

The IPTi Consortium: research for policy and action

David Schellenberg^{1,2}, Badara Cisse³ and Clara Menendez⁴

¹Department of Infectious Diseases, London School of Hygiene & Tropical Medicine, University of London, Keppel Street, London WC1E 7HT, UK

²Current address: Ifakara Health Research & Development Centre, PO Box 78373, Dar es Salaam, Tanzania

³Département de Parasitologie, Faculté de Médecine, Université de Dakar, BP 5005 Dakar Fann/16949 Dakar Fann, Sénégal

⁴Center for International Health, Hospital Clinic, University of Barcelona Villarroel 170, 08036, Barcelona, Spain, and Manhiça Health Research Center, Manhiça, Mozambique

The results of a randomized controlled trial in Tanzania suggest that intermittent preventive treatment in infants (IPTi), delivered through the Expanded Program on Immunization, might be a useful approach to controlling malaria in countries where it is endemic. An international consortium of research collaborations, involving the World Health Organization and United Nations Children's Fund, is now evaluating IPTi in a range of different settings to generate robust and compelling evidence to guide policy. This review summarizes the available information on IPTi and presents the consortium's approach to determining whether IPTi might be a valuable additional strategy in programs to control malaria.

Introduction

Malaria exacts a huge toll on the health, wealth and survival of African populations. As the third millennium gets under way, the control of malaria relies heavily on the presumptive treatment of clinical episodes and on the use of insecticide-treated mosquito nets (ITNs) [1]. While awaiting a vaccine for malaria, we need to optimize the available control tools – as a public health priority – in countries where malaria is endemic. Anti-malarial chemoprophylaxis in endemic settings has been shown to protect children from episodes of malaria, anaemia and death [2]. Chemoprophylaxis, however, is costly, might exacerbate the spread of drug resistance, is logistically complex, and might also result in the loss or delayed acquisition of acquired immunity – the so-called ‘rebound effect’ [3–5]. As a result, chemoprophylaxis has not been widely implemented for malaria control.

The first trial of intermittent preventive treatment in infants (IPTi) was conducted in an effort to harness the benefits and to minimize the problems of chemoprophylaxis. In this trial, a treatment dose of sulphadoxine–pyrimethamine was administered to children when they attended routine vaccination clinics at 2, 3 and 9 months of age. IPTi was given regardless of whether or not a child had symptoms or parasitaemia and, because fewer doses

were given than would be used in chemoprophylaxis, the cost, concerns about drug resistance and immunological effects were expected to be reduced. Furthermore, by delivering IPTi alongside routine vaccinations, the logistic considerations were eased considerably. The trial showed that it is possible to reduce clinical malaria, anaemia and hospital admissions by delivering an available and affordable anti-malarial drug at the time that routine vaccinations are given during the first year of life [6].

An international consortium of research collaborations, involving the World Health Organization (WHO) and United Nations Children's Fund (UNICEF), is now evaluating IPTi in various settings to generate evidence to guide policy.

The IPTi Consortium

The encouraging results of the first trial of IPTi led some healthcare workers to consider widespread implementation of IPTi, but others to suggest the need for a range of clinical, immunological and molecular investigations. Intermittent preventive treatment has been evaluated in pregnant women (known as IPTp) and is now recommended for malaria control in this group of the population in sub-Saharan Africa [7]. Although IPTp and IPTi have many factors in common, it was agreed that further evaluation of IPTi was necessary before a policy recommendation could be made.

The IPTi Consortium was formed in 2003 to further the development and evaluation of IPTi. It comprises 13 institutions working as six research collaborations (Box 1) across Africa, and includes the WHO and UNICEF. It aims to generate evidence to inform a policy recommendation on IPTi in a timely manner [8]. Studies were planned to answer key questions, and the Bill and Melinda Gates Foundation (<http://www.gatesfoundation.org>) was approached for funding. Information in three areas was identified as a prerequisite to informing policy.

First, the complexities of malaria epidemiology require an evaluation of treatment efficacy in different endemic settings. Accordingly, sites in west (Gabon), east (Kenya, Tanzania) and southern (Mozambique) Africa were identified. A study in Senegal was also included to shed light on the potential of an IPT-based approach to control malaria in intensely seasonal transmission settings.

Corresponding author: Schellenberg, D. (DMSchellenberg@aol.com).

