Chapter 6

Diagnostic testing and treatment of malaria

This chapter reviews (i) the extent to which national programmes have adopted policies for universal diagnostic testing of suspected malaria cases and trends in the availability and utilization of parasitological testing, (ii) the adoption of policies and implementation of programmes to expand access to, and utilization of, effective treatment for malaria, (iii) the progress made in withdrawing oral artemisinin-based monotherapies from the market, (iv) the current status of drug efficacy monitoring and the latest trends in antimalarial drug resistance, and (v) efforts to contain artemisinin resistance on the Cambodia-Thailand border.

6.1 Diagnostic testing for malaria

6.1.1 Policy adoption

WHO recommends that all persons of all ages in all epidemiological settings with suspected malaria should receive a parasitological confirmation of diagnosis by either rapid diagnostic test (RDT) or microscopy (1). National adoption and implementation of policies for diagnosis of malaria by WHO Region are shown in Table 6.1 and by country in Annex 4A. In 2010, 37 of 43 malaria-endemic countries in the WHO African Region and 53 of 63 endemic countries in other Regions reported having adopted a policy of providing parasitological diagnosis for all age groups, an increase of 4 countries in the African Region and 8 elsewhere. A total of 20 African countries are now deploying RDTs at the community level, as are 28 countries in other Regions, 10 more countries than in 2009.

6.1.2 RDTs procured and distributed

RDTs procured: In 2011, manufacturers participating in the WHO Malaria RDT Product Testing Programme supplied data on RDT sales to public and private sectors in malaria endemic regions (Figure 6.1). Sales have increased dramatically over the last 3 years, for both \( P. falciparum \)-specific tests and combination tests that can detect more than one species.

![Figure 6.1 RDT sales to public and private sectors 2008–2010](source)

Source: data provided by 31 manufacturers participating in the WHO Malaria RDT Product Testing Programme

Results of product quality testing undertaken by WHO, Foundation for Innovative New Diagnostics (FIND), Special Programme for Research and Training in Tropical Diseases, and the US Centers for Disease Control and Prevention (CDC) show an

<table>
<thead>
<tr>
<th>Policy</th>
<th>Africa</th>
<th>Americas</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients of all ages should get diagnostic test</td>
<td>37</td>
<td>19</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Only patients &gt;5 years get diagnostic test</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>RDTs used at community level</td>
<td>20</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>Malaria diagnosis is free of charge in the public sector</td>
<td>28</td>
<td>18</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>81</td>
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<tr>
<td>Number of endemic countries/areas</td>
<td>43</td>
<td>23</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>106</td>
</tr>
<tr>
<td>Number of ( P. falciparum ) endemic countries/areas</td>
<td>43</td>
<td>18</td>
<td>8</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>87</td>
</tr>
</tbody>
</table>
improvement in test quality over time (2), and, as a consequence, proportionally more high quality tests are being procured over time. The panel detection score (PDS) measures the performance of RDTs against samples of known parasite presence; WHO recommends procurement of RDTs with PDS greater than 50% against low parasite densities of *P. falciparum* in areas of high transmission, and PDS greater than 75% for areas of low to moderate transmission. According to data supplied to FIND by 17 manufacturers, nearly 90% of RDTs procured in 2011 had panel detection scores of more than 75%, compared with only 23% of RDTs procured in 2007, before the Product Testing Programme began.

**RDTs distributed:** The reported number of RDTs delivered by NMCPs has increased rapidly, from less than 200 000 in 2005 to more than 50 million in 2010 (Figure 6.3). Most of the RDTs delivered (65%) were used in the African Region followed by the South-East Asia Region (30%) and Eastern Mediterranean Region (5%). Although these totals underestimate the total quantity of RDTs distributed (only 32 of the 44 endemic countries in Africa reported these data in 2010), the same upward trend is seen as in RDT sales, with most growth occurring in the African Region.

### 6.1.3 Microscopic examinations undertaken

The number of patients tested by microscopic examination increased to a peak of 165 million in 2010 (Figure 6.4). The global total is dominated by India, which accounted for over 100 million slide examinations in 2010. Decreases in the number of patients examined by microscopy were reported in the Americas, Eastern Mediterranean, and European Regions which may be due to a reduction in numbers of cases, particularly in the American and European Regions, and to increased use of RDTs. The number of patients examined by microscopy remains relatively low in the African Region, although it has increased over the last four years.

