Chapter 5.
Malaria diagnosis and treatment

This chapter considers the extent to which national programmes have adopted policies for universal diagnostic testing of suspected malaria cases and examines trends in the availability of parasitological testing. It then reviews the adoption of policies and implementation of programmes for improving access to effective treatment for malaria and to intermittent preventive treatment of malaria in pregnancy. Finally it reviews latest trends in drug resistance, the progress made in withdrawing oral artemisinin-based monotherapies from the market, and efforts to contain artemisinin resistance on the Cambodia-Thailand border.

5.1 Diagnosis of malaria

5.1.1 Policy adoption

In early 2010, WHO updated the recommendation on malaria diagnostic testing for suspected malaria to include children < 5 years of age. With this revision, all persons of all ages in all epidemiological settings with suspected malaria should receive a parasitological confirmation of diagnosis by either microscopy or RDT. National adoption and implementation of policies for diagnosis of malaria by WHO Region are shown in Table 5.1. Adoption of policies by country is shown in Annex 4. In 2009, 33 of 43 malaria-endemic countries in the WHO African Region and 45 of 63 endemic countries in other Regions reported having adopted a policy of providing parasitological diagnosis for all age groups. A total of 16 African countries are now deploying RDTs at the community level, as are 22 additional countries in other Regions.

5.1.2 RDTs procured and distributed

The number of RDTs delivered by ministries of health has increased rapidly from less than 200,000 in 2005 to about 30 million in 2009 (Fig. 5.1), with most RDTs (44%) being used in the African Region followed by the South-East Asia Region (41%) and Eastern Mediterranean Region (11%). These totals, however, are likely to underestimate the quantity of RDTs distributed, as only 21 of the 43 endemic countries in the African Region reported these data in 2009. The number of patients receiving an RDT is generally lower than the number of RDTs delivered to health facilities, possibly because systems for reporting the number of patients tested with an RDT have not yet been well developed in many countries.

5.1.3 Microscopic examination undertaken

The number of patients tested using microscopic examination fell from a peak of 165 million in 2005 to 151 million in 2009 (Fig. 5.2a). The global total is dominated by India which accounted for 104 million slide examinations in 2005 and 94 million in 2009. Decreases in the number of patients examined by microscopy were reported in the Region of the Americas (50%), the European Region (20%) and the African Region (14%), while there was an increase in the Eastern Medi-

TABLE 5.1
ADOPTION OF POLICIES FOR MALARIA DIAGNOSIS BY WHO REGION

<table>
<thead>
<tr>
<th>POLICY</th>
<th>AFRICAN</th>
<th>AMERICAS</th>
<th>EASTERN MEDITERRANEAN</th>
<th>EUROPEAN</th>
<th>SOUTH-EAST ASIA</th>
<th>WESTERN PACIFIC</th>
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<td>Number of endemic countries/areas</td>
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<td>RDTs are used at community level</td>
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<td>Malaria diagnosis is free of charge in the public sector</td>
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<td>8</td>
<td>10</td>
<td>9</td>
<td>74</td>
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b) Excluding India

Figure 5.2 Number of patients examined by microscopy

Figure 5.3 Proportion of suspected malaria cases attending public health facilities that receive a parasitological test by microscopy or RDT

Figure 5.4 Number of countries and cases by rate of parasitological testing

terranean Region (63%) (Fig. 5.2b). Some of the decreases appear to be due to a reduction in case-loads, particularly in the American and European Regions, and to increased use of RDTs. However, these factors do not fully explain the decrease in patients examined by microscopy in some countries, where the data may reflect weakening of diagnostic systems or deterioration in reporting.

5.1.4 Parasitological testing in the public sector

The proportion of reported suspected cases receiving a parasitological test varies considerably by Region. It is highest in the American and European Regions followed by South-East Asia (Fig. 5.3). The value for the South-East Asia Region is heavily influenced by India; if countries other than India are considered then the percentage of cases tested is lower but does show an increasing trend over the past decade, as is also the case for the Eastern Mediterranean and African Regions.

Outside Africa, most countries within each Region are able to provide a diagnostic test for more than 80% of suspected cases (Fig. 5.4a), suggesting that interventions to scale up the availability of testing in public health facilities can be focussed on a small number of countries. Of 42 countries in the African Region that reported on testing, the percentage of cases tested was less than 20% in 21 countries. Examination of the numbers of cases affected by the low testing rates (Fig. 5.4b) suggests that, with the exception of India, larger countries tend to have lower testing rates. Most countries with high rates of testing have had a policy of confirming every malaria case for several years; some countries have recently expanded the availability of diagnostic testing with some success (Boxes 5.1 and 5.2).