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Box 1. Institutions currently participating in the IPTi Consortium

- Albert Schweitzer Hospital, Lambaréne, Gabon
- Centers for Disease Control and Prevention, Atlanta, USA
- Hospital Clinic, University of Barcelona, Barcelona, Spain
- Ifakara Health Research and Development Centre, Ifakara, Tanzania
- Kenya Medical Research Institute, Kisumu, Kenya
- Kilimanjaro Christian Medical Centre, Moshi, Tanzania
- London School of Hygiene and Tropical Medicine, London, UK
- Manhica Health Research Centre, Manhica, Mozambique
- National Institute for Medical Research, Amani, Tanzania
- Swiss Tropical Institute, Basel, Switzerland
- Université Cheikh Anta Diop de Dakar, Dakar, Senegal
- University of Copenhagen, Copenhagen, Denmark
- University of Tübingen, Tübingen, Germany
- United Nations Children's Fund (UNICEF)
- World Health Organization (WHO)

(Note: Trials are carried out in collaboration with local malaria control programmes and ministries of health.)

Second, although sulphadoxine–pyrimethamine has been used to treat malaria in infants for decades, it was considered prudent to consolidate its safety profile in this age group before recommending sulphadoxine–pyrimethamine for routine IPTi in predominantly healthy infants. Third, it is necessary to ensure that IPTi does not interfere with the serological response to the vaccines alongside which it is delivered: an increase in vaccine-preventable disease would be an unacceptable price to pay for IPTi.

In addition, the Consortium is conducting a large-scale operational research project in southern Tanzania and, in conjunction with UNICEF, is planning limited implementation of IPTi in six other countries. These projects will start only when the safety and efficacy of IPTi are demonstrated in epidemiologically similar settings. The purpose of these operational activities is to generate experience of implementation in several health systems – experience that should facilitate public health action if a policy recommendation is made to implement IPTi.

The Consortium is also working to identify the optimal characteristics of drugs for IPTi. Clinical trials comparing the efficacy, when used for IPTi, of long-acting (e.g. mefloquine) and short-acting (e.g. lapdap) anti-malarial drugs, with and without the anti-malarial artesunate, are underway. During the course of the various studies, the effect of IPTi on immunological responses to *Plasmodium falciparum* infection is being evaluated, the impact of IPTi on the development of anti-malarial drug resistance is being assessed across trials, and the acceptability, cost and cost-effectiveness of IPTi are being considered. Further information on each of the trials is available from the IPTi Consortium's website (<http://www.ipti-malaria.org>).

A strength of working as a consortium is that designs, methodologies and outcome measures can, to some extent, be harmonized. Working groups have been established to coordinate approaches to evaluating statistics, drug resistance, acceptability and cost-effectiveness. Overviews of the safety and efficacy data from individual trials are generated by, respectively, the Consortium's Safety Panel and Statistical Working Group. All of the Consortium's

studies are subject to clinical monitoring to ensure the quality and integrity of the data that they submit. IPTi is also being evaluated by several non-Consortium trials, including four studies being carried out in Ghana (Navrongo, Ashanti, Kumasi and Tamale) and one in Kenya (Bungoma). Data from these trials will be also considered, providing that satisfactory clinical audit reports are available.

At its 2003 annual meeting, the Consortium developed a tentative time frame for activities. Sufficient information to inform a policy recommendation on IPTi with sulphadoxine–pyrimethamine was expected to be available by mid-2006, and information on the value of other anti-malarial drugs for IPTi would become available during 2008. The Consortium will provide information to a specially convened WHO study group as part of a platform for IPTi-related policy discussions. The aim is to sensitize policy makers to IPTi and to ensure the appropriateness and relevance of information presented by the IPTi Consortium.

Evidence from IPTi trials

The first study of IPTi was an individually randomized, placebo-controlled double blind trial involving 701 infants in Ifakara town, southern Tanzania [6]. The area has perennial malaria transmission and an entomological inoculation rate (EIR) of 29 bites per person per year. Sulphadoxine–pyrimethamine was delivered through the Expanded Programme on Immunization (EPI), alongside routine vaccinations at 2 (DPT-2), 3 (DPT-3) and 9 (measles) months of age. Sulphadoxine–pyrimethamine was used on account of its safety, efficacy, affordability and availability, and was administered in a single dose, as a directly observed treatment, by facility staff. Low-dose iron supplementation was also given between 2 and 6 months of age. Efficacy was estimated by comparing the incidence of malaria, anaemia and other clinical endpoints between IPTi recipients and placebo recipients.

