

Intermittent Preventive Treatment of malaria in infants (IPTi) – February 2009

Targeting malaria prevention in infants

The burden of malaria in African children under five years old and pregnant women is high. In some communities, infants are the group most at risk of death from malaria and associated severe anaemia.

Intermittent Preventive Treatment of malaria in infants (IPTi)

IPTi is the delivery of an antimalarial drug to infants at the time of routine vaccinations through WHO's Expanded Programme on Immunization (EPI). In the first trial of IPTi, conducted in Ifakara, Tanzania (Schellenberg *et al*, Lancet, 2001), IPTi with sulfadoxine-pyrimethamine (SP), delivered at the time of the second and third doses of Diphtheria-Tetanus-Pertussis/Oral Poliovirus Vaccine (DTP/OPV) and measles vaccination, at approximately 2, 3 and 9 months of age, reduced the incidence of clinical malaria by 59% and anaemia by 50% in the first year of life. These infants also had 36% less malaria in the second year of life (Schellenberg *et al*, Lancet, 2005).

IPTi Consortium

Based on the Ifakara study results, several centres of malaria research formed the IPTi Consortium to conduct a robust and comprehensive assessment of this promising new intervention in order to guide policy development. The Consortium also aimed to generate operational experience with IPTi in order to facilitate the translation of a positive policy recommendation for IPTi into public health action.

The IPTi Consortium consists of 19 autonomous research collaborations plus WHO and UNICEF (see list at end of fact sheet) and is supported by the Bill & Melinda Gates Foundation. During its first meeting in March 2003, the Consortium prepared a strategic plan showing how, by the end of 2006, it would generate key information to inform policy discussions. This initial information is available and focuses on the efficacy of IPTi with SP (IPTi-SP) in different malaria transmission settings. It also provides a consolidated safety profile of IPTi-SP and shows no interactions between IPTi-SP and the serological response to EPI vaccines.

Experience from a large-scale implementation studies is also available from 7 countries involving over 300,000 infants a year.

In addition, the Consortium has generated other information and insights important to national policy makers:

- the choice of antimalarial drug for IPTi,
- the relationship between IPTi and drug resistance,
- the cost-effectiveness, acceptability, and community effectiveness of IPTi,
- the applicability of IPTi delivered alongside routine vaccinations in different malaria transmission settings, and
- the effect of IPTi on the immunological response to malaria infection.

This information has been generated across a range of malaria transmission settings and health systems. Information on IPTi-SP was available in 2006, data is now available for alternative drugs and combinations.

Overview of Consortium activities

The Consortium has conducted randomized, placebo-controlled efficacy trials of IPTi-SP in Mozambique and Gabon, and with alternative medicines - including artemisinin-based combination therapies; mefloquine, chloroquine-dapsone [lapdap®] in Tanzania, artesunate +SP and artesunate +amodiaquine in Kenya, and artesunate +SP and amodiaquine +SP in Papua New Guinea (PNG). Through two sets of studies in parallel to the efficacy trials, the Consortium has generated information on operational issues, acceptability, and cost of implementation. One is a community-level effectiveness study in southern Tanzania where IPTi-SP is being given by health clinic staff along with EPI vaccines to approximately 12,000 infants per year. The other is an implementation study of IPTi-SP being undertaken by UNICEF in six African countries (Benin, Mali, Senegal, Ghana, Malawi, Madagascar) involving over 300,000 infants per year.

Working groups of the IPTi Consortium

The Consortium formed a number of working groups to standardise methodology between trials, provide oversight, and conduct pooled analyses.

1. Statistical working group (SWG): Consists of the head statistician from each trial (including non-Consortium IPTi trials) and developed an approach to a pooled statistical analysis of efficacy results.

2. Consortium safety panel (CSP): Comprises experts in pharmacovigilance, clinical epidemiology and statistics, with representation from Consortium trials' Data and Safety Monitoring Boards and provides an overview of the safety data from each Consortium trial and conducts pooled analyses of safety.

3. WHO advisory committee on EPI serology: An expert panel set up by the WHO to investigate whether there are any interactions between IPTi and the serological response to EPI vaccines.

4. Cost effectiveness working group (CEWG): Measures the cost effectiveness of IPTi in the different studies using a standardised methodology.

5. Acceptability working group (AWG): Investigates the acceptability of IPTi to infants' caregivers and clinic staff using a standardised methodology.

