodia in 2011, 95.1% of public/not-for-profit outlets surveyed had QAAct treatments available at the time of the survey.

as well. The countries that had the highest proportion of private outlets stocking nQAActs were the DRC (36.4%), Nigeria (27.1%) and Uganda (33.8%).

Traditional nATs are still widely available in both public and private facilities and across both AMFm and non-AMFm countries, despite a rapid emergence of resistance to these medicines. Across countries surveyed in 2009/10 and 2011, the DRC (93.8%), Kenya (93%), Nigeria (77%) and Zambia (95.5%) had the greatest proportion of nATs available at public sector facilities. Benin is the exception where only 37.4% of public outlets had nATs available at the time of the survey. In private facilities, the availability of nATs is high, ranging from 97.8% in the DRC (2009) to 78.6% in Kenya (2011).

While progress has been made towards minimizing the use and marketing of oral AMTs, both private and public outlets in the DRC (10.2% in the public sector and 40.5% in the private sector) and Nigeria (16.8% in the public sector and 35% in the private sector) still had stock available at the time of the survey. Across all other countries surveyed, no public sector facilities had oral AMTs in stock, and in the private sector, they were only available in less than 1% of the facilities surveyed.

**Figure 26: Availability of antimalarials, among outlets stocking at least one antimalarial at the time of survey, by sector**



Notes: Public/not-for-profit 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. Last survey round in the DRC was in 2009.

Sources: ACTwatch outlet surveys 2009/2010 and 2011.

## 5.5 Paediatric ACTs

### 5.5.1 Market characteristics of donor-procured, child-pack ACT

#### 5.5.1.1 Child-pack strengths and pack-types

As children under five years old bear a significant proportion of the malaria disease burden (77%), it is important that appropriate and high-quality antimalarials are made available to ensure efficacy and widespread use (11). 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.

For AL, solid oral child-packs contain 20 mg of artemether + 120 mg of lumefantrine and the pack-types include: 6x1 (< 15 kg); and 6x2 and 6x3 (15–34 kg). Adult-packs (> 35 kg) are the same strength as child-packs but are packed as 6x4s (Table 8). 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 five years old due to the burden of disease within this population group. For this reason and 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 five years old.

For FDC ASAQ, child-pack types come as 3x1, available in three different strengths for children under 35 kg: 25 mg AS and 67.5 mg AQ (4–8 kg); 50 mg AS and 135 mg AQ (9–17 kg); 100 mg AS and 270 mg AQ (18–35 kg). Co-blister ASAQ child-packs come in 3+3 (9–17 kg) and 6+6 (18–35 kg) and each tablet contains 50 mg AS + 153 mg AQ (59). There are also child-packs available for other ACTs; however, this section focuses on AL and ASAQ given their large market share.

**Table 8: Available AL and ASAQ formulations and pack-types**

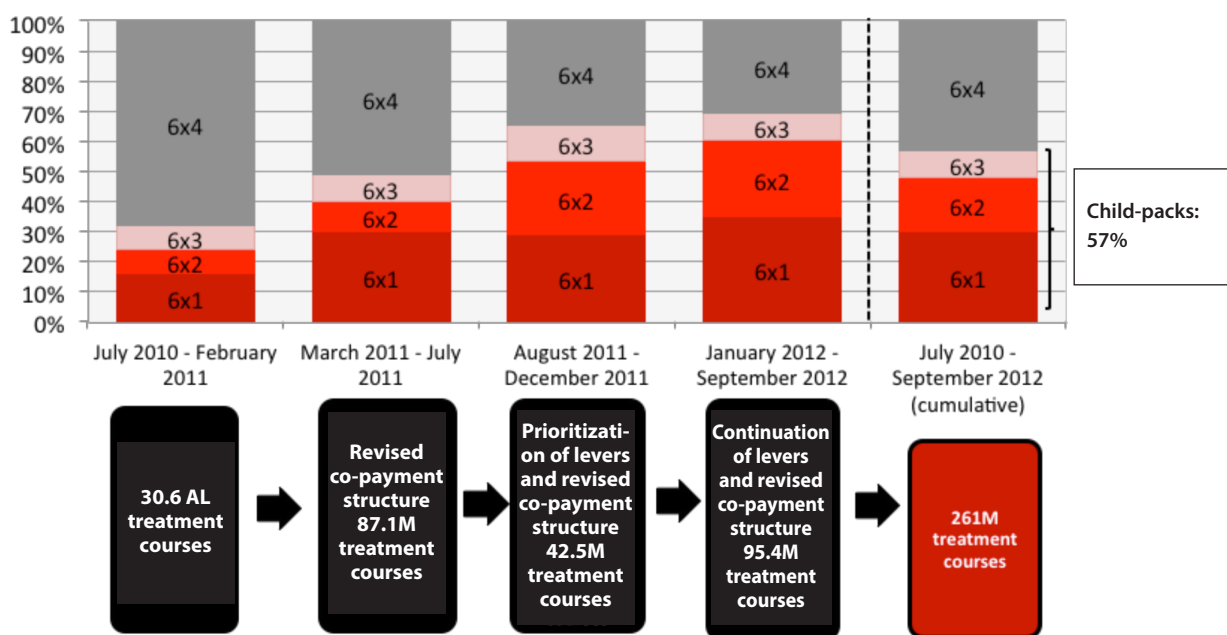
ACT	FDC or co-blister	Strength	Weight band	Pack-type
Artemether-lumefantrine (AL)	FDC	20/120 mg	Adult >35 kg	6x4
			Child 25–35 kg	6x3
			Child 15–25 kg	6x2
			Infant <15 kg	6x1
Artesunate-amodiaquine (ASAQ)	FDC	100/270 mg	Adult >35 kg	3x2
		100/270 mg	Child 18–35 kg	3x1
		50/135 mg	Child 9–17 kg	3x1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

#### 5.5.1.2 Market share of ACTs, child-pack versus adult-pack

The WMR 2013 reported that between 2005 and 2012, the number of child-packs of AL delivered to the public and private sectors has increased (11). Since 2009, child-packs of AL have accounted for the greatest volumes of AL procured (11). 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) (11).

Within AMFm, an increase in the uptake of child-packs may be attributed to the March 2011 revisions made to the co-payment structure of AMFm to favour paediatric packs. Since the revisions, levers have been put in place for managing orders to preference child-packs, where every request for a co-payment is evaluated on the basis of several criteria (for example, the ratio of cumulative approved orders to estimated demand, relative proportion of paediatric formulations/pack sizes, and sector) (23). The revisions were seen to have had an immediate effect, with child-packs of AL increasing from 32% to 49% of approved orders within the first quarter of being implemented (Figure 27) (23). Following implementation of the demand-shaping levers, further increases in the relative proportion of child-packs procured through AMFm were seen. In August–December 2011 the proportion of child-packs increased to 65%, and to 69% in January–August 2012 (23).

**Figure 27: AL relative percentage of pack-sizes, pre-revision and postrevision of co-payment structure and introduction of levers in AMFm, 2010–2012**

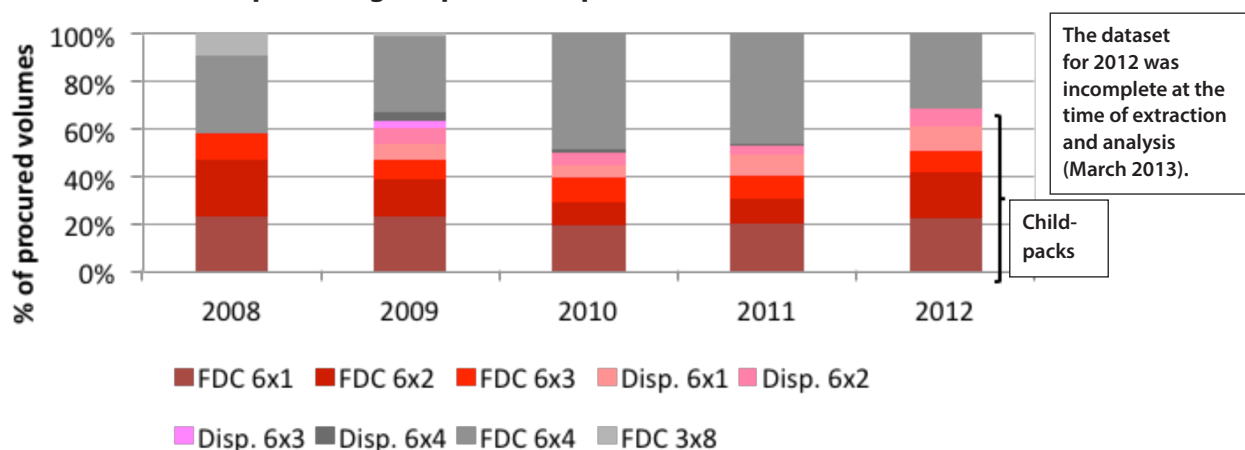


Note: artemether-lumefantrine (AL) represents 85% of all co-payment approvals; AL: solid oral and dispersible formulations 20/120 mg adult: 6x4, >35 kg; child: 6x2, 15–25 kg and 6x3, 25–35 kg; infant/toddler: 6x1, 5–15 kg.

Sources: From the GFATM in the ICF and LSHTM Independent Evaluation of the AMFm Phase 1. Data as of 28 September 2012.

Incremental increases also can be seen from the compiled GFATM PQR and AMFm datasets between 2010 and 2012, which represent approximately 73% of the donor market in 2010, 86% in 2011, and 62% in 2012 (excluding PMI volumes) (Table 5). (Figure 28). Of the total yearly AL volumes procured between 2008 and 2011, child-packs represent at least 50% each year (for example, 59%, 68%, 51%, 54% from 2008–2011, respectively). In 2012, from the ACT transactions that have been reported, packs procured for body weight < 35 kg accounted for 69% of AL treatments procured.

**Figure 28: AL relative percentage of pack-sizes procured in the donor market, 2008–2012**



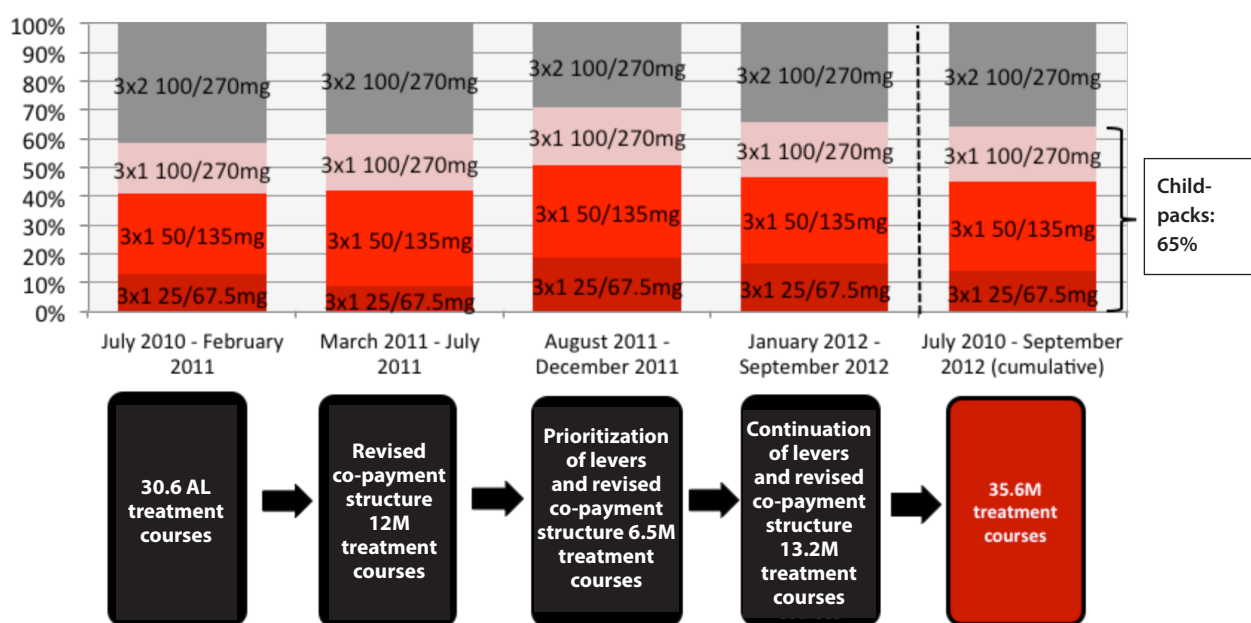
FDC = fixed-dose combination and indicates solid oral formulations; Disp. = dispersible tablets

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

For ASAQ, the proportion of child-packs versus adult-packs of both FDC and co-blister has been more in favour of child-packs since the beginning of AMFm and the share has remained stable over time (Figure

29) (23). This is thought to be caused by the fact that ASAQ comes in different strengths for different weight bands and so packs are procured along the lines of weight-based needs (i.e. there is less potential to stack child-packs ASAQ for an adult). Overall, from June 2010 to September 2012, 57% of ACTs approved for co-payment were for child-packs, and 55% of co-paid ACTs delivered to Phase 1 countries were child-packs (23).