### 6.1.4 Place of care for patients with fever

With the adoption of a new diagnostic testing policy for suspected malaria, delivery of care by trained health-care providers is increasingly important. The providers considered to be appropriate may vary by country context. Household survey data from 42 countries from 1990 to 2010, with each country weighted equally, show that more children received care from public health facilities than private in the African and American Regions, while relatively few received care from community health workers (Figure 6.5). A more recent subset of surveys indicates that the proportion seeking care from different providers differs greatly by country (Figure 6.6), which suggests that the strategy for expanding access to treatment may also need to vary by country.

### 6.1.5 Parasitological testing in the public sector

The proportion of reported suspected cases receiving a parasitological test is highest in the American and European Regions followed by South-East Asia (Figure 6.7), with the value for the South-East Asia Region heavily influenced by India. The testing rate in the Eastern Mediterranean Region rose to 80% in 2010 while in the African Region it has risen from 20% in 2005 to 45% in 2010. Much of the increase in testing in the African Region is from an increase in use of RDTs, which accounted for nearly one third of confirmed cases diagnosed in 2010. The reported testing rate may overestimate the true extent of diagnostic testing in the public sector since countries with higher testing rates may have a greater propensity to report, and therefore countries with lower testing rates are underrepresented in the overall rate.

As diagnostic testing is scaled up, the need for quality assurance monitoring becomes even more important. In 2011, WHO and global malaria partners released an operational manual on improving access to malaria diagnostic testing (3), which included guidance on quality management of malaria diagnostic testing programmes. Some malaria programmes have made special efforts to improve the quality of diagnostic testing (Box 6.1).

**BOX 6.1**

**Quality assurance for malaria microscopy in the Philippines**

The quality assurance (QA) system for malaria microscopy in the Philippines, which was first piloted in five provinces in Mindanao in 2005, has now been expanded to 31 provinces. The Philippines Department of Health coordinates and monitors the implementation of the system with stakeholders at the national, provincial and/or regional level. The Research Institute for Tropical Medicine (RITM) is the national reference centre for QA and provides a core group of trainers who conduct training at all levels of the system. Other partners include ACTMalaria and WHO, which provide experts for conducting external competency assessments and training materials, the Global Fund and the Centers for Health Development (CHD).

Microscopists are assessed at three levels: Level 1 – entry level for microbiologists who undergo the basic malaria microscopy training; Level 2 – 82 qualified validators who are assessed by RITM every 2 years; and Level 3 – the national core group of 26 trainers who are certified through the WHO regional accreditation system every two to three years.

The Level 3 core group has attained performance benchmarks of >90% score in the detection of parasitemia, >90% score in species identification, and >50% on blood film readings that fall within ±20% of the true parasite count. The Level 2 validators adopt the appropriate slide sampling scheme based on the number of slides that each microscopist had read the previous year. Following the expansion of the QA system, the 457 Level 1 trained microscopists who have achieved an average of 80%-90% proficiency are currently providing quality diagnostic services.

### 6.1.6 Utilization of parasitological tests in the private sector

Data reported by ministries of health on the number of RDTs distributed and patients examined by microscopy or RDTs generally cover the public sector only. However, approximately 40% of malaria patients worldwide seek treatment in the private sector,
Figure 6.2 RDTs sales by panel detection score (PDS)

Source: Data provided to FIND by 17 manufacturers eligible for the WHO Malaria RDT Product Testing Programme

Figure 6.3 RDTs distributed by NMCPs, by WHO Region

Source: NMCP reports

Figure 6.4 Number of patients examined by microscopy, by WHO Region

Source: NMCP reports

Figure 6.5 Proportion of febrile children seeking treatment from different sources, by WHO Region

Source: Household survey data

Figure 6.6 Proportion of febrile children seeking treatment from different sources, 2008–2010

Source: Household survey data

Figure 6.7 Proportion of suspected malaria cases attending public health facilities that receive a diagnostic test

Source: NMCP reports
which includes regulated health facilities, pharmacies and other retail outlets (4). Information on the extent of parasitological testing in the private sector is limited. Country-specific data collected by ACT Watch1 in 2009–2010 suggest that with few exceptions, both microscopy and RDTs are more widely available in the public sector. Consequently, among selected countries in Africa, the proportion of children under 5 who received a blood test for suspected malaria was higher in public than in private facilities (Figure 6.8).

