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

East Africa Regional meeting

11-12 July 2016 – Fairview Hotel – Nairobi, Kenya

MEETING REPORT

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1.Introduction

Malaria in Pregnancy: Overview

1. Introduction

The meeting was convened by the Malaria in Pregnancy (MiP) Consortium and co-funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and the Bill and Melinda Gates Foundation. The aim of the meeting was to share the latest research from the MiP Consortium's clinical trials and studies on the treatment and prevention of malaria in pregnancy in sub-Saharan Africa undertaken between 2009-2015, and to discuss with national and regional policy stakeholders any implications for malaria and reproductive health programmes. The meeting also provided an opportunity to learn from the national Malaria and Reproductive Health departments about the challenges with changing and implementing malaria in pregnancy policy in the context of Antenatal care (ANC), and to outline the type of technical support needed.

The meeting was officially opened by Dr Rebecca Kiptui, Deputy of Kenya's National Malaria Control Programme (NMCP), who emphasised the importance of malaria as a cause of maternal mortality and highlighted the need for national malaria control programs and researchers to work more closely together to improve MiP. The meeting Agenda and list of Participants are provided at Annexes 1 and 2. Presentations available at http://www.mip-consortium.org/ConferenceProgramme.htmn.

The meeting was the first of two regional meetings in Africa supported by LSTM's EDCTP-funded Implementation of Malaria in Pregnancy Policy Action Consortium (IMPPACT) project, the second will be held in West Africa in Q4 2016. The project aims to ensure the translation of the World Health Organisation (WHO) recommendations on malaria in pregnancy control policy resulting from the MiP Consortium's research into country level policy and implementation plans.

2. Burden of malaria in pregnancy - Patrick Walker, Imperial College

Malaria transmission has fallen substantially across Africa between 2000 and 2015, with estimates from the Malaria Atlas Project (MAP) of a 50% reduction in prevalence and 40% reduction in clinical disease. The risk of infection in pregnancy is estimated to have fallen more sharply in East and Southern African countries than the sub-Saharan Africa average, with a 52% reduction, however there are still 1.15m pregnancies annually potentially infected with malaria (Table 1).

Table 1. Reduction of malaria infection risk in pregnancy in East and Southern Africa

Country	2000	2015	% reduction
Kenya	0.36m	0.14m	62%
Malawi	0.28m	0.15m	47%
Mozambique	0.75m	0.48m	36%
Tanzania	0.70m	0.25m	64%
Zambia	0.25m	0.13m	47%

P. falciparum has a large infected reservoir in women of childbearing age which are often asymptomatic and also often submicroscopic. Data from recent MiP Consortium trials show that in areas of high transmission the majority of women are likely to be infected before they reach ANC.

It was suggested that, in high transmission settings, malaria in pregnancy is driven by infected women becoming pregnant rather than pregnant women becoming infected (i.e. prevalence more important than incidence, and as evidenced by high prevalence of infection at time of booking) so malaria risk falls more slowly (37% reduction since 2000 in absence of prevention). Modelling suggests that as transmission falls the risk of malaria in pregnancy will decrease but severity of infections when they occur will increase, as recently observed in data from Mozambique (Mayor et al., 2015). Lower levels of immunity to placental parasites cause low birth weight (LBW) infants and clinical disease, pre-term delivery, and miscarriage in the mother. As a result the burden of malaria in pregnancy is likely to fall more gradually than prevalence/burden of malaria in the general population.

Prevention of malaria during pregnancy remains a priority. Insecticide treated net (ITN) use in pregnancy has risen steadily in East Africa, however first time mothers (most at risk of LBW) are least likely to have slept under ITN, hence there is a need to provide ITNs to adolescents before they become pregnant. Intermittent preventative treatment in pregnancy (IPTp) uptake was quicker and is higher in East and Southern Africa than the majority of sub-Saharan Africa but still lags substantially behind ANC attendance. HIV infected women are a high risk population as they are more susceptible to adverse outcomes from malaria infections during pregnancy (in some settings, up to 50% of pregnant women are HIV-positive at time of first ANC). Preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)cannot be co-administered with cotrimoxazole, and there is some evidence of antimalarial and antiretroviral drug interactions and mother to child transmission of HIV (see Section 7.1).

Discussion

Protecting pregnant women in early pregnancy is a challenge as many attend ANC late, often as late as 5 months gestation, and are therefore unprotected by IPTp or ITNs in early pregnancy. The community has to play a role in promoting preventative services as well as effective case management.

HIV-infected women should start on preventative drugs as soon as the diagnosis is made but this does not happen in reality in which case they should receive antimalarial treatment or IPTp. However they should not be given both cotrimoxazole and sulfadoxine-pyrimethamine (SP) due to potential drug interactions

Credit: www.commons.wikimedia.org "The ideal family"

Burden

1. Infected women become pregnant, rather than pregnant becoming infected
   i.e. pre-pregnancy matters
2. Malaria transmission reduced by about 35-40% since 2010
3. Less pregnant women infected, but each infection may be more severe
4. Clinical burden will decline slower than infection burden because of reduced immunity
5. Remain vigilant

3.0 Safety and use of ACTs for case management of malaria in all trimesters of pregnancy

Credit: Malaria in Pregnancy Consortium, Michael Nambozi

Safety and Use of ACTs in all trimesters of pregnancy

1st trimester:

1. Use of ACTs in 1st trimester has similar risk of adverse pregnancy outcomes to oral quinine
2. ACTs more efficacious
3. ACTs better tolerated
4. WHO MPAC recommended to update the WHO treatment guidelines on malaria

2nd/3rd trimester:

1. All 4 four ACTs effective at clearing existing infections
2. AL best tolerated
3. DP best post treatment prophylaxis
4. AQAS, MQAS good for 2nd line

3.1 Safety and efficacy of ACTs for treatment of clinical malaria in 2nd and 3rd trimesters in Africa.

Michael Nambozi, TDRC Ndola

A multicentre, randomised, open label clinical trial involving 3428 women in Burkina Faso, Ghana, Malawi and Zambia compared the safety and efficacy of four artemisinin combination therapies (ACTs): artemether-lumefantrine (AL), amodiaquine-artesunate (AQAS), dihydroartemisinin-piperaquine (DP-PQ) and Mefloquine – artesunate (MQAS). Pregnant women in their second or third trimester (>16 weeks and <7 weeks) with *P. falciparum* infection were recruited at antenatal clinics (ANC) and followed up for 63 days. Pregnancy outcome was determined at 3-6 weeks' post-partum. Infants were followed up at 1 year (data not yet analysed).