**Figure 29: ASAQ relative percentage of pack-sizes, pre-vision and postrevision of co-payment structure and introduction of levers in AMFm, 2010–2012**

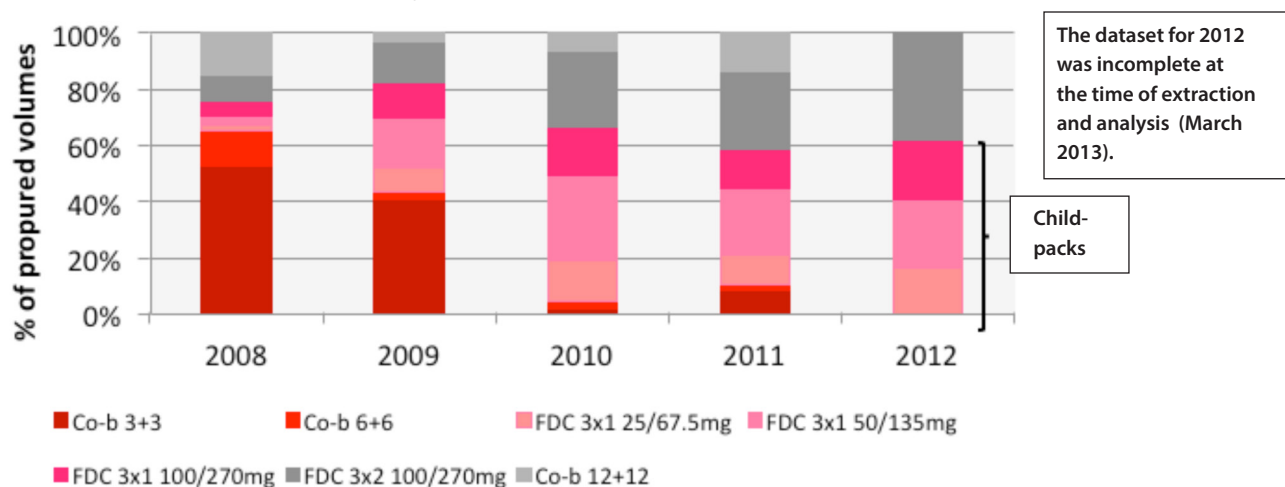


Note: artesunate-amodiaquine (ASAQ) FDC; adult: 3x2 100/270 mg, >35 kg; child: 3x1 50/135 mg, 9–17 kg, and 100/270 mg 18–35 kg; infant/toddler: 3x1 25/67.5 mg, 4–8 kg.

Sources: From the GFATM in the ICF and LSHTM Independent Evaluation of the AMFm Phase 1. Data as of 28 September 2012.

Compiled GFATM PQR and AMFm datasets also show that for ASAQ, the proportion of child-packs versus adult-packs of both FDC and co-blister has been more in favour of child-packs since 2008 (23). Child-pack ASAQ procured in 2009 accounted for 82% of the market share. Since that time, however, the proportion of child-pack ASAQ declined to 79% in 2010, 59% in 2011 and 62% in 2012.

**Figure 30: ASAQ relative percentage of pack-sizes procured in the donor market, 2008–2012**



FDC = fixed-dose combination; Co-b = co-blister

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

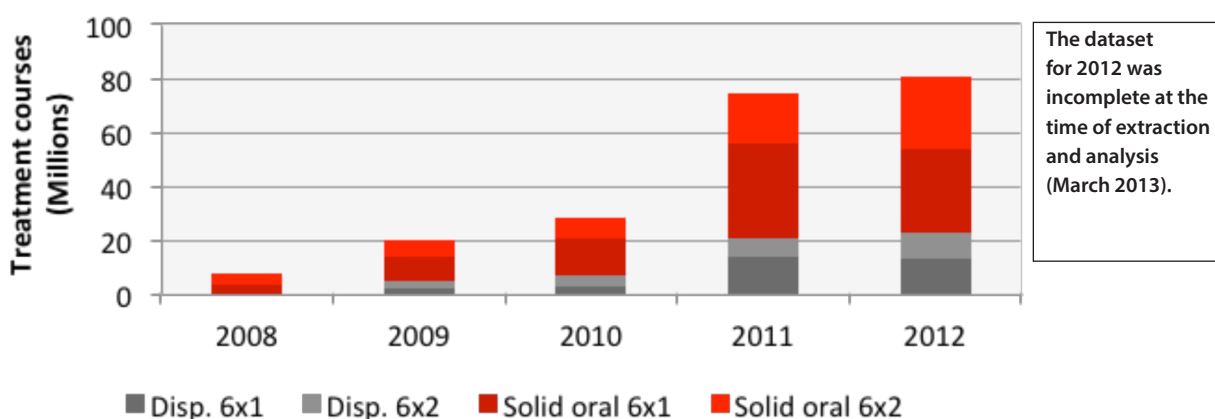


### 5.5.2 Characteristics of the paediatric ACT market

Given that the large majority (77%) of malaria cases occur in children under five years old, there has been an emphasis on scaling up ACTs that are available in formulations that facilitate their use in young children (11). 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 five years old, including malaria (26). Additionally, dispersible tablet formulations of ACTs are preferred over syrups and other forms because of their transportability and palatability (24). Two WHO prequalified dispersible tablet formulations of AL are now available; however, data indicate that uptake has been limited. While dispersible AL is available for all pack sizes, this section focuses on pack sizes targeted at children under five years old (i.e. 6x1 and 6x2 packs).<sup>16</sup>

Data from the GFATM and AMFm purchase transaction 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 21M in 2010, 53M in 2011, and 57M in 2012 for solid orals; and from 7M in 2010, 21M in 2011, and 23M in 2012 for dispersibles) (Figure 31).

**Figure 31: Volume of AL packs for children under five years old procured by international donors, 2008–2012**



AL = artemether-lumefantrine; Disp. = dispersible tablets

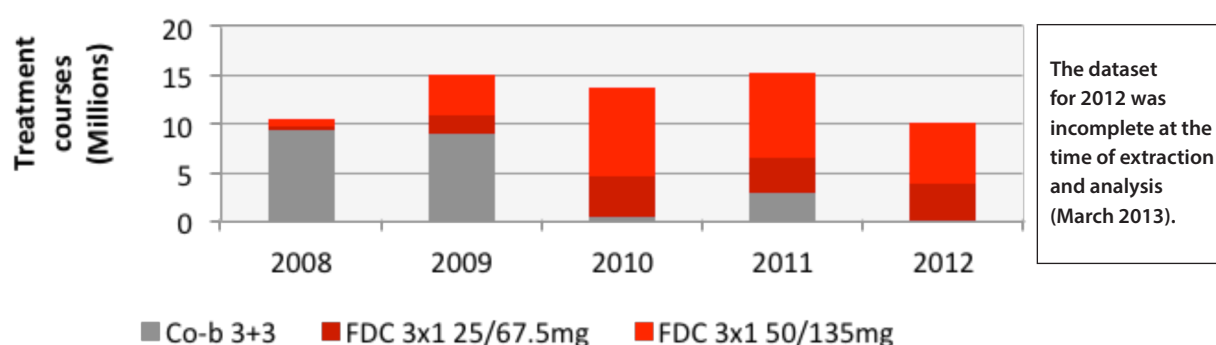
Notes: The chart only represents packs-sizes tailored for children under five years old (average weight 18 kg). It represents 6x1 and 6x2 packs-sizes; 6x3 and 6x4 packs-sizes are available for procurement but are not represented in this chart.

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

ASAQ solid oral formulations are highly soluble and, therefore, considered to be easily administrable to young children. Based on weight bands, child-packs for children under five years old include co-blisters 3 + 3 50/153 mg packs and FDC 3x1 50/135 mg and 25/67.5 mg packs. In the donor market, ASAQ packs procured for children under five 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 FDC ASAQ in October 2008 (Figure 32). Volumes of FDC ASAQ for children under five years old increased from 6M in 2009 to 13M in 2010 and 12M in 2011. Current donor procurement data show that 10M FDC courses for children under five years old have been procured in 2012 and presently no co-blisters transactions have been reported.

<sup>16</sup> Packs-sizes tailored for children under five years old are based on an average weight of 18 kg or less.

**Figure 32: Volume of ASAQ packs for children under five years old procured by international donors, 2008–2012**



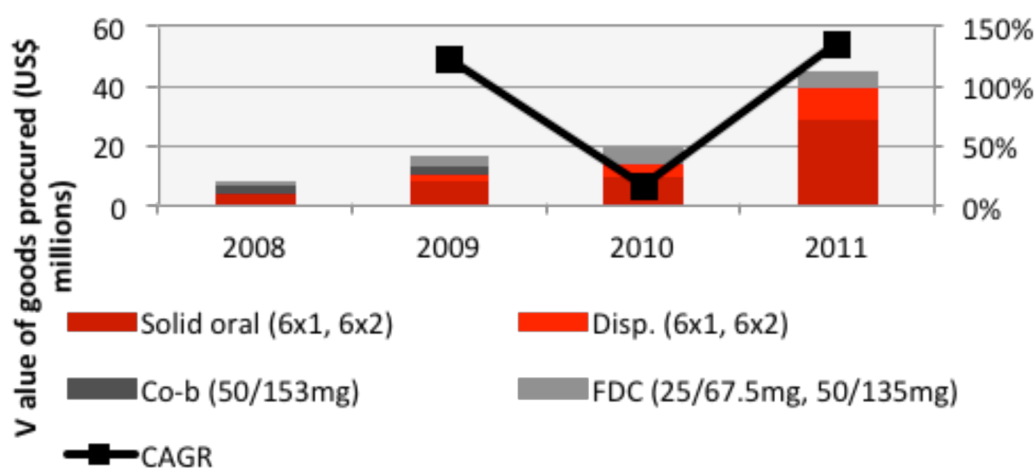
Co-b = co-blister; FDC = fixed-dose combination

Notes: The chart only represents packs-sizes tailored for children under five years old (average weight 18 kg). It represents 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 GFATM PQR data and AMFm.

Based on data from the GFATM and AMFm as a proxy for the donor market, the market value for ACTs for children under five years old has increased from approximately US\$16M in 2009 to US\$ 19M in 2010 and US\$ 45M in 2011 (Figure 33). The greatest CAGR was seen from 2010 to 2011 where this market experienced an exponential growth rate from 16% to 135%.

**Figure 33: Market value of AL and ASAQ procured in the donor market for children under five years old, 2008–2011**



AL = artemether-lumefantrine; ASAQ = artesunate-amodiaquine; Disp. = dispersible tablets; Co-b = co-blister; FDC = fixed-dose combination; CAGR = compound annual growth rate

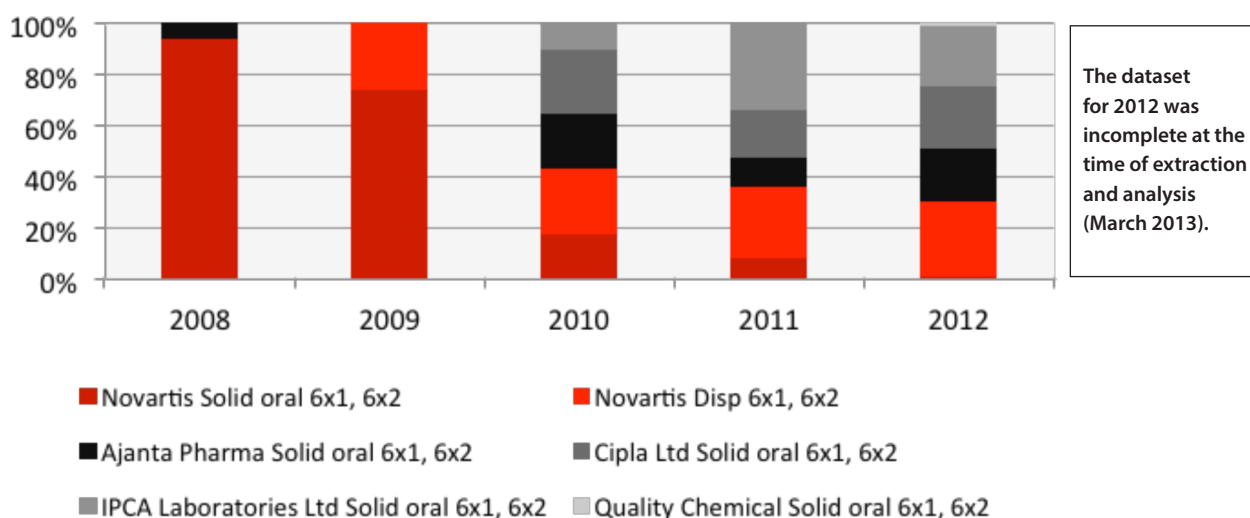
Notes: The chart only represents packs-sizes tailored for children under five years old (average weight 18 kg). It represents 6x1 and 6x2 packs-sizes; 6x3 and 6x4 packs-sizes are available for procurement but are not represented in this chart. Co-blister 3+3 pack sizes at 50/153 mg and FDC 3x1 pack sizes at 25/67.5 mg and 50/135 mg.

