



Research on the treatment and prevention of malaria in pregnancy in sub-Saharan Africa

9 October 2017 – Sheraton, Kuta Resort Hotel – Bali, Indonesia



MEETING REPORT

Dr Jenny Hill - Programme Manager, Malaria in Pregnancy Consortium

Introduction

On 10-12 Oct 2017, approximately 110 representatives from 18 malaria endemic countries including malaria researchers in the Asia-Pacific region and elsewhere came together for a 2.5-day meeting in Bali, Indonesia as part of the Asia-Pacific Malaria Elimination Network (APMEN). One full day was dedicated to malaria in pregnancy (MiP) to discuss the results of recent treatment and prevention studies that were completed in the region with potentially policy relevant findings. The meeting consisted of discussions about the burden and treatment (case-management) of malaria in pregnancy in the morning, with 4 presentations followed by a 1 hour break out session to discuss policy implications and then reporting back to plenary before lunch. In the afternoon, the focus was on prevention strategies following the same structure.



1. Burden, Dr Azucena Bardaji

Of all pregnancies occurring annually, approximately 77.4 million (61.8%) occur in the Asia-Pacific region, compared to 30m (24.2%) in Africa. Although the risk of acquiring malaria is on average considerably lower than in malaria endemic Africa, the consequences of these infections are potentially harmful to the pregnancy and associated with maternal anaemia, low birth weight, and pregnancy loss, particularly if the infections progress to become symptomatic. Dr Azucena Bardaji presented an overview of the burden of malaria in pregnancy in this region, with a special focus on recent studies looking at the burden of *P. vivax* infections in pregnancy. Earlier findings from the Asia-Pacific region showed that both *P. vivax* infections were associated with negative consequences on maternal and infant health, including low birthweight and maternal anaemia. The more recent studies show that this is primarily reflecting patent infections (those detectable by microscopy or RDTs) and particularly when they are symptomatic. There is little evidence that asymptomatic, sub-microscopic infections are associated with maternal anaemia or low birth weight, although it is not yet clear how many of these proceed to become patent infections if left undetected and untreated. It also became clear during the day, that with the use of PCR or LAMP, which are much more sensitive diagnostic tests than microscopy or RDTs, many more women in India and Indonesia were infected with malaria parasites than previously anticipated with a ratio of patent vs subpatent infections ranging between 2 to 6.



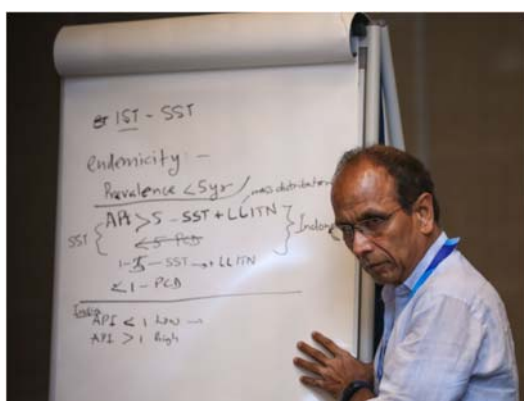
2. Case management, Professor Feiko Ter Kuile

The presentations regarding case-management focussed on three topics: the safety and efficacy of the artemisinin-based combination therapy (ACTs) compared to quinine in all trimesters, the efficacy of 2 ACTs on parasite clearance in India, and studies that evaluated primaquine disposition, including secretion of PQ and its metabolites into breast milk, with implications for radical cure in breastfeeding women. Safety of ACTs in all trimesters of pregnancy (Prof Feiko ter Kuile): The first presentation focused on the safety and efficacy of the artemisinin-based combination therapy (ACTs) compared to quinine in all trimesters and consisted of a summary of two meta-analyses published in 2016 and 2017. These showed that ACTs are much more effective than 7-day regimens with oral quinine, even when all quinine doses were provided under supervision. The risk of parasite treatment failure was 80% lower with ACTs. ACTs were also much better tolerated than oral quinine which was associated with much higher rates of tinnitus, dizziness and vomiting. Because 3-day ACT regimens are much easier to administer than 3 daily doses for 7 days of quinine, these results strongly support the current WHO recommendations that recommend ACTs for treatment in the 2nd and 3rd trimester.