All four ACTs were effective at clearing existing infections. AL had the best tolerability profile but the lowest efficacy and the shortest post–adverse treatment prophylactic period. There was a higher occurrence of events in both the AQAS and MQAS groups. DHA-PQ was considered the most suitable treatment for uncomplicated malaria in pregnancy due to good tolerability, high efficacy and long post-treatment in the Non-pregnant prophylactic period. DP has now been adopted as first line in non-pregnant population and for the treatment of MiP in 2nd and 3rd trimester in new national treatment guidelines (2014) in Zambia.

Discussion

Did women in the trial receive IPTp-SP?

Yes, women received IPTp-SP after day 63 follow-up visit until delivery.

Were lumefantrine levels assessed in the blood?

Yes, blood was collected from a proportion of patients in the study at day 7 for pharmacokinetic studies, but these have not been analysed yet.

What are the differences in cost between the antimalarials and what role did cost play in the Zambian policy decision?

Evidence of efficacy and the shifts in WHO recommendations for combined therapy were taken into consideration when making this decision. The cost was high ranging from $1 to $2.5 for AL, ASAQ cost $1.41. The prices were negotiated through WHO Novartis.

Is efficacy of ACTs monitored routinely in Zambia using WHO guidelines?

Yes, every 2 years

3.2 ACTs and quinine in early pregnancy in Africa: Feiko ter Kuile, LSTM on behalf of Stephanie Dellicour (LSTM) and Esperanca Sevene (Manhica)

Credit: MiP, Feiko Ter Kuile

The study was undertaken to address safety concerns of ACT use in the 1st trimester identified in animal models, specifically embryo-toxicity and teratogenicity of artemisinins in early pregnancy (equivalent to 6-12 weeks' gestation in humans). There is limited experience with intentional or inadvertent treatment with artemisinin in the 1st trimester, given that WHO policy states that artemisinins are contraindicated in the 1st trimester (i.e. limits intentional treatment) and difficulties of identifying women in very early pregnancy with inadvertent exposure to ACTs.

An individual patient level data (IPD) meta-analysis was conducted to compare the risk of adverse pregnancy outcomes between artemisinin and quinine exposures in 1st trimester pregnancy in Africa. Data sources included three prospective cohort studies undertaken by the MiP Consortium in Burkina Faso, Kenya and Mozambique (Tinto et al., 2015, Dellicour et al., 2015), other prospective cohort studies from sub-Saharan Africa (Mosha et al., 2014), and aggregated data from the Thai-Myanmar border (Moore et al, 2016).

The results indicate that, compared to quinine, artemisinins were not associated with an increased risk of miscarriage, stillbirths or congenital malformations. ACTs were better tolerated than quinine, and were more efficacious. Quinine is not well tolerated and poor compliance to 7-day treatment leads to untreated malaria, and malaria in 1st trimester is associated with increased risk of miscarriage. The study concluded that artemisinins should be added as a treatment option in the 1st trimester of pregnancy.

WHO's Malaria Policy Advisory Committee (MPAC) reviewed these results in 2015 and recommended that its Technical Expert Group on malaria chemotherapy review the WHO Guidelines for the treatment of malaria to consider the timely inclusion of ACT as a first-line therapeutic option for uncomplicated falciparum malaria in the 1st trimester of pregnancy (Committee and Secretariat, 2016).

Discussion

The WHO brief (November 2015) about use of ACTs in the first trimester has important programmatic implications (WHO MPAC, 2016), and it will be interesting to hear from the MOH representatives how this will work in practice. Currently, treatment for pregnant women is not always captured in ANC registers and pregnant women are not disaggregated in OPD or lab reports on malaria diagnosis and treatment. The new policy would appear to simplify practice for health providers.

3.3 Pregnancy among healthcare providers and drug outlets in western Kenya: Simon Kariuki, KEMRI

Credit: MiP, Simon Kariuki

A cross-sectional study on healthcare provider adherence to case management guidelines for MiP was conducted in 2013 in 51 health facilities and 39 drug outlets in the KEMRI/CDC Health and Demographic Surveillance System (HDSS) area in western Kenya. Results on malaria diagnosis showed that 77% of pregnant women received a diagnostic test (RDT or microscopy) on exit from health facilities, whereas only 9% of simulated clients (first trimester pregnant women or relatives of third trimester pregnant women) in drug outlets were offered an RDT or asked about previous malaria testing. On pregnancy assessment, 43% of 'not visibly pregnant' women were assessed for pregnancy in health facilities compared to 7% of the female simulated clients in drug outlets who were assessed without being prompted. Prescription of the correct drug for trimester at the correct dosage was observed in 66% of cases in health facilities and 40% in drug outlets. Among 1st trimester prescriptions, correct practice was observed in 32% of cases in health facilities and 0% in drug outlets. Among 2nd and 3rd trimester prescriptions, correct practice was found in 65% of cases in health facilities and 38% in drug outlets. Knowledge of treatment policy was higher than practice, indicating other factors affect practices but these factors were not explored. Exposures to AL in 1st trimester (unrelated to stock-out of quinine) were 16% of cases in health facilities and 51% of cases in drug outlets. SP was prescribed for treatment of acute malaria in 3% of cases in health facilities and 18% of simulations in drug outlets. Quinine dosage was inadequate in > 70% health facility patients and quinine was never prescribed in drug outlets.

Discussion

Health worker adherence to treatment guidelines in 1st trimester is worse than 2nd or 3rd trimester, have you explored reasons for this? No but perhaps we can hear from the national malaria control programme.

In Kenya, the practice by service providers for not prescribing quinine is because of the quinine intolerance. The dose is three times a day (every 8 hours) whereas it is generally taken within a 12-hour period (morning, midday and evening), and that is why clinicians prescribe AL at request of the women as it is better tolerated. Training of providers with Global Funds was done since the study so practices may have improved. Quality of care assessments are done every 6 months for public health facilities, and once every two years for private sectors, shows about 60% meet quality standards. Quality of care initiatives are needed to improve quality of treatment of MiP.