Sources: Calculated from transactions reported in GFATM PQR data and AMFm. Data from 2012 has been excluded due to the fact that the dataset was incomplete at the time of extraction and analysis (March 2013).

Until December 2012, only one prequalified dispersible AL tablet (Coartem® Novartis) was available for procurement. Additionally, Novartis announced in mid-2009 that they would reduce their prices by 5% for public sector buyers and a further 2% for prepaid orders (60). These reasons could be why Novartis has

had a monopoly on the dispersible market since 2009, and have had a dominant presence in the AL market in general. The Ajanta Pharma dispersible AL formulation became prequalified in December 2012, which will bring competition into this space (30). Despite a Novartis monopoly on dispersibles, their combined market share of 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 2011, Novartis still accounted for the greatest share of procured child-packs (37%), but the remaining share of this market was divided between Ajanta Pharma (11%), Cipla Ltd (19%) and IPCA Laboratories (33%).

**Figure 34: Proportion of dispersible and solid oral AL packs for children under five years old procured by international donors, by manufacturer, 2008–2012**



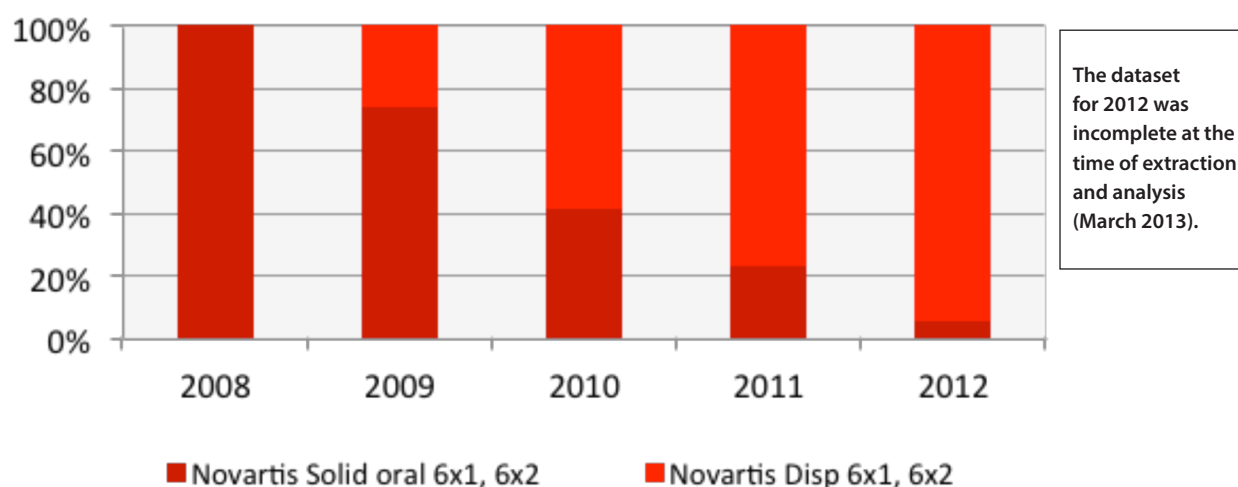
Disp = dispersible tablets

Notes: The chart only represents packs-sizes tailored for children under five years old (average weight 18 kg). It represents 6x1 and 6x2 packs-sizes; 6x3 and 6x4 packs-sizes are available for procurement but are not represented in this chart.

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

For the market leader, Coartem®, the market share of their paediatric products has been shifting to dispersibles over time. By 2012, Coartem®, was only selling low volumes of solid oral formulations in pack sizes for children (Figure 35). Dispersible 6x1 and 6x2 tablets made up 25% of Novartis sales in 2009, 77% by 2011 and an estimated 94% in 2012.

**Figure 35: Proportion of dispersible and solid oral AL packs for children under five years old procured by international donors, Novartis, 2008–2012**



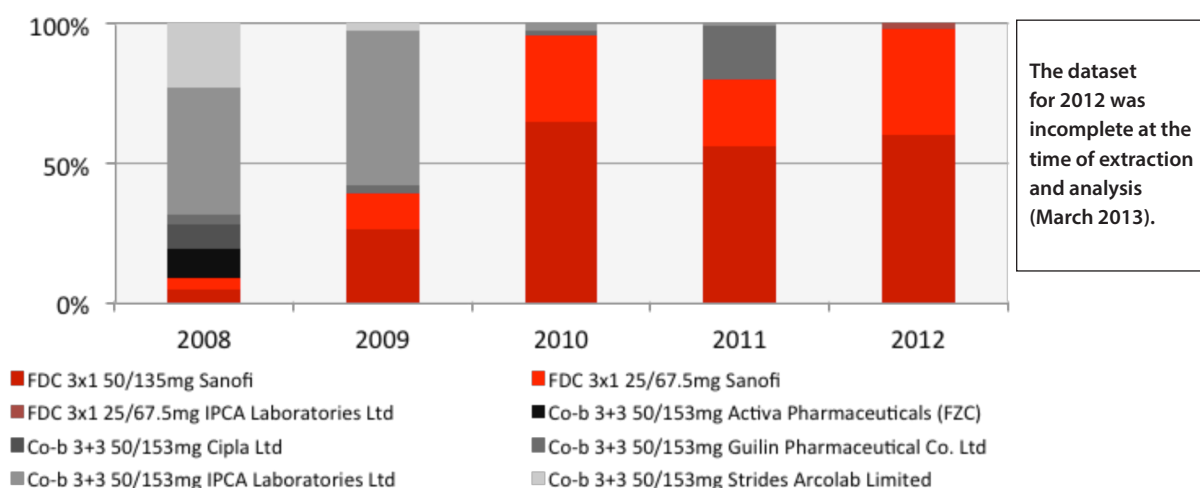
Disp. = dispersible tablets

Notes: The chart only represents packs-sizes tailored for children under five years old (average weight 18 kg). It represents 6x1 and 6x2 packs-sizes; 6x3 and 6x4 packs-sizes are available for procurement but are not represented in this chart.

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

Sanofi is the market leader of FDC ASAQ and was the sole prequalified manufacturer until 2012. As a proportion of all ASAQ available for children under five years old (including co-blisters), the Sanofi market share for child-packs, FDC ASAQ has increased from 39% in 2009 to 98% in 2012 (Figure 36). As no transactions have been reported for co-blisters ASAQ in 2012, and Guilin and IPCA are now prequalified to manufacture FDC ASAQ, the market share between manufacturers could potentially change in the future, and could possibly have a positive effect on price.

**Figure 36: Proportion of co-blisters and FDC ASAQ packs for children under five years old procured by international donors, by manufacturer, 2008–2012**



FDC = fixed-dose combination; Co-b = co-blisters

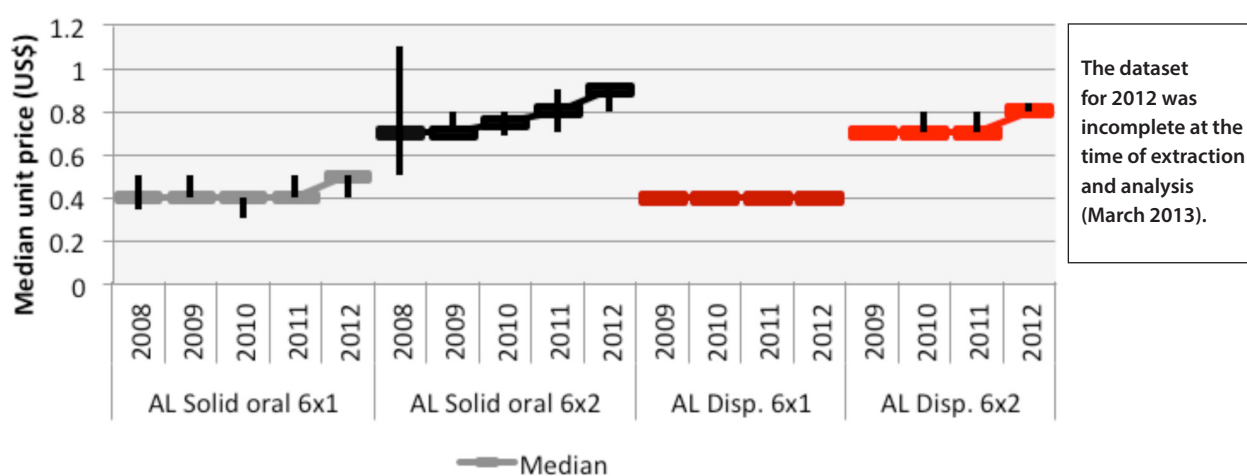
Sources: Calculated from transactions reported in GFATM PQR data and AMFm.

### 5.5.3 Procurement prices of ACTs for children under five years old in the donor-funded market

#### 5.5.3.1 Dispersible and solid oral AL procurement prices for children under five years old in the donor-funded market

Since 2009, dispersible 6x1 AL has been procured at a constant median unit price of US\$ 0.4 (Figure 37). Solid oral 6x1 AL (all brands) had the same median price as the equivalent dispersible until 2011, but in 2012 this increased to US\$ 0.5. The median price of dispersible 6x2 AL was constant between 2009 and 2011 at US\$ 0.7, and increased to US\$ 0.8 in 2012, the year when Cipla received prequalification. The median price of solid oral 6x2 AL (all brands) has steadily increased from US\$ 0.7 in 2009 to US\$ 0.9 in 2012. It is important to note that the most recent procurement transaction data from PQR are showing that prices are beginning to decrease (as low as US\$ 0.33 for 6x1 AL in March 2013) and this will be investigated further in the updated landscape in 2014 (56).

**Figure 37: Median unit price of AL for children under five years old procured by international donors, dispersible and FDC, 2008–2012**



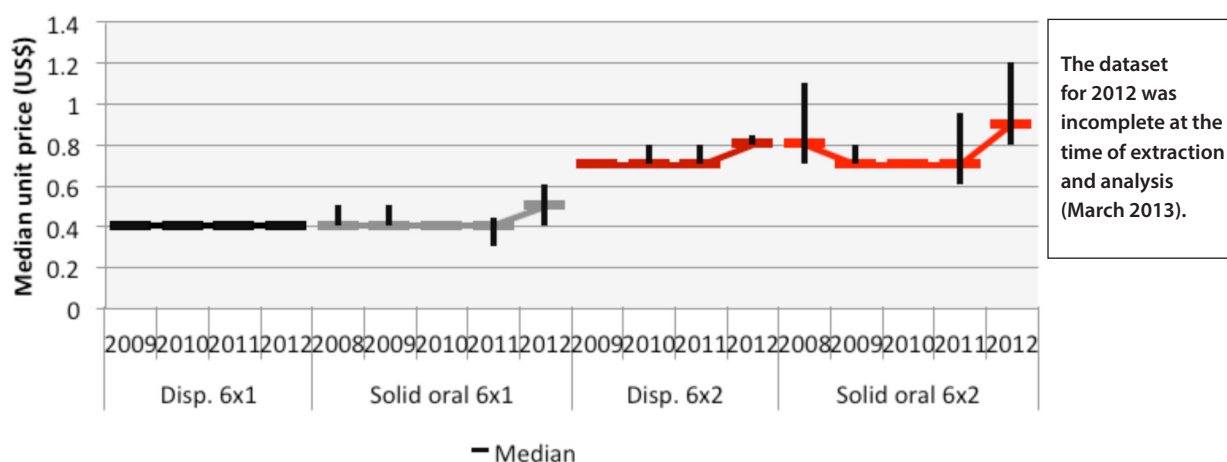
AL = artemether-lumefantrine; Disp. = dispersible tablets

Notes: 6x1 and 6x2 AL packs are tailored for children weighing less than 18 kg. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quartile. The horizontal line is the median value.

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

Novartis has committed to providing both dispersible Coartem® and solid oral Coartem® at the same price so the solid oral formulation is not preferred by procurers because of affordability issues (61). Data from PQR and AMFm show that there has been price parity between Novartis dispersible and solid oral AL formulations for children under five years old since they came on the market (e.g. US\$ 0.4 for 6x1s and US\$ 0.7 for 6x2s) (Figure 38). In 2012, there was a US\$ 0.1 increase in their solid oral 6x1 and dispersible 6x1 and 6x2 packs.

