REPORT OF THE TECHNICAL EXPERT GROUP (TEG) MEETING ON INTERMITTENT PREVENTIVE THERAPY IN INFANCY (IPTi), GENEVA, 8–10 OCTOBER 2007

Intermittent preventive treatment in infancy (IPTi) is defined as the administration of a full course of an effective antimalarial treatment at specified time points to infants at risk of malaria, regardless of whether or not they are parasitaemic, with the objective of reducing the infant malaria burden.

The World Health Organisation Technical Expert Group (WHO TEG) reviewed the evidence available on the use of sulfadoxine-pyrimethamine (SP) as IPTi. This was based on data from six published or in-press randomised, placebo-controlled, clinical trials conducted in eastern, southern and western areas of Africa, with relatively high malaria endemicity (estimated Entomological Inoculation Rate ≥ 29), which enrolled over 4000 children in the SP intervention arms [1–7]. A formal meta-analysis of these studies was precluded by the heterogeneity of the study designs, including differences in the definitions of outcomes, the dose, timing and number of SP-IPTi doses administered, the duration of follow-up, and whether or not iron supplementation was administered concurrently. These study sites also differed in intensity and pattern of malaria transmission as well as coverage with ITNs.

In addition, considerable evidence was provided as unpublished reports from the IPTi consortium on the pooled analysis of data from these six studies on protective efficacy and safety of SP-IPTi, after standardization of definitions of outcomes and time at risk; these analyses included combined estimates of protective efficacy using random effect meta-analysis [8–10]. The IPTi consortium also provided the WHO TEG with unpublished information summarising the impact of SP resistance on IPTi efficacy [11], and information on gametocyte carriage, IPTp implementation and HIV status at IPTi study sites [12].

Protective efficacy

• There was evidence of a statistically significant reduction in the incidence of clinical episodes of malaria (whether defined as symptoms in the presence of parasitaemia or parasite density above the locally defined cut-off up to 12 months of age in five of the six studies; and a parasite density above a cut-off of 20 000 asexual parasites/µl in three of the six studies). The greatest protective efficacy against clinical episodes of malaria (58.8%) was seen in the first study of IPTi in Ifakara, in 1999, with subsequent studies showing a protective efficacy of 20.1–33.3% [8].

• A prophylactic effect appears to be the main driver of the benefit seen with SP-IPTi. Prophylactic efficacy in infants for the 35 days after SP-IPTi dosing was statistically significant in five of the six study sites, with a protective efficacy of 59.9% to 83.0% after the dose given at 3 or 4 months of age, and 42.5% to 96.2% after the dose given at 9 months of age; this protective efficacy was more variable after doses given at more than 12 months of age. There was no evidence of significant protective effect during the “inter-dose” period (starting from 35 days after the last dose until just before the next SP-IPTi dose), although there was a suggestive trend towards such an effect during the inter-dose period in two of the six sites. [8]. None of these studies were designed to assess the therapeutic efficacy of SP-IPTi in infants who were parasitaemic at the time of dosing.
• There was a statistically significant reduction in the risk of anaemia in two of the six studies, with a trend towards a lower anaemia risk in a third study [8]. In a fourth study site (Navrongo), there was a significant protective efficacy (35%) for hospitalisation with anaemia (but not overall risk of anaemia) up to age 15 months [3].

• The incidence of hospital admissions with malaria parasitaemia up to 12 months of age was significantly reduced in two of the six studies, while the incidence of all-cause hospitalisations up to 12 months of age was reduced in three of the six studies, and a trend suggesting a similar effect in one other study [8]. Active follow-up of infants in three studies might have reduced this beneficial effect, as they may have prevented hospitalisations in both the active and placebo groups by facilitating earlier treatment of malaria (and possibly other illness).

• There was no difference in the number of deaths from the time of the first dose until up to three months after the last dose of IPTi (63 deaths in each of the SP-IPTi and placebo arms) [9]; including the full duration of follow-up there were a total of 152 deaths in the placebo arms and 157 deaths in the SP arms [2–7]. The WHO TEG did not have access to the details on the majority of these deaths, precluding this committee assessing independently causality and attributing mortality to possible changes in the risk of malaria, anaemia, or adverse drug effects. These trials were underpowered to show a mortality difference resulting from a protective effect against malaria. As noted above, active follow up might have reduced any mortality benefit.

• The benefits up to 12 months of age in each study site is summarised in Table 1, in terms of protective efficacy and the number of infants that need to receive IPTi to prevent one adverse outcome, as well as the combined estimates of protective efficacy using random effect meta-analysis [8].
### Table 1: Protective efficacy (number needed to treat with IPTi to prevent one adverse outcome) and the combined estimates of protective efficacy using random effect meta-analysis from unpublished analyses (unpublished).

