Technical Expert Group meeting on Preventive chemotherapy

WHO HEADQUARTERS, GENEVA, 23–24 APRIL 2009

Report of the technical consultation on Intermittent Preventive Treatment in Infants (IPTi)
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1. Background

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

In October 2006 and October 2007, WHO convened meetings of the Technical Expert Group (TEG) on Intermittent Preventive Treatment in Infants to review the available evidence on the safety, efficacy and other relevant aspects of IPTi with sulfadoxine-pyrimethamine (SP-IPTi) delivered through the Expanded Programme for Immunization (EPI). At the time, six randomised, placebo-controlled clinical trials with SP-IPTi were being, or had been, conducted in areas of Africa, south of the Sahara with relatively high malaria endemicity (see Table). TEG 2006 concluded that SP-IPTi held promise as a potential malaria control intervention, noting that three of the studies were yet ongoing or unpublished.\(^1\) At the TEG 2007, at which time the six studies had been completed, the committee concluded that, though IPTi remains a potential intervention for malaria control, the use of SP-IPTi cannot be recommended as a strategy for general deployment based on the assessment of the risks and benefits, and advised a future review of further evidence when available.\(^2\)

In the current expert review of the evidence on SP-IPTi, TEG 2009 reviewed the evidence available on SP-IPTi including additional data that were generated since the TEG-2007 meeting, with a view to making a definitive policy recommendation on this intervention for malaria control.

The new information reviewed was the following:

1. An in-depth analysis conducted by the IPTi Consortium\(^3\), of the severe skin reactions associated with SP-IPTi reported previously.\(^4,5\)

2. Two additional randomized placebo controlled trials on the safety and efficacy of IPTi, which have been submitted for publication.\(^6,7\)

3. The experience of implementation studies conducted by UNICEF in selected districts of six countries in Africa, south of the Sahara\(^8\) and another by the IPTi Consortium\(^9-11\) with respect to the feasibility of implementation, and its safety, monitored through active and passive observations on adverse reactions.
Table – Summary of site-specific information on the six published SP-IPTi trials considered for the pooled analysis*

<table>
<thead>
<tr>
<th>Study site</th>
<th>Study period</th>
<th>Transmission pattern</th>
<th>Iron supplementation</th>
<th># Infants studied SP/placebo**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifakara, UT Tanzaniai</td>
<td>1999–2000</td>
<td>Perennial</td>
<td>Yes</td>
<td>350/351</td>
</tr>
<tr>
<td>Navrongo, Ghanaii</td>
<td>2000–2004</td>
<td>Seasonal</td>
<td>Yes</td>
<td>1183/1203</td>
</tr>
<tr>
<td>Manhica, Mozambiqueiii</td>
<td>2002–2004</td>
<td>Perennial/seasonal peaks</td>
<td>None</td>
<td>748/755</td>
</tr>
<tr>
<td>Kumasi, Ghanaiv</td>
<td>2003–2005</td>
<td>Perennial</td>
<td>None</td>
<td>535/535</td>
</tr>
<tr>
<td>Tamale, Ghana</td>
<td>2003–2005</td>
<td>Perennial/seasonal peaks</td>
<td>None</td>
<td>600/600</td>
</tr>
<tr>
<td>Lambarene, Gabonvi</td>
<td>2004–2005</td>
<td>Perennial/seasonal peaks</td>
<td>None</td>
<td>504/507</td>
</tr>
</tbody>
</table>


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* The pooled analysis excludes the most recent study which was accepted for publication after the meeting, although its data were made available to the meeting.

** Who received at least the first dose of SP-IPTi
2. Conclusions

_The TEG 2009 concluded that:_

1. The previous safety concerns about SP-IPTi, specifically with respect to the reported severe skin reactions were mitigated by the evidence from the larger observational studies and retrospective in-depth examination by the Consortium of the severe skin reactions reported in previous studies.

2. The benefits of SP-IPTi in areas where SP remains effective against _Plasmodium falciparum_ malaria parasites, were upheld as providing a 30% (95% CI: 19.8%–39.4%) overall protection against clinical malaria episodes and a variable reduction (overall 21.3%) (95% CI: 8.3%–32.5%) in anaemia (< 8 g/dl) in a pooled analysis of data from 6 published studies (see Table). The reduction in all cause hospital admissions by 23% (95% CI: 10.0%–34.0%), was noted as a potential benefit. The admissions, however, were not all due to severe malaria, and this therefore cannot be equated to a similar reduction in the incidence of severe malaria. The pooled analysis excludes the most recent study which was accepted for publication after the meeting, although its data were made available to the meeting. The protective efficacy of SP-IPTi against clinical malaria episodes in this study was – 6.7% (95% CI: – 45.9–22.0).

3. Where effective, SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose. There is no evidence for an individual cumulative protective effect beyond this period until the next dose. The mechanism of action appears to be predominantly chemoprophylaxis related to the half-life of the medicine and the susceptibility of the prevalent malaria parasites.