In the African Region in 2009, the number of ACTs distributed by NMCPs exceeded the number of RDTs procured more than five-fold, and the total number of tests carried out (microscopy + RDTs) by a factor of 2.4, indicating that many patients are receiving ACTs without confirmatory diagnosis. Similarly, a review of African countries’ estimates of needs for ACTs and RDTs set out in Global Fund proposals and PMI operational plans indicated that country estimates of need for ACTs between 2009 and 2011 exceeded the need for RDTs by a factor of 2.1 (1). This is partly because 12 of the 41 countries reviewed, including the populous countries of the Democratic Republic of the Congo and Nigeria, had targeted only persons ≥ 5 years of age for diagnostic testing, in keeping with the previous WHO recommendation, which was extant at the time the review was undertaken. The review also indicated that while most of the estimated needs for ACTs were financed, the funding gap for RDTs was larger. Hence shortfalls in the availability of diagnostic testing can be at least partly attributed to the relatively recent policy change as well as failures to plan for and finance the strategy, and not necessarily to inadequate implementation.

5.1.5 Availability of parasitological tests in the private sector

Data reported by ministries of health on the number of RDTs distributed and/or patients examined by microscopy generally cover the public sector only. However, approximately 40% of malaria patients worldwide seek treatment in the private sector, which includes regulated health facilities, pharmacies and other retail outlets (2). Information on the extent of parasitological testing in the private sector is sparse. Country-specific data collected by
EXPANDING ACCESS TO DIAGNOSTIC TESTING IN SENEGAL

Malaria is endemic throughout Senegal. Until 2007, confirmatory malaria diagnosis was limited to hospitals and, of 1.5 million fever cases treated as malaria, only 3% were confirmed as malaria by microscopy. From September 2007, RDTs were incorporated into a revised national policy for management of febrile illness and introduced in all public sector health facilities beyond hospital level, i.e. in 78 health centres, 1018 health posts and subsequently in all 1640 health huts.

The RDTs were initially piloted on a limited scale by the NMCP and the University of Cheikh Anta Diop in Dakar, during which training materials were developed based on generic job-aids and training manuals available from WHO. To ensure appropriate targeting of RDTs, febrile patients were considered for malaria testing only if signs of other possible causes of fever were absent (e.g. cough, sore throat, skin rash). If positive for malaria, patients were prescribed an antimalarial, and if negative, broad spectrum antibiotics (trimethoprim-sulfamethoxazole or amoxycillin) and antipyretics were prescribed.

As part of the wide-scale introduction of RDTs, health workers were trained by district and regional management teams assisted by the NMCP and the University. Data on malaria morbidity and RDT and ACT use are reported by all health units and entered by month into a simple database (Epi Info Version 6). District supervisors cross-check reported data against health facility records during quarterly or bi-annual supervisory visits, and data received from each district are reviewed at quarterly meetings of NMCP personnel and regional and district management staff. The quality of all malaria RDTs is checked after arrival in Senegal through lot-testing at the parasitology laboratory of the University of Anta Cheikh Diop prior to distribution to the field, based on the protocol of the WHO Methods Manual (3).

From 2007 to 2009 the total number of malaria-like fevers decreased from 1.4 million in 2007 to 584 000 in 2009, possibly as a result of revised case definitions of malaria-like fever. During this period the number of patients given a parasitological test rose from 124 000 in 2007 to 503 000 in 2009, covering 86% of malaria-like fevers. The number of confirmed malaria cases rose from 53 000 in 2007 to 175 000 in 2009 because of the increased use of testing.

During this period the number of treatment courses of ACT dispensed fell from 990 000 to 184 000. Whereas ACT treatment consumption in previous years had matched the total number of fever cases, by the end of 2009 it was close to the number of confirmed malaria cases. An estimated 0.5 million courses of inappropriately prescribed ACT were averted between 2008 and 2009.

The experience in Senegal demonstrates that parasitological diagnosis with RDTs can be introduced on a national scale and that with a high level of adherence to diagnostic results, dramatic reductions in ACT consumption can be achieved. Although cost savings in ACT procurement are partly offset by the cost of RDTs, the policy allows: (i) enhanced management of non-malarial febrile illness; (ii) greater certainty on the incidence of malaria throughout Senegal, enabling the NMCP to predict accurately the antimalarial drug requirements and target programme resources to areas with greatest malaria burden; and (iii) the NMCP to assess the impact of changes in malaria control interventions such as ITN and IRS.
**BOX 5.2**

**EXPANDING ACCESS TO DIAGNOSIS AND TREATMENT IN LAO PEOPLE’S DEMOCRATIC REPUBLIC**

Malaria has long been a leading cause of mortality and morbidity in the Lao People’s Democratic Republic although the intensity of malaria transmission varies considerably across the country, ranging from very low in the plains along the Mekong River and in areas at high altitude, to intense in remote, hilly and forested areas. Between 2005 and 2008, the national malaria programme introduced a strategy to improve case management at the community level by training approximately 12 000 village health volunteers in 6202 villages. These volunteers constitute the most peripheral level of the public health care system in Lao PDR. Volunteers are selected by the village committee to provide primary health care services, including diagnosis of malaria by RDT and administration of ACT, providing health education, distributing ITNs, and reporting morbidity and mortality data to health centres and the district health office.

