Desk–based market analysis of supply side issues for antimalarial commodities

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30 May 2014
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### Acronyms

<table>
<thead>
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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
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<tr>
<td>AL</td>
<td>Artemether-lumefantrine</td>
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<td>AMFm</td>
<td>Affordable Medicines Facility - malaria</td>
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<td>API</td>
<td>Active pharmaceutical ingredient</td>
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<tr>
<td>APLMA</td>
<td>Asia Pacific Leaders Malaria Alliance</td>
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<tr>
<td>AQMTF</td>
<td>Access to Quality Medicines and Other Technologies Task Force</td>
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<tr>
<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>DDT</td>
<td>Dichloro-diphenyl-trichloroethane</td>
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<tr>
<td>DHA-PPQ</td>
<td>Dihydroartemisinin-piperaquine</td>
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<tr>
<td>G6PD</td>
<td>Glucose-6-Phosphate Dehydrogenase</td>
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<tr>
<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>IRS</td>
<td>Indoor residual spraying</td>
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<tr>
<td>ITN</td>
<td>Insecticide-treated net</td>
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<tr>
<td>LLIN</td>
<td>Long-lasting insecticide treated net</td>
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<td>MMV</td>
<td>Medicines for Malaria Venture</td>
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<td>NFM</td>
<td>Global Fund New Funding Model</td>
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<td>NMCP</td>
<td>National Malaria Control Programme</td>
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<td>P. falciparum</td>
<td>Plasmodium falciparum</td>
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<td>PMI</td>
<td>President’s Malaria Initiative (United States)</td>
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<td>PoC</td>
<td>Point-of-care</td>
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<td>PSI</td>
<td>Population Services International</td>
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<td>P. vivax</td>
<td>Plasmodium vivax</td>
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<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid Diagnostic Tests</td>
</tr>
<tr>
<td>SRA</td>
<td>Stringent Regulatory Authority</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>USD</td>
<td>US Dollar</td>
</tr>
<tr>
<td>UTN</td>
<td>Untreated nets</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHOPES</td>
<td>WHO Pesticide Evaluation Scheme</td>
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<td>WHO-PQ</td>
<td>WHO Pre-Qualification Programme</td>
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Executive summary

This paper has been prepared to support the second meeting of the Access to Quality Medicine and other Technology Task Force in June 2014. It addresses upstream supply side challenges of antimalarial medicines, diagnostics and vector control technologies and interventions related to i) market structure ii) its impact on prices, supply and innovation and iii) interventions to better align market structure with public health needs. It presents options for possible interventions, including “push” and “pull” mechanisms for technologies under development, and supply and demand interventions for existing technologies.

I. Medicines

The Asia Pacific region is important to the development and supply of antimalarial medicines. Of the nine manufacturers supplying the World Health Organization with approved artemisinin-based combination therapy (ACT), six are from the region. The Artemisia annua plant is the starting material for ACTs; it is grown principally in China and Vietnam. The Asia Pacific region is also the region from which much of the sub-standard antimalarial supply derives. Globally, key challenges to ACT adoption since mid-2000 have been supply security and pricing; both of these are influenced by the long lead time and fragmentation of players involved in the supply chain between planting and formulation.

Need to maintain transparency of demand and pooling of purchasing: Many malaria programs in the region have received funding from the Global Fund. However, the New Funding Model launched by the Global Fund in 2013 requires counterpart financing from grant recipients. Some countries are unhappy with the lack of flexibility in specification and source for products procured through the Global Fund and may opt to use their counterpart funding to procure antimalarial supplies outside Global Fund systems. This risks reducing transparency and fragmenting demand, possibly increasing prices, reducing supply security and reducing quality. Ideally countries in the region will continue to work with Global Fund systems for their antimalarial needs. If countries decide not to use Global Fund systems, an informal process should be supported among the various National Malaria Control Programmes to co-ordinate their antimalarial drug procurement. This would be linked to a market intelligence framework giving manufacturers transparency over demand and enabling them to better plan production capacity and Artemisia annual planting. This framework could be set up and run by the industry or by an independent regional organisation.

Recommendation: Develop market intelligence systems and co-ordinate procurement. Demand transparency and demand pooling must be maintained given the specific features of the upstream antimalarial supply chain, in particular the long lead time and number of players involved between planting and formulation of ACTs.

Strengthen regional regulatory capacity and support manufacturers to improve antimalarial quality standards: Resistance to artemisinin as well as to other antimalarials, originally found in Cambodia,
spread across the Greater Mekong Sub-region as far as Myanmar. A key driver of artemisinin resistance is the continuing availability of poor quality drugs, especially oral artemisinin monotherapies. Of the 30 companies still producing oral artemisinin monotherapies globally, 19 are in the region. It is important that these monotherapies are removed from the market as soon as possible. Concerns about the spread of artemisinin resistance may also affect the supply of artemisinin. Growers and extractors (principally based in the region) may well respond by exiting the market if they do not see a long-term future for artemisinin, coupled with the volatility in demand and price.

**Recommendation:** Invest in regional regulatory agency strengthening and support regional manufacturers to improve quality standards.

**Incentivise the private sector to produce quality antimalarial products, and reduce incentives to produce substandard products:** Given the demand for affordable medicines and the relatively weak levels of regulatory enforcement on imports and manufacture in many parts of Asia Pacific, the incentives for local generic manufacturers to cut corners on quality when supplying to the private sector in particular are significant. Regulatory enforcement is crucial to ensuring that poor quality and inappropriate drugs (especially monotherapies) do not reach the market. Equally, market incentives can be better leveraged to pull through better quality medicines and crowd out monotherapies. Creating demand for high quality drugs in the public sector is relatively straightforward, as the quality standards can be built into the tender specifications. Creating demand for quality in the private sector has been shown to be possible through the large scale co-payment system for medicines (Affordable Medicines Facility - malaria [AMFm] pilot) in African countries. Similarly, a programme in Myanmar showed how well the private sector can respond to (and influence) changes in care-seeker demand.

**Recommendation:** A co-payment system in the private sector could be considered, to improve affordability and crowd out monotherapies. The private sector can serve as an important incentive channel for influencing firm behaviour; it could be better leveraged to “pull” through the products desired and reduce incentives to produce substandard products.

### II. Diagnostics

Key diagnostics access issues in the Asia Pacific region are the need to scale up malaria diagnosis, in particular malaria rapid diagnostic tests (RDT) in many countries, and the need for several new diagnostic products to support malaria control and elimination.

**Improve access to quality malaria rapid diagnostic tests:** The global malaria RDT market has been rapidly growing, driven primarily by donor-funded RDT procurement in Africa. While the Asia Pacific region represents about 20-30% of the global RDT market, much of the global malaria RDT supply comes from India, China and Korea.

One challenge in the RDT market is the recent decline in prices, and resultant risks to product quality (e.g. incentives for manufacturers to cut corners, or for quality suppliers to exit the market) and to supply security (i.e. reliance on too few suppliers). In addition, regulatory systems for diagnostics are under-developed in comparison to those for vaccines and medicines, and enforcement is a challenge. While RDT
quality has improved in recent years through a WHO-led Product Evaluation, critical gaps remain, including weak quality standards at the manufacturing level and the lack of technologies that would enable checking the quality of RDTs in the field. Also, in some higher burden countries where treatment seeking in the private sector is high, the lack of access to RDTs and subsequent overtreatment with antimalarial drugs in the retail outlets is a concern. Increasing access to testing in the private sector is complex however an evidence base is emerging related to reducing barriers and disincentives to development of this market.

Recommendation: Although much of the need to increase access to RDTs relates to delivery issues, there are several supply side interventions that could contribute to improved access to quality RDTs:

- Supporting regional suppliers in upgrading manufacturing quality standards, which would have global impact on RDT market and carryover effects for diagnostcs industry in the region.
- Strengthening regulatory capacity for diagnostcs to improve access to quality tests, including capacity to confirm the quality of RDTs, mapping of existing requirements with an aim towards eventual harmonization of requirements.
- Exploring the potential to develop retail markets for RDTs.
- Improving market knowledge, e.g. RDT prices and procurement practices.

Mobilise development and production of new diagnostic products: The region’s progress in reducing malaria burdens and advancing malaria elimination, and its epidemiology are creating needs for new diagnostic technologies. There are several products in the development pipeline that could have a significant impact on the region, for instance technologies to evaluate and control RDT quality in the field, which are expected to launch within 2 years. Also, given the Asia Pacific region is home to 91% of the global population at risk for *P. vivax*, diagnostics are required to support diagnosis of *P. vivax* and safe uptake medicines for *P. vivax*. Finally, given that almost half of the Asia Pacific countries have malaria elimination strategies, the changing epidemiology and activities associated with elimination create needs for new diagnostics, such as a rapid field test to detect low levels of parasites.

