



WHO Policy recommendation on Intermittent Preventive Treatment during infancy with sulphadoxine-pyrimethamine (SP-IPTi) for *Plasmodium falciparum* malaria control in Africa

March 2010

Background

Malaria remains a leading cause of ill health, causing an estimated 243 million cases of clinical malaria and 863 thousand deaths¹. More than 85% of malaria cases and 90% of malaria deaths occur in Africa, south of Sahara. In Africa, the vast majority of cases and deaths occur in young children.

Key interventions currently recommended by WHO for the control of malaria are the use of insecticidal treated nets (ITNs) or indoor residual spraying (IRS) for vector control, and prompt access to diagnosis and treatment of clinical malaria. An additional intervention which is recommended for pregnant women – a high risk group in areas of high malaria transmission – is Intermittent Preventive Treatment in pregnancy (IPTp), which involves the administration of at least 2 doses of sulphadoxine-pyrimethamine (SP) during the second and third trimesters of pregnancy.

WHO is now recommending a new intervention against *Plasmodium falciparum* malaria: Intermittent Preventive Treatment for infants (IPTi).

Intermittent Preventive Treatment in infancy with SP (SP-IPTi) is the administration of a full therapeutic course of SP delivered through the Expanded Program on Immunization (EPI) at defined intervals corresponding to routine vaccination schedules – usually at 10 weeks, 14 weeks, and ~9 months of age – to infants at risk of malaria.

¹ World Malaria Report 2009. Geneva, World Health Organization, 2009 (ISBN 978 92 4 156390 1)
http://whqlibdoc.who.int/publications/2009/9789241563901_eng.pdf

Recommendation pour le SP-IPTi²

WHO recommends

The co-administration of SP-IPTi with DTP2, DTP3 and measles immunization to infants, through routine EPI in countries in sub-Saharan Africa, in areas:

- with moderate-to-high malaria transmission (Annual Entomological Inoculation Rates ≥ 10), and
- where parasite resistance to SP is not high – defined as a prevalence of the *pfdhps* 540 mutation of $\leq 50\%$.

Contra-indications

SP-IPTi should not be given to infants receiving a sulfa-based medication for treatment or prophylaxis, including co-trimoxazole (trimethoprim-sulfamethoxazole) which is widely used as prophylaxis against opportunistic infections in HIV-infected infants.

Considerations and caveats for implementation

- In situations where a national-scale implementation may not be feasible due to varying levels of the *pfdhps* 540 mutation, IPTi may be implemented at a provincial or district scale, targeting areas with *pfdhps* 540 mutation prevalence $\leq 50\%$.
- Programmes implementing the SP-IPTi strategy should regularly monitor and evaluate the impact on immunization services and performance.
- Pharmacovigilance systems to monitor potentially serious adverse reactions to SP should be strengthened.
- Surveillance of parasite resistance to SP should accompany the implementation of SP-IPTi as a surrogate measure of its efficacy.

² The recommendation was made at the fourth consultative meetings of the Technical Expert Group (TEG) of Preventive Chemotherapy, GMP, WHO, April 2009 (<http://malaria.who.int/docs/IPTi/TEGConsultIPTiApr2009Report.pdf>). The recommendation and programmatic experiences from 7 Africa countries was subsequently reviewed and endorsed by WHO's Strategic Advisory Group of Experts on Immunization (SAGE), in October, 2009 (<http://www.who.int/immunization/sage/previous/en/index.html>).

Expected benefits

The recommendation is based on results from 7 studies (of which 6 were included in a pooled analysis) on SP-IPTi conducted in areas of moderate to high transmission of malaria:

- SP-IPTi delivered through EPI provides an overall protection in the first year of life against clinical malaria [30.3% (95% CI: 19.8%–39.4%)], anemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital admissions [22.9% (95% CI: 10.0%–34.0%)].
- SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Safety considerations

- Skin reactions were reported in 2 of the 7 studies which, on retrospective in-depth analysis, were not classified as severe adverse reactions. Nor were they reported from larger observational studies.
- There was no evidence of adverse effects of SP-IPTi on infants' serological response to EPI vaccines (DTP, Polio, Hepatitis B, Hib, yellow fever and measles).
- A rebound effect by way of greater susceptibility to malaria following the termination of SP-IPTi, though reported for selected outcomes in some studies, was not found in the pooled analysis.

Mechanism of action

The mechanism of action of SP-IPTi appears to be predominantly one of chemoprophylaxis. Protective efficacy of SP-IPTi is related to the half-life of the medicine and the susceptibility of the malaria parasite to SP. Therefore, parasite resistance to SP in the area should serve as a guide to adoption of a policy on SP-IPTi. The recommendation of a threshold of a parasite genetic marker of SP-resistance (50% prevalence of the *pfdhps* 540) above which SP-IPTi is not recommended for use is based on the following:

- The presence of mutations at codons 437 and 540 of *pfdhps* together with the triple mutation of *pfdhfr* (quintuple mutation) is a significant predictor of SP treatment failure. The *pfdhps* 540 mutant is a useful epidemiological marker of the quintuple mutation in Africa.
- In areas with up to 50% prevalence of the *pfdhps* 540 parasite mutant in infants and children, clinical trials showed a 30% protective efficacy of SP-IPTi over one year against clinical malaria.
- One trial conducted in an area where the prevalence of the *pfdhps* 540 parasite mutant was approximately 90% found no demonstrable protective efficacy for SP-IPTi.