New Treatment Policy of Malaria as a Part of Malaria Control Program in Indonesia

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ABSTRACT

Malaria control program is one of the oldest program in the Ministry of Health (MoH) Republic of Indonesia. Started with effort to eradicate malaria in 1959 through Malaria Eradication Command well known as KOPEM (Komando Pembasmian Malaria) then it evolves to Malaria Control Program, Roll Back Malaria Program, and the current Malaria Elimination Program. In terms of diagnostic and treatment, the policy has formulated by strictly follow evidence-based principles as well as technical guided from World Health Organization (WHO).

In 2004, based on numerous researches conducted in Indonesia the use of chloroquine was stopped and artemisinin-based combination therapy (ACT) was then initiated. For severe cases the use of intravenous (iv) Artesunate for cases treated in hospitals and intramuscular (im) Artemether for cases treated in the primary care setting were also introduced. ACT, Artesunate iv, and Artemether im, all are provided nationwide through the procurement system. For radical treatment, the recommendation in Indonesia is to add primaquine (PQ) to ACT for Plasmodium vivax and Plasmodium ovale infections to prevent relapses and for Plasmodium Falciparum infection to kill the gametocytes. These recommendations put hope to reduce malaria mortality to zero and
eventually with other interventions will eliminate malaria from the country by 2030. The dissemination of this information is important for the policy to apply in practice across the country.

**Key words:** malaria, treatment, Indonesia, policy, ACT.

**INTRODUCTION**

Since the 1970’s, malaria control program in the world has been weakened by the widespread of parasite resistance to previous generations of antimalarial drugs, chloroquine (CQ) and sulfadoxine pyrimetamine (SP).¹ Whereas then multidrug resistance is established in Southeast Asia, South America, and Africa.² WHO define antimalarial drug resistance as the ability of a parasite strain to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the dose normally recommended.³ The unproper use of antimalarial drug, particularly the one that already resistance, will lead to increase morbidity and mortality.⁴ Furthermore, frequent visits due to replacements and higher cost of severe malaria will give another burden to patient and health care facilities especially in a remote area of the country.

Resistance to CQ in Indonesia was first reported in 1975 from Indonesian Papua and East Kalimantan.⁵ It was followed by numerous studies reporting resistance to CQ and SP from more places in Indonesia.⁶⁻¹⁰ The sentinel sites for drug efficacy monitoring have recorded nation wide spread of CQ resistance in Indonesia.¹¹ The report varied for CQ resistance from 10% to 80% of resistance and for SP from 0 to 15% resistance. WHO in its recommendation mention that countries should initiate change of their malaria treatment policy if the total treatment failure proportion is >10%, as assessed through in vivo monitoring of therapeutic efficacy. The selection of a new and/or alternative antimalarial medicine for use at public health level within the context of national treatment guideline should be based on an average cure rate of >95%, as assessed in clinical trial.¹¹ Pattern of anti malaria drug resistance could be seen in Figure 1.

Responding to the situation, Malaria Treatment Expert Committee was then established, the team consisted of researchers from Indonesian National Institute of Health Research and Development (NIHRD) and Leading universities; malaria experts from Indonesian Tropical Medicine Society; malaria consultants from Indonesian Internal Medicine Association; experts from pharmacology field; and the Indonesian Food and Drug Administration (FDA). The goal of the committe is to provide recommendation on malaria treatment policy.

**MALARIA TREATMENT POLICY**

Current malaria treatment policy in the country is radical treatment protocol by giving ACT and PQ to uncomplicated malaria case. For severe malaria the protocol is to give artesunate iv for cases treated in hospital or any in-patient facilities, and to give arthemeter im for cases treated in the primary health care. Both artesunate and arthemeter treatment are to be followed by oral ACT and PQ when the patient is able to take oral drug.

The new recommendation based on evidence is to use dihydroartemisinin piperaquine (DHP) and artesunate + amodiaquine (AA) as drug of choice for ACT. Both drugs are provided for free by the for nation wide use. Lately, based on reports of superiority of efficacy and prophylactic effect of DHP compared to other ACTs¹²,¹³; reports that DHP reduce vertical transmission from mothers to babies¹⁴ and the more practical fixed dose combination (FDC) preparation of DHP, the procurement of DHP will be provided more than AA and later on will start to only procure DHP.

Primaquine is contraindicated for pregnancy and ACT can only be used in 2nd and 3rd trimester of pregnancy, then the only available drug to use for the 1st trimester is quinine.

The awareness of resistance to artemisinin leads the restriction of monotherapy treatment of malaria and only to use the combination formula. Thus the government only provide ACT and will not give permit for the registration of artemisinin single preparation. The effort to improve malaria diagnosis using not only microscopy, as recommended initially, but also rapid diagnostic test (RDT) is attached along in the policy. Lastly to ensure the drug quality in the country, ACT is
distributed through the government distribution line only.