Recommendation: There is a strong case for developing a regional mechanism to encourage diagnostic development and to support new product introduction. A regional initiative would build on the Malaria 2012 Sydney Consensus Statement, calling for acceleration of high priority research and contribute to accelerated access to new products. An initiative would send a broader signal to the market and might entail: operational research to inform global and local policy on use of new products; and development of and harmonization on regulatory requirements for new products; direct investment in research and development or other incentives for product development.

III. Vector control

Indoor residual spraying (IRS) and insecticide-treated nets (ITNs) are the primary forms of vector control recommended by WHO, though there is a need for development of new tools to counter resistance and increase protection.
Influence supply of indoor residual spraying through demand shaping: In the Asia Pacific region, IRS is dominated by India’s use of dichloro-diphenyl-trichloroethane (DDT), whereas globally IRS is mostly pyrethroid-based. Globally, IRS scale-up is hampered by the cost of implementation, which is a function of demand and supply market constraints. A market intervention to influence upstream IRS supply side through demand side shaping will probably need to gain traction in Africa before the Asia Pacific would benefit.

Recommendation: Improve insecticide resistance monitoring, to contribute to the evidence base needed to develop a sound resistance management plan. Support firms in the region to develop longer lasting non-pyrethroid insecticides.

Support a diversified supply base of LLIN manufacturers in the region: Several suppliers from Japan, China, and India have products approved by the WHO Pesticide Evaluation Scheme (WHOPES), or are in the process of obtaining it, however smaller LLIN producers face barriers to entry in winning global tenders. Maintaining a diversified supply base is of benefit to the global community in terms of supply security, price competition and innovation.

Work to define, aggregate and communicate product demand requirements would likely improve value for money both of the LLINs sourced with donor funds as well as those paid for with domestic funds. If more nets are procured domestically, due to the new counterpart funding requirement of the Global Fund, countries in the region should look to work together through data sharing, aligning tender specifications, harmonising registration requirements, aggregating demand forecasts and perhaps pooled procurement. If smaller WHOPES approved suppliers in the region offer comparable value for money to larger suppliers, tenders can be structured to their advantage.

Recommendation: Priority recommendations related to existing vector control technologies are to: conduct research towards defining value for money in nets; commission a rapid survey of smaller LLIN manufacturers in the region; aggregate LLIN demand with African demand through the Global Fund or find ways of approaching to the market as a sub-group of countries in the region.

Importance of research to support supply of novel vector control products that meet regional requirements: The Asia Pacific region has urgent need for novel products for use in forest or fringe settings to control the outdoor biting and resting mosquitoes that transmit ACT drug resistant malaria. The major centres of innovation in the region can be harnessed to address this need.

Recommendations: i) provide push funding for new vector control paradigms currently in development and facilitate market entry and uptake and ii) invest in community level research to inform target product profiles for further innovations.

Conclusion

Several strategic insights emerge which are relevant across all three of the technology categories reviewed. On the demand side, the relatively smaller and fragmented demand for antimalarial technologies compared to Africa for most countries in the region raises the importance of approaching
the market strategically; this may involve aggregation of demand within or outside Global Fund systems, and in the latter case, improving and co-ordinating tender management systems in the region. Similarly, new technologies specific to the health needs of the region will need more dedicated push and pull support from the region, if they are to make it to market in time for optimal health impact. On the supply side, the continued engagement of firms in the region is crucial to supply security, price competition and innovation in the global health space, including malaria technologies. Work to reduce barriers to entry, support the growth of these firms, and improve their quality, will be an area of aligned interest with the global community. Regulatory sanctions are important but they will have more traction if linked to market incentives. There is scope to further influence the region’s supply side through shaping the private sector demand channel.
1. Introduction

This paper is focused on upstream supply side challenges of antimalarial medicines, diagnostics and vector control technologies and interventions related to i) market structure ii) its impact on prices, supply and innovation and iii) interventions to better align market structure with public health needs. Interventions to influence market structure can be categorised into “carrot” and “stick”, that is, incentive versus sanction approaches to influencing firm behaviour. Stick interventions have been covered elsewhere. Carrot options are the focus of this paper, and are sub-divided into supply or demand interventions to influence markets for existing products and “push” or “pull” interventions, for products in development. Demand/supply interventions, as well as push/pull, can be designed to work individually or in combination. Figure 1 provides a graphical depiction of illustrative options for influencing the market. Market research can elucidate the problem to be “fixed”, and then an intervention package can be tailored to the context.

Figure 1: Menu of ‘carrot’ options for influencing the market

Overall impact desired: Improved prices, supply security, delivery, quality and uptake-enhancing product features

1 For example policies, laws, regulations and enforcement influencing product availability and quality.

2 Push mechanisms are used to reduce costs and risks during development while pull mechanisms are those which add credibility to the eventual market incentive for the successful candidate.
2. Medicines

All countries in the Asia Pacific region base their national treatment policies on the World Health Organization (WHO) Guidelines for the Treatment of Malaria.\textsuperscript{1,2,3} Recommended first-line treatment of \textit{P. falciparum} malaria is artemisinin-based combination therapies (ACTs), and for \textit{P. vivax} it is chloroquine. In a few Asia Pacific countries (India, Myanmar, Papua New Guinea and Indonesia), vivax resistance to chloroquine has been reported\textsuperscript{4} with ACTs recommended instead. Primaquine is recommended for the elimination of the dormant liver stages of \textit{P. vivax}, to prevent relapse. Severe malaria should be treated with intravenous artesunate, with intravenous quinine as an alternative. Rectal artesunate is recommended for pre-referral treatment where oral drugs cannot be given.

Of the nine manufacturers that can supply quality assured ACTs, five are Indian, one is Chinese, and the remainder are international companies headquartered in Europe.

\textbf{Structure of manufacturing supply chain}

This paper restricts itself to the upstream supply chain.\textsuperscript{iv} Figure 2 outlines the process for the production of ACTs, starting from the planting of the seeds by the growers in (principally) China and Vietnam. The process for the production of the partner drugs (mefloquine, piperaquine, etc.) starts at “API production” in the figure.\textsuperscript{v} The 18-month timeline between planting and production and the number of players involved in the process makes demand forecasting relatively more important versus other medicines; this is also a key factor in historic supply insecurities. Annex 3 provides further details on the players involved at various stages of Figure 2.

\textbf{2.1 Medicines access issues}

The main issues identified in our research for the manufacturing supply chain are:

\textbf{Volatility of the artemisinin market}

The long lead time for the supply of ACTs (Figure 2) means that the supply chain cannot react quickly to significant changes in demand. This has meant that the price and the availability of artemisinin has been volatile, ranging on average from USD 1100/kg in 2005 to < USD 200/kg in 2007 back up to USD 1000/kg in 2011 (Figure 3). High prices in one year mean that farmers over-plant the following year, leading to over-supply and a fall in the price and so the cycle continues.

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\textsuperscript{ii} In Southern States of India, the treatment recommendations for \textit{P. falciparum} differ from the WHO Treatment Guidelines.

\textsuperscript{iv} A much more comprehensive overview of the global market can be found in the UNITAID Malaria Medicines Market Landscape.\textsuperscript{14} As the bulk of the disease burden and market influence is in the African region, this landscape inevitably takes an Afro-centric focus.

\textsuperscript{v} API is “active pharmaceutical ingredient”.

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2
Figure 2: ACT production process

Timeline: ‘From Artemisia to ACT’

<table>
<thead>
<tr>
<th>Months</th>
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<tbody>
<tr>
<td>Artemisia</td>
<td>SEEDS</td>
<td>New Campaign</td>
<td>SEEDS</td>
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<tr>
<td>Artemisinin production</td>
<td>Extraction, Purification</td>
<td>API Production</td>
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<tr>
<td>Drug Production</td>
<td>API Recognition, Tabletting, Packaging</td>
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<td>First Shipment</td>
<td>CO-API</td>
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<td>First Delivery</td>
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In order to avoid loss of content during storage, especially in hot climates, the extraction period may only be possible over 2-4 months, whereas other regions are able to store Artemisia leaf and extract over much of a cycle.

Figure 3: Artemisinin selling price trend 2005-2012 (USD/kg)
Particularly in China, the volatility of the market means that the number of extractors has also fluctuated. Companies have entered and left the market depending on their perceptions of the opportunities to make money compared to other chemicals.

