



RBM-WHO ROUND TABLE ON ACT SUPPLY

CROWNE PLAZA HOTEL

GENEVA

08 September 2011

Acknowledgements

The Organizers gratefully acknowledge the commitment and quality of the work of Dr Ian Boulton, TropMed Pharma Consulting, which has been the main Rapporteur of the Meeting and writer of this Report.

EXECUTIVE SUMMARY

Recently there have been reports of delays to deliveries of ACTs¹, of manufacturers being unable to accept orders with short delivery times, and of escalating prices of artemisinin on the “spot” market. This has been interpreted by some people as indicating a significant problem in the ACT supply chain. However the evidence to date remains limited. The RBM-WHO Round Table on ACT Supply was convened to bring together all the major stakeholders to discuss the situation fully and to make recommendations to address any challenges identified.

Global demand for ACTs has increased in 2011 with demand in the private sector being the major component. However forecasting this market is complex and is associated with significant uncertainties. The ACT Forecasting Consortium, working with WHO, CHAI, and A2S2 have developed a picture of the overall global situation for 2011. This shows that while the demand for and supply of ACTs have both increased substantially, there is a risk of demand exceeding supply in certain localised situations. ACT manufacturers have adequate installed capacity to meet current and forecast demand. This is provided that the orders are properly staged throughout the year and not concentrated in only a few months. The main challenge is the supply of artemisinin and the uncertainty about the levels of buffer stocks of APIs and artemisinin being held by the ACT manufacturers. Recent stories and rumours about artemisinin supplies have driven up its price on the “spot” market. Manufacturers are concerned that artemisinin suppliers are insisting on renegotiating the price in existing supply agreements to bring it closer to the “spot” market price.

The sudden success of AMFm contributes substantially to the recent increase in demand of ACTs. Learning from experience AMFm has recognised the need to more proactively manage its approvals of co-payment requests. It has introduced a series of “levers” for the review of orders before granting their approval.

The risk of malaria epidemics associated with the humanitarian disasters in the Horn of Africa is placing increased pressure on the ACT supply chain. Affected countries have made provisions to have adequate stocks of ACTs in place to meet any increased demand, but this is dependent on manufacturers meeting their agreed delivery dates.

The final balance between global supply and demand of ACTs in 2011 is tight and remains unclear at this time. The Round Table participants were not complacent. The meeting made a series of recommendations outlined in this report to:-

- Establish a small management team (“nerve centre”) under the leadership of WHO GMP, to gather real time supply and demand data that will uncover “red flag” countries where supply may not meet demand.
- Ensure communications about the supply and demand situation are carefully constructed to avoid adding unnecessarily to the challenges in the market.
- Improve forecasting and communications of the actual situation to ensure all stakeholders are making decisions on the best information possible.
- Where possible, improve systems to increase the flexibility in the supply chain to ensure that ACT supplies reach the countries and places where the need is greatest.
- Reduce demand for ACTs where possible through wider access to and use of diagnostic testing and reduced use of ACTs for non-malarial fevers.
- Maintain open communication between all major stakeholders in the supply chain.
- In the longer-term, have in place buffer stocks of ACTs and APIs to meet sudden emergencies.
- In the long-term, explore the feasibility of manufacturers' request for binding forecasts of ACT demand to minimise financial risk.

¹ Abbreviations are on the next page.

Abbreviations

| | |
|-------------|--|
| A2S2 | Assured Artemisinin Supply System |
| ACT | Artemisinin-based Combination Therapy |
| AL | Artemether/lumefantrine |
| ALMA | African Leaders' Malaria Alliance |
| AMFm | Affordable Medicines Facility – malaria |
| API | Active Pharmaceutical Ingredient |
| ASAQ | Artesunate/amodiaquine |
| BCG | Boston Consulting Group |
| CHAI | Clinton Health Access Initiative |
| FDC | Fixed Dose Combinations |
| FLB | First Line Buyers (of ACTs co-paid by the AMFm) |
| Global Fund | Global Fund to fight AIDS, Tuberculosis, and Malaria |
| GMP | Global Malaria Programme (of WHO) |
| MIT | Massachusetts Institute of Technology |
| PMI | US President's Malaria Initiative |
| PSMWG | Procurement and Supply Chain Management Working Group (of RBM) |
| RBM | Roll Back Malaria Partnership |
| RDT | Rapid Diagnostic Test |
| WHO | World Health Organisation |
| WHO-PQ | WHO Prequalified |

INTRODUCTION

Recently, several Roll Back Malaria (RBM) partners have reported longer delivery lead-times from manufacturers of artemisinin-based combination therapies (ACTs) for malaria, limited capacity of some ACT manufacturers to accept additional orders with short delivery times, and increases in the price of artemisinin on the “spot” market. These signals have been interpreted by some people as indicating the risk of either a shortage of artemisinin or a shortage of ACT formulation capacity. However the picture is complex and most of the evidence so far has been limited and anecdotal. The Round Table brought together representatives of the major stakeholders in the ACT supply chain (funders, buyers, manufacturers, implementers, other RBM partners) for a one-day meeting to discuss the situation fully and to recommend potential actions to be taken to address any challenges identified.²

The goals of the meeting set by the organisers were:-

- Improve communications about the actual situation among all stakeholders in the ACT supply chain.
- Agree on the actual situation, based upon all unbiased information available and not anecdotes.
- Discuss additional needs arising from any possible emergency or epidemic situations (as is anticipated in the Horn of Africa).
- Agree on a co-ordinated plan of action to address any supply challenges identified in the meeting.
- Agree on a co-ordinated communications plan to inform stakeholders on the real situation and the actions being undertaken to mitigate any risks.

SITUATION

ACT Demand

Global Demand Projections

The ACT Forecasting Consortium (the Consortium) funded by UNITAID is developing periodic forecasts of the global demand for ACTs.³ They produce quarterly updated 2-year global forecasts of ACT demand and artemisinin supply requirements based on the information they are able to access. The ACT market is a difficult one to forecast because it is:-

- Currently very dynamic.
- Market data is incomplete – parts of the market are difficult to access for accurate data.
- What data there is available is often hedged around with uncertainties.
- The lead-time for the market to react to demand signals is long, primarily due to the long production time for artemisinin supplies (see later discussion) and the incomplete information systems that are currently available to the main stakeholders.

