Defining and validating a measure of parasite resistance to sulfadoxine-pyrimethamine (SP) that would be indicative of the protective efficacy of SP for intermittent preventive treatment in infancy (SP-IPTi)

REPORT OF THE TECHNICAL CONSULTATION
GENEVA, 10–11 SEPTEMBER, 2009

BACKGROUND

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

In April 2009 the WHO Technical Expert Group (TEG) on IPTi reviewed the evidence on the safety, efficacy and other relevant aspects of IPTi with sulfadoxine-pyrimethamine (SP-IPTi) delivered through the Expanded Programme for Immunization (EPI). IPTi TEG recommended that SP-IPTi delivered through EPI, could be deployed as an additional malaria control intervention in African countries south of the Sahara, where transmission intensities are moderate to high and parasite resistance to SP is not high. (WHO 2009)

The protective efficacy of SP-IPTi is dependent upon the antimalarial efficacy of SP, to which there has been increasing parasite resistance in most parts of Africa. Immunity is a major contributor to therapeutic response in malaria endemic regions, and there is evidence of decreased efficacy in young children. Furthermore, the therapeutic efficacy of SP as measured in children with symptomatic malaria may not be equivalent to the protective efficacy of SP when used in IPTi. The precise threshold of resistance above which SP-IPTi ceases to provide a significant protection is yet to be defined. Prior to a decision to deploy SP-IPTi, countries would need a proxy measure of the protective efficacy of SP in IPTi as an indicator of its potential efficacy to decide when and where SP-IPTi should be deployed.

The WHO Global Malaria Programme (GMP) convened this Expert Technical Consultation to: 1) identify the most appropriate marker(s) of SP resistance that would be indicative of the protective efficacy of SP in IPTi, 2) define a threshold level of the markers prevalence to guide deployment of SP-IPTi, and 3) the methodology for surveillance of the marker(s).
CONCLUSIONS

Genetic marker of parasite resistance to SP which is most indicative of protective efficacy of SP in IPTi

- There are several combinations of mutant forms of both PfDHFR and PfDHPS which confer varying degrees of resistance to pyrimethamine and sulphadoxine, respectively. (Cowman, Morry et al. 1988; Peterson, Walliker et al. 1988; Brooks, Wang et al. 1994).

- The emergence of mutants is cumulative, and has built up from single and double to the PfDHFR triple mutation (which is now widespread in Asia, South America, and Africa), followed by PfDHPS 437 (prevalent throughout Africa) and 540 (found in East Africa in the form of 437+540 double PfDHPS mutation. (Pearce, Pota et al. 2009). Once the quintuple (PfDHFR triple + PfDHPS double) mutants are established, the rarer forms of PfDHFR and PfDHPS mutations (PfDHFR 164, PfDHPS 581, 613) appear. (Plowe 2001)

- 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. (Omar, Adagu et al. 2001; Kublin, Dzinjalamala et al. 2002; Staedke, Sendagire et al. 2004). The PfDHPS 540 mutant is a useful epidemiological marker of the quintuple mutation in Africa. (Kublin, Dzinjalamala et al. 2002).

Measure of the resistant marker

- Mutations are reported either as a frequency - defined as the ratio of quintuple/non-quintuple in the parasite population, or as a prevalence defined as the proportion of infected individuals with the quintuple mutant parasite. As prevalence counts the mutant if present (whether majority or not) in an individual, it is more appropriate as a measure from a public health perspective, as well as being easier to understand and to calculate.

Threshold level of the marker to guide decision making on the deployment of SP-IPTi

- SP-IPTi protected infants from malaria for approximately one month in areas where parasites containing the triple PfDHFR mutation and the PfDHPS 437 were prevalent.

- Only two of the SP-IPTi studies reported to date (Macete, Aide et al. 2006; Gosling, Gesase et al. 2009) were conducted in areas where the quintuple mutant parasites (with PfDHPS 540 mutation) were prevalent. The first study conducted in Manhica provided an overall protective efficacy in the first year of life of SP-IPTi of 21% where the background prevalence of PfDHPS 540 mutation was 55%. (Enosse, Magnussen et al. 2008; Mayor, Serra-Casas et al. 2008). The other study which was conducted in north-eastern Tanzania showed no measurable protection against malaria by SP-IPTi, in an area where the prevalence of PfDHPS 540 mutation was 94%. (Gosling, Gesase et al. 2009).

- There were no data from areas where the PfDHFR 164 mutant was prevalent, but only one report identifying the PfDHFR 164 mutation in Muheza district (Hastings, Bates et al. 2002) adjacent to Korogwe district where the study of IPTi did not demonstrate measurable efficacy (Gosling, Gesase et al. 2009). It was considered very unlikely that SP-IPTi would retain useful protective efficacy against parasites with this mutation.

The committee concluded that below a 21% protective efficacy as reported in the Manhica study, the public health contribution of IPTi as a malaria control tool is unknown, especially given that other effective malaria interventions are currently being deployed.
Surveillance programme for monitoring the prevalence of the marker

- Patterns of drug resistance can vary geographically and temporally. Up to date information on at least the prevalence of \textit{pfdhps} 540 mutation is required for a decision on implementing SP-IPTi. Monitoring other mutations in addition is encouraged where possible.