4. IPTp with 2 vs 3 or more doses of SP, and the impact of SP resistance

4.1 Effectiveness and cost effectiveness of 2 vs 3+ doses of IPTp with SP: Feiko ter Kuile, LSTM, on behalf of Kassoum Kayentao, MRTC

Summary

The rationale to explore 3 or more doses (3+) of SP for IPTp was to extend protection during the last 4-10 weeks of pregnancy, to compensate for moderate SP resistance which shortens duration post-treatment prophylaxis, and to improve coverage of 2-dose IPTp. It is already recommended for HIV+ women (not on cotrimoxazole) and for HIV-negative women in several countries.

A meta-analysis of the efficacy and safety of 2 versus 3+ doses of SP for IPTp using data from 6281 pregnancies from 7 trials in Burkina Faso, Kenya, Malawi (2), Mali, Tanzania and Zambia. The results showed that 3+ doses were more effective, reducing the risk of LBW by an extra 20% and increasing mean birth weight by an extra 56 gm. The 3+ dose groups also had 49% less placental malaria and 40% less severe maternal anaemia. There were no differences in rates of serious adverse events. The findings were consistent across the sites, and across subgroups including HIV status, gravidity, ITN use, SP resistance, and mean dose. Cost-effectiveness analysis shows that 3+ doses is a highly cost-effective intervention to reduce LBW (Fernandes et al., 2015). The evidence resulted in the 2012 WHO policy update of IPTp, which recommends a dose of SP at each scheduled ANC visit until delivery, at least one month apart, and the last dose can be administered up to delivery without safety concerns (World Health Organisation, 2012).

Discussion

The language in the WHO policy update is vague (monthly, i.e. number of doses not specified) and is open to interpretation (e.g. Zambia has opted for 7 doses, Mali 3 doses etc.); was this purposeful? This was to align with the new WHO guidelines on ANC which will define the recommended number of ANC visits. Publication of these guidelines has been delayed and is anticipated by October 2016.

Country participants identified two challenges which remain for implementing IPTp-SP. Complying with low dose folic acid (0.4 mg) is difficult as it is not on the national drug list and in Tanzania it is combined with iron (range 0.5 to 1.5 mg). In Kenya it took 8 years to change folic acid policy. The threshold for the folic acid effect on SP is not really known. Secondly, starting IPTp at 13 weeks is rarely possible (unless ultrasound is available) given difficulties with assessing gestational age, so in practice IPTp begins with quickening. So how important are the benefits' of reaching pregnant women early at 13 weeks' vs 20 weeks? Observational data suggest this is the period associated with foetal growth restriction. Data from the MiPc trials show that first time mothers are likely to be malaria positive at first ANC visit (detected by PCR and RDT) and would support screening of pregnant women at ANC booking with RDTs.

Prevention: IPTp with SP

What works?

1. 'Monthly' dosing
   - Early (16 wks)
   - Frequent
2. SP resistance
   - SP remarkably resilient
   - Remains beneficial if dhps 581 rare
   - Molecular surveillance useful
   - Threshold 581: 35%?
3. Low dose Folic acid (0.4-1.5 mg daily)

What's needed or what next?

1. Tools to capture IPTp 3+
   - Number of doses
   - Prevention for HIV infected women
   - Exclude non-IPTp areas from national statistics
2. How to address low uptake?
   - Concerns about tolerance
   - Concerns about resistance
   - Linkage community and ANC delivery (UNITAID)
3. New WHO RH guidelines
   - ultrasound?
   - Number of visits?
   - Use the momentum of 2012 hypenate update and evidence for continued effectiveness

4.2 Impact of SP resistance on the effectiveness of IPTp with SP in sub-Saharan Africa
Annemieke van Eijk, LSTM

Credit: MiP, Annemieke Van Eijk

Sulphadoxine-Pyrimethamine (SP) is the only antimalarial currently recommended for intermittent preventive therapy in pregnancy (IPTp) in sub-Saharan Africa. However, high level resistance threatens its efficacy in some areas. To support WHO with the design of a molecular policy decision tool for IPTp, we conducted a series of studies to determine the relationship between the population prevalence of resistance mutations in the parasite genes *Pfdhfr* and *Pfdhps* and the association between IPTp use and the risk of LBW.

In vivo studies of the efficacy of SP to clear parasitaemia in pregnant women conducted in 6 countries showed a decreased efficacy of SP in East Africa and a decrease in time to recurrence of infection with an increase of the molecular marker *Pfdhps*-K540E, as measured in the same population. However, IPTp was still associated with a significant reduction in LBW in the same 6 countries when evaluated in surveys at delivery.

Data was extracted from published literature on LBW and number of SP doses and matched with molecular markers of SP resistance by time and location. Meta-analysis showed a trend towards lower effectiveness with increasing resistance. An individual patient-level data analysis was conducted using national survey data in areas with high SP resistance, defined as >80% *Pfdhps*-K540E, whereby participants were matched for potential confounding factors. A linear decrease in effectiveness of IPTp with increasing prevalence of *Pfdhps*-K540E was observed, but even in areas with >95% *Pfdhps*-K540E, IPTp-SP remained associated with significantly less LBW. By contrast, in areas defined as super resistant (>10% *Pfdhps*-A581G), no association between IPTp and LBW was evident.

Discussion

- *What is the cut off point for SP resistance beyond which there is no benefit of IPTp-SP?* Evidence from NW Tanzania and Nyanza from 2012 with quintuple resistance shows IPTp-SP still has a benefit, whereas data from super resistant areas is not conclusive.
- *Will increased dosing with SP (new WHO policy) increase the development of SP resistance?* Yes in super resistant areas, but probably not where prevalence is <1%. More research is needed.
- *Countries need the guidance* on IPTp effectiveness to be translated into cost effectiveness in 'real life' settings for policy makers. Meanwhile WHO advises to continue using SP in these areas until a replacement drug can be recommended, as this keeps the IPTp delivery strategy in the health system functioning for the next drug.

4.3 Effectiveness of antenatal clinics to deliver IPTp-SP in context of other ANC Services
Jenny Hill, LSTM

Credit: MiP, Jenny Hill

According to 2014 DHSS surveys, only the Gambia, Sierra Leone and Zambia had exceeded 60% overage for 2 doses of IPTp, and while Malawi had achieved 60% this has now fallen. Yet most countries in Africa have 75% coverage for 2+ ANC visits.

