Technical Expert Group meeting on intermittent preventive treatment in pregnancy (IPTp)

WHO HEADQUARTERS, GENEVA, 11–13 JULY 2007

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WHO Library Cataloguing-in-Publication Data

Technical expert group meeting on intermittent preventive treatment in pregnancy (IPTp), Geneva, 11-13 July 2007.

1.Malaria - prevention and control. 2.Malaria - drug therapy. 3.Pregnancy complications, Parasitic - prevention and control. 4.Pregnancy - immunology. 5.Pyrimethamine - therapeutic use. 6. Sulfadoxine - therapeutic use. I.World Health Organization.

ISBN 978 92 4 159664 0 (NLM classification: WC 765)

1. Background

Plasmodium falciparum malaria poses an enormous threat to global health. Most of the clinical cases (approximately 90%) occur in sub-Saharan Africa where young children and pregnant women bear most of the disease burden. Adverse effects of malaria infection during pregnancy include stillbirth, miscarriage, or maternal death among women with little or no immunity resident in areas where the transmission intensities of falciparum malaria are low and unstable, and maternal anaemia, placental parasitaemia and low birth weight (LBW) among women with considerable acquired immunity living in areas of high and stable falciparum malaria transmission (*1*). In the latter situations, primi- and secundi-gravidae women have the highest prevalence of maternal malaria infection (peripheral and placental parasitaemia) and their babies are at higher risk of LBW (*2,3,4*). The current WHO recommended strategies for controlling malaria in pregnancy include both curative (effective case management) and preventive (insecticide treated nets and preventive chemotherapy) measures.

Preventive chemotherapy entails the administration of an effective antimalarial medicine at specified time points to a population at risk regardless of whether or not they are infected with malaria. One of the early uses of preventive treatment was the prophylactic use of chloroquine by pregnant women living in malaria endemic areas – a strategy which has been abandoned in many situations because of the widespread resistance of *P. falciparum* to chloroquine and the low compliance with the weekly regimen of administration. It has been superseded, by intermittent preventive treatment with sulfadoxine-pyrimethamine for pregnant women (IPTp) living in areas of high malaria transmission where the risks of malaria in pregnancy are greatest.

IPTp is the administration of a complete curative dose of an antimalarial medicine at predefined intervals during pregnancy (from the 2nd trimester at least one month apart) regardless of whether or not the pregnant women are infected with malaria. IPTp with sulfadoxine-pyrimethamine (SP) delivered at routine ante-natal care visits is policy in several African countries, and is being scaled up through reproductive health programmes. Since the strategy was recommended in late 1998, there have been several significant changes to the context in which IPTp is being deployed:

1) There has been widespread and increasing resistance of the parasite, *P. falciparum,* to SP. In 2005, WHO convened a technical consultation that reviewed the efficacy of IPTp in the context of increasing SP resistance using the measure of therapeutic efficacy of SP assessed in children under 5 years of age with symptomatic malaria.
2) The consultation found that SP-IPTp remained reasonably effective despite SP efficacy for treatment of clinical malaria in children declining to 50% which was the lowest available efficacy data at the time.

3) However, because of these declining rates of the efficacy of SP and other antimalarial monotherapies, almost all the countries implementing SP-IPTp have abandoned SP as a treatment option for malaria and switched to ACT, so it is no longer feasible to continue to evaluate the efficacy of SP in children as a surrogate for IPTp efficacy.

4) There is a rapid and progressive scale up of other effective malaria intervention strategies in these countries. The added benefit of SP-IPTp under these conditions needs to be assessed.

2. Review process

The Global Malaria Programme/WHO held a technical consultation in Geneva on 11–13 July 2007 to appraise available evidence on IPTp against the background of the various limitations and changing environment described above, with the primary objective of:

1. Developing a framework, plan, and methodology to monitor and evaluate the efficacy and effectiveness of on going SP-IPTp:
   a) in relation to SP therapeutic efficacy;
   b) against a background of improved levels of coverage with vector control interventions and access to ACTs for the treatment of malaria.
2. Reviewing the evidence on efficacy and safety of SP-IPTp, with a view to updating WHO guidelines on IPTp.
3. Identifying gaps in knowledge and defining a research agenda for IPTp for guiding future policy direction.

The panel comprised of 15 independent Experts. The Consultation was attended by observers from UNICEF, the Bill and Melinda Gates foundation, and the IPTi Consortium (Appendix 1, List of participants).

3. Summary and recommendations

The Committee acknowledged that there have been two significant changes to the context in which SP-IPTp is deployed that may impact on its effectiveness and cost-effectiveness:

◊ *SP resistance*

SP-IPTp is threatened by the spread of SP-resistant parasites. Although there must be a relationship between the level of parasite resistance to SP and the benefit provided by SP-IPTp, data on in vivo therapeutic efficacy of SP in young children with symptomatic malaria cannot be extrapolated to protective efficacy of IPTp in pregnant women because of differences in therapeutic efficacy between young children, and pregnant women-related immunity and possibly pharmacokinetics (*5*). Available evidence suggest that SP-IPTp remains beneficial even after SP therapeutic efficacy, as measured in children with symptomatic malaria has fallen to 61% at 14 days (*6*). However, in vivo therapeutic efficacy[1] and protective efficacy[2] of SP (and antimalarials in general) used for IPTp need to be determined specifically in pregnant women.