- From the few studies performed on the relationship between age and patterns of \textit{Pfdhfr} and \textit{Pfdhps} genotypes there is a clear trend towards a higher prevalence of mutant types in the younger age groups. (Mockenhaupt, May et al. 1999; Kublin, Dzinjalamala et al. 2002; Macete, Aide et al. 2006)

- Parasite samples for monitoring the marker(s) can be obtained through community cross sectional studies, on day 0 of in vivo antimalarial efficacy studies in 6–59 months old children (i.e. before treatment with any drug) or from subjects receiving IPTi at EPI clinics.

Monitoring the protective efficacy of SP-IPTi

- Under programmatic condition, it will not be possible assess the protective efficacy of SP-IPTi using a comparator group as was done during the IPTi clinical studies. However, methods that could be explored include the following:
  - Monitor protective efficacy using children receiving SP-IPTi as their own controls. This would require monitoring breakthrough episodes of malaria during a period after IPTi dosing in which few episodes would be expected if IPTi is efficacious. The “protective window” needs to be defined by re-analysis of existing data from placebo-controlled trials but is likely to be around 4–5 weeks. The malaria incidence in this period is expected to increase (i.e. as the protective window shortens) as resistance to SP worsens and effectiveness of SP-IPTi decreases.
  - Alternatively, case-control studies could be conducted measuring the odds of having received SP-IPTi within the “protective window” in infants who present to the clinic with confirmed malaria and comparing these to the incidence outside the protective window of matched healthy controls. With declining SP-IPTi efficacy, the odds of having received SP-IPTi should increase in those presenting with malaria.

RECOMMENDATIONS

- The \textit{Pfdhps} 540 mutant is a useful epidemiological marker of the quintuple mutation in Africa, and should thus be used as a marker of parasite resistance to SP which is indicative of protective efficacy of SP in IPTI

- Clinical trials in several sub-Saharan African countries found SP-IPTi protective efficacy over one year against clinical malaria of 30% (95% CI:19.8%–39.4%), in settings with a prevalence of \textit{P. falciparum} parasites in infants and children bearing the \textit{Pfdhps} 540 mutation (a surrogate marker of the quintuple mutant) of below 55%. However, one trial where the prevalence was ~ 90% found no demonstrable protective efficacy for SP-IPTI. Based on this limited evidence, the committee recommends not implementing SP-IPTi in settings with prevalence of \textit{Pfdhps} 540 exceeding 50%.

- Up to date estimates of \textit{Pfdhps} 540 prevalence should be obtained in infants and children participating in antimalarial drug efficacy trials or malaria surveys.

- Insufficient evidence exists to set specific SP-IPTi implementation thresholds for prevalence of less common \textit{Pfdhfr} and \textit{Pfdhps} mutations associated with high-level resistance notably the \textit{dhfr} 164 and \textit{dhps} 581, but prevalence levels of these mutations of more than 10% should be cause for serious
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...concern, and would cast doubt on the value of using IPTi even if the prevalence of Pf dhps 540 mutations were less than 50%.

- The potential of monitoring the protective efficacy of SP-IPTi through a measure of the duration of protection following SP-IPTi should be further explored and developed as it is difficult to measure the benefits of SP-IPTi once implemented.

- An alternative method to explore is the use of case-control studies measuring the odds of having received SP-IPTi time within a defined period before children present to clinic with confirmed malaria compared to children who present with non-malaria illness.


Additional supporting recommendations

1. Within countries, SP should be used exclusively for IPT indications
2. Countries adopting and implementing SP-IPTi should not use AS+SP for the treatment of uncomplicated falciparum malaria
3. National Malaria Programmes should routinely include monitoring of molecular markers of SP resistance in therapeutic efficacy studies and malaria surveys.
4. Urgent development of monitoring protocol is needed (this will involve further analysis of existing IPTi study cohorts).
5. Countries are encouraged to participate in and share data on molecular markers for the WWARN database
6. Development of alternative antimalarial medicines to SP for IPTi, and methodologies for dose optimization.

Outstanding research questions

1. Monitor the prevalence of both the existing mutations associated with SP resistance (Pfdhfr 51, 59, 108, 164, and Pfdhps 437, 540, 581 & 613) and the predictive value of Pfdhps 540 for the quintuple mutation in different settings and populations (including cross-sectional surveys and individuals with uncomplicated malaria), and look for new mutations.
2. How do patterns of SP-associated mutations change over time in different epidemiological settings when SP is no longer the first-line treatment?
3. How to monitor IPTi protective efficacy of new medicines – when to start and end the use of new medicines for IPTi.
4. Antimicrobial resistance to sulfonamides in infants, e.g. in nasal/enteric carriers who received SP-IPTi vs non-receivers.
5. Better understand whether parasites after treatment with SP-IPTi (breakthrough infections) are more resistant and how this relates to the spread of resistance in the parasite population.
6. Additional IPTi trials should not be precluded if evidence is required for implementation, e.g. alternative dosing regimens, etc.
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References