**Availability of semi-synthetic artemisinin**

Supplies of semi-synthetic artemisinin from Sanofi started to become available in 2013. Their maximum capacity is stated to be 60 tonnes per year, with a target price of USD 380/kg, and much of this will be used by Sanofi for its own ACT production. The most recent forecast for artemisinin predicts a total global demand of at least 170 tonnes in 2014. Therefore significant amounts of plant-derived artemisinin will be required for some time to come and extractors and growers need to be able to see this. The semi-synthetic product may be able to contribute to smoothing out the peaks-and-troughs but it will not completely remove the risk.

**ACT affordability**

A key challenge since the widespread adoption of ACTs globally in the mid-2000s has been their affordability to end-users. Due to the large increase in donor funding and agreements by the large manufacturers to supply at “no profit, no loss”, ex-manufacturer prices have fallen considerably, and have stabilised over the last five years at around USD 1.50/adult treatment course for quality-assured artemether-lumefantrine and USD 1.00 for artesunate-amodiaquine. However the price volatility of artemisinin threatens the stability of the ex-manufacturer prices.

Normally in the public sector, drugs are supplied free-of-charge, but in the private retail sector their price can be over USD 5.00. These prices are well above those for older ineffective drugs (like chloroquine and mefloquine). Exceptions are those countries where social marketing programmes or price subsidies have been introduced (e.g. the Affordable Medicines Facility - malaria [AMFm] in African countries, and the PSI program in Myanmar) to reduce prices to affordable levels. A full review of the global pricing trends can be found in the latest UNITAID Malaria Medicines Landscape, but data specific to the Asia Pacific region is limited.

### 2.2 Regional specific issues

**Emergence of drug resistance**

Resistance to artemisinin was originally found in Cambodia and has now spread across the Greater Mekong Sub-region as far as Myanmar. In addition the emergence of pyronaridine resistance, along with pre-existing resistance to mefloquine in the area, is removing key effective ACTs.

The manufacturers of alternative drugs need to be informed of these changes with enough warning to be able to respond. Any changes to national drug policies will take time to implement (especially in the private retail sector) as pipelines will need to be cleared, stocks adjusted, and all stakeholders (including care-seekers) are educated about the new regimens.

A key driver of artemisinin resistance is the continuing availability of poor quality drugs, especially oral artemisinin monotherapies. WHO has identified 11 companies in India, 3 each in China and Pakistan, and 1 each in Bangladesh and Vietnam which are still offering monotherapies for sale. It is important that these are removed from the market as soon as possible.
Importance of private sector in drug distribution

The importance of the private sector in delivering antimalarial treatment has already been extensively reviewed.\textsuperscript{19, 20} As much as 80\% of healthcare in the Asia Pacific is delivered through this sector.\textsuperscript{19} Private retailers buy relatively small quantities of products from local distributors. Demand for these small demand “packages” is then aggregated back through the distribution chain to the manufacturers and importers. The manufacturer normally only has sight of the demand from its immediate distributor or importer. However the choice available to the care-seeker, especially the most disadvantaged, is governed by availability and price, which means that manufacturers supplying cheap (often poor quality drugs) can be favoured in the private sector.\textsuperscript{15}

Raising and maintaining quality standards

The 2012 Sydney Consensus Statement set as one of its targets “identify and implement options to increase regional production capacity for and access to medicines and technologies that meet international standards”.\textsuperscript{21} There is already significant manufacturing capacity in Asia Pacific, primarily in India and China, but also in Indonesia, Korea, Pakistan, the Philippines, Taiwan, Thailand, and Vietnam. Existing capacity for most antimalarials is adequate to meet demand. The challenge is to get existing companies to improve their quality to international standards. Any efforts to increase and improve regional production capacity must be as part of a properly co-ordinated industrial policy, as has recently been reviewed for Africa.\textsuperscript{22}

The challenges faced by the regulatory systems have already been reviewed by Lalvani \textit{et al.}\textsuperscript{23} However regulatory enforcement is crucial to ensuring that poor quality and inappropriate drugs (especially monotherapies) do not reach the market, especially in the private retail sector.

Manufacturing to internationally acceptable quality standards will incur additional costs. In order to ensure that production standards are raised and maintained, a mechanism is needed to align the price paid to the quality manufacturer and paid by the care-seeker.

Creating demand for high quality and appropriate drugs

Creating demand for high quality drugs in the public sector is relatively straightforward, as the quality standards can be built into the tender specifications. However if demand is fragmented across many uncoordinated tenders, prices will be higher. Pooling, co-ordination of demand, and guaranteed orders, as the Global Fund has started to develop, can improve the situation.

Several Asia Pacific countries have called for more regional or country appropriateness in the ACT dosage levels, formulations, and packaging received from donor agencies. The challenge is to define what is needed, so the manufacturers can respond. Too much diversity will, however, lead to higher prices and/or unreliable supply due to fragmented demand.

Because of the wide dispersal of demand among many private sector players and their closeness to the ultimate customer, the private sector can respond very rapidly to changes in care-seeker demand. The recent AMFm pilot showed that availability, affordability, and supply of ACTs in the private sector could be significantly improved with the appropriate interventions.\textsuperscript{24} It was also true in
more remote and difficult to access areas. An intervention in Myanmar has also shown how quickly the private sector can respond to (and influence) changes in care-seeker demand.\textsuperscript{25,26}

**Global Fund New Funding Model counterpart financing**

The Global Fund’s New Funding Model (NFM) has significant requirements for counterpart financing from participating countries, depending on their national income levels. Countries have to decide whether to spread their counterpart financing across all components of their malaria programmes or remove certain elements completely. In Asia Pacific malaria-endemic countries the requirements are:\textsuperscript{27}

<table>
<thead>
<tr>
<th>Table 1: Global Fund New Funding Model</th>
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<tr>
<td><strong>Lower Income Countries (LICs)</strong></td>
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<td>5% counterpart financing</td>
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The major constraint on high quality drug manufacturers and on the producers of artemisinin is the lack of transparency of ACT demand over a 3-5 year time period. The Global Fund’s NFM requires countries submitting grant applications to supply national malaria 5-year plans.\textsuperscript{27} Once the NFM process is fully up-and-running, and all countries have developed 5-year strategic plans, it should be possible to develop longer-term demand forecasts for key commodities.

If countries choose to use counterpart funding to procure antimalarial drugs outside of the Global Fund systems, this could reduce transparency and fragment demand, with the risk of increasing costs, as well as risking the quality of drugs procured in the absence of strong quality control and regulatory enforcement.

### 3. Diagnostics

There are two primary gaps in access to testing in the Asia Pacific region:

\textsuperscript{26} The Myanmar programme has been was explained in the previous APLMA paper referenced.\textsuperscript{26} Key learnings from AMFm are provided in Annex 4.
1) There is a need to scale up diagnosis. Access varies by country,\textsuperscript{vii} and is particularly low in the private sector where experts suggest presumptive treatment continues to be common. Both microscopy and Rapid Diagnostic Tests (RDTs) are used to diagnose malaria. There is a regional bias towards microscopy, however, given its many advantages, RDT use is increasing, especially where quality microscopy is less well established (e.g. periphery, in hard to reach populations).

2) New diagnostics are needed. The region’s progress in reducing malaria burdens and advancing malaria elimination, and its epidemiology (e.g. high \textit{P. vivax} and G6PD deficiency risks) are creating needs for new diagnostic technologies.

Based on these priorities, this report focuses on three products: malaria RDTs for routine diagnosis of malaria; new point-of-care (PoC) G6PD tests to enable greater access to anti-relapse medicines for \textit{P. vivax}; and new highly sensitive field tests for elimination. Annex 4 provides an overview of these three diagnostics as well as other malaria diagnostics, along with commentary on the relative importance of each.

### 3.1 Malaria RDTs

Globally, the malaria RDT market has been rapidly growing, driven primarily by donor-funded RDT procurement in Africa. While the Asia Pacific region represents about 20-30\% of global RDT market, much of the global malaria RDT supply comes from India, China and Korea. Other key features of the malaria RDT market are described in Annex 5.

#### Global market challenges

**Viability of RDT market:** The most urgent challenge in the malaria RDT market relates to the long-term health and sustainability of the market. Current pricing appears to be approaching the cost of production, leaving little incentive for investment in quality or in innovation, at a time when both are public health priorities. In addition, the large donor-funded market has consolidated around three suppliers (with one supplying semi-finished product to another), resulting in a highly concentrated supply base despite an abundance of RDT suppliers meeting WHO recommendations.

