Consolidated key recommendations

The following set of core principles, held by the guideline panel, form the foundation for the recommendations.

A: Prompt diagnosis and effective treatment

- Universal access to parasitological diagnosis of malaria beyond the reach of quality controlled microscopy, is possible with deployment of quality assured rapid diagnostic tests (RDTs), appropriate for use in primary healthcare and community settings.

- Uncomplicated malaria can progress rapidly to severe forms of the disease if left untreated, especially in people with no or low immunity. Severe malaria is almost always fatal without treatment and patients may die within hours. Therefore, programs should ensure access to prompt diagnosis and effective treatments within 24–48 hours of the onset of malaria symptoms.
B: Combination therapy

- Preventing or delaying resistance is essential to the success of both national and global malaria control strategies. To help protect the current and future antimalarial medicines, all episodes of malaria should be treated with at least two antimalarials with different mechanisms of action (combination therapy). To improve adherence to treatment fixed-dose combinations are highly preferable to blistered or co-dispensed combinations.

C: Rational use of antimalarials

- To reduce the spread of drug resistance, limit wastage of precious artemisinin-based combination therapies and better identify other febrile illnesses in the context of changing malaria epidemiology, there is a strong need to dispense antimalarials only to those who truly have malaria and promote adherence to full treatment course.
Diagnosing malaria

- All people with suspected malaria should have a parasitological test to confirm the diagnosis.

Treating uncomplicated *P. falciparum* malaria

- Treat adults and children (including infants, pregnant women in their second and third trimesters, and breastfeeding women) with uncomplicated *P. falciparum* malaria with an ACT.
- The current recommended first or second-line ACT treatment options are:
  - Artemether plus lumefantrine; Artesunate plus amodiaquine; Artesunate plus mefloquine; Dihydroartemisinin plus piperaquine; Artesunate plus sulfadoxine-pyrimethamine.

Strong recommendation, High quality evidence
Treating uncomplicated *P. falciparum* malaria

- All ACTs should contain at least three days treatment with an artemisinin-derivative.

  Strong recommendation, High quality evidence

- In low transmission areas, also provide a single dose of 0.25mg/kg primaquine to reduce onward transmission of *P. falciparum*, without the need for G6PD testing (excluding pregnant and breastfeeding women and infants aged < 1 year).

  Strong recommendation, Low quality evidence
Treating uncomplicated *P. Falciparum* malaria in special risk groups

- Treat pregnant women with uncomplicated *P. falciparum* or chloroquine resistant *P. vivax* malaria in the first trimester with seven days of quinine plus clindamycin (if unavailable use an ACT).

- Treat infants weighing less than 5 kg with uncomplicated *P. falciparum* malaria with an ACT dosed at the same mg/kg target as for children weighing 5 kg.

Conditional recommendation, Low quality evidence
Treating uncomplicated *P. falciparum* malaria in special risk groups

- In HIV positive people with uncomplicated *P. falciparum* malaria avoid AS+SP if on treatment with co-trimoxazole, and avoid AS+AQ if on treatment with efavirenz.

- Treat travellers returning to non-endemic settings with uncomplicated *P. falciparum* malaria with an ACT.

- People with *P. falciparum* hyperparasitaemia are at increased risk of death and require close monitoring in addition to an ACT.

Conditional recommendation, Low quality evidence
Treating uncomplicated non-falciparum malaria

- In areas with chloroquine susceptible *P. vivax*, treat adults and children with uncomplicated non-falciparum malaria using either an ACT or chloroquine.

  Strong recommendation, High quality evidence

- In areas with chloroquine resistant *P. vivax*, treat adults and children with uncomplicated *P. vivax* malaria with an ACT (including infants, lactating women, and pregnant women in their second and third trimesters).

