

Intermittent Preventive Treatment for infants (IPTi): a 'new' malaria control strategy

New studies show real benefits from intermittent preventive treatments where prophylaxis is not practical. Professor William Brieger reports

Background

Medicine has played an important role in disease prevention, and malaria is no exception. In the past, chemoprophylaxis played a larger role in the prevention of malaria than it does today. Now most concern for this preventive approach is focused on people who travel from non-endemic into endemic areas. The simple definition of chemoprophylaxis is 'The use of a chemical agent to prevent the development of a disease.'¹ Traditionally there is the additional aspect of the definition that such agents are given in sub-therapeutic doses on a regular basis, e.g. daily or weekly. Even now the US Centers for Disease Control and Prevention shows that distinction with the drug Malarone as seen below.²

- Treatment: four tablets (each dose contains 1000mg atovaquone and 400mg proguanil) orally as a single daily dose for 3 consecutive days.
- Chemoprophylaxis: one adult tablet containing 250mg atovaquone and 100mg proguanil hydrochloride taken orally, daily.

Chemoprophylaxis together with non-adherence to the full course of treatment have been blamed for the spread of malaria parasite resistance to the common, inexpensive drug, chloroquine. In either case when people are in an endemic area and take less than the amount to drug to cure the disease, the parasites are able to survive and pass that genetic advantage on to subsequent generations.³ A particular lesson drawn from the experience of drug resistance is that when individual medicines are used alone, the likelihood of resistance increases. Now recommended treatment for malaria consists only of combination drugs, particularly artemisinin-based combination therapy (ACT), since use of artesunate drugs alone put pressure on the parasites to develop resistance.⁴

There was a time when chemoprophylaxis with chloroquine was recommended weekly for pregnant women living in endemic areas.⁵ As chemoprophylaxis for people indigenous to malaria endemic areas dropped out of use, malaria control experts developed a different medicine-based approach known as intermittent preventive treatment (IPT), which consisted of a full treatment dose of medicine, in this case sulfadoxine-

pyrimethamine (SP).

IPT with SP was tested in the late 1990s and found effective for preventing malaria during pregnancy in areas of stable malaria transmission.⁶⁻⁸ Tanzania was one of the first countries to adopt IPTp as part of its national malaria control strategy.^{9,10} IPTp in pregnancy thus, became known as IPTp.

A clear policy for IPTp⁵ was articulated by WHO's African Region in 2004 saying that: *All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening. The World Health Organization recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT with each scheduled visit after quickening will assure that a high proportion of women receive at least two doses. IPT-SP doses should not be given more frequently than monthly.*

The full treatment dose of SP serves two purposes. First it clears any parasites, even in people with asymptomatic disease. Secondly, if a drug with a long half-life is used, the person taking IPT can be protected from re-infection for an extended period.

While there have been concerns raised about the effectiveness of IPTp where resistance to SP is developing,¹¹ there is yet to be a reason to stop SP use for IPTp, especially when an appropriate alternative is yet to be found. Studies have shown that even where SP resistance has been documented in children, IPTp with SP is still effective for protecting mothers and their newborns



Community treatment of malaria possible – why not IPTi?

Professor William R Brieger is from the Department of International Health, The Johns Hopkins University Bloomberg School of Public Health; and Senior Malaria Adviser, Jhpiego, an affiliate of the Johns Hopkins University

from anaemia and low birthweight respectively.¹² Thus researchers recommend reserving the use of SP for IPT as a way to reduce drug pressure and hopefully prolong longevity of SP until an alternative can be found. In the meantime, the use of IPTp together with sleeping under insecticide-treated bednets is recommended to ensure full protection of the pregnant woman.⁵

IPTi: efficacy, effectiveness, safety

With the success in preventing malaria morbidity using IPTp, it was decided to investigate IPT in infants and children, IPTi. The first trial of IPTi took place in Ifakara, Tanzania in 2001.¹³ Subsequently the IPTi Consortium conducted research in Mozambique, Ghana, Gabon, Kenya, Papua New Guinea, Benin, Malawi, Madagascar, Mali, Senegal, and continued work in Tanzania.¹⁴ Unicef actively participated in six of the countries.

IPT itself has been described as a 'proactive' malaria control strategy, and this intervention in the early stages of testing showed 'protective efficacy of IPTi in altering the frequency of severe anaemia, malaria illness, and hospital admissions,' across several sites.¹⁵

Gosling and colleagues¹⁶ recently outlined in a review how IPTi protects children, based on a six-site review of IPTi research in the *Lancet*.¹⁷ These benefits include:

- When given to an asymptomatic child IPTi will clear existing parasites (treatment effect).

- IPTi will also prevent new blood stage infections (prophylactic effect) for up to a year.
- The prophylactic effect may also be called a 'vaccination effect' because persistence of low levels of parasitaemia provide prolonged stimulation of the immune system.
- IPTi can result in reduced hospitalisation for malaria and possibly general levels of admission for children.
- Anemia is also reduced, which might eventually be linked to reductions in general hospital admissions for children.

An important finding is that very few adverse events have been reported over the years of IPTi research.¹⁷

IPTi is cost-effective, with reduced health system costs and significant savings to households from malaria cases averted. According to the IPTi Consortium, 'Results showed that IPTi with SP when delivered alongside the EPI is a highly cost-effective intervention; ranging from US\$1.36 to US\$4.03 per malaria episode averted, and from US\$2.90 to US\$8.63 per Disability-Adjusted Life-Year (DALY) averted.'¹⁸

IPTi: delivery regimen and mechanisms

The investigations of IPTi so far have offered SP at three points in time. The choices have included varying combinations at 2, 3, 9, 12, and 15 months of age.¹⁶ Links with distribution through child immunisation programmes may determine a feasible regimen.