**Figure 38: Median unit price of dispersible Coartem® and solid oral Coartem®, for children under five years old, procured by international donors, 2008–2012**



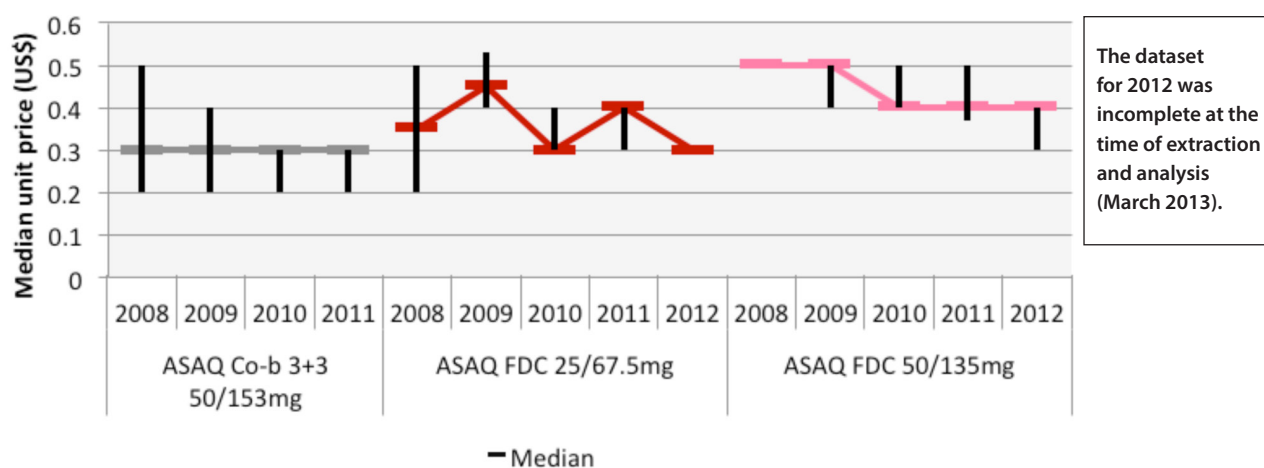
Disp. = dispersible tablets

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

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

The price of FDC ASAQ for infants has fluctuated over time, while the price for toddlers has decreased (Figure 39). In 2011, the median price of FDC ASAQ for both weight groups was US\$ 0.4. The median price of co-blister formulations remained constant (US\$ 0.3) between 2008 and 2011.

**Figure 39: Median unit price of ASAQ for children under five years old procured by international donors, co-blister and FDC, 2008–2012**



ASAQ = artesunate-amodiaquine; Co-b= co-blister; FDC = fixed-dose combination

Notes: ASAQ co-b 3+3 and FDC 25/67.5 mg, 50/135 mg AL packs are tailored for children weighing less than 18 kg. The top and bottom of the vertical lines are the 90<sup>th</sup> and 10<sup>th</sup> quartile. The horizontal line is the median value.

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

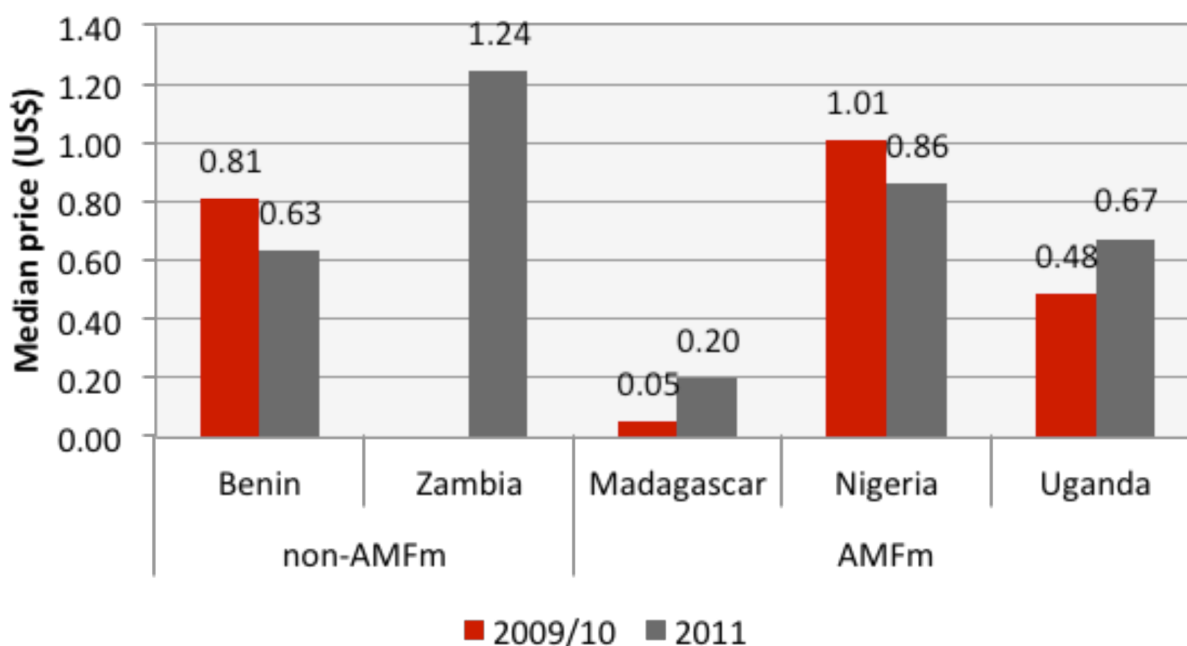
#### 5.5.4 Retail availability and child-dose retail price of quality-assured ACTs

Similar to the low uptake of dispersible formulations in the donor market, their availability in facilities and outlets is also low. Specifically, limited data from AMFm show that their availability to patients in registered pharmacies is low (11–14%), and is lower than that of paediatric packs of solid tablets (42–48%) (23).

ACTwatch outlet surveys from five African countries surveyed in 2009/10 and 2011, provide estimates on the median patient price of QAACTs in the private sector for a child under two years old. It is important to note that the QAACT prices reported below represent a mix of subsidized QAACTs (i.e. QAACTs with the AMFm logo), unsubsidized QAACTs and includes a number of different brands (4).

In non-AMFm countries, the retail price of QAACTs for children under two years old ranged between US\$ 0.63 (Benin) to US\$ 1.24 (Zambia) (Figure 40). In AMFm countries, the price ranged from US\$ 0.20 (Madagascar) and US\$ 0.86 (Nigeria). Price increases were seen between survey rounds in both Madagascar and Uganda, which could be related to a shift in product mix (e.g. possibly more dispersible formulations available on the market). Further research has shown that the median price of a QAACT child dose in the private sector in 2011 was around 1.5–2.5 times higher than that of an nAT adult dose of SP or CQ. The exception is Madagascar, where the child doses were around half the price adult nATs (4).

**Figure 40: Median patient price of QAACT tablets for a child under two years old in the private sector, including informal private sector**



Note: Prices are standardized to 2010 using the consumer price indexes in each country to adjust for inflation/deflation.

Sources: ACTwatch outlet surveys 2009/2010 and 2011.



## 5.6 Severe malaria

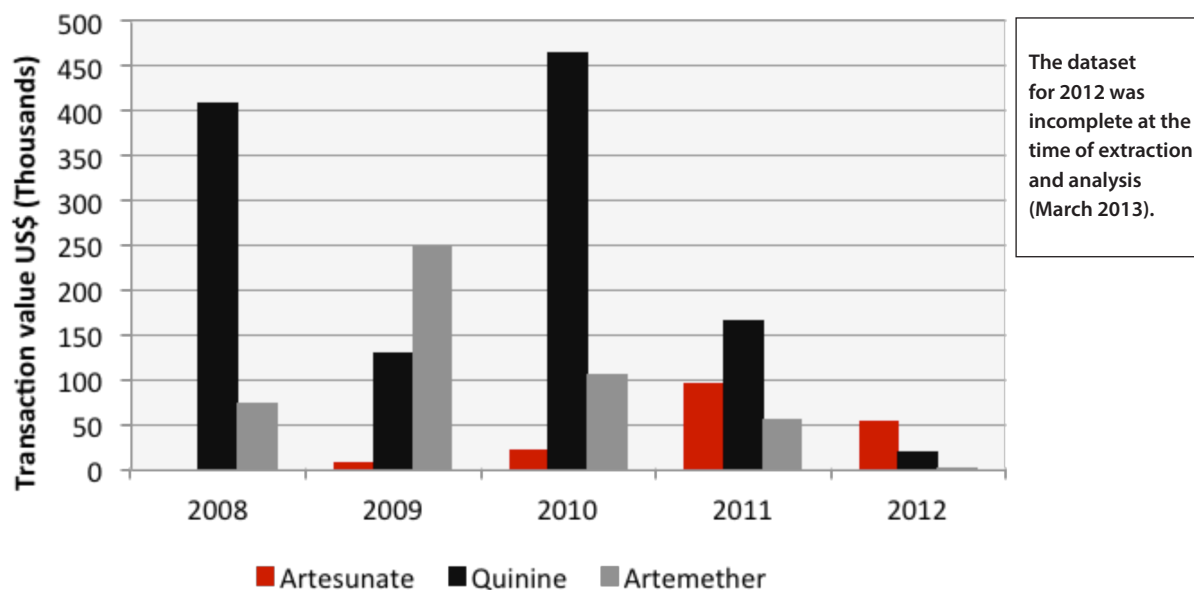
### 5.6.1 Injectable therapies for severe malaria market overview

Since WHO recommended IVAS as the preferred treatment of severe malaria in 2011 (13), uptake has been low. There is currently only one WHO prequalified IVAS product available (Guilin Pharmaceuticals). In 2012, quantities procured were less than 10% of the total needed to treat global annual cases. Approximately 3.2M vials (roughly 750,000–1M treatments for children under five years old) were procured out of an estimated 48–50M vials that would be needed to treat global annual cases (27). It is important to note that although the average treatment course cost of INJAS is currently higher than QN (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 (14). Despite this, reasons for low-level procurement of IVAS include a higher price over parenteral QN (IVQ), the absence of catalytic financing incentives to purchase IVAS, unfamiliarity with the product and buyer concerns over a single-prequalified supplier.

Countries often procure IVQ with national funding, so QN is rarely financed by international donations. This factor contributes to shortages in data availability on the use and uptake of injectable antimalarials for severe malaria and as a result, today, there is no global reporting consolidated among donors about the use of IVQ. However, limited information is available from the GFATM PQR dataset. Figure 41 shows the value of transactions for injectable antimalarials in the donor-funded market over time. IVQ accounted for the greatest value of transactions in 2008 (US\$ 410K) and 2010 (US\$ 465K). In 2011, the value of transactions for injectable antimalarial medicine was split across IVQ (US\$ 166K), artemether (US\$ 55K) and IVAS (US\$ 95K). 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<sup>17</sup> (62), 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. Moreover, the current trend shows that the total transaction value for IVAS (US\$ 53K) was more than double that of IVQ (US\$ 20K) in 2012.

A recent UNITAID-supported project attempts to address these market shortcomings. The Improving Severe Malaria Outcomes project aims to expand access to quality-assured INJAS by increasing public sector acceptance and use, encouraging market entry of a second supplier and securing lower prices through negotiation and increased competition.

<sup>17</sup> Parenteral quinine is estimated to cost US\$ 0.27 per ampoule and is widely available in health facilities across sub-Saharan Africa compared to artesunate costing around US\$ 1.06 per vial.

**Figure 41: Total value (US\$) of PQR transactions for INJAS, artemether and QN, 2008–2012**

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

### 5.6.2 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 (13). However, the lack of a WHO prequalified product or approval by an SRA, has limited access and hampered widespread use of this product. For this reason, many donors and organizations do not procure RAS. The UNITAID-supported Improving Severe Malaria Outcomes aims to address this issue by evaluating market demand for pre-referral treatment of severe malaria (rectal artesunate) and supporting the market entry of a WHO prequalified product.

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 quality-assured by Médecins sans Frontières and PMI, and it has been widely used by Médecins sans Frontières in its country programmes since 2007.<sup>18</sup> In 2009 and 2010, PQR records indicate that Mepha RAS suppositories also were procured through the GFATM from Eritrea, Sierra Leone and the Sudan. Information from the UNICEF supply catalogue, where Mepha 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 been used by Médecins sans Frontières in Sierra Leone, but it is not widely registered. There is a third RAS, as mentioned in Section 4.2, which is currently in the registration phase.

To add to barriers impeding RAS uptake, there is evidence of inappropriate use, especially the use of RAS as a monotherapy for uncomplicated *P. falciparum*. Furthermore, it is not clear as to what extent suppositories are socially or culturally acceptable and feasible across a range of societies, and so this is an important factor to consider when deploying RAS strategies. Some evidence from Papua New Guinea found that lack of spousal approval and fear of side-effects were the most common reasons for refusal of suppositories, and that shame, embarrassment and hygiene were not significant concerns (63).