  Strong recommendation, High quality evidence

- Treat adults and children with proven uncomplicated *P. ovale*, *P. malariae*, or *P. knowlesi* malaria with either a three-day course of an ACT known to be effective in the region or chloroquine.
Preventing relapse in *P. vivax* or *P. ovale* malaria

- In addition to the ACT or chloroquine treat people with *P. vivax* or *P. ovale* malaria (excluding pregnant or breastfeeding women, infants <6 months, and people with G6PD deficiency) with a 14-day course of primaquine to prevent future relapse.

  **Strong recommendation, Moderate quality evidence**

- In people with mild to moderate G6PD deficiency, consider relapse prevention with primaquine 0.75 mg base/kg once a week for 8 weeks.

  **Conditional recommendation, Very low quality evidence**

- In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding is complete, then treat with 14 days of primaquine to prevent future relapse.

  **Conditional recommendation, Moderate quality evidence**
Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment)

- Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment).

- In settings where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single dose of intramuscular artesunate and refer to an appropriate facility for further care. Use artemether or quinine if artesunate is not available.

  Strong recommendation, Moderate quality evidence

- In settings where intramuscular injections are unavailable, treat children below the age of six years with a single dose of rectal artesunate and refer immediately to an appropriate facility for further care.

  Strong recommendation, Moderate quality evidence
Treating severe malaria

- Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 hours (including infants, pregnant women in all trimesters, and lactating women).

  Strong recommendation, High quality evidence

- Children weighing less than 20 kg should receive a higher dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure an equivalent drug exposure.

  Strong recommendation based on pharmacokinetic evaluation

- Once the patient has received at least 24 hours of parenteral therapy, AND is able to tolerate oral therapy, complete treatment with three-days of an ACT.

  Strong recommendation, High quality evidence
Treating severe malaria

Figure 3  Simulated total first-dose exposure levels (AUC_{0-12h}) of (a) ARS and (b) DHA after the standard 2.4 mg/kg dosing in children at different body weights. Simulated total first-dose exposure levels (AUC_{0-12h}) of (c) ARS and (d) DHA after the suggested adjusted dose regimen (Table 3). Open circles represent median values, and bars indicate the 25th to 75th percentiles of simulations (1,000 simulations at each body weight). The broken line represents the median exposure for the largest weight group (i.e., 700 h x ng/ml and 1,230 h x ng/ml for ARS and DHA, respectively). ARS, artemesunate; AUC_{0-12h}, area under the concentration–time curve from time point 0 to 12 h; DHA, dihydroartesinin.
Treating severe malaria

Population Pharmacokinetics of Intramuscular Artesunate in African Children with Severe Malaria: Implications for a Practical Dosing Regimen

ICE Hendriksen1,2, G Mvote3, A Kent4, S Gesase5, H Reyburn6, MM Lemnge6, N Lindegardh1,2, NPJ Day1,2, L von Seidlein6, NJ White1,2, AM Dondorp1,2 and JT Tarning1,2

Table 4: Study site, number of patients, study population, study design and ARS dosing scheme(s) for all routes of ARS administration (i.e. intravenously (IV), intramuscularly (IM)) and each study contributing data to the pooled analysis.

