WHO Global Malaria Programme

Q&A on antimalarial drug efficacy and drug resistance

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What is meant by 'resistance to an antimalarial medicine'?

- Resistance to an antimalarial medicine is defined as the ability of *Plasmodium* parasites to survive despite an adequate blood concentration of antimalarial medicines. Patients who are infected with resistant strains will fail to clear parasites and / or resolve clinical symptoms despite correct and complete administration of treatment.

What is meant by 'resistance to artemisinin'?

- Artemisinin resistance is at a very early stage of development. Resistance to artemisinins has only been confirmed in one area, the Cambodia-Thailand border. In this area, patients are still able to recover after treatment, however it now takes three to four days to clear the parasite, instead of one to two days. At this early stage, artemisinins are still effective in curing the disease, provided they are used with an effective partner drug; however, it takes longer to completely clear the parasites than it did five years ago.

Why is artemisinin so important in the fight against malaria?

- Artemisinin and its derivatives are a class of plant-based antimalarial medicines, first developed by the Chinese. Artemisinins are very potent medicines which can very quickly reduce the number of malaria parasites in humans. Artemisinin compounds are part of all of the five artemisinin-based combination therapies (ACTs) recommended by WHO for the treatment of uncomplicated *P. falciparum* malaria.

Why combination therapy?

- The use of combination therapy helps to prevent the development of resistance and cures patients more rapidly. Parasites resistant to one of the medicines are unlikely to be resistant to the other, and so will be killed by the combination. Similar approaches are used for the treatment of HIV and tuberculosis.
- To protect artemisinins from the development of resistance, they are only recommended for use to treat uncomplicated malaria in combination with a partner drug. WHO has called on countries to halt the use of oral artemisinin-based monotherapies for the treatment of uncomplicated falciparum malaria.

WHO has confirmed the emergence of artemisinin resistance at the Cambodia-Thailand border; has resistance spread further?

- WHO and its partners have intensified monitoring antimalarial drug efficacy in neighbouring countries in South-East Asia and also in Africa. Delayed parasite clearance time after treatment with an artemisinin-based combination therapy (ACT) has been observed at the border between Myanmar and Thailand and in one province in Viet Nam. This is not yet confirmed as resistance, but additional studies are ongoing.

Resistance to chloroquine and pyrimethamine also emerged on the Cambodia-Thailand border; what is so special about this area?

- It is true that the Cambodia-Thailand border is the epicenter for malaria resistance in Asia. Nevertheless, chloroquine and pyrimethamine resistance also emerged independently in other places, such as South America. One study quoted in the report suggested that *P. falciparum* in South-East-Asia has an inherent tendency to develop drug resistance through genetic mutation. However the emergence and spread of resistance is influenced by many factors, including: inappropriate use of drugs (e.g., inadequate or incomplete dose), use of sub-standard drugs, or use of oral artemisinin-based monotherapy.

What can be done to prevent the spread of resistance?

- After the emergence of artemisinin resistance at the Cambodia-Thailand border, WHO and partners implemented a containment strategy which focuses on diagnosing patients, treating them with appropriate medicines, using a fixed-dose combination (also called co-formulated) ACT, and halting the use artemisinin-based monotherapies for the treatment of uncomplicated falciparum malaria.
- The containment strategy has also aggressively scaled up vector control using insecticide treated nets, insecticide treated hammocks and hammock nets, as well as information, education and communication campaigns regarding the risks of malaria, the use of nets for prevention and appropriate diagnosis and treatment.
- In preparation for the emergence or spread of artemisinin resistance elsewhere, WHO and its partners have developed a *Global plan for artemisinin resistance containment* (GPARC), which will be released in January 2011. This global plan will helps countries and partners to protect ACTs as highly effective treatment for falciparum malaria.

ACTs are used as first-line treatment in most endemic countries. What does resistance to artemisinin mean for the efficacy of ACTs in treating malaria?

- In an ACT, each component has a specific role. The artemisinin derivative given over three days will reduce the main parasite load and the partner medicine will kill the remaining parasites. The overall efficacy of the ACTs is highly dependent on the efficacy of the partner drug. Even where resistance to artemisinin exists, ACTs can still be effective, as long as resistance to the partner drug has not developed.
- Despite the development of artemisinin resistance, ACTs remain the most effective treatment for uncomplicated falciparum malaria around the world.

According to the report, only 34% of countries are compliant with WHO recommended monitoring of drug efficacy. What should countries do to become compliant, what are the main challenges and what are the implication of monitoring drug efficacy and national policy?

- Most of the countries have developed a network of study sites to monitor antimalarial drug efficacy. In these sites, every two years countries should monitor the efficacy of the first- and second- line antimalarial medicines.
- The main challenge is sustainable funding and commitment to monitoring.
- Monitoring antimalarial drug efficacy is essential for timely changes to treatment policy in countries, which should be initiated when the treatment failure rate exceeds 10%. Countries currently facing failure rates above 10% with their first line antimalarial treatment have already started to implement a new treatment policy based on another ACT.

The report includes data on treatment with 7 days of artesunate. Is this a WHO-recommended treatment for uncomplicated malaria?

- No. Since 2006, WHO has called for the halting of the use of oral artemisinin-based monotherapy for the treatment of uncomplicated falciparum malaria (artesunate is a derivative of artemisinin).
- The results provided in the report on the efficacy of 7-day artesunate treatment come from rigorous clinical trials to confirm artemisinin resistance. Testing a compound in isolation (which is normally used as part of a combination treatment), is the only way to confirm resistance, in particular when tools such as molecular markers are not available and validated. All patients in such trials were followed carefully to ensure cure, and those not fully cured were subsequently treated with an ACT.

Is it ever acceptable to use artemisinins alone?

For patients who are severely ill, artemisinins may be used alone for initial treatment, either rectally (as a suppository) or parenterally (intravenous or intramuscular injection). Such treatment has been demonstrated to be life-saving. All such patients should eventually receive a full course of an ACT once they are sufficiently recovered to be able to take an oral medication.

What guidance does WHO provide to countries regarding monitoring drug efficacy and changing drug policy?

WHO has the following documents available to guide countries in their efforts to monitor drug efficacy and to update their national policy for the treatment of malaria:

Methods for surveillance of antimalarial drug efficacy.
(http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf)

Guidelines for the treatment of malaria.
(http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf)

For further information:

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