The projections that could be presented at the Round Table were single point-of-time forecasts utilising the data that has been available to the Consortium, currently developing its 3rd quarterly iteration of the 2011 - 2012 forecast. The forecast combines available market data from all major funding and procurement agencies placing orders of prequalified ACTs, with corrective factors based on disbursement levels and procurement lead times, as well as modelled inputs on expected consumer demand in both public and private sectors. The

² Participants are listed in Annex 1.

³ The ACT Forecasting Consortium was set up and is sponsored by UNITAID, managed by Boston Consulting Group (BCG) and gathers forecasting experts from BCG, Clinton Health Access Initiatives (CHAI), and the International Logistics Programme at MIT-Zaragoza. It operates under the auspices of the RBM Partnership and at the request of the Global Fund. The methodologies and forecasts are reviewed and validated on a quarterly basis (and in between as needed) by a Steering Committee composed of representatives of the Global Fund, RBM, UNITAID, and WHO Secretariats.

combination of these multiple factors places some quite significant uncertainties around the numbers that can be presented. At the moment the projections are summary pictures of the global expected annual ACT demand, but work is also underway to develop analysis of quarterly variations in demand. This may be more useful in identifying sudden challenges to the balance between artemisinin/API supply and ACT demand in this difficult-to-predict situation.

It is important also when reviewing figures of the supply and demand situation to have clarity about the differences between the demand from the ultimate consumers (patients, carers, health care facilities) and intermediaries in the supply chain (the first line buyers [FLB] and wholesalers for the private sector: national and international procurement agencies for the public sector). Over the long-term, the demand from consumers and intermediaries will be aligned, but in a dynamic market situation, with rapid but difficult-to-forecast growth in demand, there may be misalignments between the two.

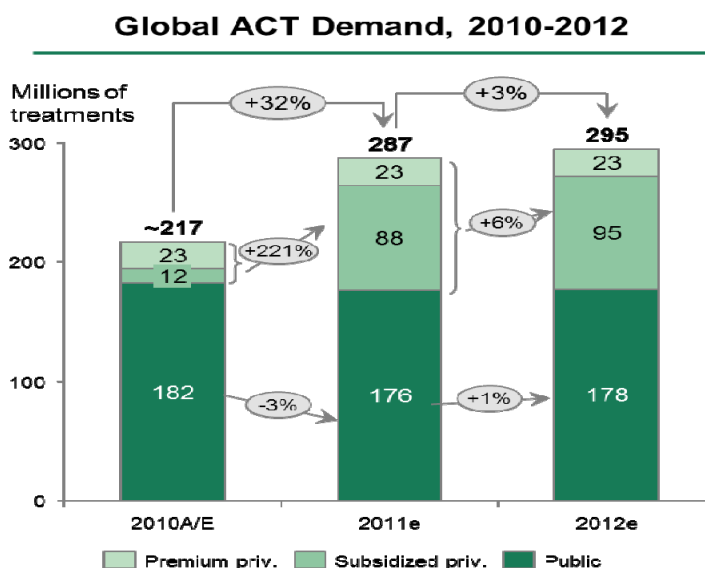


Figure 1

Based on the best information available, the Consortium presented the latest forecasts (Fig 1 and 2) showing that global WHO Pre-Qualified (WHO PQ) ACT consumer demand for 2011 will be 287 million treatments, a 32% increase over 2010. The forecast for 2012 is for 295 million treatments. While the demand via the public sector seems to plateau after several years of scaling up, the main driver of this increase is the significant growth of demand for ACTs in the private sector, where most malaria patients seek treatment. This increase is the effect of Phase I of the Affordable Medicines Facility - malaria (AMFm). This was launched in 2010 by the Global Fund to fight AIDS, Tuberculosis, and Malaria (the Global Fund). The AMFm Phase I currently offers co-paid ACTs to public and private First Line Buyers (FLBs) in 7 African countries, accounting for almost half the population at risk of malaria in Africa and all of them among the countries with the highest malaria burden. The demand due to AMFm is in line with the forecast presented to the Global Fund Board in 2008⁴. The premium private ACT market (*i.e.* for non-subsidized ACTs) is estimated to be at 23 million treatments worldwide and flat, although this may be decreasing in AMFm pilot countries as consumers shift to buying AMFm co-paid ACTs.

⁴ Report of the Global Fund Board AMFm Ad Hoc Committee to the Global Fund Board for approval of AMFm Phase 1 (Global Fund AMFm webpages)

Global ACT Consumer Demand, 2011-2012

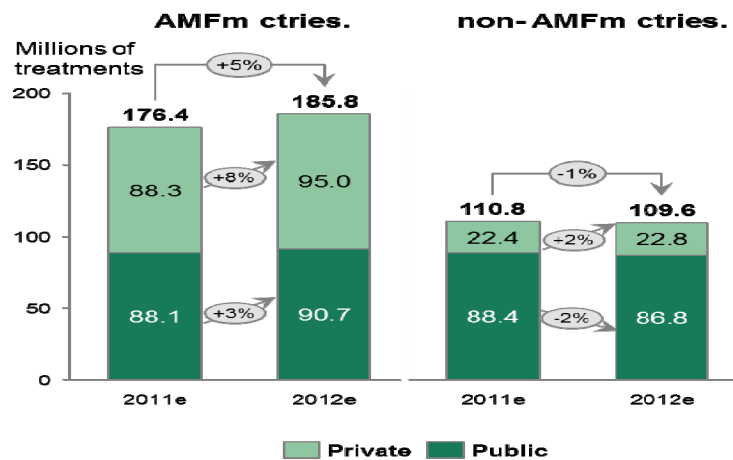


Figure 2

When quantifying their public sector ACT demand for 2011-2012, most countries assumed that current malaria diagnostic practices would not change significantly, *i.e.* only small proportions of suspected malaria cases would be tested by microscopy or rapid diagnostic tests (RDTs), and many RDT negative patients would still continue to receive ACTs, particularly in Africa. Therefore the global forecast, based on the sum of country forecasts, does not take into account the reduction of ACT demand which one could expect as RDTs are used more widely and their results influence prescribing.