Studies using household surveys and health facility surveys to assess programme effectiveness in Mali and Kenya identified key missed opportunities at ANC. In Kenya, receiving any dose of IPTp and receiving it by DOT were ineffective. In Mali, receiving IPTp by DOT was not practiced in the main referral hospital due to an institutionalised decision not to give SP to women on an empty stomach. A systematic review of 98 studies (Hill et al., 2013) identified widespread confusion about timing and dosing of SP and low knowledge of IPTp strategy, side effects and contraindications of SP and a common perception that women will not take SP on empty stomach. SP was distributed regardless of gestational age and/or estimation of gestational age was imprecise. Many of the obstacles to IPTp-SP delivery were relatively simple (health provider or organisational level at the health facility) barriers that can be resolved in the short term with improved training, guidance and reporting. The second study used an enhanced system of routine data (less expensive, timely) for assessing programme effectiveness, which introduced a series of new MiP indicators into HMIS in two districts in Mali and Kenya (trimester, IPTp DOT/non-DOT, IPTp doses 1-4+, diagnosis and treatment of MiP). While completeness for the enhanced MiP indicators in Kenya was high, inaccuracy levels were significant. Analysis on data validity is ongoing.

Discussion

Increasing IPTp coverage has been a challenge. We need to unpick the barriers to delivery of IPTp. This includes problems with acceptability to IPTp-SP among health providers and pregnant women.

Dr Chico: We reviewed barriers to IPTp delivery in Tanzania using discrete choice experiments. There needs to be a supply and demand relationship between provider and client. Pregnant women want treatment that protects them, but providers are not giving IPTp-SP as they wish to "do no harm". Dr Webster: That was in a particular site, and representative (depending upon sampling) of that site, and is not necessarily the same in other parts of Tanzania or other countries of sub-Saharan Africa.

5. Session 3: Experiences of implementing current MiP policies – national programme perspectives

Experiences of implementing current MiP policies: National programme perspectives

Credit: MiP, Peter Njiri

5.1 Kenya, Peter Njiri (NMCP)

Kenya has 14 malaria endemic counties, 8 around Lake Victoria and 6 in Coastal Province. The Kenya Malaria Strategy 2009-2018 (revised 2014) states that IPTp shall only be implemented in the malaria endemic zones in addition to ITNs and appropriate case management. All pregnant women in the 14 malaria endemic counties should receive at least three doses of IPTp with SP at ANC. Community Health Volunteers (CHVs) and health workers will sensitize pregnant women on early ANC attendance to receive IPTp doses under observation. To boost coverage with the previous policy (at least two doses), a memo from both Directors (Medical Services and Public Health and Sanitation) was issued in April 2011 reinforcing the national policy (at least two doses, by DOT). The memo included a statement on folic acid tablets to ONLY be administered 14 days following administration of SP as IPTp (high dose of folic acid-5 mg). Subsequently the National policy for iron and folic acid supplementation in pregnant mothers in Kenya, January 2013 stipulates low dose folic acid (0.5 mg).

The National guidelines for diagnosis, treatment and prevention of malaria in Kenya 2016 stipulate treatment of uncomplicated malaria in pregnancy in the first trimester is a 7-day therapy of quinine and not to withhold AL or any other treatment in 1st trimester if quinine is not available. AL is recommended in the 2nd and 3rd trimesters. Oral quinine may also be used but compliance must be ensured. Treatment of severe malaria in pregnancy is parenteral artesunate; in the absence of artesunate, artemether or quinine can be given. Dissemination of this policy has not yet taken place.

MiP, Busiku Hamainza

5.3 Zambia: Busiku Hamainza (NMCP)

Since 2003 MiP has been delivered as a package under the guiding principles of focused antenatal care. In 2014 the policy was updated and IPTp-SP is recommended on a monthly basis at all scheduled ANC visits during 2nd and 3rd trimesters, with a minimum of 3 doses. However the HMIS services integration form is limited to 3 doses of IPTp. ITNs are given free for each pregnancy at first ANC visit and another ITN is given at 8 months at infant's measles vaccination.

Treatment of uncomplicated malaria is quinine in the 1st trimester and AL in 2nd and 3rd trimesters, and quinine for any treatment failures. Treatment of severe malaria is quinine in 1st trimester and injectable artesunate in 2nd /3rd trimesters. HMIS captures all suspected and confirmed cases of malaria, including MiP

MiP, Shadreck Mulenga

5.2 Malawi: Diana Khonje (RH) & Shadreck Mulenga (NMCP)

Since 1993, Malawi has advocated 2 doses of SP for IPT under DOT in all health facilities. The IPTp policy was revised in 2014 to stipulate at least 3 doses of SP starting at 16 weeks with quickening, and 99.9% health workers providing ANC services have been trained on the revised policy. The 2014 Malawi Malaria Indicator Survey (MMIS) results show increased IPTp coverage since 2010: from 83% to 90% for any SP; from 60% to 64% for 2+ doses of SP; from 60% to 63% for 2+ doses at least one received at ANC also slightly increased. Coverage with 3 doses of IPTp has increased from 12% in 2010 to 30% in 2014 according to Malawi DHS surveys.

Challenges for IPTp delivery include: late attendance for ANC (only 12% start ANC in 1st trimester) as culturally, women believe that they have to start ANC when pregnancy is visible; health workers use SP for treatment when AL is out of stock; and overall quality of ANC is compromised in the absence of crucial equipment and supplies (pregnancy test kits, Hemoglobin testing, BP machines in some clinics).

Regarding treatment, pregnant women with malaria are now captured in OPD registers and are encouraged to report to ANC if not feeling well in order to capture malaria in pregnancy.

MiP, Baltazar Candrinho

5.4 Mozambique: Baltazar Candrinho (NMCP)

Mozambique approved IPTp policy in 2004 and began implementation in 2006. The policy was revised in 2014 to reflect the WHO 2012 updated IPTp policy. There have been several challenges to implementation. It takes one year for new guidelines to be developed and implemented in health facilities. MCH tools and monthly reports have to be adapted to accommodate 4+ doses, however the MCH programme has many other projects which do vertical training which compete with each other. The District Health Information Software (DHIS-2) indicator for IPTp-SP is now 4+ doses. The challenge is very few women make 4 ANC visits because distances are very far, they come late, and they are not motivated. SP supplies are an issue, so far they have used the push system, which leads to insufficient stocks of SP, however this will now be combined with the pull system using requisitions.

6. SUMMARY & DISCUSSION: Implications of sessions 1&2 on policies and programmes, and priorities for research

6.1: Q&A - ACTs in first trimester (pending WHO policy)

What issues would programmes face to adopt ACTs in first trimester?