**RDT quality:** Although significant progress has been made in recent years through the WHO/FIND Product Testing Programs, gaps in RDT quality remain. Notably, there is no practical way to check quality at the point of use, due to a lack of available quality control technologies (described further below). Upstream quality assurance (QA) is also inadequate: although the WHO Diagnostics Pre-Qualification Program has been reviewing malaria RDTs since 2010, with only two prequalified suppliers, progress has been slow and this program is not yet impacting the market. Notably, many of the RDT suppliers, the majority of them located in the Asia Pacific region, are struggling with manufacturing quality inspections due in large part to their lack of experience with stringent regulatory standards for diagnostics.

\textsuperscript{vii} For example, according to the 2013 World Malaria Report, in the SEARO region (WHO South East Asia Region) in 2012, 99\% of suspected cases in the public sector were tested including India. Excluding India, only 56\% of suspected cases in the region are tested. In the WPRO region (WHO Western Pacific Region), public sector testing rates have been steadily increasing over the past five years and in 2012 >90\% of suspected cases were tested.
Limited RDT market relative to need: In the public sector, there is insufficient uptake of RDTs compared to the need, due to a variety of delivery issues (in-country supply chains, inadequate training, lack of health worker supervision) and limited acceptance of RDTs in some areas. In the future, potential funding reductions and changes at the Global Fund may also limit RDT scale-up. Although the private sector plays a large role in treating fever, diagnosis is minimal in the retail private sector (e.g. outlets where medicines are sold) contributing to significant overtreatment of malaria.

Regulation of RDTs: In many countries regulatory systems for diagnostics are undeveloped relative to those for pharmaceuticals and vaccines, and where they exist their enforcement is a challenge. This leads to sale of suboptimal RDTs, and can discourage suppliers of higher performing products from entering the market. Where registration is required, it differs by country and presents a time consuming burden for suppliers to determine if and how they need to register their product. There are also few systems in place for post-market surveillance of malaria RDTs.

These global market challenges are also applicable to the Asia Pacific region. Other potential challenges require more investigation, including the extent to which the market has benefited from global RDT price declines, the effect of changes at the Global Fund (New Funding Model and anticipated changes to RDT procurement) on RDT quality and pricing, and the impact of local procurement practices and product registration requirements on RDT access.

3.2 New malaria diagnostic technologies

For the Asia Pacific region, there are three priority areas for diagnostic technology development:

Quality Controls for RDTs: Currently there is no practical way to confirm the accuracy of RDTs in the field. Quality control technologies for use at both the point of service (positive control wells, individually packaged) and at central laboratories (calibrated panels of quality controls) are needed to ensure the quality of tests. FIND is leading efforts to develop these; suitable products are expected in the next 2-3 years.

Diagnostics to support P. vivax: The Asia Pacific region is home to 91% of the global population at risk for P. vivax and this is contributing to the need for several new diagnostics. First, improvement in the sensitivity of P. vivax detecting malaria RDTs is needed. A second need relates to enabling safe...
scale-up of medicines that prevent relapse in *P. vivax*. These medicines (primaquine and tafenoquine) belong to a class of drugs (8-aminoquinolines) that can cause severe adverse reaction (haemolysis) in individuals with G6PD deficiency. A recent analysis classified countries in the Asia Pacific region as “high risk” for G6PD deficiency. Although G6PD screening is recommended prior to use of these medicines, there is yet no PoC test for G6PD. As a result, providers frequently forgo the medicine completely, putting the patient at risk of relapse, or provide the medicine without knowing G6PD status, putting the patient at risk of adverse reaction. In addition to preventing illness in the population, these medicines are key to reducing the potential reservoir of parasites contributing to onward transmission.

Currently, one qualitative PoC test for G6PD is undergoing clinical evaluations. Tafenoquine (in Phase 3 trials, GlaxoSmithKline and the Medicines for Malaria Venture) is likely to require a quantitative G6PD test to measure enzyme activity; PATH is supporting development of these tests with expected availability in 2017.

**Highly sensitive field tests for elimination:** Almost half of the Asia Pacific countries have malaria elimination strategies; the changing epidemiology and activities associated with elimination create needs for new diagnostics. Although advances are possible in several areas, the primary need is for a rapid, field test to detect low levels of parasites. These tests support surveillance activities in elimination and containment of resistance settings, whereby health workers, working at the household level, screen (symptomatic and asymptomatic) populations and treat infected individuals in order to wipe out foci of transmission.

PATH and the Bill and Melinda Gates Foundation (BMGF) are supporting development of a *P. falciparum*-only infection detection test for rapid screening of asymptomatic and symptomatic infections.

While a range of product development efforts is underway to address these access gaps (Figure 4), the pipeline is relatively thin and several research and development (R&D) gaps remain. Notably for the Asia Pacific region, there are several gaps related to *P. vivax*, including improving the sensitivity of RDTs, development of highly sensitive rapid field tests, and development of a biomarker and tests that can detect the relapse causing stage of *P. vivax*. While technologies in the broader malaria diagnostics pipeline may fit the needs of elimination settings, few are close to market, and progress has slowed due to limited R&D funding for malaria diagnostics and a lack of pull from the market.

In addition, without treatment for the liver stage, *P. vivax* can lie dormant for an extended period of time, with relapses causing illness and onward transmission of *P. vivax*. Treatment for *P. vivax* therefore requires a drug to treat the blood stage infection (e.g. ACT, chloroquine) as well as primaquine (and in the future tafenoquine) to treat the liver stage. These medicines targeting the liver stage however can cause mild to severe hemolysis in people with G6PD deficiency, which is a common enzymatic deficiency. Although there are many laboratory-based methods for G6PD testing, these formats are not appropriate for patient management due to delays with getting results and complexity of implementation.

Increased clustering of parasites in small geographic areas, among certain populations (often men, related to occupational factors), and in harder to reach populations that may have lower access to health services. Also, the proportion of *P. vivax* cases generally increases because *P. falciparum* responds more quickly to control measures.

As countries move towards elimination, programs begin additional activities aimed at detecting, responding to and reporting all infections, including asymptomatic infections, because these can contribute to onward transmission of malaria. These active case detection strategies complement routine malaria care (i.e. passive case detection) in health facilities. In addition, central reference laboratories support population surveys using highly sensitive diagnostics (PCR, LAMP) to monitor transmission.
although some products are near to market, significant work is required to facilitate adoption and scale-up of new products; optimally this market readiness work begins well before product availability.

Figure 4: Malaria diagnostic technology pipeline overview

4. Vector control

Given their demonstrated impact in reducing malaria, insecticide-treated nets (ITNs) or indoor residual spraying (IRS) are recommended by WHO for use in protecting all persons at risk in areas targeted for malaria vector control. In addition to these established paradigms, there is a need for development of new vector control tools to counter resistance and increase protection.

4.1 Insecticides

IRS is one of the primary vector control interventions recommended by the WHO Global Malaria Programme, and four classes of insecticides are in use. Many malaria-endemic countries have replaced dichloro-diphenyl-trichloroethane (DDT) with alternative insecticides, mostly pyrethroids. IRS use in the Asia Pacific region is dominated by India’s use of DDT - 53 million people were protected in 2012. India is the last remaining DDT manufacturing country and the only country still using large quantities. Pakistan is the second largest IRS market in the region, with 14 million people protected in 2012. IRS is not recommended as an effective intervention in some forested areas in South East Asia, where there are no structures to spray and where it is not aligned with targeting outdoor biting mosquitoes insect behaviour. The major market for pyrethroid-based IRS is Africa, with 58 million people protected by IRS in 2012. Globally, only 4% to 5% of at-risk populations are protected with IRS in any given year, so there is scope for market growth if the supply/demand challenges can be overcome.
Global access issues and existing interventions

IRS scale-up is hampered by the cost of implementation, which is a function of i) logistical and operational constraints in government delivered IRS campaigns ii) capacity to conduct insecticide resistance monitoring iii) lack of long lasting IRS formulations, and iv) pricing of non-pyrethroid insecticides. According to the WHO Global Plan for Insecticide Resistance Management (GPIRM), countries should be improving their monitoring and evaluation related to insecticide resistance as well as implementing strategies to delay resistance, such as insecticide rotation, using combinations, and using mixtures. However, non-pyrethroid IRS is caught in a classic market dynamics trap: insufficient monitoring and evaluation fails to identify the need for new products; therefore uptake remains low; insecticide prices are high because scale is low; the high price impedes uptake, and the negative cycle continues. There is a need for global supply side work to influence the prices of resistance breaking insecticides – and firms in the region may be able to contribute to this. But market impact will require overcoming demand side barriers in Africa, in partnership with The President’s Malaria Initiative (PMI) and the Global Fund in lower income countries in Africa.