Forecast demand by age/weight bands indicates that paediatric forms should make up $\approx 60\%$ of the demand for treatments, and that by product, the split should be $\approx 70\%$ for artemether/lumefantrine (AL) and $\approx 25\%$ for amodiaquine/artesunate (ASAQ). Both of these are forecasted as fixed dose combinations (FDCs). The balance of the demand is made up of small quantities of other ACTs (*e.g.* artesunate + sulphadoxine/pyrimethamine, artesunate/mefloquine and dihydroartemisinin/piperazine).

There was some discussion of the impact of AMFm on the overall situation. Delays in delivery for both AMFm and non-AMFm orders have been reported, to a variable extent, for all ACT manufacturers. A survey conducted for the Consortium by CHAI concluded the following (*care needs to be taken in interpreting these survey results as they are based on interviews and are not quantified*):-

Public Sector:

- Demand is growing in the public sector, with in some countries local or regional public health authorities buying AMFm co-paid ACTs from the local private sector via tenders. This is to get around problems of central procurement and supply chain inefficiencies and delays.
- There is no evidence of unusual stock-out situations in the public sector, but some evidence of orders out-pacing deliveries. This may indicate impending shortages in supply, but may also indicate orders being increased and/or brought forward in response to concerns about shortages. The latter would produce unwanted short-term pressures on the global supply chain for needlessly increasing in-country stocks.
- In the public sector, distribution from central stocks to the field remains slow and “spotty”. Global Fund mapping of the situation in Nigeria found field-level availability of ACTs “remains very low”. This shortage in the field does not seem to be due to a shortage in the overall supply of ACTs to Nigeria.

Private Sector:

There are no reports of stock-outs of AMFm co-paid ACTs at FLBs. FLBs did however raise concerns that if global supply constraints became severe this might put at risk the affordability and access objectives of AMFm.

Affordable Medicines Facility – malaria

The AMFm was launched by the Global Fund as a pilot in seven African countries and operations initiated in June 2010. The initial estimates of demand under the AMFm, which the Global Fund Board considered in November 2008, were 290 million ACTs over a two-year period⁵. If this demand was equally divided up monthly, ACT orders would have resulted in co-payments for about 169.2 million treatments by end August 2011 (about 14 months after operations started in June 2010)⁶. As of end August 2011, AMFm Phase 1 had approved co-payments for a total of about 159.5 million treatments (including 29.4 million in 2010), slightly less than indicated in the 2008 projections. However, the demand for AMFm co-paid ACTs has increased sharply over the past six months. This is typical of sigmoidal uptake curves seen with new products introductions. However by end August only 84.9 million treatments have been delivered in the same period. This is due to the fact that many approved orders are scheduled to be delivered in several parts spread over time, but also to delays in deliveries due to other causes (see below).

The Global Fund AMFm Unit confirmed the Consortium’s finding that the readier availability of co-paid ACTs via AMFm, and delays in the central public sector procurement processes, has resulted in local public sector procurement from the private sector supply chains (FLBs and others) in Ghana, Kenya, Niger, and Nigeria.

Based on the data available on the private sector from the AMFm, there appears to be some level of delayed deliveries and backlog of orders across all manufacturers, albeit at different levels. The factors responsible for delays in deliveries are complex and it would be misleading to only attribute this to manufacturing capacity and artemisinin supply problems. The ordering patterns of FLB is influenced by marketing considerations, as well as by challenges of bureaucracy, regulatory approvals, customs clearances, internal distribution, foreign exchange availability, obtaining letter of credit, and others may also contribute to this problem. Deliveries may also be under-stated in the last few months due to delays in reporting them.

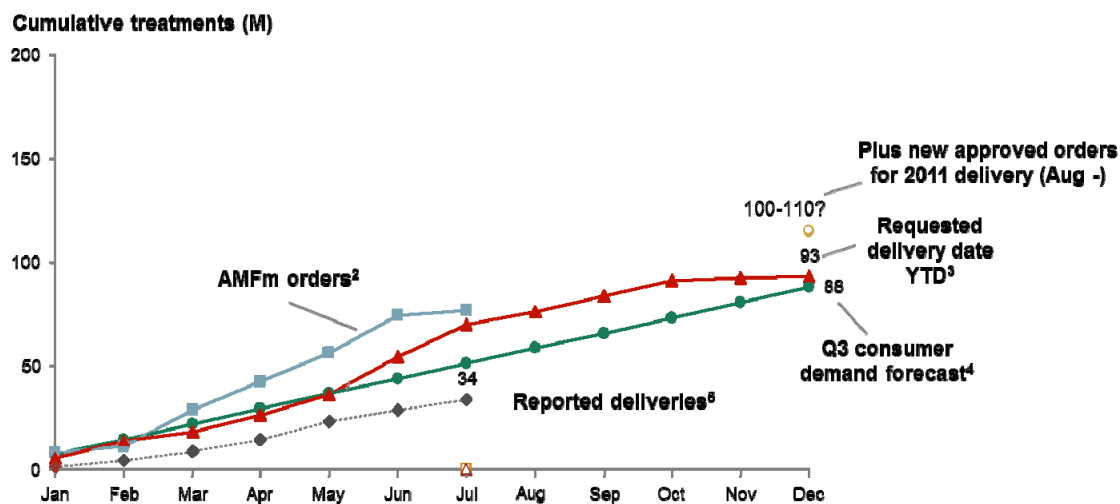


Figure 3

⁵ Report of the Global Fund Board AMFm Ad Hoc Committee to the Global Fund Board for approval of AMFm Phase 1 (Global Fund AMFm webpages)

⁶ 14 months’ forecast demand on a straight line projection of a 24 month demand of 290 million treatments would be $290 \times (14/24) = 169.2$ million.