6. Drug resistance working group (DRWG): Investigates the effect of IPTi on drug resistance. Each Consortium trial collected samples in cross-sectional surveys and from clinical malaria cases in trial participants. Molecular markers of resistance have been used to assess the effect of IPTi on the selection of drug resistant parasites. Trials are conducted using standard WHO *in vivo* procedures in 6 to 59 month old children with symptomatic malaria and relate *in vivo* resistance levels to the efficacy of these drugs when used for IPTi. The southern Tanzania effectiveness study has also investigated the effect of IPTi on the spread of resistance in all age groups in the community. Modelling techniques are being used to estimate the effect that IPTi has on drug resistance.

7. Applicability of IPTi working group: This group has generated an overview of the age pattern of malaria disease and death in sub-Saharan Africa and developed mathematical models to link this information to IPTi efficacy study results in order to estimate the benefits of IPTi in specific countries and malaria transmission settings.

Pooled analysis of IPTi-SP

Safety and efficacy data are available from six placebo-controlled randomised trials of IPTi-SP. This includes the two Consortium trials conducted in Mozambique (Manhiça) and Gabon (Lambaréné) and four trials not conducted by the Consortium but which have made their data available for analysis. These include the first trial of IPTi, in Ifakara, Tanzania and three trials in Ghana - Navrongo, Kumasi, and Tamale. All Consortium trials were conducted according to good clinical practice (GCP) standards and were subject to regular clinical monitoring. The four non-Consortium trials were audited to confirm the quality of the trials and their data.

Results of the pooled analyses of IPTi-SP:

Efficacy (analysis at 12 month of age of all infants that received at least one dose of IPTi)

In the first trial of IPTi in Ifakara, the protective efficacy against the incidence of **clinical malaria** was 59%. In the subsequent 5 trials efficacy ranged from 20 to 33% (a statistically non-significant effect was obtained in Lambaréné). The pooled analysis of the 6 trials showed a 30% reduction in the incidence of clinical malaria.

In addition, there was a 38% reduction in **hospital admissions of infants with malaria parasitemia** in a pooled analysis of the 6 trials, and a 22% reduction in **all-cause hospitalisations**.

There was a 15% reduction in the risk of **anaemia** in a pooled analysis of the 6 trials. The risk of anaemia decreased in Ifakara by 50% and in Lambaréné by 26%. There was also a trend for a reduction in the risk of anaemia in Tamale by 15% ($p=0.06$). In the individual trial analysis, Navrongo had a 35% reduction in hospital admissions for anaemia. In Manhiça, there was a reduction in the risk of hospital admission for anaemia in the month after IPTi dosing for the first (by 71%) and second (by 85%) dose but not

overall. In Kumasi, there was a 30% reduction in anaemia after the first dose but not overall. In Tamale there was 24% reduction in anaemia in the analysis at 18 months of age.

There was no significant rebound in episodes of clinical malaria, anaemia or hospital admissions in the pooled analysis of the 5 month period after the IPTi schedule was finished. However, in three studies in Ghana, there was an increase in high parasitemia density clinical malaria (Navrongo), in anaemia (Kumasi) and in severe malaria and severe anaemia (Tamale). In the initial trial in Ifakara there was sustained protection against clinical malaria into the second year of life with infants receiving IPTi-SP having 36% less malaria in the second year of life.

Safety

Approximately 4,000 infants received 12,000 doses of IPTi-SP in the six trials. The total number of deaths in the IPTi-SP group and in the control group was similar. While the trials were not powered to measure the effect of IPTi on mortality, this result shows that there is no increased risk of mortality with the use of IPTi-SP. One death in the SP group and one death in the placebo group in the six trials (both in the Kumasi trial) were possibly attributable to IPTi as this trial rates all events that occur within 40 days of IPTi administration as possibly related.

The Lambaréné, Kumasi and Tamale trials noted some hospitalisations that could be attributable to IPTi that occurred in both the SP and placebo treated groups. Overall, there were significantly fewer (22%) serious adverse events (SAEs) hospitalisations in the SP group than in placebo recipients.

No skin reactions considered due to IPTi were observed except in Kumasi. Two cases of Stevens Johnson Syndrome (SJS) occurred in two children in the SP group – this was after a third dose given outside the EPI at 15 months of age – a dose that would not be given in IPTi which focuses on the first year of life. These infants were not hospitalised and recovered. There was also a dermatological SAE in infant in the placebo group considered related to IPTi. There was a case of SJS in an infant that received placebo which was not considered related to IPTi. It is unlikely that non-hospitalised cases of SJS in Africa would self-solve and the

diagnosis is under question and currently being investigated.