◊ *Added benefit of IPTp in the presence of other interventions*

There has been a rapid scale up of other malaria control strategies, particularly insecticide nets (and indoor residual insecticide spraying) for vector control. Early evidence has shown that the impact of IPTp becomes less evident in pregnant woman in the presence of a high coverage with ITNs (*7*) (personal communication, C. Menendez). However, this information is still limited and needs to be confirmed by more studies. Improved access to effective antimalarial medicines (ACTs) is also being increasingly made available for malarial illness. Yet, data on the interaction between IPTp and these other malaria control strategies is currently limited.

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1. **Therapeutic efficacy:** is defined as elimination of parasitaemia without recrudescence of those parasites within the following 28 days of administration of IPTp.

2. **Protective efficacy:** is defined as the duration for which a pregnant women remains aparasiatemic following administration of IPTp irrespective of whether the pregnant woman is parasitaemic or not at the time of the IPTp

Recommendations of the panel

1. In sub-Saharan African countries with stable malaria transmission, SP-IPTp remains a strategy along with ITNs and access to effective treatment; that should be continued on the grounds that the available evidence to date suggests that the benefits outweigh the risks. This evidence shows that SP-IPTp, given 2 or 3 times during pregnancy to women residing in areas of stable malaria transmission reduces the risk of low birth weight in babies born to primi- and secundi-gravidae, and HIV positive multi-gravidae, thus increasing the probability of child survival; and that it reduces the incidence of malarial anaemia in primi- and secundi-gravidae women.

2. Monitoring of the effectiveness of IPTp at sentinel sites and on a continuous basis is essential, and for this to be made possible, the necessary methodology must be developed. This should include *i)* in vivo monitoring of therapeutic and protective efficacy of SP in asymptomatic pregnant women, *ii)* the correlation of this protective efficacy with molecular markers of SP resistance, and *iii)* the impact of IPTp on the clinically important parameters, such as birth weight, maternal anaemia and clinical malaria episodes, and on parasitological parameters such as peripheral and placental parasitaemia, wherever possible. The clinical parameters reflect the combined effectiveness of the package of interventions provided through the reproductive health programme (including ITNs, iron and folate supplementation) and not the effectiveness of IPT alone.

3. Carefully designed yet simple assessment and analysis methods, which adjust for timing of IPTp administration, gravidity, HIV status and use of ITNs, are required. Analysis should focus on the lower ranges in the birth weight (and haemoglobin) distribution curves and the proportion below key threshold levels, as these (rather than their averages) are the changes that would be expected to have the greatest public health impact. Large sample sizes will be needed, which could be most efficiently achieved by systematically reviewing individual patient data from many sentinel sites.

Five priorities for further research were identified among numerous research questions raised:

1. Studies on SP-IPTp to:

a) optimize its dose, dosage interval and timing;

b) determine the effect of the malaria transmission pattern, specifically in areas of highly seasonal malaria or unstable malaria transmission, on SP-IPTp effectiveness and cost-effectiveness; and

c) determine best preventive strategy in HIV positive pregnant women taking antiretrovirals and /or co-trimoxazole.

2. The correlation between therapeutic and protective efficacy of IPTp and the clinically important parameters, namely low birth weight, maternal anaemia, and clinical episodes of malaria and their relationship to peripheral and placental parasitaemia, needs to be validated and accurately calibrated. This calibration will inform the use of future in vivo efficacy studies to determine when SP should be replaced with a more effective antimalarial.

3. The potential role of the population prevalence of molecular markers associated with drug resistance, as a surrogate measure of therapeutic and or protective efficacy of IPTp, needs to be assessed. Of pressing concern is the efficacy of SP-IPTp against increasing prevalent quintiple pfdhr/dhps mutant *P. falciparum*.

4. A systematic approach and strategy for the urgent assessment of alternative antimalarials (or combinations) for future use in IPTp, preceded by the establishment of a "target product profile" to inform selection of key antimalarials to be studied, followed by dose and regimen finding studies, assessment of therapeutic efficacy as case management and then therapeutic and protective efficacy as IPTp, and lastly effectiveness as IPTp.

5. Studies to optimize the uptake of IPTp are needed, while acknowledging that some underlying problems and solutions may not be widely generalisable. Any approach to reducing the burden of malaria in pregnancy and its monitoring and evaluation must be well integrated with overall reproductive health initiatives, including HIV management.

Conclusions

The Technical Expert Group considered and concluded that,

1. Eventhough the IPTp policy was recommended and adopted in 1998 based on limited data, subsequent evidence has confirmed that IPTp is a useful intervention.

2. Given the possible detrimental effect that increasing SP resistance would have on the benefits and cost-effectiveness of SP-IPTp, there is uncertainty as to how long this intervention with SP will remain useful.

3. Currently available SP efficacy data are insufficient to make specific and meaningful changes to current WHO recommendations on SP-IPTp. SP efficacy as currently measured in children cannot be extrapolated directly to the efficacy of IPTp. Therefore, in the absence of new data, the recommendation be streamlined to state that all countries in stable malaria transmission situations should deploy and scale up the strategy of SP-IPTp, until relevant data on its effectiveness under current conditions becomes available for WHO to review this recommendation.

4. This demands,
- the urgent evaluation of the in vivo therapeutic and protective efficacy of SP in asymptomatic pregnant women, and its correlation with molecular markers of SP resistance, and the continuous monitoring of effectiveness of SP-IPTp.
- the urgent and comprehensive evaluation of alternative antimalarials for IPTp so as to inform the review of WHO recommendations and ensure an evidence-based IPTp strategy.

5. WHO provide methodological guidelines and protocols for these evaluations.

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