### 6.1.7 Malaria diagnostics in the community

A total of 42 countries report deployment of RDTs at the community level and 11 million patients were tested in 2010, including 10 million patients tested with RDTs in India. However, patients tested using RDTs in the community represent a relatively small proportion (5%) of the total number of patients receiving a parasitologic test. For 10 countries, information on RDT positivity rates was available from NMCP reports for the community and at public health facilities (Figure 6.9). Although community diagnosed cases accounted for a low proportion of all cases, in most of the countries, test positivity rates for these cases were similar to or higher than those reported for outpatient cases. A reporting bias cannot be excluded, however, this suggests that further expansion of diagnostic testing to the community level could potentially identify many additional confirmed malaria cases.

### 6.1.8 Scaling up diagnostics

Despite recent expansion of malaria diagnostic testing, many patients still do not receive a parasitological test. In the African Region in 2010, the number of ACTs distributed by NMCPs was more than twice the total number of tests (microscopy + RDTs) carried out in 2010, indicating that many patients receive ACTs without confirmatory diagnosis. Shortfalls in the availability of diagnostic testing can be attributed at least in part to the relatively recent policy change and the expected lag time in securing financing and subsequent procurement of RDTs.

The use of RDTs provides the most feasible means of rapidly expanding diagnostic testing, especially in peripheral health facilities and at community level in remote rural areas. The introduction of RDTs can significantly reduce expenditures on antimalarial drugs.

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1 www.actwatch.info

### TABLE 6.2

**Adoption of Policies for Malaria Treatment by WHO Region**

<table>
<thead>
<tr>
<th>Policy</th>
<th>Africa</th>
<th>Americas</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT is used for treatment of <em>P. falciparum</em></td>
<td>42</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>ACT is free of charge for all age groups in public sector</td>
<td>28</td>
<td>10</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>60</td>
</tr>
<tr>
<td>ACT is free of charge only for under 5 years old in the public sector</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>ACT is delivered at community level</td>
<td>24</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>Pre-referral treatment with quinine/artemether IM/artesunate suppositories</td>
<td>34</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>Therapeutic efficacy monitoring is undertaken</td>
<td>27</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td><strong>Number of endemic countries/areas</strong></td>
<td>43</td>
<td>23</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>106</td>
</tr>
<tr>
<td><strong>Number of P. falciparum endemic countries/areas</strong></td>
<td>43</td>
<td>18</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>87</td>
</tr>
</tbody>
</table>

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**Figure 6.8** Proportion of children under 5 with fever receiving a blood test for malaria

**Figure 6.9** RDT positivity rate among patients tested in outpatient facilities and in the community for 10 countries, 2010

**Figure 6.10** ACT sales to the public sector, 2005–2010

Source: data provided by 8 companies eligible for procurement by WHO/UNICEF
Malaria remains a public health problem in Zambia, despite recent progress in its control. ACTs were introduced in 2004 and RDTs at the village level in 2007. Diagnostic testing before starting antimalarial treatment is compulsory, where capacity exists, for patients above five years of age and recommended where possible for patients under five years of age. RDTs are made available primarily at health centres and health posts, with priority given to facilities without microscopy.

The results of a scale up in diagnostic testing can be seen in data for the period January 2004 to August 2009 from Kazungula, Mumbwa and Mwense districts in southern, central and northern Zambia respectively. After RDTs were introduced, testing rates have gradually increased over time with a corresponding reduction in the number of reported cases of malaria (which were previously diagnosed symptomatically and included non-malaria fevers) and consumption of antimalarial drugs.

There were differences between districts, with the two lower prevalence districts, Kazungula and Mumbwa, showing large reductions in both the proportion of patients reported as having malaria and those given antimalarial treatment, while in Mwense district no clear trends were discernable. It is possible that testing excluded fewer patients from malaria diagnosis and treatment in Mwense owing to the higher incidence of malaria in that district.

The data from Mumbwa and Kazungula districts show that reductions in ACT consumption did not occur until 6–18 months after the introduction of RDTs. This delay could be due in part to improved acceptance of test results over time, as clinicians gradually gained confidence in the new tests. Across the three districts, RDTs led to an approximate 9% reduction in prescriptions of antimalarial drugs which led to an overall reduction in commodity costs of approximately US$ 500 per facility per year, at current RDT and ACT prices.

but usually this cost saving does not fully compensate for the cost of the tests. (5) Moreover, as diagnostic testing is expanded, the decrease in antimalarial use is likely to be gradual and programmes will experience a transition period in which the needs for treatment may equal those for diagnostic testing (Box 6.2). While any overall cost-savings will depend on the intensity of malaria transmission and other factors, RDTs appear to be cost-effective compared to presumptive treatment, largely due to improved patient outcomes for non-malarial febrile illness (6).