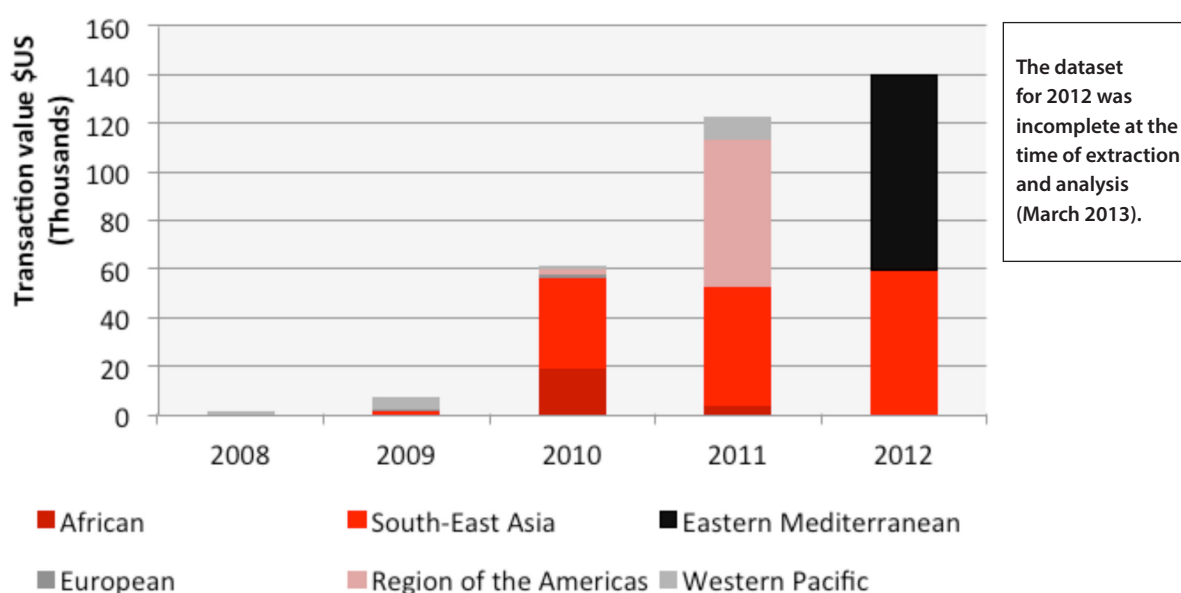
<sup>18</sup> To assess and validate the quality of a medicinal product, Médecins sans Frontières and procurement agency pharmacists have developed a qualification procedure based on WHO recommendations. From the analysis of parameters linked with the production site to the product itself, the entire production chain is checked before being validated. No information is available on the PMI quality assurance process.

### 5.7 CQ and *P. vivax* market overview

In most areas where *P. vivax* is endemic, particularly South-East Asia, CQ is the recommended first-line antimalarial medicine (13). CQ also is recommended to treat both *P. ovale* and *P. malariae*. The South-East Asia Region has the second highest number of estimated cases and deaths after the African Region. In 2012, there were an estimated 27M cases and 42 000 malaria deaths (11). Assessing the size and share of the CQ market is limited to transactional data available from the PQR database. Figure 42 shows that South-East Asia has consistently been purchasing SRA-approved CQ through donor-funded procurement channels since 2009. However, in 2011, the value of transactions for CQ was greater in the Region of the Americas, and in 2012 transactions for Pakistan alone were greater than that for South-East Asia Region.

The epidemiological situation of *P. vivax* in South-East Asia varies from the situation in the Region of the Americas. For example, in India and Pakistan, *P. vivax* and *P. falciparum* coexist and the epidemiology is fast changing between them due to a generation of resistant alleles (64), (65). 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*. For this reason, emphasis on scaling up ACTs where CQ resistance has been detected in this region should be made a priority (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 and its shortcomings.

**Figure 42: Total value (US\$) of PQR transactions for CQ, by WHO region, 2009–2012**



Note: African: Chad, Dominican Republic, Eritrea; Eastern Mediterranean: Pakistan; European: Azerbaijan, Georgia; Region of the Americas: Haiti, Multicountry Americas (Andean); South-East Asia: Korea (Democratic People's Republic), Myanmar, Thailand; Western Pacific: Philippines.

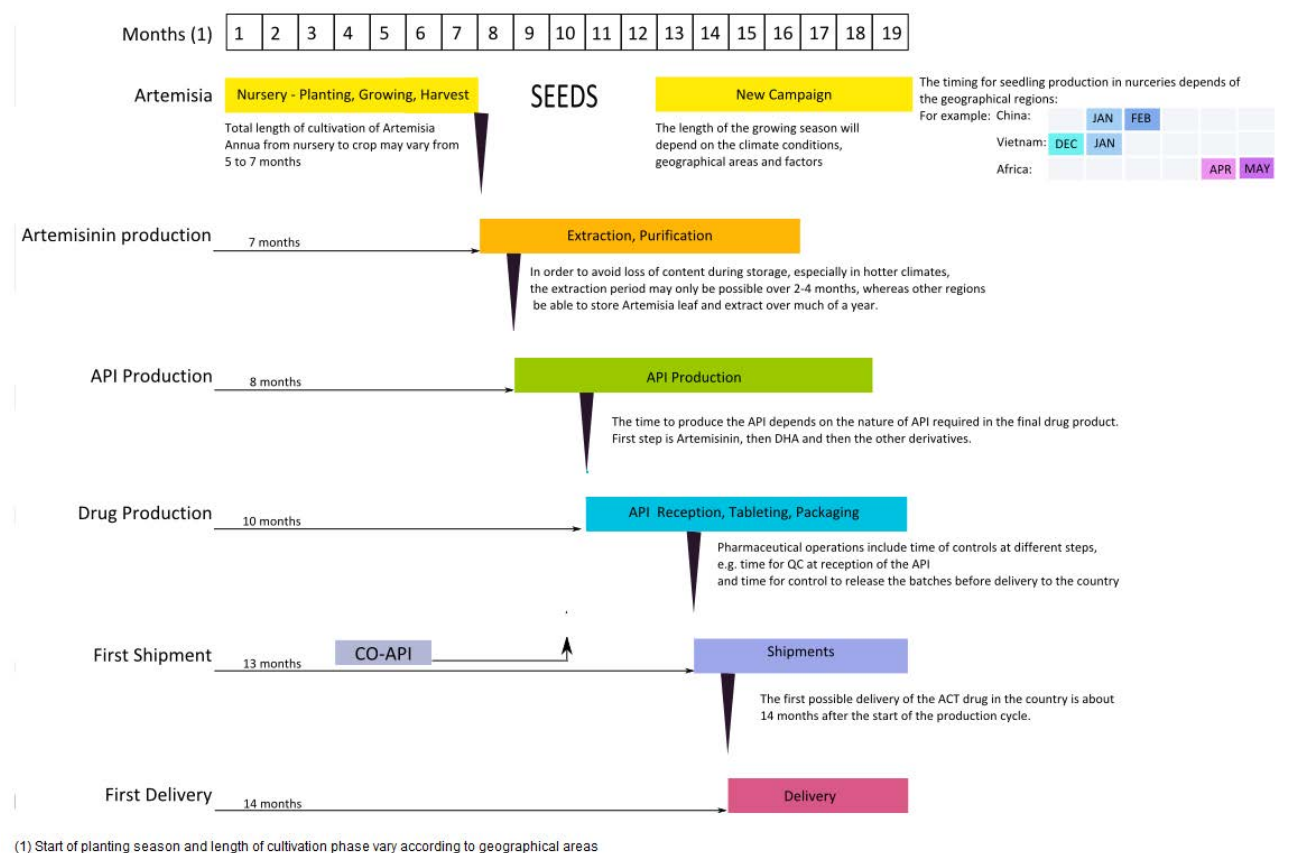
Sources: Calculated from transactions reported in GFATM PQR data and AMFm data.

## 5.8 Artemisinin market overview

### 5.8.1 Artemisinin supply chain

The upstream supply of artemisinin is based on a long and complex agricultural process; the entire cycle from planting *Artemisia annua* crops to final production of ACTs takes approximately 12–18 months (Figure 43). Upstream production begins with the planting and harvesting of *Artemisia 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 43: Timeline for artemisinin and ACT production**



Oteci/Artepal 2010 (J. Pillay)

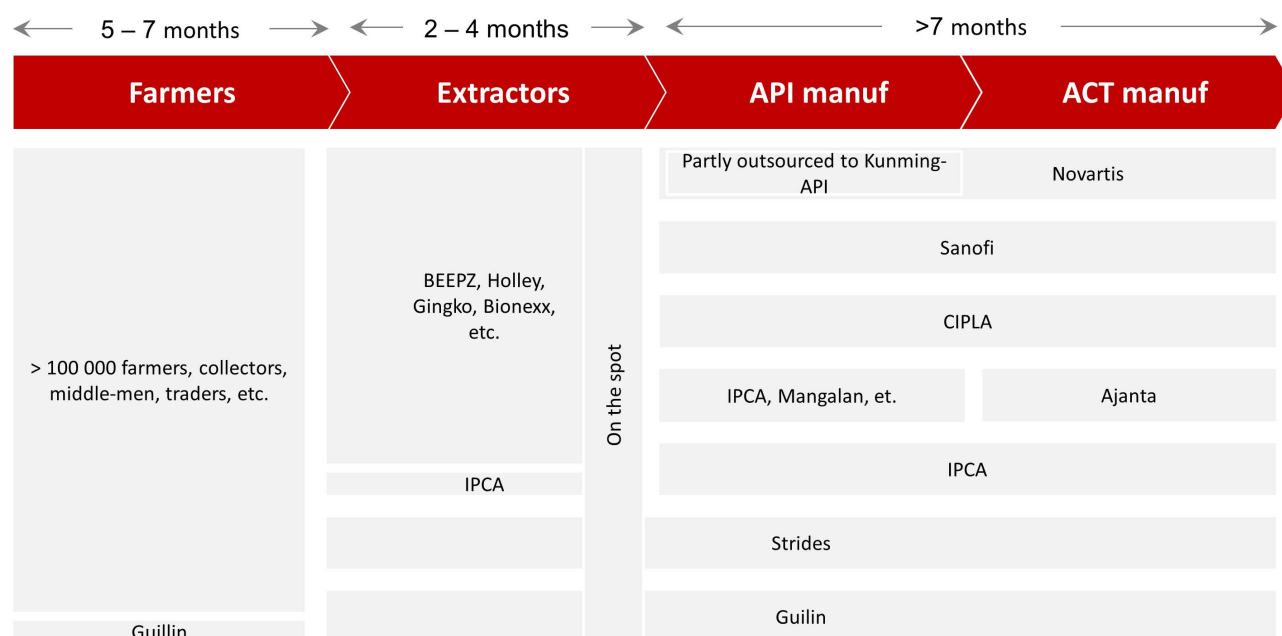
ACT = artemisinin-based combination therapy; API = active pharmaceutical ingredient; DHA = dihydroartemisinin; QC = Quality Control.

Source: A2S2 website.

The supply chain of artemisinin involves many players, which contributes to its complexity (Figure 44). The cultivation of *Artemisia annua* requires thousands of farmers, with an average area per farmer in Africa and China of approximately 0.2 hectares (54). Globally, 15 companies extract and purify artemisinin, while a number of smaller companies extract artemisinin without purifying it. Among the major companies, BEEPZ, Bionexx, Holley and Mediplantex sell to prequalified manufacturers. China, which represents 85–90% of annual (natural) artemisinin output, has in recent years seen high levels of fluctuation with regard to the number of active extractors in the market, which have entered or exited the market depending on the prevailing market conditions. There are currently six extractors, each with a capacity of over 20 metric tonnes per year, which account for roughly 80% of output in China (66). Most prequalified ACT manufacturers produce their own API. Ajanta is the exception and purchases API from IPCA, Mangalam,

and others, which it then formulates into an ACT. To fill the artemisinin supply gaps, most manufacturers buy artemisinin “on-the-spot”.

**Figure 44: Supply chain of artemisinin for prequalified manufacturers, 2011**



manuf = manufacturer

Source: Artemisia/artemisinin industry supply chain mapping, Malcolm Cutler – FSC Development Services Ltd, 2009, A2S2 website.

### 5.8.2 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 pre-set 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 9 displays an overview of the approximate artemisinin production costs for Africa, China and Viet Nam.

**Table 9: Approximate artemisinin production costs for 2012**

	China, 2012	Africa, 2012 <sup>a</sup>	Viet Nam, 2012
Cost of cultivated leaves USD/tonne	1200–1600	1200–1,400	900–1400
Cost of wild leaves USD/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 (USD/tonne leaves)	950–1050	1350–1400	500–1000
Extraction/purification efficiency	75%–80%	65%±5%	55%
Total cost/tonne leaves (USD)	2050–2400	2550–2800	1400–2400
Kg artemisinin/tonne leaves	5.1–5.4	6–7	3.3–3.9
Cost per kg artemisinin (USD/kg)	380–470	365–465	360–727

<sup>a</sup> Figures for East Africa and Madagascar are similar and for this reason are aggregated here.