IPTi was found to be safe and well-tolerated, and was associated with significant reductions in the first or only episode of clinical malaria (protective efficacy, PtdEtn 59% [95% confidence intervals (CI) 41;72%]), severe anaemia episodes (PtdEtn 50% [95% CI 8;73%]) and all-cause admission to hospital (PtdEtn 30% [95% CI 8;47%]). An analysis carried out to investigate whether a rebound effect would occur after cessation of IPTi showed the contrary: namely, a sustained reduction in the risk of clinical malaria (PtdEtn 36% [95% CI 11;53%]) between the ages of 10 months and 2 years [9]. This reduction extended well beyond the duration of the pharmacological effects of sulphadoxine–pyrimethamine, raising the possibility that IPTi might facilitate the development of anti-malarial immunity.

The results of a second study of IPTi conducted in Muheza, northern Tanzania, were reported in 2003 [10]. Amodiaquine, the anti-malarial used, was given three times during the first year of life but was not linked with routine vaccinations. The Muheza area has perennial transmission of malaria and an EIR of 405 bites per person per year. The trial involved 291 infants and produced results comparable to those from Ifakara: namely, a 65%

(95% CI 42;77%) reduction in clinical malaria and a 67% (95% CI 34;83%) reduction in anaemia during the first year of life. No extended follow-up results are available from this trial. The need to give each treatment course over 3 days is likely to increase logistic and compliance issues, and most of the other studies evaluating IPTi are using sulphadoxine–pyrimethamine.

Another non-consortium IPTi study has been conducted in Navrongo, northern Ghana [11]. This cluster-randomized trial involved 2485 children enrolled to receive sulphadoxine–pyrimethamine or placebo alongside the EPI vaccinations DPT-2, DPT-3 and measles. An additional dose of sulphadoxine–pyrimethamine was administered at 12 months of age. The EIR in the area was estimated to be 418 infective bites per person per year with strong seasonality. In Navrongo, IPTi was associated with a 25% (95% CI 14;34%) reduction in malaria episodes and a 35% (95% CI 10;53%) reduction in hospital admissions owing to anaemia in children up to 15 months of age. In this study, there was an increase in the risk of malaria episodes with a parasite density in peripheral blood of more than $5000 \mu\text{l}^{-1}$ in the 8 months after cessation of the intervention (PtdEtn -20% [95% CI -2 ; -40%). This increase was not accompanied by an increase in the risk of anaemia, and the overall rates of malaria (PtdEtn 16% [95% CI 7 ; 25%]), including high parasite density malaria (PtdEtn 12% [95% CI 0.5 ; 22%]), malaria and anaemia (PtdEtn 39% [95% CI 6 ; 60%]) and malaria admission (PtdEtn 31% [95% CI 5 ; 50%]), were all reduced between 2 and 24 months of age.

So far, the only IPTi Consortium trial to have been reported was an individually randomized, double blind placebo controlled trial carried out in Manhiça, Mozambique [12]. This area has moderate perennial transmission of malaria that peaks in the rainy season and an annual EIR of 38 bites per person per year. In this study, sulphadoxine–pyrimethamine or placebo was administered to 1,503 infants, at 3, 4 and 9 months of age, alongside routine vaccinations delivered through the EPI. Although IPTi was associated with a 22% (95% CI 4;37; $P=0.020$) reduction in the incidence of clinical malaria and a 19% (95% CI 4;31%) reduction in hospital admissions, the incidence of severe anaemia was similar in the IPTi and control groups (PtdEtn 13% [95% CI -17 ; -35%], $P=0.36$).

So far, preliminary assessments in these studies have found no evidence that the serological responses to EPI vaccines are modified by IPTi. Definitive assessments of the effect, if any, of IPTi on EPI vaccines will be made by a specially convened expert WHO advisory committee. In terms of safety, no serious adverse events have been related to the intervention in any trial.

Results are due imminently from two trials: one in Lambaréné, Gabon, and one in Kumasi, Ghana. These studies have adopted a slightly different dosing regimen in which sulphadoxine–pyrimethamine is being given at 3, 9 and 15 months – a reflection of the older age group predominantly affected by malaria in these trial sites.