The composition of cases has changed radically since the beginning of the decade. Whereas the vast majority used to be diagnosed only on a clinical basis (“probable cases”) almost all cases of *P. falciparum* malaria are now confirmed. Although records of drug consumption are not available, confirmation of cases is likely to have reduced the consumption of ACTs.

While changing diagnostic practices make it difficult to discern trends, large reductions in numbers of cases are believed to have occurred as a result of increased ITN coverage (81% of children < 5 years slept under ITNs in 2009) and improved access to treatment. The number of recorded deaths from malaria has fallen from 350 in 2000 to 5 in 2009.

Diagnosis will be extended at village level to include *P. vivax* through the use of combination RDTs, and radical treatment is to be introduced in parallel to an expansion of a private-public mix initiative for malaria diagnosis and treatment in the private sector.

ACT Watch\(^1\) in 2009–2010 suggest that: (i) in four countries (Benin, Cambodia, Madagascar and Zambia) RDTs are available in more than 60% of public facilities; (ii) with few exceptions, both microscopy and RDTs are more widely available in the public sector; and (iii) apart for Cambodia, availability of RDTs in the private sector remains low (Fig. 5.5).

### 5.2 Treatment of malaria

#### 5.2.1 Policy adoption for malaria treatment

By the end of 2009, ACTs had been adopted as national policy for first-line treatment in 77 of 86 countries with *P. falciparum*; chloroquine is still used in some countries in the Region of the Americas. By mid-2010, 70 countries were deploying these medicines within their general health services, with varying levels of coverage.\(^2\) Table 5.2 and Annex 4 summarize, respectively, the adoption of policies for the treatment of malaria by WHO Region and by country.

#### 5.2.2 Quantity of ACTs procured and distributed

The number of ACT treatment courses procured increased greatly from 11.2 million in 2005 to 76 million in 2006, and reached 158 million in 2009. Procurement of four WHO-recommended ACTs by ministries of health from 2005 to 2009 is shown in Figure 5.6. Artemether-lumefantrine (AL) accounts for the largest volume of ACTs procured by the public sector (67%) in 2009.\(^3\) The second ACT in terms of volumes procured is artesunate + amodiaquine, which increased from less than 1 million treatment courses in 2007 to 23.2 million in 2009.

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. In 2009, a changing trend was observed, with an increasing proportion procured for patients with a body weight over 35 kg and a corresponding decrease in supplies for young children weighing less than 15 kg.\(^4\) (Fig. 5.7).

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1. www.actwatch.info
2. 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_afro/en/index.html](http://www.who.int/malaria/am_drug_policies_by_region_afro/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.
3. 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.
4. Information on past AL sales for public sector use was obtained from manufacturers eligible for procurement by WHO in 2009, i.e. Ajanta, Cipla, Ipca, Novartis.
ARTEMISININ MARKET SITUATION

The agricultural production of Artemisia annua and the extraction and supply of artemisinin are still characterized by market instability. The major investments and expansion in cultivation of Artemisia annua and production of artemisinin in 2006–2007 were not matched by a similar increase in demand for artemisinin by ACT manufacturers and suppliers of artemisinin-based active pharmaceutical ingredients. The resulting production surplus of artemisinin led to a reduction in the prices of artemisinin raw material, even falling below production costs, reaching as low as US$ 170 per kg by the end of 2007. This led to the withdrawal of many artemisinin producers from the market in 2008 and 2009, creating a progressive reduction in existing inventories and a relative decrease in supply. Together with the increasing global demand for ACTs, this produced a progressive increase in the spot prices of artemisinin, reaching US$ 350 per kg by the end of 2009.

To stabilize these market dynamics, in 2009 a UNITAID-funded initiative was introduced, the Assured Artemisinin Supply System (A2S2), to provide low interest rate credits to artemisinin extractors who are linked to ACT manufacturers eligible for procurement by WHO and UNICEF. Production of artemisinin-based antimalarial medicines will remain dependent on cultivation of Artemisia annua, as production of semi-synthetic artemisinin derived from yeast cultures will not become available until at least 2012, and will only cover part of the global market requirements.
5.2.3 ACTs distributed by ministries of health

The number of ACTs distributed by NMCPs also appears to have increased between 2007 and 2009 but reporting by countries is incomplete so that totals do not match those delivered by manufacturers. Nevertheless, country reports indicate that by the end of 2009, 11 African countries were providing sufficient courses of ACTs to cover more than 100% of malaria cases seen in the public sector; a further 8 African countries delivered sufficient courses to treat 50%–100% of cases. These figures represent a substantial increase since 2005, when only 5 countries were providing sufficient courses of ACT to cover more than 50% of patients treated in the public sector.