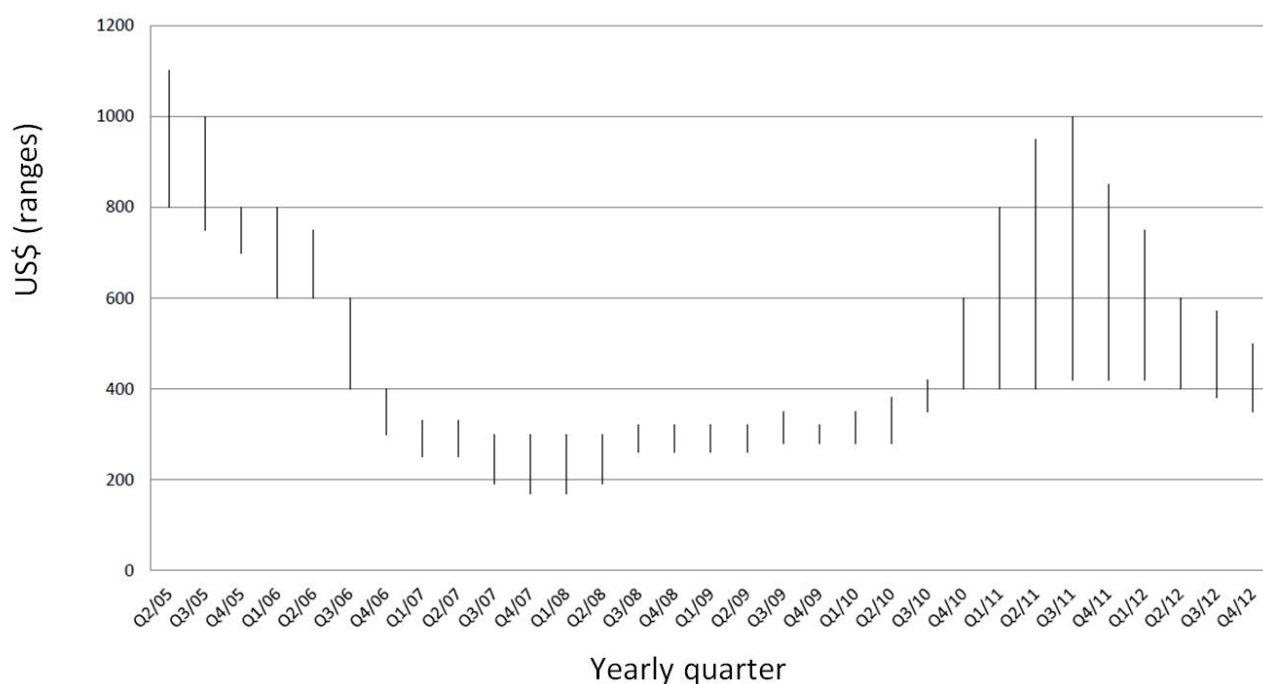
Source: Assured Artemisinin Supply System (A2S2) Y13Q2 Market Intelligence Update. July 2013.

### 5.8.3 Artemisinin prices

Artemisinin prices 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 (Figure 45). 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. In contrast to 2011/2012, in which there were concerns about possible artemisinin shortages, in 2013 there are concerns of surplus fuelled by:

- a “bumper” crop from the 2012 harvest, with high levels of cultivated artemisia, combined with favourable climatic conditions;
- a cautiousness on the behalf of the buyers of artemisinin, who were awaiting clarity on future levels of funding for ACTs, particularly through AMFm;
- the introduction in 2013 of semi-synthetic artemisinin (SSA) from Sanofi/OneWorld Health (Box 1) (66).

**Figure 45: Artemisinin selling prices (ranges)**

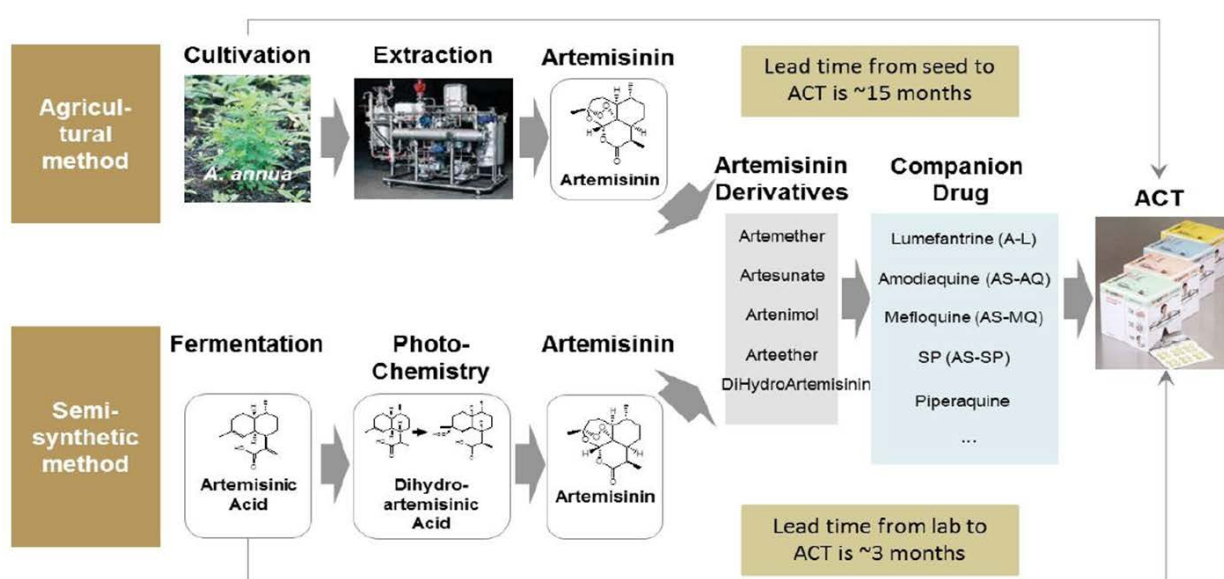


Source: Artemisinin market. Jacques Pilloy Oteci/AEDES. Presentation at the Artemisinin Conference, Nairobi, Kenya, 15–16 January 2013.



**Box 1: SSA**

SSA, uses biological and chemical processes to replicate the internal production of *A. annua*, offers an alternative source of artemisinin supply. The process, which was initially developed by the University of California, Berkeley, Amryis Biosciences and the Institute for OneWorld Health, was subsequently licensed to Sanofi for commercial scale-up and production. The aim of producing SSA is to provide a complementary source of non-seasonal, high-quality affordable artemisinin to supplement the current plant-based artemisinin and contribute to stabilizing the price of ACTs (67). 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

The master file for SSA was submitted to the WHO PQP in October 2012 (67) and was accepted in May 2013 for use in the manufacture of APIs or finished pharmaceutical products (FPPs) (68). The manufacturers of prequalified antimalarial FPPs who wish to use this new API source, will need to submit a variation to their prequalified FPP to PQP. Similarly, manufacturers of prequalified artemisinin APIs (artesunate, artemether or dihydroartemisinin) who wish to use this new source of artemisinin will need to submit an amendment to PQP.

In contrast to naturally produced artemisinin, which is considered as a “starting material” before being derivatized, SSA has been classified as an “intermediate”. In February 2013, PQP issued guidance on the proposed regulatory procedure for API manufacturers to introduce a source of non-plant-derived-artemisinin (69). In brief, manufacturers of non-plant-derived-artemisinin would submit to PQP a stand-alone master file (open and closed parts), and API manufacturers wishing to source this material may request that PQP refer to the confidential sections of the master file (with the permission of the supplier) and only need include within their regulatory documents limited details regarding this material.

Production capacity for SSA is estimated at 35 metric tonnes for 2013 for Sanofi use, with a total production capacity of 50–60 metric tonnes in 2014 (66). The current price estimate, based on a “no profit, no loss” model, is US\$ 350–400/kg for a routine production schedule (66). 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. Given that significant volumes of both SSA and agricultural artemisinin will be needed to meet demand for ACTs, a careful rollout of SSA will be required to ensure that it does not trigger agricultural suppliers to exit the market.



#### 5.8.4 Artemisinin supply and demand forecasts

In 2012, with increased *Artemisia annua* plantings and good weather conditions during the growing season, the global production of artemisinin increased considerably. Agricultural artemisinin supply for 2013 has been estimated at 238-264 metric tonnes (Table 10) (66). Current demand estimates for quality-assured ACTs in 2013 (319–334M treatment courses, equivalent to 148–155 metric tonnes of artemisinin) (48), suggest a surplus of artemisinin in 2013 (Figure 46).

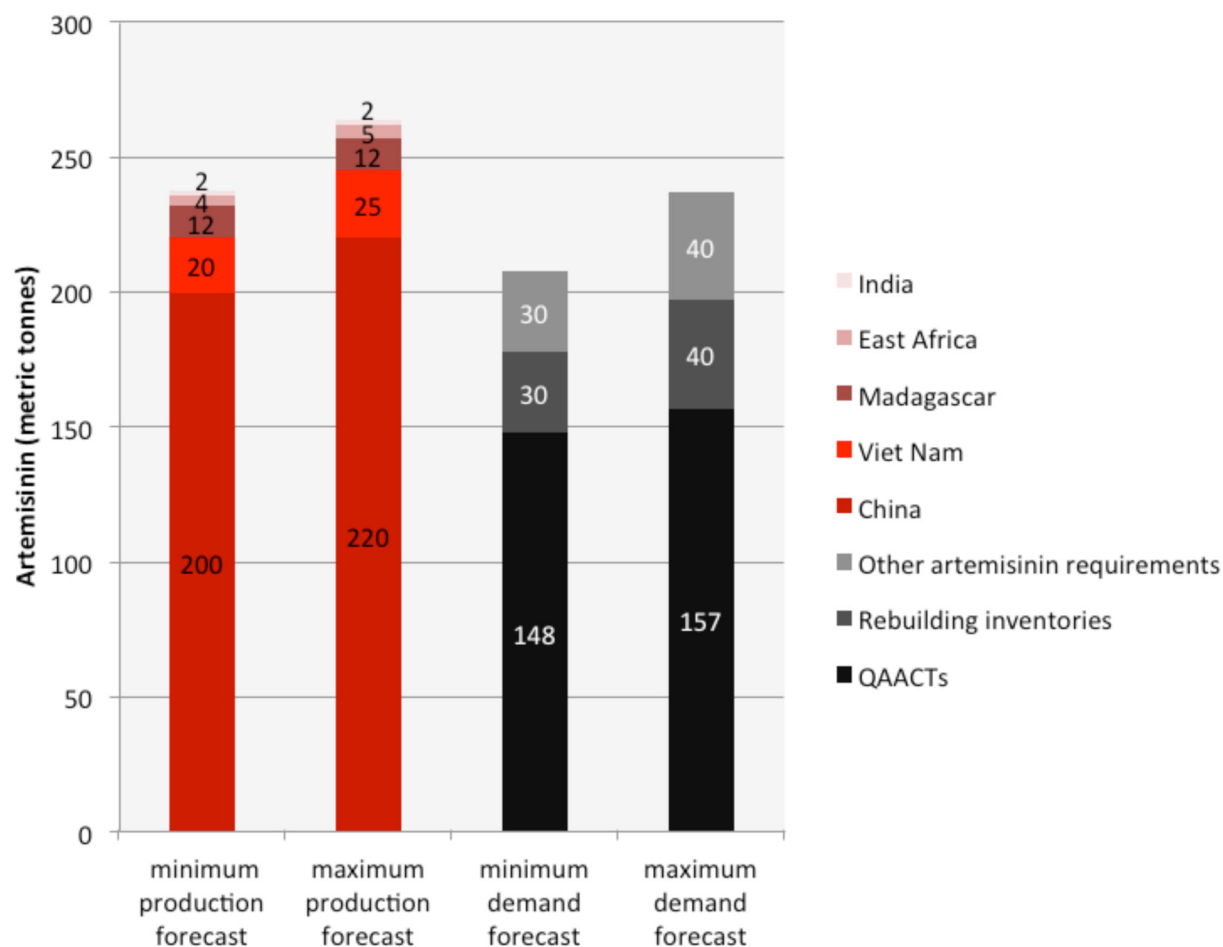
**Table 10: Artemisia planting areas and artemisinin production in 2012 (2013 supply)**

Country	Planting area (ha)	Artemisinin (kg/ha)	Estimated Artemisinin production (MT) in 2012
China	16,000 – 18,000	11kg/ha	200-220
Viet Nam	1,700 – 2,000	12kg/ha	20-25
East Africa	400-500	10kg/ha	4-5
Madagascar	800	15kg/ha	12
India	170	12kg/ha	2
Sub-total natural artemisinin	19,070 – 21,470		238 – 264
Semi-synthetic (for use by Sanofi)		Not applicable	10*
Total			248-274

\* To be used for regulatory processes

Source: Assured Artemisinin Supply System (A2S2) Y13Q1 Market Intelligence Update. February 2013.

Figure 46: Artemisinin supply and demand forecasts, 2013



Sources: Adapted from Assured Artemisinin Supply System (A2S2) Y13Q1 Market Intelligence Update, February 2013. Estimates for QAACTs taken from: ACT forecast Q3 2012 (unpublished draft).