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Malaria Incidence</th>
<th>&gt; 20000/µl incidence</th>
<th>Anaemia Risk</th>
<th>Incidence of Hospitalisation with Malaria</th>
<th>Incidence of All Cause Hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifakara, UR Tanzaniaa</td>
<td>58.8% (3.2)</td>
<td>56.5% (8.3)</td>
<td>49.9% (23.3)</td>
<td>58.5% (9.1)</td>
<td>29.2% (5.9)</td>
</tr>
<tr>
<td>Navrongo, Ghanaa</td>
<td>29.3% (3.3)</td>
<td>33.5% (10.0)</td>
<td>10%* (66.7*)</td>
<td>50.2% (33.3)</td>
<td>17.7% (16.7*)</td>
</tr>
<tr>
<td>Manhica, Mozambique</td>
<td>20.1% (9.1)</td>
<td>28.0% (10.0)</td>
<td>9.9%* (83.3*)</td>
<td>22.5%* (50.0*)</td>
<td>24.6% (9.1)</td>
</tr>
<tr>
<td>Kumasi, Ghanab</td>
<td>20.9% (3.8)</td>
<td>18.5%* (25.0)</td>
<td>10.5%* (24.4*)</td>
<td>No difference*</td>
<td>17.7%* (33.3*)</td>
</tr>
<tr>
<td>Lambarene, Gabonb</td>
<td>22.0%* (33.3*)</td>
<td>26.2%* (50.0*)</td>
<td>25.7% (22.2)</td>
<td>NA</td>
<td>−35.8%* [NNH=50]*</td>
</tr>
<tr>
<td>Tamale, Ghanaob</td>
<td>33.3% (3.2)</td>
<td>29.5%* (33.3)</td>
<td>15.3%* (19.6*)</td>
<td>44.5%* (100*)</td>
<td>49.8% (14.3)</td>
</tr>
<tr>
<td><strong>Combined estimates</strong></td>
<td><strong>30%</strong></td>
<td><strong>NA</strong></td>
<td><strong>15.1%</strong></td>
<td><strong>37.6%</strong></td>
<td><strong>22.7%</strong></td>
</tr>
</tbody>
</table>

* Difference between SP-IPTi and placebo arm not statistically significant (p > 0.05)

a Concurrent administration of iron

b Sites with active follow-up of study infants (every 1–3 months)

NA: Confirmation of presence of parasitaemia not possible in a substantial proportion of hospital records.

NNH: Number needed to harm, reported when the risk of an adverse outcome is more common in the SP-IPTi arm than the placebo arm (i.e. when protective efficacy has a negative value).

### Sustained protective efficacy/rebound effect

There were variable outcomes seen in the 5 to 11-month period starting one month after the last dose of IPTi was administered (i.e. well beyond the duration of SP pharmacological action):

- In Ifakara, there was a protective efficacy of 36% against clinical malaria following the last dose of SP-IPTi in children aged 10 months to 2 years [2].
- In Navrongo, the incidence of clinical malaria with a parasite density ≥ 5000/µl between 16 and 24 months of age was 19.5% higher (statistically significant) in the SP-IPTi arm than the placebo arm [3].
- In Manhica, neither evidence of sustained protective efficacy nor a “rebound” effect was observed up to 24 months of age [4].
- In Kumasi, there was a significant increase (24%) in the number of anaemia episodes during the eight months starting five weeks after the last SP-IPTi dose (i.e. 16 to 24 months of age), although this effect was strongly dependent on the pre-defined haemoglobin cut-off level (< 7.5 g/dl) by which anaemia was defined [5].
- In Tamale, the risk and incidence of severe malaria and (virtually overlapping) severe anaemia (Hb < 5 g/dl) were approximately doubled in children who received SP-IPTi during the 8 months starting one month after the last SP-IPTi dose (i.e. 16 to 24 months of age) i.e. 25 episodes in 338 person years at
risk in infants given SP-IPTi compared with 13 episodes per 344 person years at risk in infants given placebo [6].

- In Lambarene the protective efficacy against anaemia was sustained until 18 months of age [7].

Given the variability in these results, the overall public health significance of any potential rebound effect is difficult to ascertain. A total measure of the incidence of clinical malaria with a parasite density \( \geq 5000/\mu l \), risk of anaemia, incidence of severe malaria and/or severe anaemia, and incidence of malaria-related and all cause hospital admissions over the full duration of follow-up is needed to inform the risk-benefit assessment of SP-IPTi. As noted above, the number of deaths during the complete duration of follow up was similar between the placebo group \( n = 152 \) and the SP-IPTi group \( n = 157 \).