5.2.4 Availability of ACTs in treatment outlets

ACT Watch data summarizes the availability of antimalarial medicines in public and private sector treatment facilities in 7 countries in 2009–2010). The results suggest that, although disruptions in supplies are common in both the public and private sectors, there is wide variation in the availability of antimalarials by country and type of facility/outlet. In 4 countries, the first-line treatment is available in more than 80% of public health facilities and at lesser rates in the 3 other countries. In the private sector, there is 30% availability or less of the first-line treatment. Unfortunately, artemisinin monotherapies are also being stocked in some countries and in some instances are available in more than 30% of private outlets (Fig. 5.8).

In most countries, the private sector dispensed the predominant proportion of antimalarials. The first-line treatment represented less than 10% of the drugs dispensed through the private sector (except Cambodia at 17%) with non-artemisinin monotherapies representing the largest proportion of volumes. In the public sector, sulfadoxine-pyrimethamine accounts for the majority of non-artemisinin drugs dispensed (Fig. 5.9).

First-line treatments were found to be 4–22 times more expensive (median price US$ 4.96) than the most commonly dispensed drug, which for all countries is a non-artemisinin treatment (median price US$ 0.37). Since the price of an antimalarial will greatly affect its utilization, efforts are being made to reduce the price of ACTs to a consumer price equivalent to that of non-artemisinin therapies, by enabling wholesalers to buy ACTs at a subsidized price though a pilot initiative known as the Affordable Medicine Facility – malaria (AMFm) (Box 5.4).

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5. Treatment outlets comprise any place where patients seek treatment for malaria such as hospitals, health centres, health posts, pharmacies, shops or kiosks.

6. Stock-out of first-line treatment for one week within past three months.
**5.2.5 Utilization of antimalarial medicines to treat febrile children**

**Policy.** A central question regarding the utilization of antimalarial medicines is whether people in need of these medicines actually receive them. The need for antimalarial medicines will depend on diagnostic practices and the treatment policies existing within a country. WHO recommends that antimalarial medicines should be given only to patients who have had a positive parasitological test. The price reductions and subsidies that buyers will only pay approximately US$ 0.05 for each course of ACTs. For patients who currently pay for treatment, this is expected to result in a significant reduction in the price of ACTs from about US$ 6–10 per treatment to about US$ 0.20–0.50. The increased availability of affordable ACTs is intended to save lives by making ACTs more readily available and reducing the use of less effective treatments to which malaria parasites are becoming increasingly resistant. It also aims to reduce the use of oral artemisinin monotherapies, thereby delaying the onset of resistance to that drug and preserving its effectiveness. The current AMFm model does not include the routine use of diagnostic testing, which could result in the overuse of ACTs among patients with non-malarial febrile illnesses, especially in countries with declining malaria transmission.

A pilot trial of AMFm has been launched in a small group of countries to enable lessons to be learnt before any expansion of the initiative to other malaria-endemic countries is envisaged. The countries participating are Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, UR Tanzania (mainland and Zanzibar) and Uganda. The pilot study will operate for approximately 24 months and will be reviewed through an independent evaluation. The Global Fund Board will consider the results of the evaluation and determine whether to expand, accelerate, modify or suspend AMFm. It is expected that the Board will make this decision in 2012.

**Meeting the treatment needs.** Figure 5.10 summarises information from 37 countries (18 in sub-Saharan Africa) in which household survey information on antimalarial use and concurrent information on diagnostic testing in public sector health facilities is available. It shows that the percentage of patients attending public health facilities who need an antimalarial medicine varies enormously by country and year, being lower in less endemic countries outside Africa where the percentage requiring an antimalarial is often less than 20%.

Some countries such as Chad (2004), Liberia (2007), Rwanda (2007), United Republic of Tanzania (2004), and Zimbabwe (2005) appeared to be fulfilling antimalarial needs (the percentage of children requiring an antimalarial being close to the percentage of patients receiving one). However, whereas almost all cases received a diagnostic test in Liberia and Rwanda, only 45% did so in United Republic of Tanzania and less than 1% in Chad. Hence the percentage of patients requiring an antimalarial in Chad and in United Republic of Tanzania could have been reduced if diagnostic testing were made more widely available in the public sector.

In some countries, such as Congo (2007), Sierra Leone (2008), and Uganda (2002), the percentage of children that received an antimalarial (<20%) appears to be much less than the percentage requiring one (>60%) suggesting shortfalls in the availability of antimalarial medicines in the public sector at the time of the survey.

**Patients not using public sector health facilities.** It is more difficult to determine what percentage of fever cases should receive an antimalarial among those attending private sector facilities, or among those who do not seek treatment in any health facility. It is nevertheless instructive to compare the percentage of febrile children receiving an antimalarial in the private sector with that observed for the public sector. Figure 5.11 shows that febrile children attending private sector treatment facilities are generally only 75% as likely to receive an antimalarial medicine as those attending public sector facilities, and that the corresponding rate for children who are not treated in any health facility is 40%. Evidently, a significant proportion of those not treated in a health facility have access to antimalarial medicines at home. Information on the percentage of children receiving an ACT is less readily available, as relevant questions were not asked in household surveys until more recent years. However, children attending private sector facilities also appear less likely to
receive an ACT than in the public sector (on average about 70% as likely) while those not treated in a health facility are only 15% as likely to receive an ACT.