6.2 Treatment of malaria

6.2.1 Policy adoption

By the end of 2010, ACTs had been adopted as national policy for first-line treatment in 84 countries. In some cases P. falciparum cases will be exclusively imported. Chloroquine is still used in some countries in the Region of the Americas where it still remains efficacious. By mid-2010, 70 countries were deploying these medicines within their general health services, with varying levels of coverage. The adoption of policies for the treatment of malaria is summarized by WHO Region in Table 6.2 and by country in Annex 4A and 4B.

ACTs procured: The number of ACT treatment courses procured by the public sector increased greatly from 11 million in 2005 to 76 million in 2006, and reached 181 million in 2010 (Figure 6.10).

1 Information on adoption of the WHO policy on ACTs and their deployment (i) country adoption of ACTs: the WHO/GMP Antimalarial Drug Policies Database (http://www.who.int/malaria/am_drug_policies_by_region_africa/en/index.html); and (ii) country deployment of ACTs to general health services: compiled by the GMP Supply Chain Management Unit on the basis of reports from WHO regional and country offices.
Artemether-lumefantrine (AL) accounted for the largest volume of ACTs procured by the public sector (70%) in 2010. The second ACT in terms of volumes procured was artesunate + amodiaquine, which increased from fewer than 1 million treatment courses in 2007 to 41 million in 2010.\(^1\) The proportion of fixed-dose combination ACTs (with the two medicines combined in the same tablet), which are preferred because of improved patient adherence to the recommended regimen, has been increasing and in 2010 accounted for 97% of all ACT sales.

Between 2006 and 2008, most AL was procured for young children weighing less than 15 kg, and the smallest proportion was supplied for patients with a body weight of 25–34 kg. Compared with previous years, in 2010 an increased amount of AL was procured for patients with a body weight over 35 kg, while supplies procured for young children weighing less than 15 kg\(^2\) were unchanged (Figure 6.11). Whether this represents a response to changing epidemiology and age distribution of cases in endemic countries, or to other market forces, is unclear.

### Figure 6.11 Artemether-lumefantrine sales to the public sector by weight-based treatment course

<table>
<thead>
<tr>
<th>Weight Group</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL 5-14 kg</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>AL 15-24 kg</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>AL 25-34 kg</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>AL 35+ kg</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

Source: data provided by 4 companies prequalified by WHO.

Forecasting future demand for ACTs is crucial for planning by manufacturers, funding agencies, and malaria control programme managers. In forecasts of global ACT demand (Figure 6.12), the proportion of ACT sales in the public sector compared to the private sector is changing, largely as a consequence of the implementation of the Affordable Medicines Facility-malaria (AMFm) initiative (Box 6.3). Overall ACT demand is estimated to reach 287 million treatments in 2011, an increase of 32% over that in 2010. The driver of this increase is the almost 10-fold increase in subsidized private sales through the AMFm while estimated premium (non-subsidized) private sales remain unchanged.

### 6.2.3 Utilization of appropriate antimalarial medicines to treat febrile children

It has been difficult to track the extent to which malaria cases confirmed by RDT or microscopy receive antimalarial medicines because information on diagnostic testing has not generally been included in household surveys, and diagnostic test results are usually not linked to the treatment given to patients. Similarly, while routine information systems generally include data on diagnostic confirmation, they rarely track treatments given to patients diagnosed with malaria. The development of routine systems that track febrile patients, testing, results, and treatments given, would enable better tracking of antimalarial utilization. However, such systems seldom exist, especially in Africa, and comprehensive information on the relationship between diagnostic test results and treatments given is therefore lacking.

On the basis of the available data it is possible to examine the proportion of current antimalarial treatments that use an ACT. ACTWatch conducted household surveys in selected countries during 2009–2010 and collected information on antimalarial medicines received by patients in different health sectors (Figure 6.13). Among those surveyed in six countries, a higher proportion of patients attending a public facility received an antimalarial (of any type) than those attending private facilities, and among those who received an antimalarial, patients attending public facilities were more likely to receive an ACT. These results are consistent with those reported by WHO from an analysis of antimalarial treatments in 37 nationally representative household surveys (7) and suggest that ensuring access to ACTs remains a challenge in both public and private health care sectors.

Expanding malaria diagnostic testing and treatment to the community level would further improve access to appropriate antimalarial therapy. Programmes implementing community case management of malaria have been evolving (Box 6.4) and many now appropriately favour an integrated approach that includes other major childhood illnesses, namely pneumonia and diarrhea.