Asia Pacific priority needs and options

Although IRS use is high in a few countries in the Asia Pacific region, the market that needs shaping relates to insecticides other than DDT and pyrethroids. A market intervention to influence upstream IRS supply side will likely need to gain traction in Africa before South East Asia would benefit. Countries in Asia can take action now to benefit from future market evolution of non-pyrethroid insecticides through implementing effective insecticide resistance monitoring, which will provide a sound basis for decision making and guidance on drafting a resistance management plan. See also the section under R&D for relevant points on the region’s possible role in the IRS supply side.

4.2 Nets

Nets can be divided into untreated nets (UTNs), insecticide-treated nets (ITNs – which are UTNs dipped into insecticide which lasts 6 to 12 months) and long lasting insecticide-treated nets (LLINs), which can be categorised into three levels of approval according to the WHO Pesticide Evaluation Scheme (WHOPES). WHO primarily recommends use of WHOPES-recommended LLINs and WHOPES approval is a requirement of the major LLIN funders, the Global Fund and PMI, which fund 80% of LLIN purchases.

The concentrated donor/funding base, requirement to gain WHOPES approval, infrequent purchase every 3 to 5 years, and limitation of market size to malaria endemic countries combine to create conditions raising the importance of each tender and the entry barriers for new firms. As a result, the supplier base is concentrated and power imbalance between suppliers is high, however the recent

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xv Tom McClean, personal communication.
xvi Interim recommendation = Phase I (measuring insecticidal efficacy in a lab) and Phase II approved (measuring insecticidal efficacy in experimental field huts). Full recommendation = Phase III approved (minimum three-year review of overall performance in the field, measuring insecticide efficacy, net longevity, fabric integrity, community acceptance and safety).
xvii John Milliner, Net Mapping Project data.
xviii The market has traditionally been dominated by two suppliers for LLINs: Vestergaard (55% market share) and Sumitomo (30% market share). Bayer and Sumitomo are the only two producers making both insecticides and nets.
Access to Quality Medicines and Other Technologies Task Force

and rapid scale-up of donor finance has brought forward latent demand, allowed market expansion, and has enabled several new producers to enter the market. As compared with 4 WHOPES certified LLIN vendors in 2004,\textsuperscript{33} there are now 13 approved LLIN products from 11 suppliers, several of which are based in the Asia Pacific region.\textsuperscript{32} LLIN price has also evolved; average price to global programmes was more than USD 5 in 2009,\textsuperscript{33} and is USD 2.90 now.\textsuperscript{54} Nonetheless, specific features and requirements of international tenders have been noted to place smaller producers at a disadvantage.\textsuperscript{33, 45}

Global access issues and existing interventions

Unpredictable funding patterns or delayed disbursements have been an issue affecting supply security and pricing during recent years of rapid LLIN scale-up.\textsuperscript{35} Prices and price comparability is affected by i) order placement timing relative to production availability, ii) market leverage (volume, procurement method and management) and iii) product heterogeneity (shapes, sizes, colour, labelling, leaflets, hooks, fabric strength and weave density).\textsuperscript{33} Fragmentation in specifications increases costs as well as procurement lead times. A PMI study found price mostly correlated with shape and size and concluded that the tender process is the most important factor in influencing price. There has been a tendency to buy cheaper nets with fast delivery over more durable and expensive nets with specifications in demand by users. Systematic quote requests to all pre-selected vendors offers the best approach according to PMI.\textsuperscript{35} Since at least 2009, there has been recognition of a need to raise the bar above just WHOPES approval as minimum standard, looking beyond tender prices to encapsulate value for money, as provided by increased durability and net acceptability to users, for example.\textsuperscript{33} The Vector Control Advisory Group (VCAG) at WHO has been studying usage and performance in country, with the goal to influence rational purchasing based on value for money, and incentivise development of improved technologies. Since 2012, UNICEF’s tender evaluation criteria have included end-to-end supply chain value for money and optimisation considerations.\textsuperscript{60} The Global Fund has also recently operationalised its new procurement framework in partnership with other major LLIN purchasers. This includes joint forecasting, improved standard specification, simplified procurement and production, larger scale purchasing power and long term contracts to achieve reduced prices. Under this new model, the Global Fund signed contracts with seven manufacturers.\textsuperscript{32}

Commercial markets in UTNs are strong, although varied between countries and within countries. One study across 26 African countries found uptake of untreated nets to be surprisingly equitable and, despite lower efficacy vs. treated nets, their high distribution and high usage contributed more than expected to public health.\textsuperscript{31} There is limited knowledge of how the LLIN scale-up in recent years has influenced this market globally, for example the proportion of treated to untreated nets in use.

Asia Pacific priority needs and options

On the supply side, most LLINs are sourced from the region (mostly Vietnam and Cambodia) even if shipped to Europe or Japan for insecticide treatment.\textsuperscript{xix} Suppliers from the region which already have

\textsuperscript{xix} Tom McClean and Jo Lines, personal communication.
WHOPES approval include Shobikaa Impex Pvt (India), Sumitomo (Japan), Tinajin Yorkoo International (China), and Disease Control Technologies (India). Suppliers with products currently under evaluation by WHOPES are Kuse Lace Co (Japan), A to Z (Tanzania), Life Ideas Textiles (China), Fujian Yemein Industries (China). In the interest of supply security, price competition and potential for product design in line with consumer preferences, it is in the interest of the global community as well as the region to maintain the interest of a diversified LLIN supply base.

A number of market challenges face smaller LLIN suppliers. The large size of donor funded tenders is an impediment to firms with more limited production capacity or capital constraints. A range of options may be considered to minimise risk of supplier exit and maintain a diversified supply base - including splitting tenders, dividing large orders into smaller lots, establishing a consortium among smaller manufacturers so that they can apply for larger tenders. Advance purchase commitments may also be considered. Further insight is required into the priority constraints faced by smaller LLIN suppliers based in the region before an appropriate intervention can be tailored.

On the demand side, sub-Saharan Africa represents more than 80% of the LLIN market. Donors have prioritised vector control funding to Africa, in line with highest disease burden, and have not focused efforts on populations that have the potential to purchase protection products on their own (i.e. population segments in South East Asia). Inefficiencies at the global level in LLIN procurement and provision have been recognised and remedies are in progress currently. As with IRS, the major influence in LLIN market shaping comes from African demand; the smaller Asia Pacific LLIN demand will benefit from (ideally) linking with this African demand or alternatively, aggregating its own demand as a region.

Although globally most of the donor funded LLINs go to Africa, some countries in the region receive a large share of their total LLIN need from donors and there are complaints that Global Fund procured nets are not aligned with local preferences; there is some recent data to support this claim. The collection of additional systematic evidence would give the region more leverage with the Global Fund.

Although the focus of this paper is on upstream supply, the importance of commercial net markets within countries in the region needs to be acknowledged. A 2012 study documented the continued vibrancy of local markets providing UTNs and ITNs purchased out of pocket for three countries in the Greater Mekong Sub-region; approximately 90% of households owned a net that had been purchased. Further leveraging the private sector would support objectives for continuous rather than campaign distribution, as well as support to a sustainable channel which has proved responsive to consumer preferences. Value for money studies, comparing purchased nets with donor funded LLINs, would reveal relative cost per effective use per net year and inform strategies for further leveraging the private sector.

xx Spring 2013.
xxi Outside of Africa, six countries account for 70% of the total 78 million nets in use: India 18.4 million; Indonesia 6.5 million; Afghanistan 4.6 million; Myanmar 3.6 million; Philippines 3.0 million; China 2.2 million.
4.3 Global R&D needs and pipeline

The global R&D need is for improved insecticides/pesticides for both IRS and LLINs, including mechanisms for their application, as well as new consumer products.\textsuperscript{40} Current spending on R&D for malaria vector control products was USD 28.6 million in 2011, representing only 5.1% of the overall R&D spending on malaria. BMGF funds 78% of the vector control R&D work at present.\textsuperscript{41} Manufacturers are hesitant to invest in R&D for vector control since R&D costs are difficult to recover in a very price-sensitive market with easy “me too” approval processes and uncertainty around market size going forward.\textsuperscript{xii 32}

The existing R&D pipeline is focused on new insecticides and incremental improvements to existing products such as longer-lasting products. Four nets that contain synergists, or chemicals to block the resistance mechanisms in the malaria vectors, are currently in the WHOPES evaluation process. Further back in the R&D pipeline, the Innovative Vector Control Consortium (IVCC) has new insecticides in development.\textsuperscript{40}

**R&D: Asia Pacific priority needs and options\textsuperscript{xiii}**

The R&D need specific to vector control in the Asia Pacific region is for novel products for use in forest or fringe settings to control the outdoor biting and resting mosquitoes that transmit ACT drug resistant malaria. The region would also benefit from new insecticides and incremental innovations to existing products. Although most of the demand incentivising incremental innovations comes from Africa, the major source of innovation in research and product development in vector control, indeed in malaria in general, comes from the Asia Pacific region.\textsuperscript{44}

5. Summary of findings and recommendations

In this final section, key findings and recommended interventions are presented by technology category, in line with the organisation of this paper. Intervention options have been chosen according to the following criteria: alignment with disease burden of the region; meeting a recognised gap in upstream supply side issues relevant to the Asia Pacific region; amenable to influence by Asia Pacific Leaders Malaria Alliance (APLMA) members and levers at their disposal; builds on/leverages current actors and systems in the global health architecture, in order to facilitate ease of implementation, value for money, and sustainability; potential for near term impact. APLMA members are best positioned to discuss the political feasibility of the intervention options, and once these have been short-listed, the next stage of work could entail a detailed options appraisal.