The lower proportion of children who received an antimalarial when treated at home may be appropriate if fevers are transient, or considered by caregivers to be less serious and not requiring medication, but may be of concern if the reason were lack of access to facilities or too high a cost for treatment. In settings where active case detection has been conducted, slide positivity rates are generally about 50% of the rates observed during passive case detection. Hence, the lower rate of treatment utilization among those who are not treated in a health facility may be appropriate. However, from the information available there is no assurance that children who receive antimalarial medicines are those who are parasite-positive and in need of treatment.

**BOX 5.5**

**ESTIMATING NEEDS FOR ANTIMALARIAL MEDICINES IN THE PUBLIC SECTOR AND COMPARISON WITH USE**

An estimate of the need for antimalarial medicines among patients attending public health facilities can be obtained from routine information on the percentage of patients receiving a parasitological test and the percentage testing positive. The estimated need can then be compared with the percentage of febrile children actually receiving an antimalarial medicine as recorded in a DHS or other heath survey.

For example, in Rwanda in 2005 health facility records indicated that 87% of suspected malaria cases attending public health facilities received a parasitological test, of which 48% tested positive. Hence, it can be estimated that 55% of children attending public health facilities in Rwanda required an antimalarial (13% who were not tested plus 87% x 48% who tested positive). This can be compared to the 31% of children attending public health facilities who actually received an antimalarial medicine. It therefore appears that the percentage of children receiving an antimalarial medicine compared to those needing one was 57% (31%/55%).

A comparison of the results in 2005 with those obtained in 2008 shows important developments over this period. The percentage of patients with suspected malaria who received a parasitological test increased to 100% while only 22% were test positive. Thus the percentage of patients attending public sector facilities that needed an antimalarial medicine was 100% x 22% or just 22%. The percentage of children attending public facilities who received an antimalarial was recorded as 16%. The percentage of need that had been fulfilled had therefore increased to 75% (16%/22%) despite the overall percentage of children receiving an antimalarial having decreased. This is largely because the percentage of suspected malaria cases testing positive for malaria had dropped from 48% to 22% owing to decreasing incidence of malaria as a result of control activities.

In general a national estimate of the percentage of patients requiring an antimalarial, Mf, in public health facilities can be calculated from routine data as:

\[ M_f = (S_t \times T) + S_n \]

where:
- \( S_t \) = percentage of suspected cases tested
- \( T \) = percentage of tests positive
- \( S_n \) = percentage of suspected cases not tested and treated presumptively

This indicator can then be compared with the percentage receiving an antimalarial in public sector facilities, Mf, as measured in a household survey:

\[ M_s = A \div R \]

where:
- \( A \) = percentage of febrile children taken to public health facilities that receive an antimalarial medicine
- \( R \) = population at risk of malaria

Such a comparison provides a rough assessment of whether the need for antimalarial medicines in public health facilities is being fulfilled. It does not consider the specific test results of individuals or the treatment they were given but simply examines statistics at an aggregate level. In addition household survey data are restricted to children under 5, whereas data on the percentage of suspected malaria cases that are test positive are usually only available for all age groups combined. Moreover the analysis does not consider whether health workers withheld a test because other symptoms were present and another diagnosis given.

It is more difficult to determine whether the percentage of febrile children receiving an antimalarial is appropriate for those treated in private sector facilities or those who are not treated in any health facility. More information is required on both the extent of parasitological diagnosis in the private sector and the proportion of tested cases which are positive. Information on the incidence of malaria among those who do not seek treatment is also required; some insight could be derived from malaria indicator surveys that undertake parasitological testing. Unfortunately datasets from many of such surveys are not readily available for analysis.

*Figure Box 5.5* Percentages of fever cases attending public sector facilities that (i) receive a diagnostic test, (ii) require an antimalarial medicine and (iii) receive one, Rwanda 2005 and 2008.
5.3 Intermittent preventive treatment

A total of 33 of 43 endemic countries in the African Region had adopted intermittent preventive treatment for pregnant women (IPTp) as national policy by the end of 2009, with two in the Eastern Mediterranean Region (Somalia and Sudan), and one in the Western Pacific Region (Papua New Guinea) (Table 5.3). No country has yet adopted a national policy of intermittent preventive treatment for infants (IPTi).

For 22 of the 35 high-burden countries, consistent data were available on both the second dose of IPTp (numerator) and the number of women who had attended antenatal care at least once (denominator) for 2009. The median percentage of women attending antenatal care receiving the second dose of IPTp was 55% (inter-quartile range 47%–61%) (Fig. 5.12). Thus half of women attending antenatal clinics received a second dose of IPTp in those countries responding.