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\(^1\) WHO monitors the global supply of and demand for the artemether-lumefantrine fixed-dose combination as part of the requirements of the Memorandum of Understanding signed with the manufacturer Novartis in 2001, in order to make Coartem® available at cost price for distribution in the public sector of malaria-endemic developing countries.

\(^2\) Information on past AL sales for public sector use was obtained from manufacturers of ACTs which have been prequalified by in 2010.
BOX 6.3
Forecasting global ACT demand

The ACT Forecasting Consortium was created to develop regular forecasts of the global demand for ACTs and artemisinin requirements; it is sponsored by UNITAID, managed by Boston Consulting Group (BCG) and involves forecasting experts from BCG, Clinton Health Access Initiative (CHAI), and the International Logistics Programme at MIT-Zaragoza. The Consortium produces quarterly updates of a 2-year global forecast of ACT demand and artemisinin supply, providing important information to the main funding agencies and the pharmaceutical companies which supply ACTs.

Forecasting the ACT market is difficult because market data are incomplete, and there is often only limited access to country data on past consumption, current procurement, and projected demand. In addition, the lead time for the market to react to changes in demand is lengthy, primarily due to the long production time for artemisinin, which is currently derived exclusively from plants. 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 modeled inputs on expected consumer demand in both public and private sectors. The combination of these multiple factors introduces significant uncertainties around the estimates.

Based on the best information available, the Consortium presented the latest forecasts at the recent RBM-WHO Round Table on ACT Supply in September, 2011 (Figure 6.12). Global WHO Pre-Qualified ACT consumer demand for 2011 is estimated at 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 have reached a plateau after several years of annual increases, the main driver of this recent increase is the significant growth of demand for ACTs in the procurement for the Affordable Medicine Facility for malaria (AMFm). The AMFm was launched in 2010, hosted by the Global Fund, and is currently in Phase I, offering subsidies for purchase of ACTs by public and private First Line Buyers (FLBs) in 7 African countries. In addition to the demand for the private sector via AMFm, the premium private ACT market (i.e. for non-subsidized ACTs) requires an estimated additional 23 million treatments worldwide and has remained relatively constant.

BOX 6.4
From Community Case Management of Malaria (CCM) to integrated Community Case Management (iCCM)

Community Case Management of Malaria (previously known as Home Management of Malaria) has been evolving beyond malaria over the last several years into a more comprehensive strategy that addresses the three main killer diseases of children: malaria, pneumonia and diarrhoea. This new approach is termed integrated Community Case Management, iCCM.

While the former strategy was based on the presumption that most fever cases in malaria endemic countries were due to malaria (and consequently the recommendation was to administer antimalarial medicines to all febrile children indiscriminately), iCCM incorporates the updated malaria treatment guidelines recommendation to confirm malaria infection in all patients prior to treatment. The availability of high-quality RDTs for malaria has made testing for malaria at the community level possible. This places a higher demand for high quality integrated treatment, so that when febrile children are found not to have malaria, there are other treatment options. The significant overlap in the clinical manifestation of pneumonia and malaria, often simultaneous with diarrhoeal disease and malnutrition, further justifies an integrated diagnostic and therapeutic approach.

As part of the iCCM approach, front-line workers at the community level are trained, supplied and supervised to treat children for malaria and pneumonia and diarrhoea, using ACT, oral antibiotics, and oral rehydration salts and zinc. All patients are screened for the three diseases and treatment is administered based on the results of diagnostic tests that include malaria RDTs, disease history, and respiratory rate.

The first experiences with iCCM are encouraging. In Ghana, nearly all carers of sick children (92%) sought treatment from community-based agents trained to manage pneumonia and malaria (8). Indeed, most (77%) sought care for their children with fever within 24 hours of onset. In Zambia, an iCCM study for pneumonia and malaria found that 68% of children with pneumonia received early and appropriate treatment from community health workers, and overtreatment of malaria significantly declined (9). In Ethiopia, iCCM workers deployed in remote communities delivered 2.5 times as many treatments for the three diseases than all the district’s facility-based providers combined (10). The evidence for impact on mortality is still being collected, but programmatic experience suggests that the iCCM strategy can be effective in achieving high treatment coverage and delivering high quality care for sick children in the community.