The current WHO policy for treatment of malaria in the first trimester is quinine + clindamycin in the first trimester. However, this appears to be almost never implemented in pregnancy and either quinine alone is used or ACTs are given. Results from a meta-analysis of prospective studies designed to determine the safety of inadvertent exposure to artemisinins in the first trimester, showed that compared to quinine, artemisinin treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they also indicate no difference in the prevalence of major congenital anomalies between treatment groups. Overall, the benefits of 3-day artemisinin combination therapy regimens to treat malaria in early pregnancy are likely to outweigh the adverse outcomes of partially treated malaria, which can occur with oral quinine because of the known poor adherence to 7-day regimens. These recommendations for use of ACTs in the first trimester are currently under review by WHO's Technical Expert Group on malaria chemotherapy to determine if the WHO treatment guidelines for malaria in the first trimester should be updated. In subsequent breakout sessions it became clear that all countries represented at the meeting have treatment guidelines that more or less follow the current WHO recommendations to use ACTs in the 2nd and 3rd trimester and quinine, alone or combined with clindamycin (albeit rarely) in the first trimester (or chloroquine in case of *P. vivax* mono-infections). Malaysia used weekly CQ prophylaxis following ACT treatment of *P. vivax* infections. Almost all countries that had a strategy for radical cure of *P. vivax* infections deferred primaquine to 6 months post-breastfeeding (per WHO recommendations). It was also recognised that use of artemisinin in the first trimester is likely to be very common in real life settings despite current WHO recommendations, and countries were interested to update their guidelines as soon as the outcome from the deliberations at WHO were available (expected in the first quarter of 2018). Indonesia, which was one of the first countries to use dihydroartemisinin-piperazine in the general population and in the 2nd and 3rd trimester, has gone ahead and is now recommending dihydroartemisinin-piperazine in the first trimester.

Case management trial India (Prof Daniel Chandramohan): This presentation was about a treatment trial comparing SP-artesunate and mefloquine-artesunate in pregnant women with uncomplicated malaria in their 2nd and 3rd trimester. The trial showed excellent efficacy in terms of clearance of parasites by day 63 with both regimens. DHA-piperazine could not be included in the trial as the drug was not registered in India at the time the study was designed.

Primaquine and breastfeeding (Prof Joel Tarning): Lastly, Prof Tarning presented the preliminary results of a study that was designed to evaluate 14-days of the hypnozoitocidal antimalarial primaquine for the radical cure of *P. vivax* (killing of the hypnozoites, the dormant liver stage). The current recommendations by WHO and in most countries in areas where *P. vivax* occurs, include withholding primaquine during pregnancy (all trimesters) as well as during lactation (because of concerns about G6PD associated haemolysis in breast-fed infants). For some women, this implies they don't become eligible for radical cure for several years and remain at risk of relapse of *P. vivax*. The study showed that although primaquine is transferred into breast milk, the levels of primaquine and carboxyprimaquine were very low, and exposure for suckling infants appears safe. There was great interest in this study, which has important potential treatment implications. The study is still unpublished. The study team will contact WHO to evaluate whether this can be discussed in the upcoming policy making meetings.



Professor Daniel Chandramohan



Professor Joel Tarning,

In the breakout, the main implementation impediments to adherence to treatment guidelines for pregnant women were discussed. Private sectors practices (Nepal, India, Philippines), MCH service guidelines that require referral of all pregnant mothers with malaria to a clinical doctor (Thailand, Philippines), and pregnant women's attitudes towards drug use during pregnancy (Indonesia) were considered the main impediments for adherence to MIP treatment guidelines. Private sector providers tend to buy cheaper drugs and RDTs (compromising quality considering counterfeit drugs in the region); often do not follow National Guidelines (e.g. use of parenteral artemisinin for uncomplicated malaria, including in the first trimester); and often both private and public sectors have problems with stock-outs. The requirement to refer all pregnant women with malaria to Medical Doctors is a major impediment to access timely treatment, and it should be explored for community health workers to provide malaria treatment for MIP (i.e. closer to the community thereby increasing access). It was suggested that for countries to ensure treatment guidelines are implemented in all health facilities, countries should work towards ensuring access to ACTs in private sector facilities (example from Indonesia, where private sector providers could access ACT for free from the MoH system); enforcing treatment policy to private sectors through regulation, supervision/monitoring, reporting (to MoH), and training. Awareness of the national treatment guideline among clinic staff should be improved, as well as awareness by village based staff on MIP. Pregnant mothers should be provided with good information and education on how to take drugs and the safety to increase adherence.

The breakout group also suggested that monitoring should be done through both routine monitoring and supervisory visits. It is suggested that MCH and malaria control program both include MIP indicators in their program indicators. Data could be recorded through the MCH system (ANC) and shared with the Malaria Program. It was recognised that in many countries, the number of pregnant women with malaria is low and they are often only recorded as malaria cases without documenting pregnancy status. Supervisory visits protocol of three programs: MCH, Malaria, and Health Centre Program, should include MIP component.



3. Prevention

In the afternoon, the results were presented of 3 prevention trials conducted in India, Papua New Guinea and Indonesia. These were the first trials assessing the safety and efficacy of new approaches to controlling malaria in pregnancy using single screen and treat strategies (SST), monthly intermittent screening and treatment (IST) and monthly intermittent preventive therapy (IPTp) in this region.



IPT with SP-azithromycin in PNG, Prof Stephen Rogerson

Prof Rogerson presented the results from the first IPTp trial in the Asia-Pacific region. This trial compared the prevention policy at that time in PNG at the time, a single course of SP-chloroquine, with 3 courses of IPTp with the combination of SP plus 3g of azithromycin (SP-AZ). SP-AZ was efficacious and safe in reducing LBW, possibly acting through multiple mechanisms including the effect on malaria and on sexually transmitted infections. PNG has since introduced IPTp with SP as national policy.