\textsuperscript{xii} The market failure in vector control R&D is driven by shift in target product profiles for agrochemical insecticides, which had previously been the source of all public health pesticides. As a result, none of the insecticides developed over the past three decades are appropriate for repurposing for the public health market. The small market size means little incentive to invest in R&D specifically for public health. The market failure in the bednet market is over-reliance on pyrethroids, which are used as monotherapy, making resistance an inevitable bi-product of mass distribution campaigns.\textsuperscript{40}

\textsuperscript{xiii} This section draws on conversations with Dr Tom McClean.
5.1 Summary medicines findings

There is already significant malaria medicine manufacturing capacity in Asia Pacific, primarily in India and China, but also in Indonesia, Korea, Pakistan, the Philippines, Taiwan, Thailand, and Vietnam. The continued engagement of these suppliers is important to supply security, price competition and innovation – not only for the benefit of the region but also for global health worldwide.

WHO has identified 11 companies in India, 3 each in China and Pakistan, and 1 each in Bangladesh and Vietnam who are still offering artemisinin oral monotherapies for sale. The priority need is to drive out poor quality drug products, which can be achieved through regulatory sanctions, loss of a market, or support to raise standards.

Due to the long lead times and number of players involved in upstream ACT production, prices and supply security can suffer when demand is unpredictable and/or fragmented across many uncoordinated tenders. With the Global Fund’s New Funding Model, countries might choose to use counterpart funding to procure antimalarial drugs outside of the Global Fund systems, which would reduce transparency and fragment demand, with the risk of increasing prices, as well as risking the quality of drugs procured in the absence of strong quality control and regulatory enforcement.

Several Asia Pacific countries have called for more regional or country appropriateness in the ACT dosage levels, formulations, and packaging received from donor agencies.

Medicines recommendations

Possible interventions to address the challenges outlined are as follows:

1. **Increase transparency of demand:** A market intelligence framework could give the manufacturers transparency over demand and enable them to better plan production capacity and *Artemisia annua* planting. This framework could be set up and run by the industry or by an independent regional organisation.

2. **Pool demand:** The Global Fund is already developing a system for pooling demand for ACTs, and has already completed such an exercise with bednets. However, as mentioned above, some countries may consider not using Global Fund systems. Ideally countries in the region will continue to work with Global Fund systems for their ACTs needs. If countries decide not to use Global Fund systems, an informal process should be supported among the various National Malaria Control Programmes (NMCPs) to co-ordinate their antimalarial drug procurement. This could then also feed into the market intelligence framework outlined above. This would have the potential benefit of reducing drug prices as order quantities are increased, further reducing demand uncertainties, and allowing for guaranteed supply commitments to be agreed.

3. **Establish a co-payment system:** to subsidise appropriate products and shift demand away from monotherapies and other poor quality antimalarials. Affordability is a key barrier to access to high quality and appropriate antimalarials in countries with a significant involvement of the private sector – especially for the most disadvantaged and hard to reach patients. The AMFm co-payment pilot showed that this model could deliver greater access and
affordability but has only been trialled in Africa. However the experience of social marketing of drugs through the private sector has also been reviewed for Myanmar, Cambodia, and globally. These reviews show that there are several models for increasing the affordability of high quality medicines in the private sector. This system might be linked not only to medicines but also to diagnosis (especially RDTs).

4. **Investment in regional regulatory agency strengthening:** Most of the reduction in the use and availability of monotherapies around the world is due to better enforcement of the prohibitions on their use. There will always remain the need for improved and strengthened regulatory agencies. As WHO has noted, this needs to cover exports as well as domestic supply. The development of more regional regulatory collaboration and harmonisation would need to be supplemented by investment in robust national enforcement. Some donor funding could be directed towards such investment.

5. **Support to regional manufacturers:** A major barrier for regional and local manufacturers is to earn an adequate return on their investment in improving quality. A recent survey of African-based pharmaceutical manufacturers identified a lack of access to affordable long-term finance as a major barrier. Several options could be considered for supporting regional pharmaceutical manufacturers to invest in raising production standards – loans or grants, where capital is the constraint; technical assistance in meeting good manufacturing practice and preparing regulatory dossiers; brokering discussions of demand and finance projections and business case modelling; and advance purchase commitments. A better understanding of the specific constraints faced by producers in the region is required before tailoring a solution. This approach would have to be thought of as part of a wider industrial strategy and not merely as a health-related issue. It would also have to address the eligibility criteria for companies to access support, based upon some measure of their ability to improve and maintain globally recognised quality standards.

5.2 **Summary diagnostics findings**

Global and Asia Pacific access challenges in malaria diagnostics share some common features: presumptive treatment continues to be common in the absence of diagnostic scale up; current RDT pricing appears to be approaching the cost of production, leaving little incentive for investment in quality or in innovation, at a time when both are public health priorities; and there is no practical way to check RDT quality at the point of use, due to a lack of available quality control technologies.

A challenge particular to the Asia Pacific region is the need for new diagnostics related to the region’s epidemiology (e.g. presence of *P. vivax*, progress in reducing malaria burdens and advancing malaria elimination). Product development efforts are underway to address region-specific access gaps; some of these products are near to market and require significant work to be developed and scaled up.

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xxiv The AMFm experience revealed the importance of appropriate communication programmes to go alongside price subsidisation. This is to create demand from the care-seekers to pull the product through the system.

xxv Although Cambodia was one of the pilot countries, delays in accessing WHO-PQ standard DHA-PPQ meant that the programme could not be implemented in time for its inclusion in the pilot’s evaluation.

xxvi Best practice on the introduction of diagnosis in the private sector is being collected by the Roll Back Malaria Partnership (RBM) Case Management Working Group for publication shortly.

xxvii See related recommendations by Lalvani et al. and the Outcome Statement from the Regulator’s meeting. 23, 57
facilitate adoption and scale-up. This market readiness work ideally begins well before product availability.

The pipeline is relatively thin and several R&D gaps remain in other areas, notably including improving the sensitivity of RDTs for *P. vivax*, development of highly sensitive rapid field tests for elimination, and development of a biomarker and tests that can detect the relapse causing stage of *P. vivax*.

**Diagnostics recommendations**

**Rapid diagnostic tests:** Several supply side interventions could contribute to improved access to quality RDTs:

1. **Build supplier capacity in manufacturing quality systems.** This includes providing technical assistance to RDT manufacturers to raise manufacturing quality standards. Qualified consultants would provide assistance (e.g. mock site inspections, dossier reviews) to companies meeting eligibility criteria. Building capacity in manufacturing quality would benefit the global market for RDTs and would have carry over effects for other diagnostics.

2. **Strengthen regulatory capacity for diagnostics.** Development of stronger, harmonized regulations for diagnostics should be a priority for the region, including development of systems for post-marketing surveillance and enforcing regulation in private sector markets. In the near term, each country’s RDT related regulatory requirements can be surveyed and results compared to inform regional collaboration on improving the regulatory environment.

3. **Explore development of retail markets for RDTs.** Developing private sector markets for RDTs is complex; however, given the important role of the private sector in fever management and the need to improve targeting of medicines in the region, there is a case for exploring this channel in some settings. The Roll Back Malaria Partnership (RBM) Case Management Working Group is working to synthesize experience to date on where and how malaria RDTs might be supported and implemented in retail markets. A regional leadership and coordination body could advance work and decision-making on opportunities to develop the private sector market for diagnosis in the Asia Pacific region. Initially, it might engage with the Roll Back Malaria Partnership in dissemination of learning, oversee formative research, and map local policy regarding testing in the private sector. Additionally, if momentum develops, a regional body could establish a catalytic fund to support operational research in multiple countries and support development of a funding mechanism to support private sector initiatives in the region.