<table>
<thead>
<tr>
<th>Research team</th>
<th>Study site</th>
<th>No. of patients</th>
<th>Study population</th>
<th>Study design</th>
<th>Dosing scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramar et al.</td>
<td>Gabon, Malawi</td>
<td>182/177</td>
<td>Children with severe malaria</td>
<td>Randomised Controlled Trial</td>
<td>I (2.4) mg/kg at 0, 12, 24, 48, 72 hrs&lt;br&gt;II (4) mg/kg at 0, 24, 48 hrs</td>
</tr>
<tr>
<td>Krishna et al.</td>
<td>Ghana</td>
<td>34</td>
<td>Children with moderately severe malaria</td>
<td>Cross-over Trial</td>
<td>I (10) mg/kg at 0 hrs&lt;br&gt;II (20) mg/kg at 0 hrs&lt;br&gt;III (2.4) mg/kg IV at 12 hrs&lt;br&gt;IV (20) mg/kg at 0 hrs&lt;br&gt;V (2.4) mg/kg IV at 12 hrs</td>
</tr>
<tr>
<td>Nealan et al.</td>
<td>Gabon</td>
<td>28</td>
<td>Children with severe malaria</td>
<td>Cross-over Trial</td>
<td>I (2.4) mg/kg IV at 0 hrs&lt;br&gt;II (1.3) mg/kg IM at 12 hrs&lt;br&gt;III (2.4) mg/kg IV at 0 hrs&lt;br&gt;IV (1.2) mg/kg IV at 12 hrs</td>
</tr>
<tr>
<td>Mnde et al.</td>
<td>Bangladesh</td>
<td>21</td>
<td>Adults with severe malaria</td>
<td>Clinical Study</td>
<td>I (2.4) mg/kg at 0, 12, 24, 48 hrs etc</td>
</tr>
<tr>
<td>WHO</td>
<td>Bangkok, Thailand</td>
<td>48</td>
<td>Adults with moderately severe malaria</td>
<td>Cross-over Trial</td>
<td>I (10) mg/kg at 0 hrs&lt;br&gt;II (20) mg/kg at 0 hrs&lt;br&gt;III (2.4) mg/kg IV at 12 hrs&lt;br&gt;IV (20) mg/kg at 0 hrs&lt;br&gt;V (2.4) mg/kg IV at 12 hrs</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>Vietnam</td>
<td>30</td>
<td>Adults with either severe or moderately severe malaria</td>
<td>Phase 1 – Clinical Study&lt;br&gt;Phase 2 – Randomised Controlled Trial</td>
<td>Phase 1 (120) mg/kg IV at 0 hrs&lt;br&gt;Phase 2 (I (120) mg/kg IV at 0 and 4 hrs&lt;br&gt;II (240) mg/kg IV infusion over 4 hrs at 0 hrs</td>
</tr>
</tbody>
</table>

\*Number reported in published paper or internal WHO report. \*ITT – intention to treat; \*PP – per protocol
Treating severe malaria

OLD

2.4 mg/kg

NEW

<20 kg: 3.0 mg/kg
Chemoprevention for special risk groups

- In areas with highly seasonal malaria transmission, provide seasonal malaria chemoprevention with monthly AQ+SP for all children below the age of six years during each transmission season.

  Strong recommendation, High quality evidence

- In areas of moderate to high malaria transmission where SP is still effective, provide intermittent preventive treatment of infants with SP (SP-IPTi) alongside DTP2, DTP3, and measles vaccinations.

  Evidence not graded

- In malaria endemic areas, give Intermittent Preventive Treatment with SP to all pregnant women in their first or second pregnancies at every scheduled antenatal visit commencing at the start of the second trimester. Each SP dose should be given at least one month apart.

  Strong recommendation, High quality evidence
Dosing

All patients deserve an equal chance of being cured

Artemether-Lumefantrine

DHA-piperaquine

75th percentile – adults

25th percentile – adults

Body weight (kg)

Day 7 concentration (ng/mL)
## Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exposure in young children</th>
<th>Predictable relationship between dosing and exposure?</th>
<th>Dose increase?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumefantrine</td>
<td>Reduced</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>Reduced</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Piperaquine dose response

<table>
<thead>
<tr>
<th>Recrudescence</th>
<th>N (n)</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PIP dose (every 5 mg/kg increase)</td>
<td>7,070 [127]</td>
<td>0.87</td>
<td>[0.79–0.95]</td>
<td>0.002</td>
</tr>
<tr>
<td>Parasitaemia (Log10)</td>
<td>7,070 [127]</td>
<td>1.23</td>
<td>[1.08–1.41]</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (ref ≥12 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>439 [7]</td>
<td>2.36</td>
<td>[0.79–7.06]</td>
<td>0.200</td>
</tr>
<tr>
<td>1-&lt;5 years</td>
<td>3,429 [9]</td>
<td>3.71</td>
<td>[1.66–8.26]</td>
<td>0.002</td>
</tr>
<tr>
<td>5-&lt;12 years</td>
<td>943 [7]</td>
<td>1.48</td>
<td>[0.56–3.91]</td>
<td>0.610</td>
</tr>
</tbody>
</table>
By day 42, the risk of recrudescence in patients receiving a PIP dose below 59 mg/kg was 5.5% (95% CI 4.2–6.7) compared to 2.1% (95%: 1.1–3.0) in patients receiving a higher dose, [p < 0.001].