Intermittent screening and treatment (IST) studies India

Professor Danial Chandramohan

Prof Chandramohan presented the results of a large trial comparing the impact of intermittent screening and treatment using RDTs and treatment of RDT positive women with SP-AS. The control group consisted of passive case detection (PCD), the policy in most parts of India at the time of the trial. ISTp detected a significantly higher number of women with malaria in pregnancy compared to PCD, indicating that malaria in pregnancy is mostly asymptomatic even in this very low transmission setting. However, this intervention did not reduce the risk of placental malaria or adverse birth outcomes compared to PCD. IST was well accepted by women and clinic staff. IST has been policy in India since 2016.



STOPMIP Indonesia,

Dr Jeanne Rini Poespoprodjo & Dr Rukhsana Ahmed

Lastly the results of a large 3-arm cluster randomised trial conducted in two sites (SW Sumba and Papua) in Indonesia was presented by Dr Rukhsana Ahmed and Dr Jeanne Rini Poespoprodjo. The study compared the current policy in Indonesia consisting of single screening and treatment (SST) at antenatal booking (enrolment) with IST and IPTp. All arms used DHA-piperazine. The study found that IST did not detect more infections than SST, but IPTp resulted in marked reduction in the incidence of malaria during pregnancy and a halving of the risk of placental malaria, but only in Papua, the site with moderate malaria transmission, and not in Sumba, which had low malaria transmission.

In the break-out sessions there was one group that mapped the current strategies for malaria prevention in pregnancy in the region. Countries included Indonesia, Laos, Malaysia, PNG, Vanuatu and Solomon Islands. Long Lasting Insecticide Nets (LLINs) distribution has been the main focus of malaria prevention programs in pregnancy in all countries represented in the group. IPT is policy in a single country, Papua New Guinea, and uses SP. In Vanuatu and Solomon Islands, weekly chloroquine is given to pregnant women. Indonesia's National Policy includes single screening and treatment for pregnant women in low to moderate malaria endemic area. Malaysia is screening all pregnant women at risk on their first ANC visit and after delivery (those with vivax malaria) will be given primaquine for radical cure following G6PD testing. Migrants in Malaysia and Laos are also screened at first ANC visit and treated according to the National Guidelines.

There were also discussions about whether SST, IST and IPTp should be considered for policy and in which areas. Many countries were already applying single screen and treat strategies. There was a discussion about which parameter (prevalence or API) to define the threshold to use IST, with a consensus towards API to be considered, and suggestions varied from API1 in India, to 5 in other countries. Indonesia is considering piloting the implementation of IPTp with DHA-piperazine in one high transmission district in Papua Indonesia in 2018 and if this is successful to expand this to other high transmission districts in Papua with an API >100. Five such districts exist in Indonesia, with a population of about 500,000. India and Indonesia agreed that there might be challenges with acceptance by women of giving antimalarials without prior testing. In Indonesian Papua, there are difficulties with access as well. It was agreed that roll out would be easier if linked with the country's ANC schedule, rather than monthly dosing, so a consideration was to link it with 'every scheduled visit', similar to WHO's current recommendations for IPTp with SP in Africa.

Another breakout group discussed the question of the role of malaria in pregnancy in the context of malaria elimination, with representatives from Vietnam, Nepal, Indonesia, Ethiopia, PNG and India. Generally, it was felt that there should not be special consideration for prevention of malaria in pregnant women in pre-elimination settings. In these settings, malaria is often more of an issue for migrant workers and marginal groups, and males are over-represented in these groups. Pregnant women are more likely to stay in the villages, but are not perceived to be at increased risk to warrant specific interventions, such as special screening programs. Rather, programs such as focal screening and treatment (around index cases) are expected to find infected pregnant women. In one or two cases, whole families move for short periods e.g. into forests to cut bamboo (Vietnam) and there, these families including pregnant women are encouraged to take ITNs with them. In all the relevant settings, LLINs continue to be recommended. The role of using malaria prevalence data routinely collected at the first antenatal clinics visit as part of existing SST or planned IST strategies, such as in India, for surveillance purposes to track transmission was also discussed. India has introduced regular blood slide screening of pregnant women. At present this data is under control of Maternal Child Services, and is not being collated; if it could be extracted and collated it could be a good way to monitor transmission at each of the three tiers that India identifies, from low to medium to high. There was not a lot of support for excluding women of childbearing age (WOCBAs) from e.g. MST or MDA with DHA-piperazine, although if *P. vivax* was detected then a mechanism to detect (early or any) pregnancy to withhold primaquine was seen as important. There was less of a concern expressed about using DHA PQ in early pregnancy.





Malaria in Pregnancy Consortium, Bill and Melinda Gates Foundation



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