4. **Improve market knowledge surrounding diagnostics.** A regional market study would highlight issues around demand fragmentation, procurement practices, and registration requirements. Additionally, the impact of the Global Fund New Funding Model on the region should be analyzed, as donor leverage to shape markets may decrease, and a regional mechanism for influencing the markets might become more important.

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xxviii Similar capacity building approaches have been undertaken in medicines, led by CHAI and MMV for example.
New diagnostics: Given the acute need for new diagnostics, and pipeline of products that are particularly relevant to the region, there is a strong case for developing a regional mechanism to support introduction of new diagnostic technologies. A regional initiative would build on the 2012 Sydney Consensus Statement, calling for acceleration of high priority research\textsuperscript{53} and contribute to accelerated access to new products. A detailed landscaping analysis, including mapping of work underway globally, for each of the areas should be undertaken to inform development of a regional initiative; among the possible activities to consider are:

- Operational research to inform policy recommendations regarding use of new products (e.g. research to inform optimal delivery of PoC G6PD testing, optimal strategies for active case detection in elimination settings).
- Regional mechanisms to support market-entry, including support for regional evaluations and demonstration projects, as well as awareness raising, information dissemination and policy work. This could take the form of funding for agencies that provide technical support or hiring regional “uptake coordinators” to support countries.
- Development of and harmonization on regulatory requirements for new products.
- Analysis of the need for funding to support scale-up of technologies, in cases where cost may be a potential barrier to access (e.g. G6PD testing + tafenoquine), explore the role of co-funding initial demand until production economies of scale are achieved.
- Leverage the region’s several centres of excellence to facilitate access to expertise, well-characterized samples, and clinical trial sites for product development. These centres could also be involved in the establishment of global external QA systems for nucleic acid based testing used for research, trials, and surveillance purposes.
- Provide funding for product development, or other incentives for R&D, where the existing pipeline is thin (e.g. improving \textit{P. vivax} RDTs) and for markets where demand may be small or less predictable (e.g. highly sensitive tests for elimination settings).

5.3 Summary vector control findings

Globally, IRS scale-up is hampered by the cost of implementation, which is a function of i) logistical and operational constraints in government delivered IRS campaigns ii) capacity to conduct insecticide resistance monitoring iii) lack of long lasting IRS formulations, and iv) pricing of non-pyrethroid insecticides. There is a need for global supply side work to influence the prices of resistance breaking insecticides – and firms in the region may be able to contribute to this. Market impact will require overcoming demand side barriers in Africa, given its relatively higher volumes of IRS consumption.

The Asia Pacific region is important to the global supply of treated and untreated mosquito nets, however market conditions are not favourable to competition and smaller firms face considerable hurdles to continued engagement in the WHOPES-approved LLIN segment. In the interest of supply security, price competition and potential for product design in line with consumer preferences, it is in the interest of the global community as well as the region to maintain a diversified LLIN supply base. Further insight is required into the priority constraints faced by smaller LLIN suppliers based in the region before an appropriate intervention can be tailored.
Access to Quality Medicines and Other Technologies Task Force

As with IRS, the major influence in LLIN market shaping comes from African demand; the smaller Asia Pacific LLIN demand will benefit from (ideally) linking with this African demand or alternatively, aggregating its own demand as a region.

Although globally most of the donor funded LLINs go to Africa, some countries in the region receive a large share of their total LLIN need from donors and there are complaints that Global Fund procured nets are not aligned with local preferences; there is some recent data to support this claim.

Commercial markets for untreated nets continue to be important in many countries in the region. Further leveraging the private sector would support objectives for continuous rather than campaign distribution, as well as a sustainable channel which has proved responsive to consumer preferences.

There are R&D needs specific to the Asia Pacific region as well as those which are shared with Africa; the region has strong contributions to make towards R&D.

Vector control recommendations

1. Countries in Asia can take action now to benefit from future market evolution of non-pyrethroid insecticides through creating the correct “pull” conditions for uptake. This includes coordinating and harmonising regulatory processes across a group of countries, implementing effective insecticide resistance monitoring, which will provide a sound basis for decision making and guidance on drafting a resistance management plan, and forecasting the emergent marketplace linked to a financial guarantee supporting the forecast. This will create a market. On the supply side, there is a near-term opportunity to leverage Indian formulation expertise in producing longer lasting non-pyrethroid insecticides. Push funding to selected firms might be considered to reduce their development risks.

2. Conduct research towards defining value for money in nets, in order to i) advocate with the Global Fund for procurement of nets with increased acceptability and durability ii) make the best use of domestic funds (where applicable), where nets are procured with Ministry of Health or Global Fund counterpart funding and iii) to inform policy and practice with regard to influencing nets in commercial circulation. This would involve gathering data to evaluate net longevity and use in different settings, using the data to guide tender specifications beyond WHOPES approval and unit price, thereby reducing the fragmentation of packaging and specifications. This work should be linked in with similar studies underway by WHO, major funders and procurers.

3. A rapid survey of smaller LLIN manufacturers in the region is recommended; this will inform APLMA leaders as to the most promising combination of supply or demand side interventions for enhancing both LLIN supplier business viability and their public health contributions. The data gathered may be included and disseminated in UNITAID’s new vector control landscape study due to be published later in 2014.

4. Given the relatively small demand for LLINs, as a proportion of global demand, value for money is likely to be superior when countries in the region ideally aggregate the region’s LLIN demand with African demand through the Global Fund. In cases where this is not achievable,
and LLINs are procured with domestic funds, countries can find ways of working together or approaching the market as a sub-group. Lessons can be learned from other regional initiatives on medicines, the African Medicines Regulatory Harmonisation (AMRH) and the Southern Africa Regional Programme on Access to Medicines and Diagnostics (SARPAM). Generating market intelligence is the starting point, which can proceed to co-ordinated information exchange, work sharing and potentially leading eventually to some version of pooled procurement. Specific options include:

- Address information gaps that affect buyers and sellers, making it easier to learn about new suppliers, their prices or acceptable standards and improving chances of effective competition in the tendering process. This can include a central mechanism of collecting data on pricing and WHOPES-approved supplier performance.
- Align tendering specifications and decision-making processes in the region; this could be linked with point 2 – incorporating value for money in the tendering decision-making criteria.
- Harmonise regulatory processes and/or registration requirements to lower barriers to entry and enhance supply base from which to choose.
- If some countries in the region decide to engage in pooled procurement, group contracting or co-ordinated informed buying, the tender could be scaled appropriately to advantage the many Asia Pacific region firms who have now made the investment to gain WHOPES approval.

5. **Provide push funding for new vector control paradigms currently in development and facilitate market entry and uptake once developed:** There is a concern that new technologies currently in development are not moving along the pipeline fast enough to meet the resistance challenges foreseen in 12 to 18 months. Increased push funding is required to initiate and hasten efficacy studies and speed development and registration. Countries in the region can also prepare groundwork for introduction of these close to market technologies, to facilitate market entry and uptake once developed.

6. **Invest in community level research to inform target product profiles for further innovations:** There is great need for community level research to understand which products would people use, and which channels could be used to roll them out. This would inform the target product profiles which can be used to commission R&D work. Depending on the stage of research, this process could be managed via national research councils of relevant countries, science agencies (e.g. Australia’s Commonwealth Scientific and Industrial Research Organisation) or product development partnerships such as the Innovative Vector Control Consortium.

**Conclusion**

Several strategic insights emerge which are relevant across all three of the technology categories reviewed. On the demand side, it is clear that antimalarial technology markets in the Asia Pacific region are generally small and fragmented compared to global and African demand. This limits leverage with suppliers when buying outside the Global Fund. Regional and national buying leverage is likely to lessen further over time as volume requirements fall in line with reduced disease incidence. In

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\textsuperscript{xxx} The Indian market is an exception – demand volumes for ACTs, RDTs, and LLINs is sufficiently large to give India leverage in the global demand landscape.
addition, the Global Fund’s requirement for counterpart funding may result in more countries procuring independently. Limited buying power, and perhaps inefficient national tendering, may translate to higher prices and less secure supplies. In turn, inability to secure good prices for antimalarial technologies may accentuate the trend to buy reduced quality products. To counter this, countries need to strengthen their buying power. In most cases, better value for money is likely to be achieved by continuing to participate in the Global Fund system. If countries wish to opt out of the Global Fund system, then regional collaboration on procurement (supported by regulatory harmonisation already underway) will be the second best option.

It is also clear that the private sector is important as a demand channel in many of the Asian Pacific countries, but initiatives to influence the supply side through shaping this channel remain small scale. This is true with all the commodities reviewed. Lessons can be learned from interventions within and outside the region to develop and implement larger private sector focused interventions, with greater impact. Given the complexity of these interventions, additional research and piloting in local markets is warranted.