Raising the target minimum dose of PIP in this age group to **59 mg/kg would halve the risk of treatment failure** and ensure cure of at least 95% of young children.
## Dihydroartemisinin-Piperaquine

<table>
<thead>
<tr>
<th>Body weight</th>
<th>DHA/PPQ dose given daily for 3 days</th>
<th>DHA mg/kg dose range, given daily for 3 days</th>
<th>Piperaquine mg/kg dose range, given daily for 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 7 kg</td>
<td>1 x 20 / 160 mg</td>
<td>2.9 – 4.0 mg/kg</td>
<td>23 - 32 mg/kg</td>
</tr>
<tr>
<td>8 - 10 kg</td>
<td>1.5 x 20 / 160 mg</td>
<td>3.0 – 3.8 mg/kg</td>
<td>24 - 30 mg/kg</td>
</tr>
<tr>
<td>11 - 16 kg</td>
<td>1 x 40 / 320 mg</td>
<td>2.5 - 3.6 mg/kg</td>
<td>20 - 29 mg/kg</td>
</tr>
<tr>
<td>17 - 24 kg</td>
<td>1.5 x 40 / 320 mg</td>
<td>2.5 – 3.5 mg/kg</td>
<td>20 - 28 mg/kg</td>
</tr>
<tr>
<td>25 - 35 kg</td>
<td>2 x 40 / 320 mg</td>
<td>2.3 – 3.2 mg/kg</td>
<td>18 - 26 mg/kg</td>
</tr>
<tr>
<td>36 - 59 kg</td>
<td>3 x 40 / 320 mg</td>
<td>2.0 – 3.3 mg/kg</td>
<td>16 - 27 mg/kg</td>
</tr>
<tr>
<td>60 - 79 kg</td>
<td>4 x 40 / 320 mg</td>
<td>2 – 2.6 mg/kg</td>
<td>16 - 21 mg/kg</td>
</tr>
<tr>
<td>&gt;80 kg</td>
<td>5 x 40 / 320 mg</td>
<td>2* – 2.5 mg/kg</td>
<td>16* - 20 mg/kg</td>
</tr>
</tbody>
</table>

*Weight adjusted dose range assumes a maximum weight of 100kg
Dihydroartemisinin-Piperaquine

Revised dosing regimen

Previous dosing regimen
OLD

Highest peak level

NEW

World Health Organization
Review process and timelines

- **September 2014** Approval from MPAC.
- **Q4 2014** Compilation, external review, proofing (October).
- **Q4 2014** Final clearance through the WHO GRC and other WHO in-house processes.
- **Q1 2015** Release and launching, web publication, translations and dissemination.
Definition of $\Delta \Delta QTc$

$\Delta \Delta QTc = \Delta QTc_{\text{Treatment}} - \Delta QTc_{\text{Placebo}}$

$\Delta \Delta QTc = [QTc(T_2) - QTc(T_1)] - [QTc(T_4) - QTc(T_3)]$

$T_2$ and $T_4$ is the same clock time.
ΔΔQTc modelling

Direct response model:

\[ ΔΔQTc = (θ_1 + η_1) + θ_2 \cdot CP(t) + ε_i \]

θ_1 = Baseline ΔΔQTc
θ_2 = Slope, concentration-effect relationship
Final parameter estimates:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate</th>
<th>%RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$, Baseline $\Delta \Delta QTc$ (msec)</td>
<td>5.39</td>
<td>51%</td>
</tr>
<tr>
<td>$\theta_2$, Slope (msec/(ng/mL))</td>
<td>0.0352</td>
<td>21%</td>
</tr>
<tr>
<td>$\eta_1$, IIIV of Baseline $\Delta \Delta QTc$ (msec)</td>
<td>9.48</td>
<td>40%</td>
</tr>
<tr>
<td>$\sigma$, Additive error (msec)</td>
<td>10.6</td>
<td>10%</td>
</tr>
</tbody>
</table>