Figure 3 shows the actual and forecast position for deliveries through the AMFm mechanism as at the end of July 2011, as best determined by the Consortium from all available data. All the figures are of cumulative orders and deliveries. The AMFm orders (2 – blue/grey) are all confirmed orders through the AMFm mechanism with documented 2011 co-payment dates. Requested delivery date (3 – red) shows the cumulative delivery schedule for currently approved orders based on the date indicated in the co-payment approval documentation. Q3 consumer demand (4 – green) is the expected constant consumer uptake based on the Consortium’s latest global annual forecast (assuming equal uptake in each month). Reported deliveries (5 – grey) shows the actual reported deliveries of AMFm approved ACTs.

These figures must be treated with some caution. Actual deliveries (5 – grey) are based on the reports to the AMFm team that delivery has actually taken place. The actual delivery time may differ from the original requested delivery time (3 – red) as there may have been negotiation subsequent to order placement on delivery times between the manufacturers and the FLBs, but these are still recorded as delayed deliveries. As mentioned earlier, delays in reporting delivery to the AMFm team may be understating the reported actual deliveries.

The Round Table requested an estimate of new approved orders for delivery in the rest of 2011. Based upon their public and private FLB survey referred to above, the Consortium estimates that an additional 7 – 17 million treatments may be required for delivery between August and December. This would bring up the total of AMFm-approved orders for delivery in 2011 to 100 -110 million treatments, and this is shown as a point estimate in Fig 3.

The Global Fund’s AMFm Unit has made adjustments to influence the market through incentives and to manage incoming orders. These aim to limit the growth in demand at the level of the first line buyer.

- The AMFm modified its co-payment schedule in March 2011. One of the objectives was to favour child pack sizes over adult pack sizes. For AL, 68 % of the 36 million treatments approved before the modified co-payment schedule were for the adult pack sizes (6x4 tablets). This reduced to 49% of the 98 million treatments approved after the modified co-payment schedule. The 6x1 tablet pack sizes increased from 16 to 32% and the 6x2 from 8 to 12% of approved orders over the same period. The 6x3 pack-size remained unchanged at 8%.
- While the total number of orders to date was less than projected in 2008, in July 2011 it became clear that after a very slow start in 2010 the ordering pattern had almost caught up with the initial forecast. This could lead to over-ordering as the updated forecasts became available. The AMFm therefore applied a number of adjustments to the order approval policy.

The AMFm Unit are also reviewing incoming orders for approval for co-payment using a series of “levers” to decide whether to immediately approve them or to put them on-hold until it is felt more appropriate to approve them. These “levers” are applied to the approval of orders received on a case-by-case basis. :-

- Ratio of cumulative approved orders to the Consortium’s estimated demand forecast, favouring countries and sectors where the ratio of the cumulative approved orders to estimated demand is low.
- Manufacturer delivery performance, favouring orders to manufacturers with high historical ratio of actual to planned delivery volumes by specified dates.
- Delivery date, favouring delivery in the next three to six months over delivery scheduled longer into the future.
- Formulation or pack size, favouring paediatric forms.
- Mode of transport, favouring sea over air where the mode of transport does not affect desired delivery times.
- Sector, favouring orders for the public over the private sector.

It is important to note that these levers are not applied rigidly but judgement is exercised by the AMFm team. In addition, orders are not rejected if they are not favoured by the “levers”, but are put on hold and kept under review until they are felt appropriate to approve.

The use of these levers aims to ensure that orders' delivery times are better aligned with estimated consumer demand and to reduce the pressure on the ACT supply chain from the ramping up of the AMFm demand. Since AMFm adjusted its order approval policy 87.4m orders were received out of which 20.3m were approved and 67.1m put on hold.

However, it should be remembered that total AMFm approved ACT orders to-date are in line with the original forecast number of 290 million in the first two years, as explained at the beginning of this section.

Additional Demand from Horn of Africa

The Horn of Africa (Ethiopia, Somalia, and Northern Kenya) is currently affected by a major humanitarian emergency, due to extended droughts, affecting an estimated population of approximately 12.4 people. Many of the areas affected by the drought are also at risk of malaria epidemics - the main at-risk period is October – December. ACTs are an essential component of preparedness plans of each of these countries. The African Leaders' Malaria Alliance (ALMA) warned of possible additional pressures on the ACT supply chain from the need to put in place in the next 4-6 weeks adequate emergency buffer stocks to meet a possible epidemic. Specifically:-

Somalia:

The estimated need is 800,000 treatments in 2011 & early 2012. Only 100,000 ACT treatments are in stock and there is also a need to bring forward delivery of the 400 – 450,000 treatments currently on order with a delivery time of December. Also there is a need to find resources to purchase another 375,000 treatments to meet the estimated demand and to replenish the buffer stocks.

Kenya:

1.2 million cases are expected in the areas at high risk of malaria epidemics, and local stock-outs have been reported at central and peripheral levels. Out of 11.9 million ACTs on order for delivery in the at-risk period, approximately 5.4 million treatments have been delivered in July-August. The remaining delivery dates should not be allowed to slip.

Ethiopia:

The country has approximately 2.3 million ACTs in stock. In order to meet the projected demand of an additional 3.5 million cases in case of a possible epidemic, a total of 5.5 million ACT treatment courses are on order. However, the government would like to order a further 600,000 treatments supplied for a buffer stock. All orders must be delivered on time and preferably deliveries expected in November and December be brought forward to avoid the risk of shortages during any epidemic.

ACT & Artemisinin Supply

Artemisinin Supply

The Assured Artemisinin Supply System (A2S2) funded by UNITAID is developing artemisinin market intelligence.⁷ They produce regularly updated 2-year global forecasts of artemisinin supply based on the information they are able to access. The artemisinin market is a difficult one to forecast because it is dependent on *Artemisia annua* cultivation (the plant from which artemisinin is extracted), which is hedged around with uncertainties such as:-

- Farmers will only start growing Artemisia if they have reasonable expectations that they will be able to sell the dried leaves at a fair price to artemisinin extractors after the harvest. Firm orders and advance funding from the extractors can help a lot.
- Extractors will engage with farmers to the extent that they have reasonable expectations that they will be able to sell the artemisinin at a fair price to API/ACT manufacturers after the harvest and extraction. Firm orders, long term arrangements, and advance payment are normally very effective.
- ACT manufacturers will engage with extractors to the extent that they have reasonable expectations that they will be able to win tenders issued by public ACT procurement agencies or receive orders from private buyers.
- Nowadays 75-80% of global cultivation takes place in China, 10-15% in Vietnam and 10% in Africa, mainly Madagascar.
- The level of what is a fair price is mainly determined by the price farmers can expect for food crops.

