Essential medicines

Intensified efforts required to withdraw oral artemisinin-based monotherapies

The emergence and spread of artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapy (oAMT) from the markets. Despite substantial progress, oAMTs are still available in many countries.

Intensified action is needed to protect the therapeutic life of artemisinin-based combination therapy (ACT), the mainstay of treatment for malaria caused by Plasmodium falciparum. No alternative medicine is ready to enter the market in the next few years to replace ACTs. The loss of this lifesaving class of medicines would have devastating consequences.

Background
Most malaria deaths occur as a result of infection with the P. falciparum parasite (1). P. falciparum has thus far developed resistance to all classes of medicines used in its treatment. The emergence of resistance took several decades for quinine, 12 years for chloroquine, 5 years for mefloquine and approximately 1 year for proguanil, sulfadoxine-pyrimethamine and atovaquone (2).

Artemisinins constitute the only class of medicines that are still widely effective against P. falciparum. However, they must be combined with a longer-acting partner medicine to ensure that no parasites survive the 3-day treatment course and become resistant. WHO recommends five artemisinin-based combination therapies (ACTs) as the mainstay of treatment for uncomplicated P. falciparum malaria (3).

In 2008, scientists confirmed the first cases of P. falciparum resistance to artemisinin derivatives in the western Cambodian province of Pailin (4), which in the past has already been the focus area for the initial development of resistance to other antimalarial compounds. In this particular province, artemisinins were extensively used as monotherapy during the past decade, and this – together with other, so far unidentified factors (5, 6) – contributed to the development of resistance.

WHO recommendations on phasing out oAMT
Based on observations of the biological mechanisms of resistance to other...
antimalarial compounds, it is expected that the removal of oAMT products will help slow down the spread of *P. falciparum* resistance to artemisinins and that the prevalence of newly emerged resistant strains might decline over time. Both mechanisms will extend the time during which ACTs remain an effective weapon in the fight against malaria.

WHO therefore urges Member States to cease the marketing and use of oAMT products (see definition in Box 1) in the public and private sectors and to promote the rational use of ACTs. This recommendation was endorsed by all WHO Member States at the Sixtieth World Health Assembly in May 2007 (Resolution WHA60.18) (7), and reaffirmed in 2011 (Resolution WHA64.17) (8).

**Box 1: Oral artemisinin-based monotherapy**

- The recommendation to phase out artemisinin-based monotherapy refers only to oral formulations.
- Rectal and injectable formulations (e.g. artesunate suppositories and artesunate injectables) are still required for pre-referral treatment and for the treatment of severe malaria, respectively (3).
- In very few and exceptional cases, oral formulations of artesunate or other artemisinin-derivatives might still be manufactured for co-packaging with a partner medicine in ACT products that are not yet available as fixed-dose combinations.

**Latest evidence on artemisinin resistance**

In January 2014, the WHO Global Malaria Programme published the latest status report on artemisinin resistance (9). Foci of artemisinin resistance have meanwhile been identified in five countries in the Greater Mekong sub-region, mainly along international borders: Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. Additional foci of resistance are suspected in Suriname, Guyana and French Guiana (France); the initial findings are pending confirmation by in-depth studies in these three areas.

There is cause for great concern that artemisinin resistance may spread beyond the Greater Mekong sub-region or emerge independently on other continents. The spread of artemisinin resistance would threaten people’s health and lives in malaria-endemic countries, and would reverse the recent progress in malaria control achieved in many countries.