Conclusion: 95% of patients will be below 60 msec QTc at 850 ng/mL
Piperaquine has effects ≤ to chloroquine on the QTc interval

Randomized Dose-Ranging Controlled Trial of AQ-13, a Candidate Antimalarial, and Chloroquine in Healthy Volunteers

Fawaz Mzayek1,2,3, Haiyan Deng1,3, Frances J. Mather4, Elizabeth C. Wasilewic1,2,3,as, Huayan Liu1,3, Christiane M. Had3, David H. Chansolme4,5,6,7,9,9, Holly A. Murphy1,3,5, Bekir H. Melek5, Alan N. Tenaglia5,6,7,9, David M. Mushatt1,3,9, Albert W. Dreisbach5,6,7,9, Juan J. L. Lertora5,6,7,9, Donald J. Krogstad1,3,5,9*

Panel C 600 mg Dose of CQ (n=24)

Figure 3. Pharmacokinetics of AQ-13 and CQ at Doses Equivalent to 600 and 700 mg CQ Base

Table 6. Effects of AQ-13 and CQ on the QTc Interval

<table>
<thead>
<tr>
<th>Time of QTc Measurement</th>
<th>600/700 mg AQ-13, 600 mg CQ</th>
<th>1,750 mg AQ-13, 1,500 mg CQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQ-13 (n = 25)</td>
<td>CQ (n = 24)</td>
<td>AQ-13 (n = 13)</td>
</tr>
<tr>
<td>Baseline</td>
<td>403 ± 17</td>
<td>406 ± 19</td>
</tr>
<tr>
<td>4-5 h post-dose (day 1)</td>
<td>414 ± 17</td>
<td>421 ± 20</td>
</tr>
<tr>
<td>4-5 h post-dose (day 2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4-5 h post-dose (day 3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 wk follow-up</td>
<td>405 ± 18</td>
<td>403 ± 15</td>
</tr>
</tbody>
</table>

All data are presented in milliseconds as mean ± standard deviation. Data presented in columns 3 and 4 are for 12 volunteers randomized to AQ-13 at the 600 mg dose, plus an additional 13 volunteers who received 700 mg AQ-13; for 12 volunteers randomized to 600 mg CQ as capsules and an additional 12 volunteers randomized to 600 mg CQ as the commercially available Sanofi-Winthrop tablets (Aralen). Data in columns 4 and 5 are for 13 volunteers randomized to 1,750 mg AQ-13 and 13 volunteers randomized to 1,500 mg CQ. NA, not applicable.
Pharmacokinetic Interactions and Safety Evaluations of Coadministered Tafenoquine and Chloroquine in Healthy Subjects

Ann K. Miller, PhD, Emma Harrell, BSc, Li Ye, MS, Sharon Baptiste-Brown, MSN, Jörg-Peter Klein, PhD, Colin Ohrt, MD, MPH, Stephan Duparc, MD, Jörg J. Möhrle, PhD, Alison Webster, MD, Sandra Stinnett, MS, Arlene Hughes, PhD, Sandy Griffith, PharmD, Andrew P. Beelen, MD

Chloroquine (25 mg/kg)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg CQ</td>
<td>600 mg CQ</td>
<td>300 mg CQ</td>
</tr>
</tbody>
</table>

Higher QTc prolongation at standard dose compared to PQ

CQ alone

CQ + TQ

Clinical trial of extended-dose chloroquine for treatment of resistant falciparum malaria among Afghan refugees in Pakistan

Natalia Howard*, Naem Darani*, Sandra Sanchez, Khalid Beshir*, Rachel Halley and Mark Rowland*