A key challenge for matching supply and demand in the ACT market is the long lead time between the planting of *Artemisia annua* and the completion of the final manufacture of the ACTs. This is summarised in Fig. 4 below:

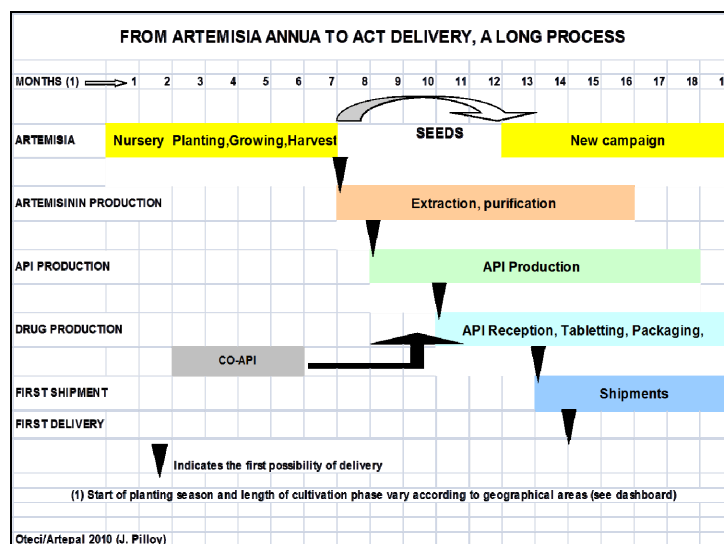


Figure 4

In summary, there is a 14 – 18 month lead-time between the planting of seed to the availability of final ACTs. This means that the supply of ACTs must be based on forecasts developed at least 24 months ahead of the

⁷ The Assured Artemisinin Supply System (A2S2) was set up in 2009 and is sponsored by UNITAID, managed by i+solutions, gathers artemisinin intelligence experts from Artepal and FSC, and runs an US\$8 million loan facility for artemisinin extractors administrated by the Triodos Bank. They operate in regular consultation with an Advisory Board composed of representatives from Médecins sans Frontières, RBM Secretariat, and WHO.

desired delivery dates. Rolling 24 month quarterly forecasts of demand for all artemisinin derivatives are needed to ensure that adequate planting can take place, with a particular focus on the timing of planting of *A annua* in different parts of the world. For example, in China planting can only take place in January – March.

Based on interviews conducted by A2S2 with growers and artemisinin extractors, the 2010 harvest would have made some additional 115 metric tons of artemisinin available for ACT production in 2011. To meet the ACT forecast for 2011 some 133 tons would be required. While there remain key uncertainties around these figures, both around the demand and supply forecasts, it is likely that existing inventories of artemisinin and its derivatives held in the manufacturing supply chain will also be used to meet the demand. This is further discussed in more detail in Fig. 8 below. The situation is expected to be much more aligned in 2012, where supply should be 21% above demand (as shown in Fig. 5) and artemisinin inventories could be replenished somehow.

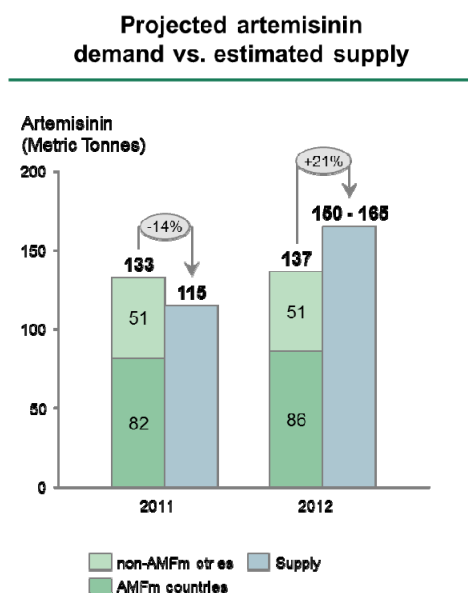


Figure 5

In the past, shortfalls in supply have been filled by extractors, formulators, and ACT manufacturers running down their stocks of dried leaves, extracted artemisinin, and APIs (artemisinin derivatives). The current supply situation is unclear as there is no accurate information on the inventory levels and buffer stocks of artemisinin and its derivatives being held in the ACT supply chain. A2S2 have no evidence of any inventories of leaves or artemisinin in buffer stocks held outside the ACT manufacturers. Recently there have been reports of ACT manufacturers experiencing problems accessing artemisinin supplies and having to buy on the “spot” market. Artemisinin prices have escalated from the US\$ 400 / Kg of 12 months ago to US\$500 and even US\$600/Kg. One recent deal was reported at as high as US\$950/kg. Some manufacturers had supply contracts with artemisinin suppliers dating back to 2010 at a price of about US\$ 400/kg, but the artemisinin suppliers now seem to be reneging on these agreements and insisting they will only supply at prices close to the “spot” market price. This is disrupting the supply and stock situation at individual ACT manufacturers as well as seriously affecting their margins. However, some ACT manufacturers reported that they have adequate stocks of artemisinin to meet their needs in 2011. Their only concern is the price at which they will have to buy API in 2012.

Artemisinin production is still heavily concentrated in China, responsible for about 80% of the global supply. Vietnam and Africa (especially Madagascar) supply another 10% each. Planting in China has increased in 2011 and adverse weather has only affected artemisinin production in limited geographical areas. The effects of additional supply of artemisinin from China on the ACT supply situation are not expected to be seen until 2012.

The concentration of supply in a few countries does place artemisinin suppliers in a strong negotiating position if there are global shortages and/or price increases.