Although not all pregnant women attend antenatal clinics, information on the percentage of all pregnant women receiving the second dose of IPTp can be derived from household surveys. Data on IPTp for pregnant women from surveys in 2007–2009 were available for 8 countries in Africa representing a combined population of 270 million. In 2007–2009, the percentage of women who received two doses of treatment during pregnancy ranged from 2.4% in Angola to 62% in Zambia (Fig. 5.13); the weighted average remained low, at 12% due to low coverage rates in Nigeria.

Table 5.3

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<tr>
<th>POLICY</th>
<th>AFRICAN</th>
<th>AMERICAS</th>
<th>EASTERN MEDITERRANEAN</th>
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5.4 Antimalarial drug resistance

5.4.1 Oral artemisinin-based monotherapy medicines

The use of oral artemisinin-based monotherapies threatens the therapeutic life of ACTs by fostering the spread of resistance to artemisinin. To contain this risk and to ensure high cure rates for \textit{P. falciparum} malaria, WHO recommends the withdrawal of oral artemisinin-based monotherapies from the market and the use of ACTs instead, as endorsed by the World Health Assembly in 2007 (Box 5.6). It also calls upon manufacturers to cease production and marketing of oral artemisinin-based monotherapies.

WHO compiles data on both manufacturers’ compliance and the regulatory action taken by malaria-endemic countries and the data are posted on the Internet.\(^8\) Nearly all companies which have a consistent market share in public sector procurement funded by international agencies have de-listed oral artemisinin-based monotherapy medicines from their product catalogues. However, smaller companies mainly targeting private sector markets are less likely to comply with the WHO appeal. When responsible companies withdraw their monotherapy products, they leave “niche markets” which are rapidly exploited by other companies manufacturing monotherapies. One of the main reasons for the limited success in phasing out oral artemisinin-based monotherapy is the weak regulation of pharmaceutical markets in malaria-endemic countries. By November 2010, 25 countries were still allowing the marketing of these products and 39 pharmaceutical companies were manufacturing these products. Most of the countries that still allow the marketing of monotherapies are located in the African Region, while most of the manufacturers of these medicines are located in India (Fig. 5.14).

Greater collaboration and involvement of national regulatory authorities is required to ensure complete withdrawal of oral artemisinin-based monotherapies from all countries. Progress made by several pharmaceutical companies and regulatory authorities at country level shows that phasing out oral artemisinin-based monotherapy medicines from the market is possible through a range of interventions. Based on their experience, a generic series of actions has been developed to remove oral artemisinin-based monotherapy medicines from the market (Box 5.7).

5.4.2 Drug efficacy monitoring

Therapeutic efficacy studies remain the gold standard for guiding drug policy. WHO compiles the results of efficacy tests conducted by national malaria programmes in the WHO Global Database on Antimalarial Drug Efficacy. The database, which now contains over 4000 studies conducted between 1996 and 2010, formed the basis of the Global report on antimalarial drug efficacy and drug resistance: 2000–2010 (5), from which the following summary has been extracted.

\textbf{Treatment of \textit{P. falciparum} malaria:} major findings related to the development of drug resistance for the treatment of \textit{P. falciparum} globally are:

- Among the 21 African countries that have adopted artesunate-amodiaquine, 6 countries have reported at least one study with a high level of treatment failure (> 10%). A high level of treatment failure for this combination was also observed in four Indonesian studies.
- The efficacy of artemunate-mefloquine is lowest in those areas where mefloquine resistance is prevalent, for example in the Greater Mekong region. In Africa and the Americas, the combination remains highly effective.
- Artesunate-sulfadoxine-pyrimethamine remains particularly effective in those countries that are using this combination as a first-line treatment. Failure rates remain high in those regions where resistance to sulfadoxine-pyrimethamine is high.
- Artemether-lumefantrine remains highly effective in most parts of the world, with the exception of Cambodia. More studies are needed to determine the current state of the efficacy of artemether-lumefantrine in Africa, as over 85% of the studies included in the database were completed in 2007 or earlier.
- Data on the therapeutic efficacy of dihydroartemisinin-piperazine are limited and come mainly from studies carried out in some parts of Africa and in the Greater Mekong subregion. More studies are needed before drawing conclusions about its overall efficacy in endemic countries.

\textbf{BOX 5.6}

\textbf{WORLD HEALTH ASSEMBLY RESOLUTION WHA60.18}

In May 2007, the 60th World Health Assembly resolved to take strong action against oral artemisinin-based monotherapies and adopted resolution WHA60.18, which:

- urges Member States to cease progressively the provision in both the public and private sectors of oral artemisinin-based monotherapies, to promote the use of ACTs, and to implement policies that prohibit the production, marketing, distribution and the use of counterfeit antimalarial medicines;
- requests international organizations and financing bodies to adjust their policies so as progressively to cease to fund the provision and distribution of oral artemisinin monotherapies, and to join in campaigns to prohibit the production, marketing, distribution and use of counterfeit antimalarial medicines.