Explaining heterogeneity

The heterogeneity in the above results might be the result of the varying characteristics of the trial sites. At face

value, if the prophylactic effect of sulphadoxine–pyrimethamine lasts about a month and children are given three doses of IPTi between 2 and 12 months of age, one would expect the protective efficacy to be $\sim 30\%$. However, sites vary in the intensity and seasonality of malaria transmission; in the availability of other interventions for malaria control, such as ITNs and anti-malarial treatment; in the provision of iron supplementation; and in the level of resistance to the anti-malarial drug used for IPTi, as reflected by the percentage of the population showing an ‘adequate clinical and parasitological response’ (ACPR; Figure 1). All of these factors might influence the effect of IPTi.

The reason why the efficacy of IPTi was so high in Ifakara is not known, although the coverage of ITNs might be an important factor: ITN coverage was 68% in Ifakara, as compared with less than 10% in Navrongo and none in Manhiça. Further information from the other IPTi trials using sulphadoxine–pyrimethamine will help to build up a picture and to show whether or not IPTi needs to be implemented with ITNs to maximize its effect.

Applicability of IPTi

Determining where IPTi should be implemented will be a function of its cost, efficacy and potential benefits in different settings. Although the ‘protective efficacy’ of IPTi in Navrongo (25%) is considerably lower than that in Ifakara (59%), the intensity of malaria transmission is much higher in Navrongo than in Ifakara and the absolute number of malaria episodes that could be prevented by IPTi in the two settings is similar [11]. The Consortium will generate an overview of trial results, initially concentrating on the effect of sulphadoxine–pyrimethamine when used for IPTi (Figure 1), and will evaluate the cost and cost-effectiveness of IPTi and the epidemiology of malaria to help inform the policy-making process.

Epidemiologists have so far failed to describe the age pattern of malaria disease and death in sub-Saharan Africa, which makes it difficult to estimate the potential of IPTi to control malaria because the burden of disease in infants is unknown. In areas where the most frequent age of individuals with malaria is more than 1 year, the impact of IPTi might be rather limited. Although infants might continue to bear the brunt of malaria mortality in such settings [13], the general picture is unclear. The IPTi Consortium is therefore working to summarize available epidemiological information to help inform this discussion. The picture is clearer in most of the Sahel and in other areas where malaria transmission is intensely seasonal and where there might effectively be no transmission for many months of the year. In such regions, it would make little sense to deliver IPTi year-round through the EPI system, and other approaches to the intermittent use of anti-malarial drugs might be more effective.

Seasonally administered IPT

Seasonal IPT (sIPT) is the administration of anti-malarial drugs at curative doses on a monthly or bi-monthly basis at the time of peak malaria transmission. sIPT targets children under 5 years of age with the aim of reducing the