ACT Formulation Capacity

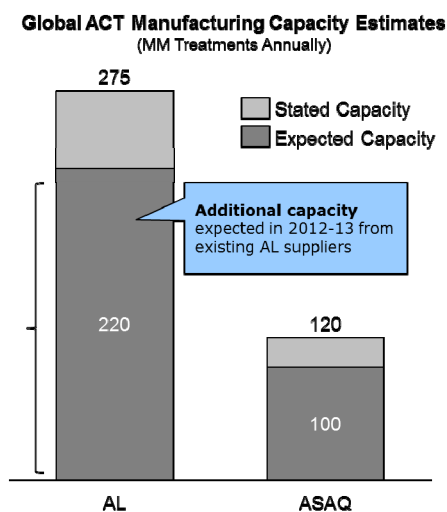


Figure 6

WHO & CHAI have jointly estimated the installed ACT manufacturing capacity, shown in Fig. 6. They have reduced the stated capacities to an expected capacity, based on past performance and WHO experience. This reduction is about 20%. Capacity will increase as new suppliers come on-stream in 2012 and new ACTs are made available, and with expansion of manufacturing facilities by several existing ACT producers. ACT manufacturing capacity does not seem to be a bottleneck in the supply chain. However their margins are under severe pressure due to the recent price increases of artemisinin. Other API prices (*e.g.* lumefantrine) are also increasing, but not at the same rate and this can be managed under the current AMFm pricing review system.

However the Round Table was reminded that annual manufacturing capacity can be misleading if the monthly capacity is not fully utilised. If orders are not spread out across a year, then under-utilisation in the early months cannot be made up in the later months. This is illustrated in Fig. 7 (**N.B.**: non-AMFm orders are provided as illustrative data only):-

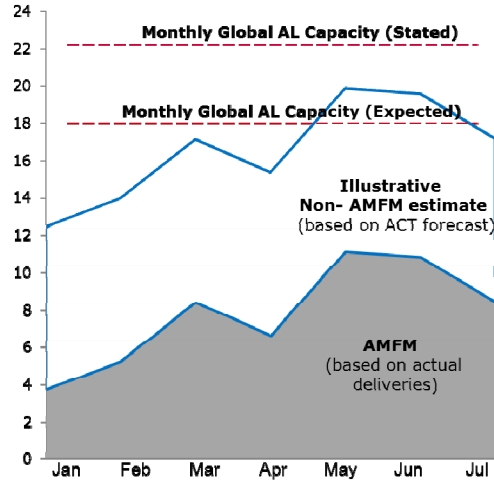


Figure 7

This figure illustrates the need to ensure that manufacturers are able to use their available capacity to the fullest extent. This requires that information on large orders for both public and private sector be properly shared so that consultation can take place if needed and that risks of production problems for individual manufacturers can be mitigated. Advance planning and earlier firm orders will also enable manufacturers to secure access to all the artemisinin/API they need at the appropriate time to meet expected delivery dates on ACT orders. It also shows that there is adequate production capacity needed for manufacturers to meet the expected monthly orders, provided all orders are received well in advance and individual suppliers have improved their performance to maximise their use of the available production capacity.

An additional problem that needs to be borne in mind is that there may be contractual or regulatory reasons why it would not be easy to switch between manufacturers in the event of one being unable to supply to a particular order. In addition, countries require different ACTs: if a particular country uses AL as its first-line antimalarial, and supplies are constrained, then it is not easy for it to switch to ASAQ even if there is spare capacity in the system to supply this alternative ACT.

The WHO-PQ ACT manufacturers present were asked to give their view on the situation. All were concerned about the escalating price of artemisinin in the market. They were particularly concerned by the attitude of some artemisinin suppliers, who seemed to be able to break their supply contracts which had been agreed 12-24 months previously. This was clearly escalating prices on the spot market, disrupting manufacturers supply plans as well as damaging their own margins. Most manufacturers stated that they had adequate installed capacity to meet future demands until another major step change in the demand curve.

The manufacturers' main problem is the level of financial risk that they have to take well ahead of firm orders being placed in order to try and ensure artemisinin supplies through supply agreements with the extractors. Some companies were more able to support this level of risk. Given the long lead time on API supplies the companies were concerned that they needed to bear all the financial risk and a proper risk sharing mechanism needed to be developed. If a certain proportion of the forecast demand could be pre-ordered 12 months in advance, this would reduce the risk to manufacturers when buying their artemisinin supplies. It would also permit more efficiency in planning production and so allow for capacity utilisation to be better spread across the year. It was also suggested that in the short term there is a need for a mechanism of linking the price budgeted by donors for ACTs to the market price of artemisinin to ensure that manufacturers would be able to stay as suppliers because their overhead recovery could be assured.

Manufacturers were also concerned about over-forecasting demand and communication about possible shortages. They felt that this had fed into the vicious circle of price speculation and escalation, delayed supply, shortages, and more price escalation. There needed to be great care in how ACT forecasts and artemisinin

supply requirements were communicated to the wider world so as not to stoke speculation in the market. It was also acknowledged that the decision of the November 2012 Global Fund Board with regard to the future of the AMFm and all communications around it will have major consequences for the future global ACT supply.

Semi-synthetic Artemisinin

A consortium of One World Health, Amyris, and sanofi aventis is developing a semi-synthetic method to produce artemisinin derivatives that does not depend on growing *Artemisia annua*. Once developed, sanofi aventis reported that this will be a source of non-seasonal, high-quality, and affordable artemisinin to supplement the current plant-derived supply. It is not intended to replace plant-derived material. It should also help to stabilise the prices of artemisinin.

The production facility in France is now coming on-stream. In Summer 2011, 150 kg have been produced, and in 2012 capacity will be increased to produce 11.5 tonnes. After that production will continue to be scaled up to reach 60 tonnes by 2014. Sanofi aventis are committed to producing the material from this method at a “fair” price for the market, expected to be around US\$ 350 – 400 /Kg. This will be a not-for-profit price.