Frequent changes to treatment guidelines can be confusing to health workers if countries don't have good strategies for dissemination and training. This needs resources and clear guidance. It may be too late to revise national treatment guidelines if already printed and distributed e.g. Kenya is disseminating a 2016 version now. It should be possible to distribute an addendum.

Clear guidance and communication from WHO will be critical to help countries implement the policy. For example, when WHO enforced 7 days of quinine, but some countries then reduced the regimen to 3 days when quinine was combined with clindamycin. Quinine stock that have been pre-ordered would need to be re-purposed and may expire. An alternative to quinine that has fewer side effects would be welcomed by providers and users, who already prescribe/use ACTs.

Process of dissemination of WHO policies, what is needed?

WHO needs a more active dissemination process and to provide implementation support in countries. Geneva first sends policies to regions and country offices. There is supposed to be an implementation process, which is usually very minimal, due to limited resources. Most policy recommendations and guidelines were supported by partners (e.g. systematic reviews and review processes). Dissemination to countries needs to emphasize: what is new, what the implications are, and what are the costs.

What role will pharmaceutical companies play in any change in policy?

Pharmaceutical companies have not yet recommended ACTs in the first trimester, but this has not happened for any other antimalarial. It is only very recently that industry has become involved in clinical trials of malaria in pregnancy (e.g. chloroquine-azithromycin). Regulators now push for the pharmaceutical industry to take pregnancy into account when developing new drugs. It may take a while to change the label. Industry ultimately wants to have safety information by brand, but this is not feasible for countries to collect. Medicines for Malaria (MMV) may be in the best position to set up post-marketing surveillance.

How can drug quality be ensured?

Several countries have local antimalarial drug manufacturers that are not approved by WHO. Systems need to be put in place to monitor and ensure drug quality.

How good is malaria diagnosis? Do we expect community health workers to test and treat pregnant women?

In Zambia, community workers are paid to diagnose malaria with RDTs (from WHO list), and pregnant women who test positive for malaria are referred to health facilities for treatment. Microscopy is only available at first and second level health facilities however there are a few mixed infections. Internal quality control assurance through supervisory visits and spot checks works well. Ghana also trained community volunteers to test, treat and track malaria, and this has reduced antimalarial use. Treatment of negative cases is on the decline.

Can we consider screening of pregnant women in the 1st trimester?

There was support for this from countries where women first attend ANC late.

Photo Credit: MiP,

6.2: Monthly doses of IPTp-SP

Did the switch from 2 to 3+ dose help to increase coverage?

This is still a fairly recent policy and while there does seem to have been an increase in IPTp coverage (e.g. Zambia has seen an increase in 3+ doses) it is not clear if it is because of the policy change. The challenge remains I early and frequent ANC visits, raising the importance of effective IEC. In Malawi, in some districts women who attend ANC early are given cash and early attendance has risen from 12 to 20%.

Importance of starting IPTp as early as possible in the 2nd trimester and problems with assessing gestational age. In the new WHO ANC guidelines due out October 2016 one recommendation will be the use of ultrasound to help countries to address the issue of gestational age. Jhpiego and partners are developing a toolkit to assess gestational age in the absence of ultrasound.

Is it difficult to change DHIS-2 indicator or in ANC registers with regard to the denominator used for IPTp coverage, which currently doesn't exclude women who would be ineligible to receive IPTp (e.g. HIV+ women taking cotrimoxazole)?

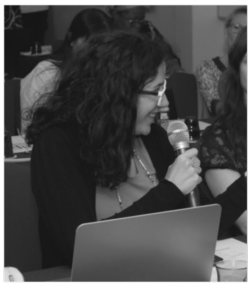
It appears there is need for countries to adapt the DHIS-2 data tables to allow malaria and HIV indicators to be combined for this specific analysis.

How can you improve ITN coverage among young women in their first pregnancy, since they cannot receive IPTp?

ITNs are important as well but are not given much attention; however, countries use ITNs in their MiP program. They can be used throughout pregnancy. Room for improvement would include paying attention to with special messaging to women of childbearing age (WOCBA) during nationwide universal campaigns.

7.0: Alternative drugs for IPTp and alternative screen and treat approaches (ISTp)

7.1 Lessons learnt from IPTp with mefloquine clinical trials in Benin, Gabon, Kenya, Mozambique and Tanzania: Raquel Gonzales, IS Global



Two randomised controlled trials were undertaken in five countries to: 1) evaluate the safety and efficacy of MQ as IPTp in HIV-negative women in the context of long lasting insecticide treated nets (LLITNs) use; 2) evaluate the safety and efficacy of MQ as IPTp in HIV-infected women taking daily CTXp and in the context of LLITNs.

The results of the trial in HIV-negative women showed that MQ had a better antimalarial prophylactic efficacy than SP and had a comparable safety profile on pregnancy outcomes. However, the tolerability of MQ (15mg/kg) was worse than that of IPTp-SP, even when splitting the dose over two days. MQ is therefore not a suitable alternative to SP for IPTp at the dose used in this study. The one year follow up of infants showed no differences between study arms.

The results of the trial in HIV-positive women showed that the addition of an effective antimalarial drug to daily CTXp and LLITN halved the risk of maternal parasitaemia at delivery and reduced the incidence of hospital admissions. However, tolerability of MQ (15mg/kg) was worse compared with that of CTXp alone, and the HIV viral load and the risk of mother-to-child transmission of HIV was increased in MQ recipients, indicating that MQ should not be used for IPTp in this group. Therefore there remains an urgent need to address the prevention of malaria in HIV-infected pregnant women.

Discussion

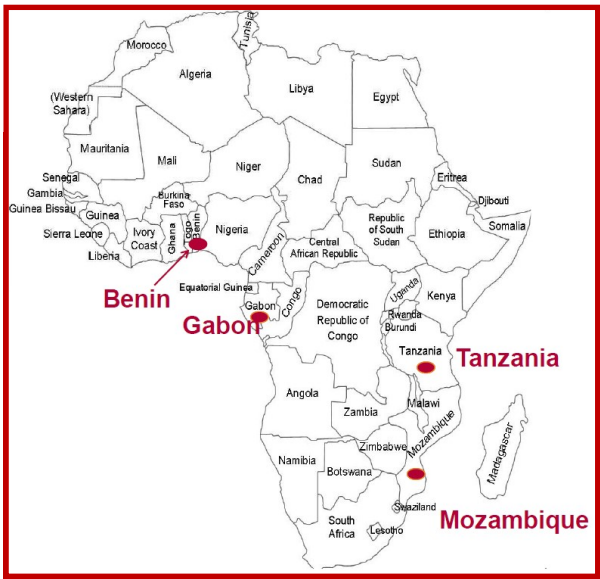
Was CTX given under supervision?