The full text of the resolution can be found on the Internet at: http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf.
**BOX 5.7**

**RECOMMENDED STEPS TO REMOVE ORAL ARTEMISININ-BASED MONOTHERAPY MEDICINES FROM THE MARKET**

<table>
<thead>
<tr>
<th>ACTION</th>
<th>TASK</th>
<th>TIMELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on time frame for phasing out oral artemisinin-based monotherapies in synchrony with larg-scale implementation of artemisinin-based combination therapies (ACTs).</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oral artemisinin-based monotherapies.</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 3</td>
<td>Suspension of import licences for artemisinin or its derivatives (as Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Products (FPP)) to domestic companies exclusively marketing oral artemisinin-based monotherapies.</td>
<td>3–4 months</td>
</tr>
<tr>
<td>Step 4</td>
<td>Large-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapies, generally associated with external funding for procurement (e.g. from Global Fund or other sources). All subsequent timelines are conditional on this.</td>
<td>Time X</td>
</tr>
<tr>
<td>Step 5</td>
<td>Widespread availability and affordability of subsidized ACTs in the private sector, as expected in countries participating in the Affordable Medicine Facility.</td>
<td>Time Z</td>
</tr>
<tr>
<td>Step 6</td>
<td>Withdrawal of marketing authorization and of manufacturing licences for oral artemisinin-based monotherapies as FPPs.</td>
<td>6 months after time X</td>
</tr>
<tr>
<td>Step 7</td>
<td>Suspension of export license for oral artemisinin-based monotherapies as FPPs.</td>
<td>6 months after time X</td>
</tr>
<tr>
<td>Step 8</td>
<td>Complete elimination of oral artemisinin-based monotherapy medicines as FPPs from the market.</td>
<td>10–12 months after time X</td>
</tr>
<tr>
<td>Step 9</td>
<td>Active recall of oral artemisinin-monotherapies from the market.</td>
<td>3 months after time Z</td>
</tr>
</tbody>
</table>

**BOX 5.8**

**THE ARTEMISININ RESISTANCE CONTAINMENT PROJECT**

The first evidence of resistance to artemisinins on the Cambodia-Thailand border emerged from routine efficacy testing in 2006. This finding prompted WHO, the health ministries of Cambodia and Thailand, and other partners to develop a project aiming to contain and eliminate resistant parasites from the area. The Bill & Melinda Gates Foundation provided US$ 22.5 million to fund the first two years of activities, starting in 2009.

The project uses a combination of prevention and treatment methods and is implemented in two zones. Zone 1 covers populations in which artemisinin tolerance has been detected, including about 270 000 people in Cambodia and 110 000 people in Thailand. Zone 2 covers areas where there is as yet no evidence of tolerance, but the risk is high because it is close to Zone 1; it covers more than 4 million people in Thailand and 150 000 people in Cambodia.

The project has distributed more than 260 000 LLINs in Zone 1, allowing every person to sleep under a mosquito net each night. In Zone 2, where 320 000 LLINs have been distributed, 100% coverage has also been achieved in the high-risk villages. The sale of artemisinin monotherapies was banned by the Cambodian Department of Drugs and Food in March 2009. Approximately 250 “justice police” were trained to enforce the law against counterfeit drugs and the ban on the sale of monotherapies. All private pharmacies, shops and outlets dispensing drugs in Pailin were registered and are regularly inspected. Workshops were held with retailers of antimalarial medicines to raise awareness of the ban and the problems associated with monotherapies.

All villages in Zone 1 and all high-risk villages in Zone 2 have access to early diagnosis and treatment provided free of charge by trained village malaria workers – about 2900 were trained in Cambodia and 326 in Thailand. The volunteer malaria workers also provide community-based education programmes, raising awareness about the use of mosquito nets, the dangers of fake drugs, and how to access reliable treatment. Education materials such as posters, brochures, and billboards have been produced in both Thai and Khmer, with the Khmer materials available on both sides of the border.

Systems to monitor the cross-border movements of Cambodians and Thais have been developed in order to track possible movement of the malaria parasites. The health departments of Cambodia and Thailand share information to coordinate actions and follow up cases.

An intense screening and treatment programme is being conducted in 20 high-risk villages in Pailin which screens all men, women and children in a village, even those not showing symptoms of malaria. Samples are sent by taxi to the Pasteur Institute in Phnom Penh where they are examined using PCR to determine whether malaria parasites are present. In the first seven villages screened – from May to late June 2010 – almost 2800 people were tested and only two cases of *P. falciparum* malaria were found. Six of the seven villages had no cases of *P. falciparum* malaria. Only one year previously these seven villages were among the most affected by malaria in the border area. Two other sources of data – from the Cambodian Ministry of Health and from the village malaria workers – also showed that cases of *P. falciparum* malaria in the zone targeted by the project had fallen dramatically. The interventions to combat malaria in the target area therefore appear to be having an impact.

For more details see: http://www.who.int/malaria/diagnosis _ treatment/arcp/en/ index.html
The critical role of monitoring drug efficacy has been demonstrated on 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, AFRIM detected two cases of artemisinin resistance in Tasan, Cambodia, providing the first evidence of artemisinin resistance. Since 2008, WHO has been coordinating containment activities in this area, making significant progress in limiting the spread of artemisinin-resistant parasites (Box 5.8).