4. The protective efficacy of SP-IPTi is dependent upon the efficacy of SP, to which there is increasing parasite resistance in Africa and worldwide, but the threshold of parasite resistance to SP at which IPTi ceases to be effective is still not known. SP-IPTi was reported to provide benefit when the _in vivo_ therapeutic failure rate of SP at day 14 was 31% (measured
in children with symptomatic malaria\textsuperscript{13} and the population prevalence of \textit{Pfdhps + Pfdhfr} quintuple mutants (molecular markers of parasite resistance to SP) was 50\%\textsuperscript{14} but there was no benefit when the \textit{in vivo} SP therapeutic failure rate was 82\% at day 28, and the prevalence of the quintuple mutants was 90\%.\textsuperscript{6}

5. Uncertainties remain on the potential impact, or lack thereof, of SP-IPTi on the incidence of severe malaria or malaria mortality.

6. Uncertainties also remain on the impact of SP-IPTi at low levels of malaria transmission (either natural or resulting from effective control interventions).

7. A rebound effect by way of greater susceptibility to malaria following the termination of SP-IPTi was not evident in the pooled analysis. However, this warrants further observation in view of the fact that three of the studies reported an increase in either malaria infections associated high density parasitaemia\textsuperscript{15}; anaemia (< 7.5 g/dl)\textsuperscript{4}; or severe malaria and severe malarial anaemia (Hb < 5g/dl)\textsuperscript{5} during the post-intervention period in children who had received SP compared to the placebo group.

8. SP-IPTi was deemed a safe addition to EPI because there was no evidence of an adverse effect of SP-IPTi on infants’ serological response to EPI vaccines against DTP, Polio, Hepatitis B, Hib, yellow fever and measles.\textsuperscript{16} Limited implementation studies suggest that SP-IPTi incurs only marginally additional costs to EPI, and that it has a favorable effect on EPI coverage.

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. Recommendations

Considering that the benefits of SP-IPTi to infants are in providing a protection against clinical malaria from – 6.7% to 59.4%, and in view of increasing parasite resistance to SP, the TEG 2009 recommended that,

1. SP-IPTi delivered through EPI be considered for implementation as an additional malaria control intervention in countries in Africa, south of the Sahara under the following specific conditions,
   a. In areas with moderate to high transmission (Annual Entomological Inoculation Rates [EIR] beyond 10).
   b. When parasite resistance to SP in the area is not high. Precise cut-offs cannot be defined on the basis of available data. More information is needed on the relationship between the prevalence of molecular markers (mutations in Pfdhfr and Pfdhps) and the duration of malaria protection provided by SP-IPTi.
   c. If its implementation does not detract from efforts to scale-up access to artemisinin-based combination therapies (ACT) for early treatment, and to insecticide-treated bednets (ITN) and indoor residual spraying (IRS) as preventive measures, all of which have significantly greater efficacy in malaria control.

2. Where SP-IPTi is used,
   a. Continuous surveillance of parasite resistance to SP must accompany the implementation of SP-IPTi as a surrogate measure of its efficacy. Methodologies for monitoring the efficacy of SP-IPTi should be developed urgently to guide countries on when the intervention should no longer be deployed.
b. SP-IPTi should not be given to infants receiving a sulfa medication for treatment or prophylaxis against an infection, including co-trimoxazole (trimethoprim-sulfamethoxazole) which is widely used as a prophylactic against opportunistic infections in HIV-infected infants.

c. Surveillance for drug safety must be strengthened with effective pharmaco-vigilance systems to monitor serious adverse reactions to SP which may be exacerbated because SP-IPTi is likely to be implemented against a background of co-trimoxazole use for the treatment of acute respiratory infections in infants and for prevention of opportunistic infections in HIV-infected infants.
4. Other Considerations

The Technical Expert Group,

- Considered the seasonality of malaria transmission, and whether areas of seasonal malaria should be excluded for the implementation of SP-IPTi given that the optimal protective effect lasts for 35 days post treatment, but concluded that the evidence base did not support such an inference.

- Recognized the need to develop tools to monitor the effectiveness of SP-IPTi and validate a measure of parasite resistance to SP which can define a threshold at which SP-IPTi should not be implemented, and recommended that WHO GMP be financially supported to undertake this development as a priority.

- Urged the development of new alternative medicines for IPTi as replacements for SP, with properties conferring an optimum therapeutic profile for IPTi (single dose, excellent tolerability and long half-life) and reliably provide prophylaxis for a period of at least 4 weeks; new medicines for IPTi should preferably be different from those deployed for chemotherapeutic purposes, and should also be suitably formulated for the paediatric age group.

- Warned that the efficacy of SP is decreasing in many areas. Though desirable, the development of a paediatric formulation for SP might take longer than its useful residual therapeutic life for IPTi and hence the simpler option of producing scored SP tablets should be considered.

- Requested that the following questions be addressed:
  - What are the optimum pharmacokinetic and pharmacodynamic properties required for medicines used for IPTi?
  - What are the optimum ages for administering IPTi taking into account operational realities and burden of disease in relation to transmission intensity?

- Recommended that the assessment of impact on mortality should be considered among the endpoints for efficacy of the next candidate medicine for IPTi.
5. References


11. Maokola W et al. The safety of sulphadoxine-pyrimethamine for intermittent preventive treatment of malaria in infants: evidence from large-scale operational research in southern Tanzania *(unpublished)*.


16. WHO (2006). Interim report on IPTi with SP. WHO Advisory Committee on Serological responses to EPI vaccines in Infants receiving IPTi.
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