An inter-agency iCCM task force has recently been established with the participation of international partners including WHO, UNICEF and USAID, NGOs (Save the Children, BASICS, International Rescue Committee) and research institutions (Karolinska Institute, Boston University, University of Dakar, and the Special Programme for Research and Training in Tropical Diseases, TDR). More information on iCCM and programme support tools can be found at the task force web site: www.ccmcentral.com
6.3 Antimalarial drug resistance

6.3.1 Policy adoption: withdrawal of oral artemisinin-based monotherapy medicines

The use of oral artemisinin-based monotherapies threatens the long-term usefulness of ACTs by fostering the emergence and/or spread of resistance to artemisinin. To contain this risk and to ensure high cure rates for *P. falciparum* malaria, WHO recommends the withdrawal of oral artemisinin-based monotherapies from the market and their replacement by ACTs, as indicated by the World Health Assembly in 2007. WHO also calls upon manufacturers to cease the marketing of oral artemisinin-based monotherapies. (For the full text of the WHA resolution, see http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf.)

WHO compiles data on the marketing of oral artemisinin-based monotherapies by manufacturers and on the regulatory action taken by malaria-endemic countries; these data are posted on the Internet.¹ By November 2011, 25 countries were still allowing the marketing of these products and 28 pharmaceutical companies were manufacturing these products, down from 39 one year ago. Most of the countries that still allow the marketing of monotherapies are located in the African Region (Fig. 6.14), while most of the manufacturers are located in India. One of the main reasons for the limited success in phasing out oral artemisinin-based monotherapies is the weak regulation of pharmaceutical markets in many malaria-endemic countries. Greater collaboration and involvement of national regulatory authorities is required to ensure complete withdrawal of oral artemisinin-based monotherapies from all countries.

6.3.2 Drug efficacy monitoring

Status of drug efficacy monitoring: Therapeutic efficacy studies remain the gold standard for guiding drug policy; the standard WHO protocol was updated in 2009 (11). WHO compiles the results of efficacy tests conducted by national malaria programmes and research institutes in the WHO Global Database on Antimalarial Drug Efficacy. The database currently contains over 4000 studies carried out between 1996 and 2011 and it formed the basis of the Global report on antimalarial drug efficacy and drug resistance: 2000–2010 (12). Experience with previous antimalarial treatments shows that significant levels of resistance can develop within a short time, and therefore WHO recommends that the efficacy of first- and second-line antimalarial treatments be monitored at least once every two years.

In 2008–2009 studies of first- or second-line antimalarial treatments were completed in 31 of 75 countries where *P. falciparum* efficacy studies are possible (Fig. 6.15). In 17 countries, efficacy studies are impractical because of low malaria incidence, and 15 countries are endemic for *P. vivax* only. In 32 countries in which therapeutic efficacy studies are feasible, studies were last conducted more than three years ago, longer than recommended by WHO.

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¹ Information is available on the internet via the following links:
- Manufacturing companies: http://www.who.int/malaria/monotherapy_manufacturers.pdf
- National Regulatory Authorities: http://www.who.int/malaria/monotherapy_NDRAs.pdf
Treatment of *P. falciparum* malaria: major findings related to the development of drug resistance concerning the treatment of *P. falciparum* globally are as follows:

- Artemether-lumefantrine is first- or second-line treatment in 56 countries worldwide and remains highly effective in most parts of the world, with the exception of Cambodia. However, more studies are needed to monitor the efficacy of artemether-lumefantrine, especially in Africa where the treatment is widely used.

- Among the 21 African countries which have adopted artesunate-amodiaquine, six countries have reported at least one study showing a high level of treatment failure (>10%). A high treatment failure rate for this combination was also observed in four Indonesian studies.

- The efficacy of artesunate-mefloquine is lowest in areas where mefloquine resistance is prevalent in Thailand and Cambodia. In Africa and the Americas, the combination remains highly effective.

**BOX 6.5**  
**Containment of artemisinin resistance**

The Global Plan for Artemisinin Resistance Containment (GPARC) recommends that in areas with evidence of artemisinin resistance, an immediate, multifaceted response should be launched with the aim of containing and, if feasible, eliminating the resistant parasites.