**Web-based WHO monitoring system**

In order to track compliance with resolution WHA60.18, the WHO Global Malaria Programme has established a web-based monitoring system that contains regularly updated information on:

- **Regulatory actions** undertaken by national medicines regulatory authorities, available at www.who.int/malaria/monotherapy_NDRAs.pdf; and
- **Pharmaceutical companies** involved in the production and marketing of oAMTs, available at www.who.int/malaria/monotherapy_manufacturers.pdf. Since 2005 – based on product catalogues published on the web, printed advertisements in English and French, and samples of finished pharmaceutical products available to WHO – the Global Malaria Programme has identified about 100 companies involved in the production and marketing of oAMTs. Most likely this is not the complete list of companies and the real number is probably far higher. Where product information was no longer available on companies’ websites, the companies were removed from the WHO monitoring web page, although it is not clear whether they are still involved in the production and marketing of oAMTs.
Progress in phasing out oAMT

**Regulatory action.** The setting of regulations by national medicines regulatory authorities is a major determinant of successfully phasing out oAMTs from the markets. As of May 2014, substantial progress has been achieved. However, nine of the 78 national medicines regulatory authorities of falciparum-endemic countries do not yet comply with WHO recommendations; most of them are located in Africa (Figure 1).

**Pharmaceutical companies.** Despite substantial progress on the regulatory side and good cooperation of a number of pharmaceutical manufacturers, 30 of the 86 manufacturing companies currently listed in the WHO monitoring tool have not yet disclosed their intention to withdraw oAMTs from the market (Figure 2). WHO contacts companies regularly on the basis of the information collected to clarify their positions with regard to WHO recommendations.

**Challenges**
A number of challenges have been encountered in implementing regulatory actions at country level, particularly in countries with a federal state structure: while appropriate regulatory decisions were endorsed at the federal level, an adequate enforcement mechanism was required at the state level to adopt and implement the same regulations. India, for example, took regulatory steps to withdraw oAMTs from the market in 2008/9; however, regulatory action followed in only a few states, and the largest number of oAMTs manufacturers continues to be located in India (see Figure 2).

Another challenge is that in many malaria-endemic countries a flourishing informal private sector continues to sell oral monotherapy. This practice must be counteracted through a functional supply management system that can make effective and quality-assured medicines available at affordable prices.

**The way forward**
Success in removing oAMTs from the market depends ultimately on effective regulation of medicines at country level. Measures must be integrated with the complex domestic and international market dynamics and regulatory frameworks involved at each step in the production of artemisinin-based medicines: planting of seeds, extraction of raw material from the plant’s leaves, derivatization of active pharmaceutical ingredients and manufacture of the finished products.

Experience has shown that a variety of interventions can be used successfully to
interrupt the manufacture, export, import, sale and use of oAMTs. It is crucial to ensure at the same time that quality ACTs are widely available in both the public and private sectors.

- **Domestic markets.** To protect domestic markets, the most effective strategy is to refuse new and suspend existing marketing authorization and to stop issuing import licenses for such products. Domestic manufacturers should be regulated more stringently with regard to import licenses for APIs, for instance refusing API import licenses to companies that manufacture oAMTs only. In addition, FPP import licenses should be suspended for companies that market oAMTs only in order to prevent the re-packaging or re-branding of artemisinin-based FPPs produced in other countries.

- **Export markets.** Many countries have protected their domestic markets as described above; however, the manufacture and export of oAMTs have not been regulated with the same stringency. Consequently, oAMTs continue to be manufactured for export only and can easily enter malaria-endemic countries with weak regulatory systems. It is crucial, therefore, that countries protect not only their domestic markets but also the export markets by withdrawing manufacture and export licenses.

**Targets and timelines for regulatory action**

Derived from successful country experiences, Annex 1 proposes targets and timelines for the progressive removal of oAMTs from the market, which countries can adapt to their national context. Annex 2 is based on this generic guide and summarizes the minimum requirements for tracking progress in the form of a checklist.

Besides the widespread use of oAMTs, a number of other factors contribute to the emergence and spread of resistance. Annex 3 shows the main factors that should also be taken into consideration when regulating the market; potential solutions are described.

**Conclusion**

In view of the latest evidence on artemisinin resistance, and in the absence of safe, effective alternative medicines for the treatment of *P. falciparum* malaria, urgent action is required to protect this important class of life-saving medicines. Prevention of the development and spread of artemisinin resistance is crucially important, and oAMTs must therefore entirely be withdrawn from the markets.