No, adherence was checked at every study clinic visit and was over 75%.

What is known about the Interaction between MQ and ARVs*, and how can it be explained?*

There are some reports indicating interactions between MQ and some protease inhibitors ARV drugs, but when study was designed a comprehensive literature search did not find any prior studies indicating such contraindication, and studies are needed to understand the mechanisms. One alternative explanation for MTCT was that MQ women were vomiting more and this may have affected the ARV drug levels and increased viral load, thus vertical transmission. However, MQ-related vomiting was mild and transient thus unlikely to have significantly affected absorption of drugs taken throughout pregnancy.

Tolerance of MQ appears to be dose related, as side effects reduced with subsequent courses. There was no difference in birth weight despite a strong effect of MQ on malaria, which may have been due to other factors affecting birth weight (e.g. everybody received ITNs). There were no differences in infant outcomes at 1 year between groups.



Credit: Raquel Gonzalas, IS Global

ISTp as an Alternative strategy to replace IPTp-SP?

ISTp not as good

1. ISTp not better than IPTp-SP
2. Limited RDT performance later in pregnancy and multigravidae
3. Resilient effect of SP properties need replicating

The good news

1. RDT performance good at ANC booking
2. Screening is well accepted
3. Hybrid options: add screening at ANC booking in very high resistance areas?

7.2 Intermittent screening and treatment (ISTp) compared to IPTp-SP in Kenya and Malawi - Mwayi Madanitsa, CoM Malawi

The concept of intermittent screening and treatment (ISTp) in pregnancy is to provide scheduled malaria screening using an RDT and treating positive women with a long acting ACT thereby clearing existing infections, providing additional post-treatment prophylaxis for up to six weeks, and ensuring that only women with detectable malaria infection receive treatment.

Results from a pooled result of two trials in 2902 women in Kenya and Malawi showed ISTp with dihydroartemisinin-piperaquine (DP) was not superior to 3 doses of IPTp-SP. Women receiving ISTp-DP had a 31% higher risk of any malaria infection at delivery, 14% higher risk of any malaria infection during pregnancy, 19% higher risk of placental malaria, and 52-gram lower birth weight in paucigravidae. Results suggested a higher risk of any adverse live birth outcome. However, DP was well tolerated.

There are two possible explanations for the ineffectiveness of ISTp. The first is lack of sensitivity of RDTs; sensitivity was high at 1st ANC visit, but substantially dropped in subsequent visits. The strategy therefore missed many low density infections and these women did not receive DP and did not benefit from its post treatment prophylaxis resulting in persistent sub-patent infections. The second is the continued effectiveness of IPTp-SP despite prevalent SP resistance. 3+ doses of SP mitigates the shortening of post treatment prophylaxis by SP resistance and may continue to supress low parasite densities, in addition SP may have a beneficial broad antimicrobial activity.

Discussion

How was tolerance assessed and did you look at the QC interval of DP?

Tolerance was measured by observing the 1st dose by DOT and observing 30min-1 hour for any vomiting (99% of women did not vomit). QC interval was not measured in the trial but studies measuring QC intervals in children given repeated DP doses did not show any problems.

Given RDT sensitivity at 1st ANC visit was very high, is it possible to combine RDT test at 1st ANC visit and subsequent IPTp?

Yes, this may be an option in areas with very high SP resistance but not currently recommended by WHO. Tanzania has already implemented this hybrid strategy throughout the country.

Were all DP doses observed?

In Malawi, every dose was observed and in Kenya only first dose was observed, with subsequent doses taken at home followed by random checks. However, no differences in outcomes were seen.

Given most infections were not detected by RDTs and are submicroscopic, would the strategy work with a more sensitive test e.g. LAMP?

Modelling has shown that increasing test sensitivity does not make a difference to the outcomes. Also LAMP is not practical, it takes a lot longer and is expensive.

7.3 Alternative drugs for IPTp in Kenya and Uganda- Meghna Desai, CDC

Credit: MiP, Meghna Desai

Results from previous trials of several alternative drugs to SP have been disappointing, including MQ, chloroquine-azithromycin, SP- azithromycin and SP-amodiaquine.

Two recent randomised controlled trials in areas of high SP resistance in Kenya and Uganda compared IPTp with dihydroartemisinin-piperaquine (DP) with IPTp-SP. DP offers an attractive alternative due to the long half-life of piperaquine, once-daily dosing, demonstrated efficacy and safety in pregnancy. The trial in Kenya was a 3 arm trial comparing IST-DP and IPTp-DP vs IPTp-SP and included 515 women in the IPTp-SP arm and 516 in IPTp-DP (Desai et al., 2015). In the trial in Uganda ~100 women in each of 3 arms comparing IPTp-SP, IPTp-DP 3 doses, IPTp-DP monthly (Kakuru et al., 2016).

Results showed that IPTp-DP was very effective in preventing several adverse malaria in pregnancy outcomes across all gravidae (see Table 2) and the monthly (3-4 courses) of DP was well tolerated. There was little to no impact of DP on foetal growth but neither trial was powered to detect impact on birth outcomes (e.g. birthweight). On the basis of these results, IPTp-DP is a promising potential replacement to SP in areas where the efficacy of IPTp with SP is threatened and WHO's MPAC recommended a larger confirmatory trial on safety and efficacy, together with studies on acceptability, feasibility and cost effectiveness.

Table 2. Relative risk of pregnancy outcomes in IPTp-DP vs IPTp-SP

Outcome	Kenya	Uganda
Malaria infection at delivery	68%*	59%*
Incidence of clinical malaria during pregnancy	84%*	67%*
Maternal anemia at delivery	22%*	13%
Fetal loss + early neonatal death	61%*	47%

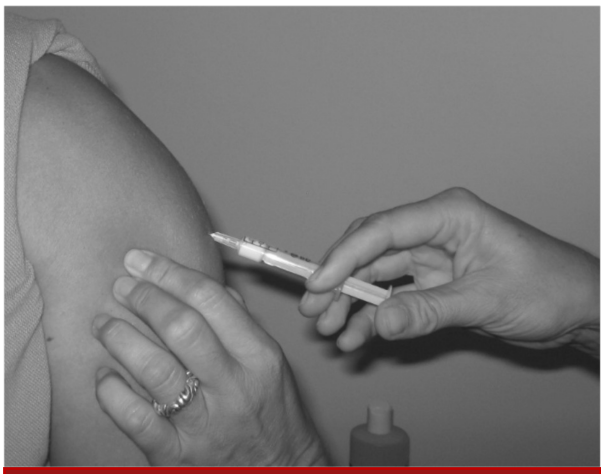
Discussion

When will next trials be done and what will they test?