**Safety**

- Up to three months after the actual last dose received, there were a total of 6 serious dermatological adverse events observed in the SP-IPTi arms and 14 in the placebo arms, of which the IPTi consortium investigators considered 2 in the SP-IPTi arm and 1 in the placebo arm as “most likely related to treatment” [9].

- The serious adverse dermatological events known to be associated with SP were considered to be of the greatest concern. In a study with active monthly follow-up of infants in Kumasi (Ghana), where the estimated HIV prevalence is < 3\%, two cases of Steven Johnson Syndrome (SJS) considered related to IPTi-SP were detected following the 3rd dose of SP given at 15 months of age, among 535 infants in the SP-IPTi arm (and 1 case of SJS in an HIV-positive infant recently treated with antituberculosis drugs and cotrimoxazole in the placebo arm that was not considered related to IPTi). Both infants in the SP-IPTi arm recovered fully; the infant in the placebo arm died at the age of 5 months from multi-organ failure. Another infant in the placebo group had a dermatological SAE considered related to IPTi. The infant developed bullous skin lesions three weeks after the second dose of placebo – IPTi. On the day that the infant received the second dose of placebo – IPTi, the infant had clinical malaria and received artesunate-amodiaquine. There was one case in the IPTi arm of exfoliative dermatitis in Tamale (Ghana), which was considered by the investigators to be moderately severe as it had reportedly resolved within four days of symptomatic treatment (with calamine lotion) [5,6]. No cases of SJS, or other serious adverse dermatological reactions, related to treatment were detected in the remaining studies [1–7], giving a total of two treatment-associated cases of SJS in 4071 infants administered at least one dose of SP-IPTi (and a total of approximately 12 000 SP-IPTi doses). No cases of SJS have been reported so far from the on-going Southern UR Tanzania effectiveness trial that has been implementing IPTi and the passive spontaneous surveillance of ADRs in southern UR Tanzania. Up until August 2007, approximately 60 000 doses of IPTi-SP have been given to 20 000 infants. Only one AE (skin rash) is reported to be probably due to IPTi-SP, which was a grade-1 event [9].

- As with the deaths, the WHO TEG did not have access to the details on the majority of the SAEs and deaths, precluding this committee assessing causality independently and excluding any additional cases of severe drug related adverse effects, e.g. a rapidly progressive SJS (e.g. with pneumonitis). As SJS is a rare event, accurate quantification of this risk is not possible, so the WHO TEG had no reason to believe that risk in infants is lower (or higher) than previously seen in other populations. In travellers SP prophylaxis was withdrawn after it was associated with an incidence of SJS of 1:7000 and 1:18000 fatalities [13]. This creates the need for careful safety monitoring wherever SP-IPTi is used.
• There appears to be an increased risk of adverse effects with the number of doses administered [9]. However, as infants were not randomized to different numbers of SP-IPTi doses, a bias is possible when making these comparisons.

• There was no evidence of an adverse effect of SP-IPTi on the infants’ serological response to EPI vaccines against DTP, Polio, Hepatitis B, Hib, yellow fever and measles [14].

• There was an overall 22.7% reduction in the incidence of all cause hospital admissions in infants up to 12 months of age who received SP [8].

• As noted above, the observed mortality rates in the SP and placebo groups were not different. One death in Kumasi was considered possibly due SP-IPTi. At the visit for the second dose of SP-IPTi the infant had microscopically confirmed malaria and was treated with artesunate plus amodiaquine, iron and folic acid. The infant became very weak two weeks later and was taken to hospital where severe anaemia (4 g/dl) was diagnosed for which the infant was admitted and given a blood transfusion and penicillin, and discharged after 6 days in an apparently satisfactory condition. The infant died the next night at home [9].

• In two infants in Lambarene, Gabon, haemoglobin levels dropped markedly after SP administration; these infants both had sickle cell anaemia [7].

SP-IPTi was delivered mainly through the Expanded Programme of Immunisation in these randomised controlled trials. This method of delivery had clear advantages in terms of:

- using an established existing infrastructure with reasonably high coverage rates in most countries [15];
- allowing highly cost-effective delivery of IPTi [10];
- sound evidence that IPTi with SP has no adverse impact on serological responses to DTP, Polio, Hepatitis B, Hib, yellow fever and measles vaccines [14];
- it was reported that IPTi did not compromise EPI operations and, after adequate communication, was generally well accepted by the healthcare providers and mothers/caregivers [16].