Suspected resistance to artemisinins has been identified in four countries in the Greater Mekong subregion. Containment activities were first started in eastern Thailand and western Cambodia, following the evidence of resistance to artemisinins on the Cambodia–Thailand border that was found in therapeutic efficacy studies in 2006. The project started in 2009 and received funding from the Bill & Melinda Gates Foundation for the first two years of activities. The project covered 380 000 people on both sides of the border, in tier 1 areas, where artemisinin resistance had already been detected (Zone 1) and more than 4.1 million people in tier 2 buffer areas, where there was no evidence of resistance but the risk was deemed high (Zone 2). More than half a million LLINs were distributed to achieve universal coverage, allowing every person to sleep under a net each night. In addition, all villages in Zone 1 and all high-risk villages in Zone 2 had access to early diagnosis and treatment provided free of charge by trained village malaria workers. As a result of the project, there has been a drop in the malaria incidence in many of these areas since 2008, notably in *P. falciparum* cases diagnosed at health facilities in Pailin province. Cases declined there after interventions were implemented in 2009 (Figure Box 6.5).

*Figure Box 6.5*  
*P. falciparum* cases diagnosed by microscopy and RDT at health facilities in Pailin province, by month 2008–2011

Therapeutic efficacy studies in 2009 and 2010 in western Thailand, south-eastern Myanmar and in one province in Viet Nam found >10% of patients with parasitaemia on day 3 after treatment. Consequently, containment projects have been initiated in these areas drawing on the experience gained from the project on the Cambodia–Thailand border. Project components include increased coverage with LLINs, better access to quality assured diagnosis and treatment among local and migrant populations, and directly observed treatment and follow-up of all confirmed falciparum malaria patients, as well as strengthened monitoring and surveillance. Thailand’s containment project, which includes both eastern and western provinces, has already been approved for funding from Global Fund Round 10. All the suspected foci of artemisinin resistance are in areas close to the border where there are large numbers of migrants. A regional framework for containment in the Greater Mekong subregion is being developed to strengthen the cross-border collaboration.

In Myanmar, the Ministry of Health, and partners including funding agencies, endorsed a plan for containment of artemisinin resistance in April 2011, and containment activities have started with support from the funding consortium Three Diseases Fund and Bill & Melinda Gates Foundation. In Viet Nam, a containment project has been initiated, similar to that carried out on the Cambodia–Thailand border, and additional funding is being sought.
• Artesunate-sulfadoxine-pyrimethamine remains effective in the countries using this combination as a first-line treatment (this includes countries in the Middle East, South and Central Asia and the Horn of Africa). Failure rates remain high in regions where resistance to sulfadoxine-pyrimethamine is high.

• Data on the therapeutic efficacy of dihydroartemisinin-piperaquine are limited and come mainly from studies carried out in parts or Africa and in the Greater Mekong subregion. More studies are needed before drawing conclusions about its overall efficacy in endemic countries.

The crucial role of monitoring drug efficacy has been demonstrated in the Cambodia–Thailand border area, where studies in 2002–2005 by the Cambodia and Thailand national malaria programmes demonstrated prolonged parasite clearance times following treatment with ACTs. In 2006–2007, two cases of artemisinin resistance were detected in Tasanh, Cambodia, by the Armed Forces Research Institute of Medical Sciences, providing the first evidence of artemisinin resistance. Since 2008, WHO has been coordinating containment activities in this area.

In 2009 and 2010, therapeutic drug efficacy studies also detected suspected artemisinin resistance in western Thailand and south-eastern Myanmar, and in one province in Viet Nam, as evidenced by ≥ 10% of cases with parasites detectable on day 3 after treatment with an ACT. Day 3 parasite detection is one of the earliest signs of potential artemisinin drug resistance. Containment activities have begun in Thailand along the Myanmar border, in south-eastern Myanmar and in Viet Nam (Box 6.5).

Although the observations suggest that there are changes in parasite sensitivity to artemisinins, ACTs remain clinically and parasitologically effective, except in Pailin province, Cambodia. In Pailin, resistance to both components, artesunate and mefloquine, of a commonly used ACT have been confirmed, and resistance to piperaquine is under investigation after a study in 2010 found 27% treatment failure with dihydroartemisinin-piperaquine. Many aspects of artemisinin resistance are still not well understood and more research is needed, e.g. the importance of non-artemisinin component drugs in ACTs needs further clarification. The partner drugs usually have a longer half-life than the artemisinin component, and therefore complement and extend the therapeutic efficacy of the combination. Indiscriminate use of ACTs in patients who do not have malaria risks not only the development of artemisinin resistance but potential failure of the partner drug as well.