A confirmatory trial of IPTp-DP vs IPTP-SP is planned in 2017, and additional funding is being sought to add an arm with azithromycin. Results will be presented to WHO ERG in 2019/2020.

Atovaquone-proguanil could also be evaluated?

It has not been considered for IPTp because of poor pharmacokinetics and the requirement of daily doses (not feasible).



Credit: Wikimedia.org

New Drugs to Replace SP for IPTp

What did not work?

1. CQ-AZ
2. AQ alone or AQ-SP
3. MQ

What may work?

1. DHA-PiP assessed by WHO to be promising based on 2 small trials, and now,… more research needed
2. Larger confirmatory trial with newborn outcomes planned for 2017/2018 with
   - Feasibility IPTp-DP
   - Cost effectiveness
   - Safety of monthly dosing (e.g. cardio)

7.4 User and provider acceptability of alternative drugs for IPTp and ISTp under trial conditions in Ghana, Malawi and Kenya - Jayne Webster, LSHTM

A model of the components of acceptability of ISTp or IPTp with an ACT in comparison to IPTp-SP was developed. The model was used in a theory based evaluation to test acceptability of each of these interventions in the context of trials across four studies in Ghana (2), Kenya and Malawi assessed the acceptability of: 1) Components of each strategy; and 2) Strategy as a whole.

There were some site differences but overall the findings from the four sites were similar. Overall ISTp with an ACT was acceptable. Among pregnant women, diagnosis with a malaria test was valued but there are issues to deal with around pain due to the blood test and in Ghana assurances were needed on whether malaria could be detected in small blood samples (lancet pricks). Health providers on the other hand lacked confidence in the sensitivity and specificity of RDTs, a critical problem to be addressed if the strategy is to be adopted. DP as a replacement for SP was acceptable based on perceived efficacy, but it will be important to deal with side effects and adherence to multi -day regimens in the routine health care context. In Kenya providers were concerned about the ability to maintain supplies of both RDTs for ISTp and DP for IPTp in the routine setting.

Regarding IPTp-SP, pregnant women had low acceptability due to side effects (both sites in Ghana, and Kenya) and perceptions of lack of efficacy. Similarly health providers questioned continued efficacy of SP in an environment of increasing resistance. Discrete choice experiments in Ghana found that midwives resistance to policy change became less so with increased SP resistance. Nevertheless there was a general belief among providers that 'prevention is better than cure' (Ghana and Kenya) and providers in Kenya showed a preference for both screening/treatment at first ANC visit followed by IPTp ('hybrid strategy'). The acceptability of any of these interventions is delicate, easily reduced and should be carefully monitored.

Discussion

How do we balance the differences between providers in any one country?

- There was and is heterogeneity, and qualitative data may help identify these differences. The behaviours of health workers cluster at the health facility level, and strategies on how to improve quality needs research.
- Side effects to IPTp with SP was a problem in all sites. Kenya NMCP did address this, but other countries need to do the same to increase coverage. Research is needed on the best ways to mitigate reduced feasibility of interventions due to side effects
- Lack of acceptability of RDTs is shared by health workers and policy makers.

Is there an effect of the MiP package on the acceptability of other ANC interventions in ANC?

- Data on this not yet analysed, though one study in Tanzania reported that ITNs increased ANC attendance.
- Kenya and Tanzania had introduced screening at first ANC followed by IPTp (hybrid strategy, part of ANC profile). This practice continues in Tanzania, but has been removed from the ANC profile in high endemic provinces in Kenya.
- Health workers need convincing of the continued efficacy of SP for IPTp, given it is no longer used for treatment. If national policy clearly state IPTp-SP will improve birth outcomes, then they will accept that. This was shown in Ghana data.

8. Potential challenges for MiP policy change and implementation of new policies – national programme perspectives

All country MOH's represented at the meeting had well developed systems for policy decision making for malaria, comprising national technical working groups (TWG) on malaria (with subcommittees on different aspects such as treatment, vector control etc.) to review evidence and provide recommendations to relevant policy committee or Senior Management in the Ministry of Health. For example, in Zambia MiP is the preserve of the Case Management TWG. These technical committees are interagency and multidisciplinary, and are generally chaired by leading national experts in the field. In Tanzania, new policy guidelines are discussed within NMCP's TWG on malaria and the Reproductive and Child Health Service's Safe Motherhood Initiative TWG before being discussed with high level MOH management. Representatives of each programme (NMCP and RH) are generally obligated to attend meetings of the other TWGs.

Potential challenges for changing MiP policies at national, district, facility and community levels identified by each national programme are captured in Table 3.

9. Research priorities

1. Hybrid strategy of single screening and treatment (SST) and IPTp - evaluate.
2. Antimalarial + ARV drug interactions.
3. Malaria prevention in HIV positive women.
4. Integrated control of maternal infections (e.g. IPTp-DP with AZ).
5. Operational research on strategies to improve access and use of ITNs in women of childbearing age (WOCBA) pre-pregnancy.
6. Testing interventions to improve the effectiveness of delivery (implementation) of IPTp-SP and new alternative drugs for IPTp such as IPTp-DP.
7. Strategies to mitigate reduced feasibility of interventions due to side effects of antimalarials.