The agricultural artemisinin supply for 2014, based on production in 2013, is estimated at approximately 202-262 metric tonnes (Table 11). However, recent information suggests that artemisinin production in China may be lower than originally estimated (approximately 100 metric tonnes instead of 170 metric tonnes) due to low artemisinin prices (below \$300/kg) and a lack of orders. This would reduce the total production of natural artemisinin to 132 metric tonnes. Demand forecasts for 2014 are difficult to predict due to funding uncertainties. In particular, at the end of 2013 AMFm will be integrated into core GFATM grant management and financial processes, making private sector demand for quality-assured ACTs difficult to quantify. In terms of the needs to rebuild safety stocks in 2013/14, this demand is estimated to be limited due to the stocks being amply filled by 2012 (surplus) production. Finally, if SSA is introduced into the market as planned, it is expected that the demand for natural artemisinin will drop as a proportion of total demand.

**Table 11: Provisional supply estimates for 2014 (based on 2013 production estimates)**

Country	Planting area (ha)	Artemisinin (kg/ha)	Estimated Artemisinin production (metric tonne) in 2013
China	15 000–16 000	11 kg/ha	170 <sup>a</sup>
China wild leaves			60 possible
Viet Nam	1000–1100	12 kg/ha	12 – 13
East Africa	400–500	10 kg/ha	5
Madagascar	1500	14 kg/ha	12
India	250	12 kg/ha	3
Subtotal natural artemisinin	18 150–19 350		202 (262 possible)
Semi-synthetic (for use by Sanofi)		not applicable	35
Total			237 (297 possible)

<sup>a</sup> Estimate as of June 2013. More recent information suggests that artemisinin production in China may be lower (approximately 100 metric tonnes) due to low artemisinin prices (below \$300/kg) and a lack of orders.

Source: Assured Artemisinin Supply System (A2S2) Y13Q2 Market Intelligence Update. July 2013.

### 5.8.5 Market volatility

The long duration of the agricultural artemisinin production cycle limits market responsiveness to sudden changes in demand, and in the past has resulted in a volatile market with large price fluctuations. Resulting supply is significantly affected by price volatility in the market, and by the relative attractiveness of other crops; at times of rising food insecurity, high prices for other commodities may encourage farmers to plant crops other than *A. annua*.

Currently, falling prices and concerns regarding surpluses 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 at the beginning of 2014. 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.

Without long-term funding commitments for ACT purchases, which allow realistic production planning, it is very difficult to stabilize artemisinin prices. The imminent introduction of large volumes of SSA, without careful coordination, also could exacerbate this problem. Maintaining and communicating up-to-date market intelligence on the demand for ACTs and artemisinin, and on the market entry of SSA, has, therefore, been identified as a key mechanism for stabilizing artemisinin prices.

### 6. Market shortcomings and their reasons

Following substantial investments and efforts made in recent years to scale up the use of quality-assured ACTs, the malaria community is now faced with the challenge of sustaining, and expanding, the progress made over recent years. Following its December 2012 Board meeting, RBM issued the following press release summarizing this challenge, “Africa has made enormous progress in fighting malaria, but we have to ensure, as a continent, that this funding is sustained; we risk backsliding if we don’t act fast. The gaps in funding will have serious consequences if they are not filled; lives will be lost and our battle against poverty derailed” (70).

Through the development of this market landscape, consultations with key informants and review of other UNITAID malaria landscapes for possible cross-cutting issues, seven market issues have been identified as likely to influence access to quality-assured ACTs in the future:

- **Reliable funding:** The availability and stability of future funding to supply sufficient quantities of quality-assured ACTs to meet estimated needs, and to assist forecasting measures that will aid a better understanding of the market, including potential new ACT manufacturers.
- **Sufficient and stable supply of artemisinin:** Stability of the price and supply of plant-derived artemisinin, and coordinated introduction of SSA into the market.
- **Information on future demand:** Accurate demand forecasts to allow manufacturers to plan appropriately and ensure sufficient production capacity.
- **Effective delivery:** Better country-focused networks that can drive coordination of ACT delivery and, therefore, build delivery capacity.
- **Provision of optimal medicines:** Improvements to the quality control of ACTs and better regulation of antimalarial markets to reduce use of suboptimal products; improvements to the availability of ACTs adapted to children in terms of palatability, dosing and formulation.
- **Enhanced drug resistance monitoring:** Improved monitoring of artemisinin resistance, particularly in (West) Africa. Monitoring resistance to SP also will be important in light of its increased use in SMC in the Sahel subregion, and in the increased dosing schedule of IPTp (three doses of SP during pregnancy versus two previously).
- **Scale-up quality diagnostics:** Improved quality and expanded use of rapid diagnostic tests (RDTs) as a key contribution to improved management of non-malaria fevers, leading to rational use of ACTs, antibiotics and other medicines, and improving health-care outcomes for children at the community level.

Unless otherwise stated, reference to ACTs throughout this section refers to prequalified ACTs.

## **6.1 Market shortcomings for malaria medicines**

Several shortcomings in the malaria medicines market have been identified through the development of this landscape, as well as through discussions with key stakeholders and previous Malaria Medicines Landscapes (e.g. BCG Market Landscape of Malaria Medicines 2012 – unpublished). 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 (Table 12) 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 primaquine for treating the liver stage of <i>P. vivax</i>	<ul style="list-style-type: none"> <li>■ Research is ongoing (e.g. tafenoquine) but products are not yet available</li> <li>■ 8-aminoquinolines are the only class of drugs known to have anti-hypnozoite activity and all suffer from safety issues, especially G6PD-deficient patients</li> <li>■ Lack of incentives for manufacturers to invest in R&amp;D due to uncertainties around future demand, market size and return on investment</li> </ul>
	No single-dose ACTs to reduce current three-day dosing requirements	<ul style="list-style-type: none"> <li>■ Two candidates for a single-dose cure for uncomplicated <i>P. falciparum</i> malaria are under development but earliest availability is 2018</li> <li>■ Lack of incentives for manufacturers to invest in R&amp;D due to uncertainties around future demand, market size and return on investment</li> </ul>
Affordability	High ACT retail prices in non-AMFm countries (e.g. US\$ 4.81 in Zambia and US\$ 2.10 in Benin), with a high price differential between ACTs and nATs (ACTs are around 5–24 times more expensive than nATs)	<ul style="list-style-type: none"> <li>■ High ACT manufacturing costs, including expensive and variable raw material prices (artemisinin prices have ranged from US\$ 170–1100/kg)</li> <li>■ Despite an increase in the number of prequalified ACT suppliers in recent years, market share is still highly concentrated by a few manufacturers</li> <li>■ Future integration of AMFm into GFATM grant mechanisms suggests little scope for expansion of private sector subsidies</li> </ul>
	Limited price reductions over time of ACTs procured through the GFATM and AMFm	<ul style="list-style-type: none"> <li>■ Pricing architecture of key procurement channels</li> <li>■ Reliance on the assumption that increased market competition will stimulate competitive pricing</li> </ul>
Quality	Low market share and availability of QAACTs, particularly in the private sector of non-AMFm countries (e.g. market share of QAACTs: 3.1% in DRC, 6.3% in Zambia and 16.7% in Benin; proportion of private outlets with QAACTs in stock: <30% in Benin, DRC and Zambia)	<ul style="list-style-type: none"> <li>■ Low demand for QAACTs in the out-of-pocket market due to higher cost (see Affordability above)</li> <li>■ QAACT manufacturers have tight production capacity with low incentive for expansion due to uncertain future demand</li> <li>■ Lack of visibility on future orders and variability of raw materials prices</li> <li>■ Complexity and cost of prequalification process</li> <li>■ Weak and/or unharmonized regulatory standards in many endemic countries, which limit incentives for manufacturers to meet international drug quality standards</li> </ul>
	High quality-control failure rates among non-prequalified ACTs (60% quality-control failure rate versus <4% for prequalified ACTs) and non-artemisinin treatments (e.g. 28% quality-control failure rate for SP)	<ul style="list-style-type: none"> <li>■ Existence of counterfeit drugs that form the basis for a profitable business, which benefits from insufficient local quality control and awareness</li> <li>■ Regulatory loopholes allow significant market penetration by substandard or non-proven therapies</li> <li>■ Technologies for on-the-spot quality control not widely used</li> </ul>

Acceptability/ adaptability	While ACTs are more widespread than in 2002–2006, their usage is still below that of non-recommended therapies (~4–44% among antimalarials given to febrile children) <sup>5</sup>	<ul style="list-style-type: none"> <li>■ Complex dosing regimen of ACTs compared to single-dose conventional therapies, which has been cited by patients and providers as a key acceptability barrier to ACTs (1)</li> <li>■ Non-availability of single-dose ACTs</li> <li>■ Limited palatable medicines for children, both for curative and preventive drug regimens</li> </ul>
Delivery	Risk of supply shortages for artemisinin	<ul style="list-style-type: none"> <li>■ The long, complex and multi-actor, upstream supply chain contributes to a volatile market and limits market responsiveness to sudden changes in demand</li> <li>■ SSA could help to stabilize the supply and price of artemisinin but ACTs made with SSA are yet to enter the market; market entry of SSA also could have a destabilizing effect on the market if shortages arise from growers and extractors of plant-based artemisinin exit the market</li> </ul>
	Public sector stockouts of prequalified ACTs	<ul style="list-style-type: none"> <li>■ Public sector supply is challenged by tight QAACT production capacity</li> <li>■ Delays in funding disbursements</li> <li>■ Demand uncertainty/unpredictability and diversion from public subsidized sector to private for-profit sector</li> <li>■ Suboptimal in-country planning and supply management and forecasting as well as uncertainty on the effect of diagnostics on treatment demand</li> </ul>
	Low availability of ACTs in private sector facilities, particularly outside AMFm Phase I countries (e.g. 20% in Zambia; <25% in Benin; <30% in DRC)	<ul style="list-style-type: none"> <li>■ Low private sector demand for ACTs is largely due to high ACT prices compared to non-artemisinin treatments (e.g. ACTs are 5–24 times more expensive than SP and CQ)</li> <li>■ Complex dosing regimen of ACTs and non-availability of single-dose ACTs, also may contribute to low demand</li> <li>■ 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</li> </ul>
	Large rates of overtreatment with all antimalarials, including ACTs, particularly in the private sector (in 2010, it is estimated that 655M treatments were delivered through the private sector in Africa alone) (2)	<ul style="list-style-type: none"> <li>■ Historical practice of presumptive treatment of fever with antimalarials</li> <li>■ Low uptake of quality, point-of-care diagnostic tools for malaria (RDTs), particularly in the private sector where presumptive dispensing prevails alongside low ACT availability</li> </ul>
	Unpredictable future demand	<ul style="list-style-type: none"> <li>■ 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</li> </ul>

<sup>5</sup> Household surveys, 2010–2011, from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe). The public health sector includes government and non-profit facilities; the formal private sector includes private clinics and providers; the community sector is community health workers; the informal private sector includes pharmacies, shops and traditional providers. Figures represent the 10th and 90th percentiles.



## 6.2 Market shortcomings for paediatric antimalarial medicines

For the most commonly used ACTs, adult and paediatric treatments consist largely of the same formulations sold as solid oral tablets in different packs sizes, though two AL dispersible tablets are WHO prequalified and different dosages of ASAQ exist for infants, toddlers and children/adults. The market shortcomings for ACTs as a whole also apply to paediatric packs sizes. In addition, the following market shortcomings have been identified (Table 13) that are specific to 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, despite being recommended by WHO for the pre-referral treatment of severe malaria	<ul style="list-style-type: none"> <li>■ One RAS product is currently under review by an SRA but has not yet been approved</li> <li>■ Lack of information on the size of the market for the pre-referral treatment of severe malaria</li> </ul>
Acceptability/adaptability	Low uptake of child-friendly ACT formulations for children under five years old (12% of the total donor-funded market for AL in 2011)	<ul style="list-style-type: none"> <li>■ Only one prequalified manufacturer of dispersible tablets until December 2012 (Novartis, and now Ajanta)</li> <li>■ Variable demand for dispersible tablets by different providers and caregivers</li> <li>■ Multiple non-prequalified paediatric formulations (e.g. suspensions) are available in local markets</li> </ul>
Delivery	Low uptake of INJAS for severe malaria	<ul style="list-style-type: none"> <li>■ Inadequate advocacy, education and training, including poor communication around the superior efficacy, leading to poor acceptance by patients and providers</li> <li>■ High treatment prices (three times more than injectable QN) due to low volumes and lack of competition</li> <li>■ Only one prequalified product (Guilin Pharmaceuticals), with buyer concerns over single-prequalified supplier; if the single supplier cannot meet the demand, then there is potential for stockouts</li> <li>■ Commercial interests around injectable QN which is often procured from local manufacturers; behavioural issues around QN use</li> </ul>

## 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. Artemisinin Conference, Malaria Market Forum, RBM Procurement and Supply Management Working Group meetings) and more exploratory interventions that require additional discussion and vetting. This section is not specific to 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. Longer-term funding commitments would, therefore, 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 “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. 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, the reported rate of RDT use in the public sector in sub-Saharan Africa was still only 47% in 2011 (6). In the same region between 2006 and 2011, the number of diagnostic tests conducted in the public sector was less than half of the ACTs distributed, when the ratio of diagnostic tests to ACTs should be  $\geq 2$  (6). 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*

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- **Support the sale of quality-assured ACTs 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 primaquine for treating the liver stage of *P. vivax*; a single-dose ACT to reduce current three-day dosing requirements; a prequalified RAS product for the pre-referral treatment of severe malaria; and an alternative to SP for IPTp. Several products are in the advanced stages of development that could address these needs and improve malaria treatment. The ongoing monitoring of high-potential products is, therefore, an important activity, including investigating any potential opportunities to speed up market entry by encouraging late-stage development, streamlining evidence review and policy/guideline modification, and preparing the market for uptake once a product becomes available.