EPI serology

Samples were collected from two (Navrongo and Manhiça) of the six of the IPTi-SP trials for the measurement of a potential adverse effect of co-administration of IPTi on the responses to EPI vaccine. Data show that IPTi-SP does not have an adverse impact on the serological responses to vaccination against measles, DTP, polio, HepB, and limited data from Navrongo suggests that there is no negative interference of IPTi-SP on yellow fever vaccination. Data for the alternative drugs and combinations is presently being analysed but results show IPTi has no impact on seroconversion to EPI vaccines.

Cost effectiveness

Cost effectiveness analysis of IPTi-SP has been conducted in two trials (Ifakara and Manhiça). IPTi delivered alongside the EPI is highly cost-effective - and even cost-saving - from the health system perspective. The cost per DALY averted was under US\$12 in Ifakara and Manhiça; a cost per DALY averted of under US\$50 is considered very good value-for-money. Data for the other trials, including alternative drugs and combinations, is presently being analysed but results show IPTi is still highly cost effective.

Acceptability

Information on acceptability from the Manhiça and southern Tanzania studies indicate that IPTi-SP is generally acceptable in these settings. This is based on the perceived seriousness of infant malaria, prior existence and acceptance of EPI, and familiarity with and perceived safety of SP. Data for the other trials, including alternative drugs and combinations, is presently being analysed but results show IPTi is acceptable with alternative drugs but a single dose is preferred.

IPTi is currently under review by the WHO for possible recommendation for the prevention of malaria in infants

IPTi-SP was reviewed by the WHO Technical Expert Group (TEG) in October 2006, the Technical Research Advisory Committee (TRAC) in December 2006 and by the TEG again in October 2007. IPTi will be reviewed again in April 2009 where a decision will be made about a policy recommendation.

IPTi underwent an independent review by the US Institute of Medicine in 2008

The committee concluded that IPTi was safe, efficacious, cost effective, and acceptable and could easily be implemented and recommended that IPTi should be taken to the next level.

Data from the pooled analyses are preliminary and unpublished

All publications on IPTi are available on the IPTi website: www.ipti-malaria.org

The IPTi Consortium consists of leading centres of malaria research in Africa, Europe and the United States, plus two United Nations agencies:

1. Albert Schweitzer Hospital, Lambaréné, Gabon
2. Barcelona Centre for International Health Research, Barcelona, Spain
3. Case Western Reserve University, Cleveland, USA
4. Centers for Disease Control and Prevention, Atlanta, USA
5. Ifakara Health Research and Development Centre, Ifakara, Tanzania
6. Institut de Recherche pour le Développement, Dakar, Sénégal
7. Kenya Medical Research Institute, Kisumu, Kenya
8. Kilimanjaro Christian Medical Centre, Moshi, Tanzania
9. London School of Hygiene and Tropical Medicine, London, UK
10. Manhica Health Research Centre, Manhica, Mozambique
11. National Institute for Medical Research, Amani, Tanzania
12. PNG Institute of Medical Research, Goroka, Papua New Guinea
13. Swiss Tropical Institute, Basel, Switzerland
14. Université Cheikh Anta Diop de Dakar, Dakar, Sénégal
15. University of Copenhagen, Copenhagen, Denmark
16. University of Tübingen, Tübingen, Germany
17. Walter and Eliza Hall Institute of Medical Research, University of Melbourne, Australia
18. World Health Organization (WHO)
19. United Nations Children's Fund (UNICEF)

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Affiliations of the non IPTi-Consortium IPTi-SP trials:

Ifakara trial

- Ifakara Health Research & Development Centre, Kilombero, Tanzania
- St Francis Designated District Hospital, Ministry of Health, Tanzania
- Barcelona Centre for International Health Research, Barcelona, Spain
- Swiss Tropical Institute, Basel, Switzerland

Kumasi trial

- Infectious Disease Epidemiology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
- Kumasi Centre for Collaborative Research in Tropical Medicine, Ghana
- Ministry of Health/Ghana Health Service, District Health Directorate, Agona, Ashanti Region, Ghana

Navrongo trial

- Navrongo Health Research Centre, Ministry of Health, Ghana
- London School of Hygiene and Tropical Medicine, UK

Tamale trial

- Institute of Tropical Medicine, Charité University Medicine Berlin, Germany
- School of Medicine and Health Sciences, University for Development Studies, Tamale, Ghana
- Ghana Health Service, Regional Health Administration, Tamale, Ghana