Status of the efficacy of artemisinin-based combination therapy (ACT) in Guyana and Suriname

Summary

Preliminary results from therapeutic efficacy studies in Suriname and Guyana are raising concerns that artemisinin resistance may be emerging in South America. The suspected resistance has been found in areas with a high number of migrants. Although many countries in South America have managed to dramatically reduce the number of malaria cases, the findings highlight the importance of all endemic countries conducting routine monitoring of therapeutic efficacy of antimalarial drugs. During a meeting held in Washington on 21 February 2013, representatives from Suriname and Guyana and malaria control partners agreed that confirmatory studies should be conducted in the two countries as soon as possible. Additional activities needed to contain artemisinin resistance in the region are currently under discussion.

Antimalarial efficacy surveillance in South America

Since 2001, USAID, in collaboration with the Pan-American Health Organization (PAHO), the World Health Organization (WHO), the US Centers for Disease Control & Prevention (CDC) and other partners, have supported the development and work of the Amazon Network for Surveillance of Antimalarial Drug Resistance (RAVREDA)\(^1\), through the Amazon Malaria Initiative (AMI). Efficacy studies undertaken with support from AMI/RAVREDA in the Amazon Basin from 2001 confirmed *Plasmodium falciparum* resistance to the standard treatments (chloroquine and sulfadoxine-pyrimethamine). These results were used in guiding changes in treatment policy. By 2008, all countries in the Amazon basin were using the WHO-recommended artemisinin-based combination therapy (ACT).

In the Americas, the malaria burden has decreased by over 50% in the past decade. *P. falciparum* accounts for approximately 25% of all cases in the region. The relatively few number of cases means that undertaking therapeutic efficacy studies of antimalarial drugs, especially for *P. falciparum*, has become logistically difficult and/or unfeasible in some settings.

Molecular markers of resistance to artemisinin have not yet been identified. Instead, the measurement of parasite clearance on day 3 after treatment with an ACT is the current method used to initially detect reduced sensitivity to the artemisinin component.

Resistance to artemisinin was first reported from the Cambodia-Thailand border in 2008, catalyzing the need for a Global Plan for Artemisinin Resistance Containment (GPARC), whose development was

\(^1\) The Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA) consists of: Brazil, Colombia, Ecuador, Guyana, Plurinational State of Bolivia, Peru, Suriname, and the Bolivarian Republic of Venezuela.
coordinated by the WHO Global Malaria Programme, in consultation with members of the constituencies of the Roll Back Malaria Partnership, and published in 2011. The GPARC calls for all endemic countries to monitor antimalarial efficacy at least once every 24 months in 4 to 6 sentinel sites. These studies include measurement of the proportion of patients positive on day 3 after treatment with an ACT.

At an AMI/RAVREDA meeting in Bogota, Colombia in September 2012, all countries using ACTs were again urged to establish sentinel sites to routinely monitor ACT efficacy including monitoring of day 3 parasitemia among treated patients. Experience from Thailand and Cambodia suggested that when more than 10% of patients have detectable parasites on day 3, confirmatory studies with artesunate monotherapy should be conducted.

A limited number of countries in South America have undertaken periodic studies to monitor the efficacy of ACTs since their introduction as a first-line treatment for P. falciparum malaria. Results have shown that ACTs continue to be efficacious in the Amazon basin. The studies include measurements of day 3 parasite densities after treatment with an ACT. The preliminary results from Suriname and Guyana described below reinforce the need for conducting therapeutic efficacy studies in all countries in the region. The findings reflect the importance of AMI/RAVREDA’s support to efforts at monitoring and combating malaria in the Americas, and must lead to further investigations.

Country data

Suriname

In 2004, Suriname changed its first line treatment for P. falciparum malaria to an artemisinin-based combination therapy (ACT), artemether-lumefantrine. This, and the distribution of long-lasting insecticidal nets, indoor residual spraying, active case detection and an improved surveillance system, resulted in a more than 90 percent decrease in malaria cases. Currently, malaria cases are mainly seen among gold miners in the interior of the country.

An efficacy study for artemether-lumefantrine was conducted between July 2005 and September 2006. The incidence of day 3 parasitaemia was 2.2%, with 95.3% of cases with a negative slide on day 28 (data not PCR corrected). A second study was undertaken to assess artemether-lumefantrine efficacy in patients with P. falciparum malaria, in the capital city of Paramaribo in April – November 20112. The treatment was directly observed; patients were followed daily until parasite clearance plus one day and then on day 7, 14, 21 and 28. Of the 67 patients enrolled, 9 were withdrawn because of protocol violations. Among the remaining 58 patients, 5 were lost to follow up before parasite clearance. Only 11 patients were followed for the full 28-day period, none of whom had recurrent parasitaemia. Among the

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53 patients that were followed at least until parasite clearance, 15 (28.8%) still had parasites on day 3. Of the 11 patients followed until day 28, only 1 had a positive slide on day 3, which became negative on day 4. All 11 patients presented with adequate clinical and parasitological response (ACPR).

All day-3 slides were reviewed by an independent microscopist outside of Suriname, who found that 16.2% rather than 28.8% of the day-3 slides were positive. Due to the many discrepancies between the two readings, a more conservative approach is to report the proportion of slides read as positive by both microscopists, which is 10.8%.