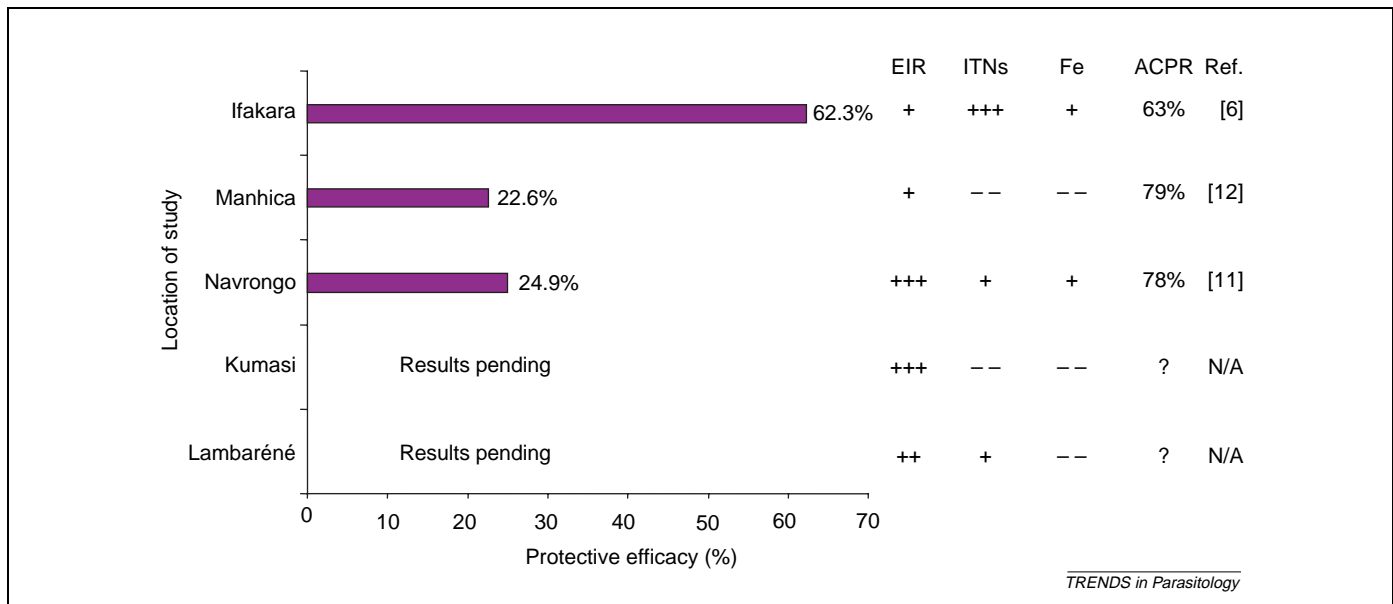


Figure 1. Protective efficacy of IPTi against malaria. Shown is the protective efficacy, against all clinical episodes of malaria, of IPTi using sulphadoxine–pyrimethamine in comparison to contemporaneous controls. The results from the trials in Ifakara [6], Manhica [12] and Navrongo [11] have been reported so far; as further data become available, the potential value of IPTi as part of malaria control policy will become clearer. Abbreviations: EIR, entomological inoculation rate; ITN, insecticide-treated net; Fe, iron supplementation; ACPR, adequate clinical and parasitological response.

incidence of clinical episodes and possibly the severity of attacks. In an initial placebo-controlled trial of sIPT conducted in Mali, children randomized to receive two doses of sulphadoxine–pyrimethamine during the transmission season suffered 40% (95% CI 25;51%) fewer episodes of malaria than controls [14].

In a double-blind, randomized placebo-controlled trial in Niakhar, Senegal, children under 5 years were given a dose of sulphadoxine–pyrimethamine plus a single dose of artesunate three times during the rainy season. This intervention was safe and well-tolerated, and produced an 86% (95% CI 80;90%) reduction in the incidence of clinical episodes of malaria [15]. Follow-up in the subsequent transmission season showed no evidence of increased malaria morbidity in children who had received sIPT the previous year.

In this trial, parasites obtained at the end of the malaria transmission season from children who had received sIPT carried molecular markers of resistance to sulphadoxine or pyrimethamine significantly more frequently than parasites obtained from control children. The dihydrofolate reductase triple mutation frequency was 95% in sIPT recipients as compared with 75% in controls, and the dihydropterate synthase 437 mutation frequency was 86% in sIPT recipients and 44% in controls, showing that a single dose of artesunate did not prevent the selection of resistant parasites [15]. Because sIPT recipients were much less likely to be parasitaemic than controls, however, fewer children overall carried resistant parasites among the IPT recipients (13%) than the controls (28%). A follow-up study is investigating alternative regimens for sIPT in the same area. These results emphasize the need to monitor drug resistance in all IPT studies.

Several other aspects of sIPT merit further assessment. Similar to IPTi, it will be important to understand its

efficacy in different epidemiological conditions. A chief challenge is the development of feasible delivery strategies, which will be linked to assessments of the acceptability of sIPT. Elucidating the best drug combination will involve consideration of cost-effectiveness, safety and tolerability. It will be also valuable to assess its impact on anti-malarial immunity and to evaluate its effect on transmission. Because sIPT requires consideration of issues that differ from those involved in IPTi, its further evaluation is not included in the portfolio of the IPTi Consortium.

Concluding remarks

The IPTi Consortium is a coordinated effort to further the development and evaluation of a promising new strategy for disease control. It aims to generate robust and compelling information to inform the policy-making process, and to do this in a timely manner. In 2003, a time-plan was drawn up that suggested sufficient information would become available during 2006 to inform a policy recommendation. Placebo-controlled safety and efficacy studies were initiated in a range of settings and, at the same time, operational research programs were planned to start in various places as safety and efficacy data became available. At the time of writing, these original targets are still expected to be met.

By running efficacy studies and operational programs in parallel, the practicalities of implementation should be understood by the time that a policy recommendation can be made. Thus, if the recommendation is to implement IPTi, it should be possible to move rapidly to public health action. The transition from proof of principle through policy to public health action will have been achieved in a relatively short time frame and the IPTi Consortium model might be relevant to other potential public health interventions.

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