Experience in a range of malaria-endemic countries has shown that phasing out oAMTs is possible. A number of critical steps should be considered to phase out oAMTs from the market. The synchronization of these steps with the large-scale deployment of quality ACTs is indispensable; enforcement mechanisms and the active recall of existing oAMTs stocks have proven to be very useful withdrawal tools. Reasonable timelines should be set that allow progressive adaptation and response of the private sector to new health directives. Government commitment and strong stewardship by national regulatory authorities are the crucial basis for achieving this.

Artemisinin resistance, which is being fuelled by the use of oral monotherapy products, is too serious a public health risk to allow their continued use.

**References**


### Annex 1.

**Generic guide with suggested timelines for phasing out oAMTs medicines from the market**

<table>
<thead>
<tr>
<th>Action</th>
<th>Task</th>
<th>Suggested approximate timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on time frame for phasing out oAMTs in synchrony with wide-scale deployment of ACTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oAMTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 3</td>
<td>Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies that exclusively market oAMTs</td>
<td>3–4 months</td>
</tr>
<tr>
<td>Step 4</td>
<td>Wide-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapy</td>
<td>Time X</td>
</tr>
<tr>
<td>Step 5</td>
<td>Widespread availability and affordability of ACTs in the private sector</td>
<td>Time Z</td>
</tr>
<tr>
<td>Step 6</td>
<td>Withdrawal of marketing authorization and of manufacturing licences for oAMTs as FPPs to protect domestic markets</td>
<td>6 months after Time X</td>
</tr>
<tr>
<td>Step 7</td>
<td>Suspension of export license for oAMTs as FPPs to protect export markets</td>
<td>6 months after Time X</td>
</tr>
<tr>
<td>Step 8</td>
<td>Active recall of oAMTs from the market</td>
<td>3 months after Time Z</td>
</tr>
<tr>
<td>Step 9</td>
<td>Enforcement activities (e.g. regular outlet inspections, confiscation and destruction of products, suspension of selling licenses, fines, prosecution)</td>
<td>Regular intervals after Step 8</td>
</tr>
<tr>
<td>Step 10</td>
<td>Monitoring to ensure complete elimination of oAMTs as FPPs from the market</td>
<td>10–12 months after Time X</td>
</tr>
</tbody>
</table>

oAMTs, oral artemisinin-based monotherapy; ACT, artemisinin-based combination therapy; API, active pharmaceutical ingredient; FPP, finished pharmaceutical product; Time X, time at which a country will deploy ACT in the public sector on a wide scale (All subsequent timelines are conditional on this.); Time Z, requires distribution of high-quality ACT at subsidized prices in the private sector.
Annex 2. Checklist for monitoring regulatory action taken by national authorities to phase out oAMTs from domestic and export markets

<table>
<thead>
<tr>
<th>Regulatory action</th>
<th>Protection of domestic market</th>
<th>Protection of export market</th>
</tr>
</thead>
</table>
| Marketing authorization                                | □ No more approvals of new marketing authorization for oAMTs FPPs  
▪ Suspension of existing marketing authorizations for oAMTs FPPs |                                                                                                                                                                                                                                                                                                                                                                     |
| Manufacturing licenses                                 | □ Suspension of manufacturing licenses for oAMTs FPPs                                                                                                                                                                                                                                                                                                       |
| Import licenses                                        | □ Suspension of API and oAMTs FPP import licences for companies exclusively marketing oAMTs or exclusively involved in re-packaging or re-branding                                                                                                                                                                                                                  |
| Export licenses                                        | □ Suspension of export licenses for APIs with clear documentation that they are exclusively used for the manufacture of oAMTs  
▪ Suspension of export licenses for oAMTs FPPs |                                                                                                                                                                                                                                                                                                                                                                     |
| Wide-scale availability of affordable, quality ACTs products | □ Public sector  
▪ Private sector  
▪ (informal private sector) |                                                                                                                                                                                                                                                                                                                                                                     |
| Active recall and disposal of existing oAMTs stocks from all outlets | □ Public sector  
▪ Private sector  
▪ (informal private sector) |                                                                                                                                                                                                                                                                                                                                                                     |
| Regular inspection of outlet systems                   | □ Public sector  
▪ Private sector  
▪ (informal private sector) | □ Regular inspection of manufacturing sites                                                                                                                                                                                                                                                                                                                     |
| Harmonization of regulations at state and federal levels (where applicable) | □ Public sector  
▪ Private sector  
▪ (Informal private sector) |                                                                                                                                                                                                                                                                                                                                                                     |
Annex 3. Main factors that contribute to the development and spread of artemisinin resistance and potential solutions