The protective efficacy of SP-IPTi was confirmed in areas in West Africa where malaria transmission is highly seasonal [3]. However, the protective efficacy was reduced for SP-IPTi doses administered during the dry season [3]. A secondary analysis extrapolating these results across areas in West Africa where malaria is highly seasonal, and EPI coverage is low in some countries, only 10% of malaria episodes in infants would be averted if SP-IPTi was delivered using this strategy with the current coverage of EPI [17]. This suggests that alternative, feasible delivery strategies may need to be evaluated in areas with highly seasonal malaria transmission patterns or where EPI coverage is relatively low.

SP has advantageous features that make it practical for IPTi, being inexpensive, familiar, and administered as a single-dose. However, there is a concern that the critical level of SP-resistance above which SP-IPTi is significantly reduced may already have been reached in some parts of Africa, although this situation may change if the deployment of ACTs as first-line treatment results in a substantial reduction in the use of SP [18,19]. The efficacy of SP for treatment of uncomplicated malaria is generally falling as a result of SP resistance. However, there is insufficient evidence to describe changes over time in the protective efficacy of SP as IPTi. Although protective efficacy has been seen in areas where 4 dhfr/dhps mutations are prevalent [5], the duration of protective efficacy, if any, against parasites with the dhfr/dhps quintuple mutation (or the dhfr164 mutation) is uncertain at this time. Available models have concluded that SP-IPT is unlikely to contribute substantially to an increase in SP resistance [20,21].
It is uncertain whether SP-IPTi is optimally dosed. There are no studies of the therapeutic efficacy or pharmacokinetics of SP in parasitaemic children aged more than 12 months [19]. This response to treatment is of particular importance to those infants who carry asymptomatic parasitaemia at the time of IPTi administration.

The WHO TEG considered it premature to comment on the relative advantage of different antimalarials for IPTi as there are only two IPT trials published to date that have evaluated antimalarials other than SP (amodiaquine for three days as IPTi and single dose artesunate plus SP given to those under 5 years of age monthly during the malaria season) [22,23].

The potential role of IPTi needs to be considered in the context of generally improving malaria control. While these SP-IPTi studies were conducted in areas where coverage with other malaria control interventions varied markedly, there were too few trials to do a stratified meta-regression for defining any potential interactions between SP-IPTi and other malaria control interventions. In areas achieving high coverage with other effective malaria control strategies a decrease in the burden of malaria in infants would increase the number of infants that need to be treated with IPTi (NNT) to prevent one case of either clinical malaria, anaemia or hospitalization, even if the protective efficacy remains constant. Since the risk associated with IPTi is constant, any decrease in malaria burden in infancy would shift the risk-benefit profile of IPTi. Thus, careful ongoing monitoring of these benefits and risks is essential wherever IPTi is used, especially in the real world context of complex programmes.
SUMMARY RECOMMENDATION

Prevention of malaria in infancy (and childhood) through intermittent preventive treatment (IPT) is a potentially valuable and cost-effective intervention. The EPI programme provides an effective existing platform for delivery of IPT to infants (IPTi). The Committee reviewed all available published information on IPTi, focusing on SP (SP-IPTi). It was concluded that in the trials conducted SP-IPTi provided protection from malaria for approximately 35 days after each dose. The preventive effects on anaemia and hospital admission varied in magnitude between studies. Extended protection (starting 35 days after the last dose of SP-IPTi until the end of the follow-up) was observed in two studies, and in three studies there was evidence of a rebound in malaria or anaemia. There remain significant safety concerns, particularly regarding the risk of severe skin reactions. Taking into account these safety concerns when IPTi would be administered to otherwise healthy children, the duration of protection against malaria, the uncertainty over the magnitude of the protective effect against anaemia and severe malaria, the uncertainty concerning the efficacy against highly SP resistant parasites and the optimal dose and timing of administration, the committee cannot recommend general deployment of SP-IPTi.

IPTi remains a promising intervention. In order for the full potential of IPT to be realized, the development of other antimalarials that are suitable for preventive treatment both in infants and other risk groups, with adequately characterized pharmacokinetic – pharmacodynamic profiles (and ideally formulations suitable for infants) is a priority.

Since the established benefits of SP-IPTi might override the safety concerns in areas where there is a very large burden of malaria in infants, carefully monitored assessments of SP-IPTi may be considered in parallel with the development of alternative medicines to SP.

We anticipate that further information will be available in the near future on SP-IPTi and IPTi using alternative antimalarials, so this recommendation will be reviewed in 2008.
References


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