The independent slide review furthermore led to the reclassification of one patient as ACPR. The patient had previously been classified as early treatment failure (ETF) based on a higher parasitaemia on day 2 than on day 0. The independent microscopist detected 6300 parasites/μl on day 0, instead of the 350/μl reported by the first microscopist.

**Guyana**

Guyana adopted artemether-lumefantrine as a first-line treatment for uncomplicated falciparum malaria in 2006. Similar to Suriname, malaria is mostly found in the interior regions. Over 90% of the malaria cases diagnosed in Guyana originate from regions where migrant populations (miners, loggers) and indigenous groups are the most affected.

Preliminary results from a study conducted in Georgetown, Guyana, from May 2011 to August 2012, also suggest a high day-3 positivity rate. Artemether-lumefantrine was given as directly observed treatment and patients were followed daily until day 3 and then on day 7, 14, 21 and 28. A total of 92 patients were included. Data before quality control showed 63/89 (70.1%) of patients were still positive at day 3. Of the 68 patients followed-up until day 28, 7 (10.3%) were still parasitemic, and were classified as treatment failure (note: these data have not been PCR corrected). Day-3 slides were double-checked at CDC Atlanta, which reported that 7/89 (7.9%) patients were confirmed to be positive at day 3. However, it should be noted that very low parasitaemia was detected. Most of these parasites were noted to be disintegrating, and therefore not likely to have been living at the time of sampling. Only 3 patients remained classified as treatment failure after microscopy quality control. One patient was classified as recrudescence after PCR correction whereas for the other patients, no amplification of DNA was possible from the filter papers collected during the trials. The treatment failure with artemether-lumefantrine was therefore 1.6%.

**Neighboring countries**

In Brazil, two therapeutic efficacy studies and three simplified studies, i.e. the follow-up of patients over 3 days without supervised treatment and with parasite count at day 0 and day 3 only, were conducted in 2010 and 2011. Only one case was reported to be positive at day 3, a patient in Manaus, who came from the mining area bordering Suriname.
French Guyana is currently compiling the data and is expected to share with PAHO and WHO soon.

Review of the literature

The Global Malaria Programme database, containing published and unpublished data on antimalarial drug efficacy from 2000 to 2012 was reviewed, and moderate day 3 positivity rates were reported in two studies:

**Bolivia**

In 2001, the day-3 positivity rate after treatment with artesunate-mefloquine was as high as 8.5%. No treatment failures were reported\(^3\). No other studies have been conducted since 2001.

**Peru**

In 2000, the day-3 positivity rate after treatment with artesunate-sulfadoxine-pyrimethamine was 2.2%\(^4\).

All the other published studies with ACTs since 2001 did not report any day 3 positive cases.

Informal consultation on the emergence of artemisinin resistance in South America, held in Washington, 21 February 2013.

A meeting was held to review the most recent data from Suriname and Guyana as described above. Representatives attended from the Ministries of Health of Guyana and Suriname, as well as from CDC, USAID, WHO PAHO and WHO Headquarters, and the chair of DRC TEG. There was a consensus that artemisinin resistance is now suspected in both Guyana and Suriname. Given the most recent quality control of microscopy, which confirmed reduced parasite clearance on day 3, participants agreed that activities to contain artemisinin resistance, as outlined in the GPARC, should now be initiated.

It was proposed that confirmatory studies be conducted in Suriname and Guyana. It was suggested that in Suriname, the study be conducted with artesunate for three days followed by mefloquine for two days. In Guyana, it was suggested to study 1) artesunate for seven days, or 2) artesunate for three days followed by an ACT. Funding for the studies in Guyana and Suriname may be available from WHO/GMP, with an estimated budget of $100,000 USD for each country. Medicines will be provided by WHO/GMP.

Clinical monitoring of all study procedures and quality control of microscopy will be available to ensure studies of extremely high quality. Blood samples taken during the studies should be made available to the Sanger Institute at Oxford University for molecular analysis. Draft protocols and a budget outline will be developed and shared by with participants of the meeting.

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A communications plan will be developed to ensure clear and consistent messages on the current situation. It was agreed that communication of messages would be managed by PAHO and AMI/RAVREDA in close consultation with WHO. A formal announcement of the findings will soon be issued by the PAHO office. Various stakeholders, including neighboring countries, donors and technical partners, should be aware of the data and its implications.

During the next AMI/RAVREDA meeting (8-11 April 2013), countries will discuss the findings and determine the most appropriate plans of action. Guyana is currently applying for Phase 2 of the Global Fund Single Stream Funding and will modify the objectives of the grant to align with GPARC recommendations. Suriname, which reports around 500 cases per year, will develop an elimination plan. However, these actions will only be effective with the commitment of the neighboring countries. In particular, there needs to be active engagement with French Guiana, who is currently not a member of AMI/RAVREDA. Therefore a “Guyana shield meeting” is planned in Suriname during the second half of 2013 which will provide an opportunity for French Guiana to be involved in the development of the action plan. Priorities for the other countries in the region will be to strengthen drug efficacy monitoring and improve national capacity in microscopy. All neighboring malaria endemic countries should conduct therapeutic efficacy studies of their first and second-line treatments.