<table>
<thead>
<tr>
<th>Factor</th>
<th>Issue</th>
<th>Potential solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient compliance / adherence to treatment</td>
<td>Artemisinin-based monotherapy would require a complete 7-day treatment course to fully clear parasitaemia (and is thus not recommended by WHO anymore; WHO recommends a three day treatment course with ACTs (3)) ⇒ Due to the rapid clearance of symptoms by the artemisinin derivative within 3 days, patients often discontinue treatment too early. Thus only sub-therapeutic levels of API are achieved which cannot fully clear parasitaemia.</td>
<td>Use ACT medicines that require a 3-day treatment regimen in line with WHO guidelines (3). Provide comprehensive information resulting in patient compliance to the full treatment course – rational use. Ensure widespread accessibility to affordable, quality, and ideally fixed-dose (co-formulated) ACTs. Eliminate oAMTs from the market.</td>
</tr>
<tr>
<td>Formulation of products (co-blistered versus co-formulated)</td>
<td>Co-blistered packs of artemisinin derivative and their partner medicine. ⇒ Rapid clearance of symptoms without complete parasite clearance by the artemisinin derivative and poor tolerability of the partner medicine result in patients often taking only the artemisinin component of the co-blistered product. ⇒ Sub-therapeutic levels of API through only one instead of two modes of action cannot achieve full clearance of parasitaemia.</td>
<td>Use fixed-dose ACTs (co-formulated products containing both partner medicines in one tablet). Ensure widespread accessibility to affordable, quality ACTs.</td>
</tr>
<tr>
<td>Quality of medicines</td>
<td>Products containing inadequate amounts of the API or degradation due to poor stability. ⇒ Sub-therapeutic levels of API cannot fully clear parasitaemia.</td>
<td>Select antimalarial medicines from pre-qualified sources for procurement. Ensure functioning quality assurance and quality control measures at country level.</td>
</tr>
<tr>
<td>Migrating populations</td>
<td>Artemisinin-resistant strains from other geographical areas are imported, which then recombine with local parasites to give rise to a pool of mutated and recombined parasites. ⇒ Contribution to development and spread of resistance.</td>
<td>Increase monitoring and surveillance, with specific attention to mass population movements from areas with high levels of resistance. Improve access to rational treatment with ACTs.</td>
</tr>
<tr>
<td>Regulatory systems</td>
<td>Lack of adequate mechanisms at country level to ensure that only high-quality medicines enter the market.</td>
<td>Strengthen national drug regulatory systems. Build capacity and introduce structural reforms.</td>
</tr>
<tr>
<td>Information</td>
<td>Insufficient knowledge of both prescriber and patient.</td>
<td>Provide adequate training and communication to change prescribing habits. Conduct information campaigns for patients.</td>
</tr>
<tr>
<td>Availability of ACTs</td>
<td>Insufficient amounts of quality ACTs at affordable prices.</td>
<td>Ensure wide-scale availability of affordable, quality ACTs and rapid diagnostic tests in both public and private sectors to crowd out oAMTs and promote rational use of ACTs.</td>
</tr>
</tbody>
</table>