Treatment of *P. vivax* malaria: Chloroquine remains the drug of choice in areas where chloroquine is still effective. Treatment failure on or before day 28 and/or prophylactic failures have been observed in Afghanistan, Brazil, Cambodia, Colombia, Guyana, Ethiopia, India, Indonesia, Madagascar, Malaysia, Myanmar, Pakistan, Papua New Guinea, Peru, the Republic of Korea, Solomon Islands, Thailand, Turkey, Sri Lanka, Vanuatu and Viet Nam. However, confirmation of true chloroquine resistance requires additional drug concentration studies and for this reason it is not entirely clear to what extent chloroquine-resistant *P. vivax* has spread. At least one case of chloroquine-resistant *P. vivax* has been confirmed in Brazil, Ethiopia, Indonesia, Malaysia, Myanmar, Solomon Islands, Thailand, Papua New Guinea, and Peru. ACTs are now recommended for the treatment of chloroquine-resistant *P. vivax*, particularly where ACTs have been adopted as the first-line treatment for *P. falciparum*.

### 6.4 Conclusions

**Utilization of parasitological testing:** There have been significant increases in the availability and use of parasitological testing in the last few years, particularly in the WHO African Region where the percentage of reported suspected cases receiving a parasitological test increased from 20% in 2005 to 45% in 2010. Further funding and technical support are required to assist countries to achieve universal diagnostic testing of suspected malaria in the public sector. Given that a substantial proportion of children currently receive care in private facilities where the frequency of diagnostic testing for malaria is generally lower, further efforts are also needed both to increase the utilization of malaria diagnostic testing in the private sector and to encourage patients to seek care from providers who can provide the full range of diagnostic services and appropriate treatment.

**Community-based diagnosis and treatment:** For the many communities with limited access to public sector or private sector facility-based health-care providers, parasitological diagnosis and treatment of malaria will need to be provided by community-based programmes as already in place in some countries. Community-based programmes may also increase access to health service delivery in urban settings (13). The limited available data on testing carried out at the community level indicate that test positivity rates are in line with those among patients seen at public facilities; this implies that expanding access to testing and treatment to the community should have a positive effect on fever management in the periphery. There is progress in integrating community-based malaria programmes with those for other childhood illnesses (iCCM), and early experience in implementation of these programmes is encouraging.

**Cost implications of improved diagnosis:** Expanded use of diagnostic testing can significantly reduce expenditures on antimalarial drugs, but this saving generally does not fully compensate for the cost of the tests themselves. ACT needs may not decrease immediately after implementation of universal diagnostic testing due to delays in the uptake of testing, inconsistent use of test results in some settings (especially among medical personnel in facilities where microscopy already exists) and the collection and utilization of those data for estimating ACT procurement needs. Countries will need to take this lag time into account when planning diagnostic scale up, and have realistic expectations about the overall cost savings and the time frame. While the likelihood of cost-savings will depend on several factors, particularly the intensity of malaria transmission, RDTs appear to be cost effective compared to presumptive treatment, largely due to the improved patient outcomes for non-malarial febrile illness (6).

**Access to treatment:** Information from manufacturers indicates that the number of ACTs procured has increased in every year since 2005. It is difficult to track the extent to which malaria cases confirmed by RDT or microscopy receive antimalarial medicines because diagnostic test results are not usually linked to the treatment given to patients, in either household surveys or routine information systems. A limited number of recent household surveys suggest that febrile patients attending public health facilities are more likely to receive an ACT than those attending private facilities. The development of routine systems that track febrile patients, testing, results, and treatments given would enable better tracking of antimalarial utilization.

**Combating drug resistance:** The spread of resistance to antimalarial drugs over the past few decades has led to an intensification of efficacy monitoring to allow early detection of resistance in order to revise
national malaria treatment policies and ensure proper management of clinical cases. Containment efforts in the Mekong subregion have shown that malaria incidence can be decreased, a key component of the overall containment plan to halt the spread of resistant parasites. Despite the observed changes in parasite sensitivity to artemisinins, the clinical and parasitological efficacy of ACTs has not yet been compromised, except in Pailin province, Cambodia, where resistance to both ACT components has been found. In other areas in this region, the efficacy of both components of the combination is put at risk. Using an ACT containing a partner drug to which there is already resistance (and is therefore not effective) can increase the risk of development or spread of artemisinin resistance. The indiscriminate use of ACTs without diagnostic testing, especially in areas with higher malaria transmission, may also hasten the development of resistance to the partner drugs in ACTs. Similarly, if the efficacy of the artemisinin component is lost, the efficacy of the partner drug could be jeopardized. It is noted that 25 countries still allow the marketing of oral artemisinin-based monotherapies which threatens the continued efficacy of artemisinin.

References