Credit: www.wordclouds.com/

Table 3. Current MiP policies and potential challenges for changing MiP policy by country

	Kenya	Malawi	Tanzania	Mozambique	Zambia
Current MiP policies	IPTp 3+ (2014) in high malaria transmission areas only (14 counties) Rx policy per WHO DP use as second line Rx (2/3 trimesters) ITNs to all PW through ANC and and children <1 via child welfare clinics	IPTp 3+ (2014) Rx policy per WHO ITNs to all PW through ANC	IPTp 3+ (2014) Rx policy per WHO ITNs to all PW through ANC	IPTp 3+ (2014) Rx policy per WHO (NB not included in the National Malaria treatment guidelines, to be incorporated in 2017 revision) ITNs to all PW through ANC	3+ doses IPTp-SP Rx policy per WHO Free ITN @ 1st ANC and @ 8 month measles vaccination
National	Dissemination of policy documents among health care workers National policy, malaria strategy and national guidelines Memos on scaling up of MIP interventions (IPTp, low dose folic acid) Cost of training staff on interventions with current training packages i.e. FANC, case management etc Supportive supervision	Lengthy development process of the new policy (advocacy meetings, agreement, and approval processes) Financial implications of marketing of new policy, trainings, printing, and community dissemination to create demand and uptake. Effects of changing policy during implementation (hangovers). Length of time before new policy becomes apparent	Involvement of Policy makers planning for a new policy (must be convinced) Having compelling efficacy and acceptability data Funding for a new strategy (drugs, test reagents)	Coordination with others Departments or Programs Timeline to implement and consolidate the policy Funds to implement Reproduction of materials Adapt the tools to collect information	Desire for policy change to be driven by locally generated evidence. Stakeholder coordination and building consensus Funding the process of implementing Development of the new policy including dissemination Trainings/orientation Technical supervisory support Procurement and storage of commodities Complexity of policy environment
County/District & sub-county/ district level	Devolution of health services to county governments with low health budget allocation (>70% human resource) Majority of malaria control coordinators are non-clinical staff			Monitoring at provincial and district level Tools in place and DHIS2	Complex administrative structure from Central level – PMO/DMO/HF/Community Require improved communication. Adequacy of staffing to drive process of technical support and implementing the new policy Pharmacovigilance

Table 3. Current MiP policies and potential challenges for changing MiP policy by country (Continued)

	Kenya	Malawi	Tanzania	Mozambique	Zambia
Facility level	Stock-out of health commodities including SP, IPC apparatus, disinfectants Workload especially at dispensary and health centre level Data management – lack of tools to capture IPTp3 for entry into DHIS2		Confidence of health workers to implement the strategy How to change the ANC programming to capture the new change Issues of integration of services Workload to Health care providers	Long time to reach peripheral health facilities	
Community level	Community level Lack of allowances is a disincentives to promotion of MIP at community level (Few CHVs on stipend from global fund) ACSM approaches (messaging) not effective for behaviour change towards uptake of interventions Result - poor utilization of available effective interventions (LLINs, SP,)				Development of communication strategy to influence behaviour change – Driven by local conditions, literacy levels, gender etc. Access to healthcare remains inadequate

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Meeting Agenda

Monday 11th July 2016

AM		**CHAIR: Meghna Desai, CDC**
08.30 - 08.40	Opening/Welcome and introductions	Dr. Rebecca Kiptui, NMCP, Ministry of Health, Kenya
08.40 - 09.00	Malaria in Pregnancy Consortium Overview & Objectives of the meeting	Feiko ter Kuile & Jenny Hill, Liverpool School of Tropical Medicine (LSTM)
09.00 – 09.30	Burden of malaria in pregnancy in the East Africa region	Patrick Walker, Imperial College London
Session 1 – Use of ACTs for case management of malaria in all trimesters of pregnancy		
09:30 – 10:00	Safety, efficacy and dosing of ACTs for treatment of clinical malaria in 2nd and 3rd trimesters in Africa	Michael Nambozi, Tropical Diseases Research Centre (TDRC), Zambia
10.00 – 10.30	Safety of ACTs and quinine in early pregnancy in Africa	Feiko ter Kuile, LSTM
10.30 - 11.00	Knowledge and adherence to national guidelines for malaria case management in pregnancy among healthcare providers and drug outlets in western Kenya	Simon Kariuki, Kenya Medical Research Institute (KEMRI)
11.00 - 11.30	COFFEE	
Session 2 – IPTp with 2 vs 3 or more doses of SP, and the impact of SP resistance		
11.30 – 12.00	Effectiveness and cost effectiveness of 2 vs 3+ doses of IPTp with SP	Feiko ter Kuile, LSTM
12.00 - 12.30	Impact of SP resistance on the effectiveness of IPTp with SP in sub-Saharan Africa	Annemieke van Eijk, LSTM
12.30 – 13.00	Effectiveness of antenatal clinics to deliver IPTp-SP in context of other ANC services	Jenny Hill, LSTM
13.00 - 14.00	LUNCH	
PM		**CHAIR: Elaine Roman, jhpiego**
14.00 - 15.00	Experiences of implementing current MiP policies – national programme perspectives	MOH representatives - Kenya, Tanzania, Malawi, Mozambique & Zambia
15.00 – 15.30	Priority areas for research and support	Chair
15.30 – 16.00	TEA	
Session 3 – Implications for current policies		
16.00 – 17.00	SUMMARY & DISCUSSION: Implications of sessions 1&2 on policies and programmes, and priorities for research	Chair

Meeting Agenda

Tuesday 12th July 2016

AM — CHAIR: Feiko ter Kuile, LSTM

Session 4 – Alternative drugs for IPTp and alternative screen and treat approaches (ISTp)

08.30 – 9.00	Lessons learnt from IPTp with Mefloquine clinical trials in Benin, Gabon, Kenya, Mozambique and Tanzania	Raquel Gonzales, IS Global
09.00 – 09.30	Intermittent screening and treatment (ISTp) compared to IPTp-SP in Kenya and Malawi	Mwayi Madanitsa, College of Medicine, Malawi
09.30– 10.00	Alternative drugs for IPTp in Kenya and Uganda	Meghna Desai, CDC
10.00 – 10.30	User and provider acceptability of alternative drugs for IPTp and ISTp under trial conditions in Ghana, Malawi and Kenya	Jayne Webster, London School of Hygiene and Tropical Medicine (LSHTM)
10.30 - 11.00	COFFEE	

Session 5 – Implications for national policies and programmes — CHAIR: Jayne Webster, LSHTM

11.00 – 12.00	Potential challenges for MiP policy change and implementation of new policies – national programme perspectives	MOH representatives - Kenya, Tanzania, Malawi, Mozambique & Zambia
12.00 - 12.30	MEETING SUMMARY: Implications for programmes & support needed to take forward WHO recommendations Research priorities	**CHAIR: Feiko ter Kuile, LSTM**
12.30 – 13.30	CLOSURE OF MEETING & LUNCH	

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