An increase in the proportion of patients still parasitaemic on day 3 following treatment with ACTs has also been reported along the Thailand-Myanmar and China-Myanmar borders, and in one province in Viet Nam where the situation is less serious than at the Cambodia-Thailand border, but still merits careful monitoring. While these observations suggest that there are changes in parasite sensitivity to artemisinins, ACTs remain clinically and parasitologically effective even in the Greater Mekong subregion. It is not yet known whether clearance times will continue to become more prolonged, or how the prolonged clearance time might put the partner drug at risk for the development of resistance.

**Treatment of P. vivax malaria**: chloroquine remains the drug of choice in areas where chloroquine remains 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 (Borneo), 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. 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 (Borneo), 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*.

5.5 Conclusions

**Availability of parasitological diagnosis**: there have been significant increases in the availability of parasitological testing in the last few years but low rates persist in the majority of African countries and in a few other countries. A review of commodity procurement plans suggests that the gap between policy and implementation appears to be partly due to a failure to adequately plan for and finance the expansion of RDTs; bottlenecks in implementation may also contribute.

A small selection of countries have shown that it is possible to rapidly scale up the availability of malaria diagnostic testing nationwide within a relatively short period of time, provided that attention is given to adequate preparation, training, monitoring, supervision and quality control.

**Cost implications of improved diagnosis**: as the incidence of malaria decreases through much of sub-Saharan Africa the need to differentiate malaria from non-malarial fevers becomes more pressing. Countries that adopt universal testing will reduce their spending on ACTs but the savings will be offset by the cost of RDTs and alternative therapies and the increased time needed by health workers to examine patients. The total costs to the health system will depend on the cost of testing, the proportion of suspected malaria cases that are parasite positive, the sensitivity and specificity of tests, clinicians’ adherence to test results, and the cost of treatment prescribed to parasite-positive and parasite-negative patients (6). Further work is needed to understand how costs will change as the availability of diagnostic testing is increased and to identify the factors NMCPs need to take into account when planning for expansion of RDT programmes.

**Benefits of expanding diagnosis**: several benefits accrue from increasing diagnostic testing: (i) patients will obtain appropriate diagnosis and treatment for their illness leading to lower mortality rates and reduced recovery times; (ii) excessive use of antimalarials can be reduced which will help to limit the development of resistance to ACTs; (iii) more accurate data on the incidence of confirmed malaria cases will enable interventions to be targeted to high priority areas and it will be possible to judge more accurately the success of programme implementation. The monetary value of such benefits is uncertain but there is consensus that these are worthwhile objectives for health systems.

**Diagnostic testing in the private sector**: the challenges involved in expanding access are likely to be greater in the private sector for several reasons: (i) the availability of testing is lower; (ii) the private sector is not so easily regulated by ministries of health; (iii) there is little experience of expanding diagnostic programmes in the private sector; (iv) incentives to use diagnostic tests and comply with test results will depend on costs which will often be borne directly by the patients. It may be more affordable for a patient to buy an ACT rather than seek an RDT particularly if the costs of ACTs in the private sector are reduced through subsidies. More information is needed on how to scale up availability of diagnostic testing in the private sector.

**Community-based diagnosis and treatment**: for some remote communities with little access to public sector or private sector health care providers, parasitological diagnosis and treatment of malaria will need to be provided by community based programmes. Very few such programmes operate on a large scale but the experience of Lao People’s Democratic Republic and some other countries suggests that an existing cadre of village health workers can be trained in the use of RDTs and in large scale provision of appropriate treatment, resulting in dramatic changes in the way malaria case reporting is undertaken.

**Access to treatment**: information from manufacturers indicates that the number of ACTs procured has increased in every year since 2005. However there is little information on whether the quantities of antimalarial medicines available in public and private sectors are sufficient to meet the needs of patients. Data provided by malaria-endemic countries on medicines delivered are often incomplete.
Household survey data currently do not examine the question directly. If survey data are combined with health facility data then it is estimated that on average 65% of treatment needs are fulfilled for patients attending public health facilities. Estimates are more difficult to construct for patients visiting private sector treatment outlets and those that stay at home, but use of antimalarial medicines appears to be lower than for patients attending public sector facilities. The scarcity of information on access to treatment highlights the need to strengthen routine monitoring systems for diagnostic testing and treatment, to gather more direct information from household surveys, and to explore other methods to monitor access such as clinic exit interviews.

**Combatting 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. Despite the observed changes in parasite sensitivity to artemisinins, the clinical and parasitological efficacy of ACTs has not yet been compromised, even in the Greater Mekong subregion. Nonetheless, both components of the combination are currently at risk and using an ACT with an ineffective partner medicine can increase the risk of development or spread of artemisinin resistance. 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 that threatens the continued efficacy of artemisinin.
References