Matching Demand and Supply

Following extensive discussions on the situation of ACT supply and demand, the meeting attempted to summarise the situation as best it could, with all the available information. This may be illustrated in Fig. 8 below. **However it is very important that this figure is read with the caveats included afterwards:-**

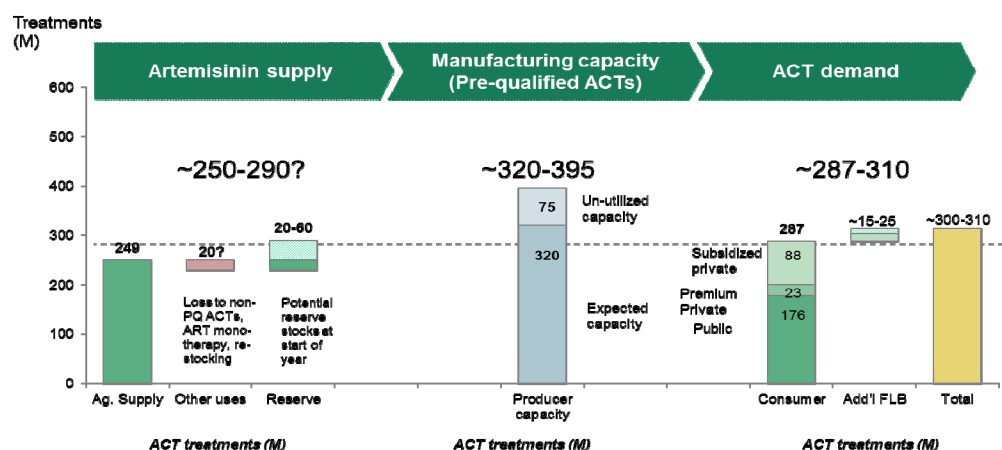


Figure 8: 2011 Estimates

Fig. 8 attempts to bring together all the information that was available to the Round Table on the supply and demand situation for ACTs in 2011. Specifically it is looking at the global situation for 2011 of WHO-PQ ACTs that can be used to supply AMFm and public sector orders - especially those funded by major international donors (Global Fund, US President’s Malaria Initiative, etc.). It is based on the forecasts produced by the ACT Forecasting Consortium and the WHO-CHAI formulation capacity tracking, and the information from A2S2 on artemisinin supplies.

Fig 8 shows on the left the estimated supply of artemisinin available for conversion in 2011 to ACTs, expressed as ACT treatment equivalents (249 million). The harvest potential has then been reduced by ~20 million treatments to account for an estimate of the usage in producing non-WHO PQ ACTs, artemisinin monotherapies, and injectable artemisinins. The Consortium has then estimated the buffer stocks held by the ACT manufacturers at 20 – 60 million treatments. This gives a total artemisinin supply of 250 – 290 million treatment equivalents. In the centre is the estimate of stated and expected capacity available at the ACT manufacturers (320 – 395 million treatments). Finally on the right is the forecast consumer demand (287

million treatments) with an additional 15-20 million treatments to account for the estimate of the buffer stocks the FLBs would like to build up (based upon the CHAI survey in mid-2011).

The Round Table was concerned that this point estimate of the situation could be very misleading for the following reasons:-

- The data as presented does not show all the uncertainties in the forecast and so gives it a misleading aura of accuracy. A 10-15 % margin of error in all this data (not considered unreasonable) would bring supply and demand into balance or even into slight over-supply. The Consortium needs to be clearer on all the error bars around each of these point estimates.
- The estimates for the consumption by non-WHO PQ ACT manufacture seemed to be on the high side and, since it could not be easily verified, could be over-estimating the challenge.
- Similarly the estimates for the buffer stocks of artemisinin/APIs held in the supply chain, especially by the ACT manufacturers, seemed to be low. Some manufacturers present stated that they had adequate buffer stocks to meet the current demand. Manufacturers' buffer stocks of artemisinin/APIs are one of the biggest unknowns and need to further investigated.
- The ACT buffer stock build-up by FLBs could be managed in the short-term through the levers being used by the AMFm team and so might be ignored in 2011 (although would need to be considered for 2012).
- Shortages indicated in this type of forecast do not automatically convert into stock-outs at the level of the consumer. All supply chains have a degree of buffer in them and this can be used for a short-time to manage supply to more closely match to demand. Close co-operation between all the players can go a long way to minimise the impact of shortages.

CONCLUSIONS

Given all the caveats mentioned here, the Round Table concluded that while there was no acute shortage of ACTs, the supply situation in the rest of 2011 could become "tight" in some local situations. The meeting was not complacent on this matter and requested (i) that a small management team under WHO leadership develop a risk management plan and monitor and address those local situations at risk, (ii) that the Roll Back Malaria PSM working group improve intelligence on ACT demand and supply and propose strategies and solutions for the medium and long term and (iii) an immediate statement on the conclusions of this meeting and an aligned communication plan. Several proposals are summarised in the relevant section of this report.

It was agreed to be essential that every effort is made to identify and address any at-risk situations.

The meeting also warned against poorly informed statements about the situation which would only serve to increase the problem. Suppliers of artemisinin would be more tempted to hold back on supplies in the expectation that a supply shortage would continue to drive up prices on the spot market and a vicious cycle of price rises (similar to what happened in 2004/05) could occur. The AMFm, Global Fund Voluntary Pooled Procurement and USPMI were congratulated on the open and transparent way they were publishing information on their orders and deliveries. It appeared however that some observers had been confused by duplicate order data on the AMFm website. The AMFm Unit informed the authors of this report that this would be rectified in the next few days.

PROPOSALS

The meeting developed a series of proposed actions that could be taken to mitigate any risk to the ACT supply.

Immediate

1. Develop an aligned communication message on the nature of the issue and on the measures being taken to mitigate any risk to ACT supplies. The full report of the meeting, and related Questions & Answers to be made available by 1 October. This plan must also include communications to First Line Buyers to minimise the risk of price increase in the private sector.
2. Establish a small management team ("nerve centre") under the leadership of WHO GMP, to identify issues for immediate attention. A high priority will be to identify "red flag" countries which are at the greatest risk of ACT supply challenges in the short term, and co-ordinate efforts to mitigate this risk. The deadline for setting up the team should be 15 September. This team will obtain accurate data on the actual pipeline and supply situation in these selected countries.
3. Under PSMWG leadership, discuss and propose medium to longer-term strategies and solutions for any challenges to the future ACT supply.
4. The RBM Executive Director together with WHO and other relevant RBM Partners, will consult with the WHO Director General and the representative from China on the RBM Board to explore how the Chinese Government could contribute to optimizing the cooperation between Chinese artemisinin producers and ACT manufacturers.
5. AMFM to correct and update the order information on the AMFm website.
6. Finalise the conclusions and recommendations from this meeting and publish them as soon as possible.