On the supply side, the Asia Pacific region is crucial to the global supply of existing treatments, vector control products and diagnostic tests. Thus, initiatives to ensure producers maintain engagement and improve quality standards will be an area of aligned interest with the global community. Industry can be influenced via sanctions or incentives. Incentives need to be designed to address specific access shortcomings identified through market research. For some of the product sectors covered here, better market data is needed before an intervention package can be tailored. “Push” or supply focused incentives can involve technical assistance, loans or grants to specific firms, while “pull” or demand focused incentives aim to make the market more transparent and credible. All of the product sectors reviewed would benefit from significant “pull” or demand side work in the region. Finally, the region’s fundamental and behaviour/social science research, as well as active pharmaceutical ingredient, formulation and clinical trials expertise, should be further leveraged to develop new technologies relevant to global health. There is also a strong case for developing co-ordinated systems to support introduction of new technologies.
Annex 1: Acknowledgements

The authors would like to acknowledge the advice of the following people who were consulted during the research for this paper:

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</table>
Annex 2: References


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The authors also acknowledge permission for the use of the following figures:

Figure 2: Jacques Pilloy (Oteci/Artepal 2010).

Figure 3: Jacques Pilloy (Oteci/AEDES). Presentation at the Artemisinin Conference, Nairobi, Kenya, 15–16 January 2013.
Annex 3: Medicines supply chain details

The main categories of players involved in the supply chain (Figure 2 of this report) are as follows:

- **Growers:** >100,000 small farmers who grow *Artemisia annua* as a crop but who can choose to replace it with other cash crops if it is more profitable for them to do so. These growers are often not bound by contracts and need good management by the “extractors”.

- **Extractors:** about 15 companies that buy the harvested leaf from the growers. They then process it to extract and purify the artemisinin. Some more companies extract but do not purify the artemisinin, selling it on directly to active pharmaceutical ingredient (API) producers.

- **API producers:** for artemisinin, the API producers process the purified artemisinin into the derivatives needed for ACT manufacture (artesunate, DHA, etc.). For the partner drugs (piperaquine, amodiaquine, lumefantrine, etc.), the API producers synthesise the chemicals from readily available chemical intermediates. 90% of the global manufacture of antimalarial APIs (including artemisinin) is in China, India and Korea.

- **Secondary producers:** these are the companies that buy the API and formulate them into the finished products, package it, undertake QA testing, and then ship to the in-country distributors. They handle the stage of “Drug Production” in Figure 2.

Secondary producers for antimalarials can be classified broadly into three groups:

- **Global innovator pharmaceutical companies:** these include Novartis and Sanofi as producers of ACTs. Their principal business is the discovery, development, and deployment of innovative drugs. In the past their involvement with malaria has been by developing novel drugs such as artemether-lumefantrine and artesunate-amodiaquine. They often operate now by supplying antimalarials on a “no profit, no loss” basis. All these companies produce to WHO-PQ or equivalent standards.

- **Major regional generic manufacturers:** these are large manufacturers operating on at least a regional, but often a global scale. Their business model is to produce drugs for which there is an identifiable market, where they can make an adequate return on their investment, and are no longer protected by intellectual property. They usually manufacture to global good manufacturing practice standards, although they may not always have obtained WHO-PQ for all their products. Among the ACT manufacturers, this group would include Guilin Pharma, IPCA, Cipla, and Ajanta.

- **Local generic manufacturers:** these are small companies who primarily manufacture for customers in a single country or a small group of adjoining countries. They often do not meet good manufacturing practice standards and do not qualify to supply to the public sector. Their main line of business is to supply to the private market. They are usually much more affordable.

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[xxx We have avoided naming all the companies involved at each stage, as it is not possible to verify information directly with all the companies in the timeframe of this work. However secondary producers’ names have been provided where appropriate.]
but can be of questionable, if not completely unacceptable, quality due to their non-adherence to generally accepted QA and good manufacturing practice procedures and standards.
Annex 4: Malaria diagnostics technologies

<table>
<thead>
<tr>
<th>Use category</th>
<th>Technology</th>
<th>Description</th>
<th>Stage of use or development (global)</th>
<th>Priority market for Asia Pacific region?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive case detection (i.e. case management of individuals who are ill and seek care)</td>
<td>Malaria RDTs</td>
<td>Disposable tests that detect antigens produced by the malaria parasite.</td>
<td>Rapidly growing market, 205 million RDTs in 2012 and growing.</td>
<td>High: Access to testing could be scaled through use of RDTs, especially in harder to reach populations, private sector.</td>
</tr>
<tr>
<td></td>
<td>PoC G6PD tests</td>
<td>PoC test to measure enzyme activity in red blood cells. May be qualitative (e.g. RDT format); semi-quantitative; or quantitative (e.g. biosensor device). Used to screen for G6PD deficiency prior to administering primaquine or tafenoquine for radical cure of <em>P. vivax</em>. and ovale.</td>
<td>• R&amp;D of PoC formats underway; several laboratory-based methods available.</td>
<td>High: Critical to ensuring radical cure of <em>P. vivax</em>.</td>
</tr>
<tr>
<td>Active infection detection (i.e. strategies that focus on screening individuals at the household level to identify and treat)</td>
<td>Rapid infection detection tests</td>
<td>PoC rapid tests to support the detection of infection (both asymptomatic and symptomatic) in elimination and in containment of resistance settings.</td>
<td>• Limited R&amp;D of new PoC, rapid tests underway.</td>
<td>High: Priority for elimination programs.</td>
</tr>
</tbody>
</table>
Infections, including those that do not present at health facilities as early as possible in order to reduce chances of onward transmission)

| Centralized laboratory testing (i.e. reference testing, surveillance, QA/QC) | Nucleic acid detection tests (PCR, LAMP) | Highly sensitive laboratory based technologies that detect parasite DNA/RNA. Limited use due to cost, infrastructure requirements and training. Time to results often too long. | • Limited use: reference, research and surveillance use.  
• Little standardization of methods, protocols etc.  
• Very limited availability of commercial test kits (exception LAMP from Eiken).  
• R&D: Improvements to existing platforms/assays; PoC products in development.  
| Low: while standardization on protocols and QA are priorities, costs are high and overall market size small. |

| Serology | Detection of antibodies to malaria parasites, signifies exposure not active infection. Several laboratory based approaches; ELISA is most common method. | • Blood banks: commercial ELISA kits.  
• Methods for surveillance/transmission monitoring in elimination settings under development.  
| Low: while standardization on protocols is a priority, commercial kits beneficial (standardization/QA) overall market size small. |

| G6PD surveys | • Tests that detect prevalence by phenotype.  
• Tests to determine genotype of deficiency. | • Commercial products currently available, but require significant capacity and training to implement.  
| Low: limited market size. Rationale for prevalence mapping as well as methodology must be well thought out. |
Annex 5: Key characteristics of the malaria RDT market

Malaria RDTs were first developed in the 1990s. Recently, the market has grown substantially, from 45 million tests sold in 2008 to 205 million in 2012. There are over 40 malaria RDT suppliers, predominantly small companies located in the Asia Pacific region. RDT suppliers vary from companies that produce the primary reagent as well as the finished product, to companies that purchase semi-finished product for repackaging and rebranding. The level of automation, manufacturing quality, and R&D capabilities varies considerably across the companies. Although RDTs are produced to order, globally, production capacity is not considered to be a limiting factor in this market.

The main quality standard is the WHO/FIND Product Testing Program, which compares the relative performance of RDTs, and is the basis of the WHO and major donors recommended RDTs lists. Although the WHO-PQ for Diagnostics began reviewing malaria RDTs in 2010, suppliers are progressing slowly through the process (only two suppliers have been prequalified) and the program has no impact on the market. Several suppliers have not engaged in the WHO/FIND Product Testing Program; even fewer suppliers are engaging in WHO-PQ.

By far, the largest market segment is the public sector market (estimated to be >80% of global market), which is driven by donor funding and has recently consolidated around three producers. Africa is the largest and fastest growing RDT market. Globally, the private sector RDT market is small. The region represents an estimated 25-30% of the global RDT market, with India dominating. Limited procurement data indicates an increasing use of combination tests, order sizes that are on average smaller than typical African volumes (with a handful of exceptions), and declining prices for RDTs in the public sector. Malaria RDTs are inexpensive: in 2013, average public sector prices were USD 0.32 for
Data on the Asia Pacific RDT market is scarce.

P. falciparum-only RDTs and USD 0.38 P.falciparum-pan RDTs. Data on the Asia Pacific RDT market is scarce.