*Market shortcoming addressed: Availability*

- **Support the production of global ACT and RDT demand forecasts that project the need of ACTs and RDTs in relation to each other, the disease burden and funding available**

Maintaining and communicating up-to-date information on the future demand for ACTs is a key mechanism for stabilizing the price of both artemisinin and ACTs and promoting a consistent supply of ACTs enabling improved global access to quality malaria treatment. Going forward, the scale-up of malaria RDTs is going to impact ACT demand and as such RDT demand should be forecasted alongside ACTs. Further to this, it will be important to clearly 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. UNITAID currently supports quarterly forecasts that predict the demand for donor-funded, prequalified ACTs and the resulting demand for artemisinin. In light of future unpredictability of supply and demand situations, UNITAID will continue to maintain a forecasting service, expanding to include both ACTs and RDTs, to ensure information is collected and communicated to all supply chain agents.

*Market shortcoming addressed: Delivery*

- **Stabilize artemisinin prices and supply through the collection and dissemination of information on supply and demand, and evaluate the need for additional targeted interventions**

Some research shows that artemisinin makes up 20–40% of the total cost of ACTs (34). Reducing the volatility of the artemisinin market is, therefore, an important mechanism to influence ACT prices and ensure that appropriate artemisinin supplies are available to meet demand, thereby avoiding long lead times and stockouts. A key mechanism to stabilize the artemisinin market is the collection and communication of up-to-date market intelligence on the supply of, and demand for, artemisinin and the market entry of SSA. While SSA has the potential to reduce price and supply volatility, it also has the potential to disrupt the market and lead to shortages if farmers and extractors exit the market. A careful and transparent rollout of SSA, with active information dissemination, is, therefore, required to allow different market actors to adapt to new dynamics that SSA brings to the artemisinin and ACT markets. While the collection and dissemination of information is an important interven-

tion, it may not be sufficient in itself to stabilize this market. Over the next few years, the artemisinin market should be carefully monitored with a view to evaluating what, if any, additional measures are needed to bring stability to this market. This could include, for example, the creation of a global natural artemisinin stock management entity using buffer stocks to compensate for demand and drastic price changes. It also could include, in time, measures to support the market entry of additional suppliers of SSA.

*Market shortcomings addressed: Affordability, Delivery*

- **Encourage the uptake of IVAS 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 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.

*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 (rectal artesunate) 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.

*Market shortcomings addressed: Quality, Delivery*

- **Support a competitive market for child-friendly ACT formulations, especially for children under five years old**

The market share of dispersible QAACTs for children under five years old is low compared to solid, oral FDCs (37% versus 63%). Incentivizing a more competitive market for child-friendly formulations could give the donor community scope to preferentially procure dispersible formulations. This could include, for example, incentivizing the prequalification of additional dispersible AL products; it also will 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 PyA). Supporting their development and/or entry into the market may be catalytic in scaling up quality-assured, child-friendly ACTs for children under five years old. The bitter taste of some antimalarial medicines, such as amodiaquine, 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 treatment delivery in future SMC projects.

*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, sulfadoxine-pyrimethamine (SP) + amodiaquine is recommended for SMC in the Sahel subregion, and SP is recommended for IPTp and IPTi (71). As such, a better understanding of the rational demand for CQ, SP and amodiaquine 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 (72) measures to support better quality control of these products are warranted. Innovative quality-control technologies, such as handheld 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*

## 8. Conclusion

The market for malaria medicines is currently very dynamic and evolving rapidly. Changes to the malaria funding landscape, notably the evolution of the GFATM round-based funding to the New Funding Model and the incorporation of AMFm into existing funding modalities, are going to be determining factors on the size and nature of malaria medicines markets over the next few years. Global policy changes, such as universal diagnostic testing and recommendation of SMC, also are having a strong impact on existing markets as well as driving the need for new products. Looking ahead, changing malaria epidemiology, emerging resistance to artemisinin and an increased focus on malaria elimination are all going to have a strong influence on future markets. The changing nature of the malaria medicines market requires that it be continuously monitored in order to understand and mitigate market inefficiencies that are contributing to access issues. A range of market-based interventions are possible, ranging from upstream interventions to stabilize the volatility of the artemisinin market, to more downstream interventions aimed at the point of delivery. Careful consideration needs to be given to the optimal suite of interventions in order to maximize market and public health impact as well as value-for-money.

## 9. Annexes

### Annex 1: Prequalified medicines WHO list of prequalified medicinal products as of April 2013<sup>19</sup>

Table created on 23 April 2013 from the website at <http://apps.who.int/prequal/>.

Applicant	Manufacturing site	INN	Strength	Formulation	Date of prequalification
Ajanta Pharma Ltd	India	AL	Tablets 20 mg+120 mg	FDC	16-Dec-08
	India	AL	Dispersible tablets 20 mg+120 mg	FDC	19-Dec-12
Artecef BV	Germany	Artemotil	Solution injection 50 mg/ml	Solution	1-Mar-06
	Germany	Artemotil	Solution injection 150 mg/ml	Solution	1-Mar-06
Cipla Ltd	India	AS+AQ	Tablets 153 mg (200 mg as hydrochloride)+tablets 50 mg	Co-blister	11-Nov-08
	Uganda	AL	Tablets 20 mg+120 mg	FDC	22-May-09
DNDi, Switzerland (Cipla Ltd)	India	AS+MQ	Tablets 25 mg+50 mg	FDC	12-Sep-12
	India	AS+MQ	Tablets 100 mg+200 mg	FDC	12-Sep-12
Guilin Pharmaceutical Co. Ltd	China	AQ	Film-coated tablets 150 mg	Tablet	30-Aug-07
	China	AS+AQ	Tablets 67.5 mg+25 mg	FDC	16-Nov-12
	China	AS+AQ	Tablets 270 mg+100 mg	FDC	16-Nov-12
	China	AS+AQ	Tablets 135 mg+50 mg	FDC	16-Nov-12
	China	AS+AQ	Tablets 150 mg+50 mg	Co-blister	30-Aug-07
	China	AS	Tablets 50 mg	Tablet	21-Dec-05
	China	AS	Powder for Injection 60 mg	Powder	5-Nov-10
	China	AS+SP	Tablets+tablets 50 mg+(500 mg+25 mg)	Co-blister	24-May-12

<sup>19</sup> Since the preparation of this landscape, an additional ACT, artemether-lumefantrine tablets 20 mg+120 mg, manufactured by Strides Arcolab Limited, achieved WHO prequalification on 24 June 2013.



Ipca Laboratories Ltd	India	AS+AQ	Tablets 67.5 mg+25 mg	FDC	1-Jun-12
	India	AS+AQ	Tablets 270 mg+100 mg	FDC	1-Jun-12
	India	AS+AQ	Tablets 135 mg+50 mg	FDC	1-Jun-12
	India	AS+AQ	Tablets 153 mg (200 mg as hydrochloride)+tablets 50 mg	Co-blister	23-Apr-08
	India	AL	Tablets 20 mg+120 mg	FDC	15-Dec-09
	India	AS	Tablets 50 mg	Tablet	30-Aug-07
Novartis Pharma	China; USA	AL	Tablets 20 mg +120 mg	FDC	26-Apr-04
	USA	AL	Dispersible tablets 20 mg + 120 mg	FDC	27-Feb-09
Sanofi	Morocco	AS+AQ	Tablets 67.5 mg+25 mg	FDC	14-Oct-08
	Morocco	AS+AQ	Tablets 270 mg+100 mg	FDC	14-Oct-08
	Morocco	AS+AQ	Tablets 135 mg+50 mg	FDC	14-Oct-08
Shin Poong Pharmaceutical Co Ltd	Republic of Korea	AS+SP	Tablets 60 mg+180 mg	Co-blister	EMA Article 58
Strides Arcolab Limited	India	AS+AQ	Tablets (co-blistered) 153 mg+50 mg	FDC	22-Dec-11

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

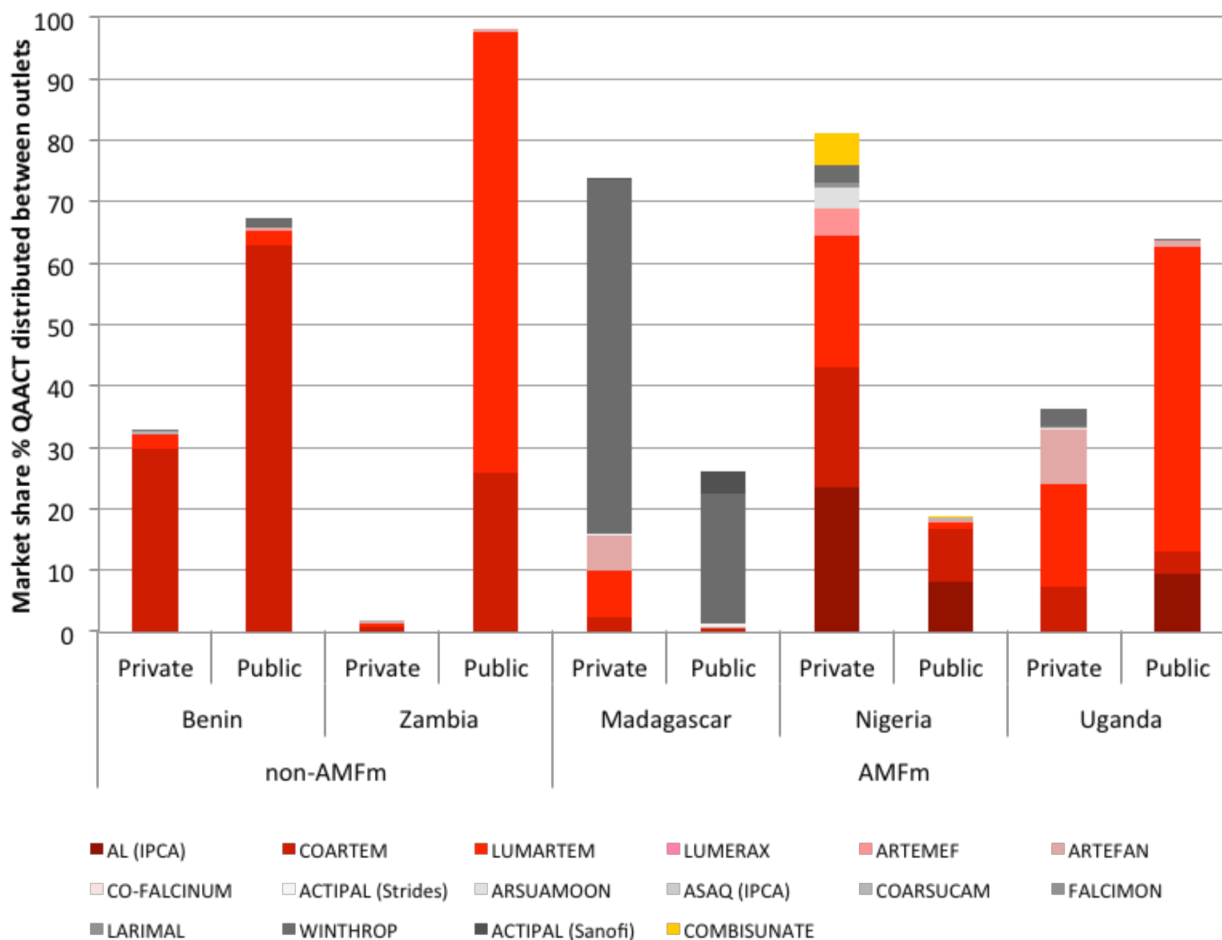
## Annex 2: Medicines under assessment for WHO prequalification

Table created on 23 April 2013 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	20 mg+120 mg	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.
AQSP	Tablet	500+25+150 mg	Additional data to be provided by the manufacturer: quality. Dossier part acceptable: efficacy/safety.
AQSP	Tablet	250+12.5+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.

**Annex 3: Relative market share of QAACT brands sold/distributed between outlets in the past seven days, by sector, 2011**



Notes: Public/not-for-profit 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. Shades of red represent artemether-lumefantrine (AL) products, shades of grey represent artesunate-amodiaquine (ASAQ) products and yellow (combisunate) represents artesunate sulfadoxine-pyrimethamine (ASSP).

Source: ACTwatch outlet surveys 2011.

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