Short-term (next 6 to 12 months)

These are proposed actions that should be able to positively impact the situation in the short-term.

1. Under the auspices of the RBM PSMWG and with WHO GMP leadership, all RBM Partners to co-ordinate their efforts to ensure that any supply chain risk is mitigated in an orderly manner. Where crisis points are identified, this mechanism should be used to prioritise orders and deliveries with particular priority for the public sector and for children (in Africa).
2. AMFm to continue to implement the 6 "levers" to manage demand through the at-risk period. PMI to continue their efforts to reschedule the less urgent orders. Other RBM partners to consider similarly proactive measures.
3. Global Fund to develop systems to enable it to contribute to the information gathering on the ACT supply situation from the extensive information it has on ACT purchases by its grant recipients.
4. WHO & RBM to work with countries to lower buffer stock levels to appropriate levels, especially in countries with large existing buffer stocks, to free up supply for countries with urgent needs (like Horn of Africa).
5. ACT Forecasting Consortium to extend their work to develop global 24 month rolling forecasts with projections of the quarterly demand. The improvements of the forecasts should also include building in more precision in delivery timings, analysis of changes in the demand curve of FLBs, proper sensitivity analysis on the demand and supply curves, and measuring drug replacement rate in private and public antimalarial market.
6. A2S2 to improve, update and disseminate information on Artemisia, artemisinin, and API production
7. PSMWG to bring together the findings of the Consortium and A2S2 for timely alignment of demand and supply information.
8. Relevant RBM partners to focus attention on large orders and to investigate if these can be split for staggered delivery, thus freeing up ACT supplies for at-risk countries.
9. Relevant RBM partners to proactively monitor actual vs. agreed upon delivery times in order to have early warning of country level delays. Through more communication with manufacturers, understand earlier and more continuously the supply situation for each manufacturer and when they have challenges in meeting agreed delivery dates.

10. Relevant RBM partners to investigate the substitutability of different ACTs and their presentations (*e.g.* for ASAQ FDC vs. co-blistered) in at-risk situations so as to maximise the level of flexibility in the supply chain.
11. Increase efforts to increase use of diagnostics, especially in the public sector, in order to reduce use of ACTs to treat non-malarial fevers. Public sector use of RDTs may be easily increased in the short-term. This could be focused in a few high potential countries which are already well prepared.
12. Investigate setting up a centrally held buffer stock of ACTs to be used for emergency or epidemic situations.
13. Establish appropriate mechanism to bring all stakeholders represented at this meeting (and others considered relevant) on a regular basis to continue to monitor the situation and to co-operatively develop solutions to new supply chain challenges. The annual RBM-WHO Artemisinin Conference may be an appropriate vehicle.

Longer-term (beyond 12 months)

These proposals are about aspects of the architecture or systems of the ACT supply chain that could be investigated. Changes to these may reduce the risk of future concerns about mismatches between supply and demand. However the meeting did not have time to look at detailed recommendations, merely to identify areas for future work.

1. Increase efforts to increase use of RDTs, especially in the private sector, in order to reduce the demand for ACTs to treat non-malarial fevers.
2. When planning of any potential expansion of AMFm to a second phase, take into account the extended response time of the ACT supply chain, as well as the need to incorporate diagnostic testing. Ensure that it has adequate time to prepare and produce enough artemisinin to meet a further step change in demand.
3. Investigate the practicality of establishing a revolving buffer stock of artemisinin to reduce the risk of artemisinin producers exploiting any shortages (real or perceived) in the supply chain.
4. Develop and put into effect a system for incentivising ACT manufacturers to produce according to longer term forecasts rather than waiting until firm orders are received.
5. All partners to follow AMFm's example and to be more transparent in publishing detailed information on the demand and supply situation. More information on country orders, manufacturer performance, and age/weight band usage would be of value for market planning.
6. The Global Fund to undertake an economic analysis of the level of the AMFm co-payment on the behaviour of the FLBs, as part of the overall review of the performance of AMFm.
7. Investigate the risk to funders of continued high artemisinin prices and possible way to reduce or mitigate the risk.

Annex 1: List of Participants

| Name | Organisation |
|--|--|
| Awa Marie Coll-Seck Rob Newman | RBM Partnership Executive Director (Co-chair) Director WHO/GMP (Co-chair) |
| Rima Shretta Prashant Yadav | PSMWG Co-Chair / MSH PSMWG Co-Chair / Univ. of Michigan |
| Jacques Pilloy Mani Kuriakose Melanie Renshaw Colin Boyle Susan Nazarro Megumi Gordon Neel Lakhani Carlton Evans Kirsten Myhr Martin Auton Scott Filler Sophie Logez Olusoji Adeyi Silas Holland Fabienne Jouberton Sarma Murali Renia Coghlan George Jagoe David Reddy Jean-Marie Kindermans Tido von Schoen-Angerer Rebecca Stevens René Cazetien Philippe Farabolini Andreas Diederhofen Alan Court Philippe Duneton Ambachew Yohannes Jennifer Murphy John Paul Clark | A2S2/OTECI Ajanta Pharma ALMA BCG Bill & Melinda Gates Foundation CHAI CHAI DFID Global Fund Board AMFm Ad Hoc Committee Global Fund Global Fund Global Fund Global Fund (AMFm) Global Fund (AMFm) Global Fund (AMFm) IPCA MMV MMV MMV MSF MSF Novartis International sanofi aventis sanofi aventis Sigma Tau UN Special Envoy's Office UNITAID UNITAID US PMI World Bank |
| Andrea Bosman Clare Courtney Clarisse Morris Pru Smith Thomas Teuscher Jan van Erps | WHO/GMP RBM Secretariat RBM Secretariat RBM Secretariat RBM Secretariat RBM Secretariat |
| Ian Boulton | TropMed Pharma Consulting (Rapporteur) |