MALARIA ELIMINATION

Since 2009, Indonesia has been embarking upon eliminating malaria in the country by 2030. The goal is to be achieved stepwise, by 2015 for Java, Bali, Riau Islands, and Aceh; and Sumatera, Kalimantan, Sulawesi, and West Nusa Tenggara by 2020; and the eastern part of Indonesia i.e. East Nusa Tenggara, Maluku, North Maluku, Papua, and West Papua by 2030. Currently, malaria cases are concentrated in the eastern part of Indonesia; contributing more than 80% of the nation’s 450,000 confirmed malaria cases in 2011. With more and more areas became moderate or low endemic, radical treatment, rigorous patient follow up, and treatment for severe malaria became a high priority for those particular areas.

People living in low endemic area have low protective immunity. While the risk to get infected is reduced in this area, the risk to develop severe malaria is increasing. Hospitals should be ready to treat severe malaria cases using Artesunate iv to achieve zero death of malaria.

Malaria elimination means reduction to zero local transmitted malaria cases in a defined geographical area. Human malaria is transmitted by sexual stages of the parasites, infecting anopheline mosquito vectors. Transmission depends on the duration of gametocytes carried in the blood, infectivity of this gametocytaemia to the local vectors, and the amount and behavior of the vectors. Anti malaria drugs which kill asexual stages also kill the early stages of P.falciparum gametocytes, as well as the mature P.vivax, malariae, and ovale gametocytes. The combination of reducing the asexual stage progenitors of sexual stages, and killing the gametocytes themselves reduce transmissibility. PQ is active against asexual stage of P.vivax, kill hypnozoites of P.vivax and P. ovale, and mature gametocytes of P.falciparum. Therefore, the importance of PQ use in clinical practices for radical treatment to achieve malaria elimination is emphasized. A rigorous patient follow up until day 28 will make sure that the infection is cleared up completely. Patient compliance and rational use of the drugs play an important role in keeping the drug effective. If drug activity against asexual stage is worsened because of antimalarial resistance, the rate at which parasitaemia is cleared up from the blood is reduced, and treatment failure rates increase. Studies have shown that increase gametocytaemia is the first warning sign of drug resistance. Thus, transmission and especially transmission of resistance would have increased before detectable changes in treatment failure. It is important for every physician to take responsibility in keeping the drug to be effective by following the treatment.
protocols set by the government.

**CHALLENGES**

Routine data collection by the government shows out of 1,322,451 suspected malaria cases; around ninety-two percent was examined using either microscope or RDT. Of the 256,592 confirmed malaria; 66% received ACT treatment.

Incoordination regarding drugs availability is stil reported from some areas. Main challenge is always proper communication between each health facility i.e hospitals, private practices, or other facility with the DHO on drug supply mechanism.

Countries in the Greater Mekong Region have reported resistance to ACT. Results from surveillance sites on the Thai-Cambodian border have shown increasing failure rate of P. falciparum to ACT. In particular, slow parasite clearance times have been detected on the third day of treatment in Pailin, in western Cambodia. In those areas, counterfeit and substandard antimalarial drugs and irrational drug use are highly prevalent, population mobility is widespread, and health service coverage is inadequate among ethnic minorities. Indonesia, while has strong policy to slow down artemisinin resistance in the area, will have to establish a system to monitor the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compositions</th>
<th>Preparations</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHP</td>
<td>40mg dihydroartemisinin + 320mg piperaquin</td>
<td>FDC</td>
<td>Dihydroartemisinin: 2–4 mg/kgBW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Piperaquin: 16–32 mg/kgBW</td>
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<tr>
<td>AA</td>
<td>50mg artesunat + 153mg amodiaquin</td>
<td>Co – blister</td>
<td>Artesunate: 4mg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Amodiaquin: 10 mg</td>
</tr>
<tr>
<td>PQ</td>
<td>15 mg</td>
<td>Tablet</td>
<td>P. vivax/P. ovale: 0.25 mg/kgBW for 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P. falciparum: 0.75 mg/kgBW single dose</td>
</tr>
<tr>
<td>Artesunate iv</td>
<td>60 mg</td>
<td>1 vial</td>
<td>2.4 mg/kgBW</td>
</tr>
<tr>
<td>Artesunate im</td>
<td>80 mg</td>
<td>1 ampul</td>
<td>3.2mg/kgBW in the 1st 24 hours continued with 1.6mg/kgBW/day</td>
</tr>
</tbody>
</table>

**FREE FROM MALARIA**

**MALARIA ENDEMICITY MAP IN INDONESIA IN 2011**

\[\text{Figure 2. Malaria endemicity}\]
efficacy of ACT and to establish strategy against counterfeit and substandard antimalarial drugs distribution. On the other hand, the appropriate clinical practice is playing a very important role in keeping the drug to be effective in Indonesia.

CONCLUSION
The Indonesian government through MoH has set a strong malaria treatment policy to reduce morbidity and mortality; to achieve malaria elimination; and to protect ACT from becoming ineffective. Aware with the challenges, the MoH is calling the clinical practices in the country to take responsibility to keep the drug effective by following the national treatment protocol and encouraging patient’s compliance. Studies and operational research need to be conducted to help the MoH formulate their strategies to provide the best treatment for malaria patients in Indonesia.

REFERENCES
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11. Routine MoH data.