Child Health clinic where IPTi could be given

Researchers on IPTi from the Mozambique reported that, 'The main comparative advantage of IPTi over other modes of delivery for malaria control is its integration within the EPI scheme.'¹⁹ Synergistic effect wherein IPTi actually attracted more children to immunisation services was observed.

Alternative distribution mechanisms are also being considered since as noted above, some of the timings used in the IPTi studies fall outside the routine immunisation schedule. The possible role of community volunteers is being considered.^{20,21} The community distributor approach appears promising for IPTip²² and hopefully will also be useful for IPTi.

SP formulation in paediatric doses is another operational concern.¹⁶ In Nigeria several years ago pre-packaging of antimalarial drugs and their promotion in treatment was undertaken by USAID partners prior to the change-over to ACTs as first-line treatment. Local pharmaceutical manufacturers produced SP in doses for children aged 2 months to 2 years and also 2+ to 6 years.²³ Other countries could easily adopt this approach.

Overall, Aponte and colleagues conclude that, 'operational experience from Tanzania and six other African countries shows that rapid large-scale deployment of IPTi is feasible. Thus, this intervention could make an important contribution to reducing the intolerable burden of malaria in infants and should be integrated with other effective control methods.'¹⁷

Current status of IPTi

The body of IPTi research has undergone reviews by two expert committees: The Technical Expert Group (TEG) convened by the WHO,²⁴ and a group of experts convened by the US Institute of Medicine (IOM).²⁵ Both committees recommended (IOM in July 2008, TEG in April 2009) that IPTi should be implemented in areas of moderate to high malaria transmission, and with SP in areas where there is not very high level resistance to SP.

The TEG confirmed that the IPTi studies showed a decrease in:

- the incidence of episodes of clinical malaria by 30% (95% CI, 19.8–39.4%);
- anaemia (haemoglobin, <8 g/dl) overall by 21.3% (95% CI, 8.3–32.5%);
- all-cause hospital admissions during the first year of life by 23% (95% CI, 10.0–34.0%).

WHO has posted the TEG report on its website,



IPTp set the stage for IPTi: a pregnant woman takes IPTp in Angola

which implies a strong degree of support. WHO has yet to produce operational guidelines and a clear policy statement of its own in support of IPTi, although rumours of its imminent publication abound. Most agencies await formal WHO approval before embarking on a new malaria strategy.

In the meantime in Ghana where Unicef supported the IPTi studies, the National Malaria Control Program has already adopted IPTi as part of its national strategy. IPTi thus features among the activities that the US President's Malaria Initiative is supporting in Ghana in the current fiscal year.²⁶

WHO's Strategic Advisory Group of Experts (SAGE) on immunisation also reviewed IPTi since routine immunisation was used as the main delivery mechanism for IPTi.²⁷ SAGE was happy to learn that:

- sulfadoxine–pyrimethamine did not have a detrimental impact on the serological responses to studied vaccines;
- EPI monitoring tools had been successfully adapted to include IPTi;
- immunisation coverage was not adversely affected;
- IPTi was generally well accepted by health-workers and mothers or caregivers within the study sites.

SAGE encouraged WHO and partners to continue monitoring delivery of IPTi within immunisation programmes, study serological responses to new vaccines like rotavirus, and consider SP formulations that would be easy for infants to swallow.

The way forward

Implementation of IPTi as an integrated part of both malaria control and child health services is now within the power of countries who have participated in the IPTi Consortium research, as evidenced by Ghana's proactive approach. Other countries are encouraged to read up on the existing IPTi research studies which are available on the IPTi Consortium website, and make their programming plans accordingly.

The IPTi Consortium has developed a decision making tool 'to assist national and sub-national policy makers in making decisions about whether Intermittent Preventive Treatment in infants is an appropriate intervention for a given country or region, and to provide relevant information to support IPTi-related policy discussions. This tool is restricted to sub-Saharan Africa and selected Ocean Pacific countries (Papua New Guinea, the Solomon Islands, Vanuatu) where the burden of malaria is focussed on children.'²⁸

It is important to ensure that when IPTi is adopted that it operates on a platform of routine child health services like immunisation. This will ensure proper monitoring and data reporting to document achievement of malaria control targets. Involving community volunteers can be part of this process as long as the volunteer programmes are linked into the nearest health facility and its child health programmes. The TEG also encourages countries that use cotrimoxazole, another common sulfa drug, for treatment of child pneumonia or as prophylaxis for HIV+ children, to monitor the use of SP for IPTi to avoid overdosing of this medication family.²⁴

Two issues will affect use of IPTi into the future. One, as mentioned, is the potential negative effect of parasite resistance to SP. Therefore research is focusing on other drugs that might substitute for SP, e.g. amodiaquine.²⁹

Ultimately as all malaria interventions generally become more effective and malaria more rare, use of IPT either for pregnant women of infants/children will no longer be needed as malaria transmission in formerly stable area becomes more sporadic. As countries move into the pre-elimination phase of malaria control and drop IPT, they must ensure that strong surveillance, diagnosis and treatment services are available to save lives. Hopefully, IPTi, if adopted soon as part of integrated malaria control, will speed the arrival of the day when children are no longer dying from malaria.

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