

Editorial: Intermittent preventive treatment for malaria control in infants: moving towards evidence-based policy and public health action

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From proof of principle to public health application

It is important to balance the urgency of implementing a new, efficacious intervention on a public health scale against the need to acquire convincing evidence on safety and efficacy. Two studies in Tanzania have shown that intermittent preventive treatment in infants (IPTi), the administration of antimalarial drugs at pre-specified times during the first year of life, regardless of the presence of clinical symptoms or *Plasmodium falciparum* parasitaemia, reduces episodes of malaria and anaemia by over 50% (Schellenberg *et al.* 2001; Massaga *et al.* 2003). Children followed up to the age of 2 years showed a sustained 36% reduction in the risk of malaria (Schellenberg *et al.* 2005). IPTi has the potential to become a major tool for malaria control in Africa as it may be delivered at the time of routine vaccination – through the Expanded Programme on Immunisation (EPI) – which increases the chance of long-term sustainability. Should IPTi now be recommended as a malaria control strategy for Africa?

A group of research scientists, WHO and UNICEF reviewed the evidence that was available in 2002 and agreed that information would be required in three key areas before a recommendation on the role of IPTi in national malaria control strategies could be made. First, the efficacy of IPTi in reducing episodes of clinical malaria and anaemia in different epidemiological settings should be known. Secondly, it should be demonstrated that IPTi has no adverse impact on serological responses to EPI vaccines. Thirdly, the reassuring safety data that is currently available on IPTi with sulphadoxine-pyrimethamine (SP) should be consolidated.

The IPTi Consortium was established in 2003 with support from the Bill and Melinda Gates Foundation. By conducting a co-ordinated series of clinical trials in a range of settings, the Consortium aims at generating the scientific evidence that is required to inform policy. Experience with operationalization of the IPTi strategy will be obtained from community effectiveness studies, and will facilitate prompt public health action if a positive WHO policy recommendation is made. The Consortium expects to have sufficient data on which to base a recommendation by late 2006.

Key issues being addressed by the IPTi Consortium

Efficacy against malaria in different settings

The complexities of malaria epidemiology make it essential to assess the efficacy of IPTi in settings with different transmission intensities. This information may help to modify the IPTi strategy in parts of Africa where the main burden of malaria is not in the first year of life. The Consortium is also generating data on the impact of IPTi in settings with different insecticide treated nets (ITNs) coverage, levels of drug resistance, health service delivery and community practices.

Safety

SP and the other antimalarial drugs being considered for use as IPTi have been licensed for therapeutic, not preventive, use in infants, and there are relatively few safety data available specifically in this age group. It would be unacceptable for EPI programmes if the introduction of IPTi resulted in severe adverse reactions or deaths, which would then decrease the acceptance of EPI vaccines. For this reason, consolidation of antimalarial safety data in this age group is a priority.

* The institutions currently participating in the IPTi Consortium are listed in the Appendix.

Immune responses to EPI vaccines

The impact of IPTi on serological responses to EPI vaccines is being assessed using a range of antimalarial drug options, and will include data on the newer quadravalent [diphtheria-tetanus-pertussis (DTP) – hepatitis B] and pentavalent (DTP-hepatitis B-*Haemophilus influenzae* b) vaccines currently being introduced through the EPI in some countries. An expert WHO Advisory Committee will assess all the serological data arising from the IPTi Consortium studies, and will advise WHO accordingly.

Drug resistance and drug choice

Resistance to SP is increasing across Africa and it is important to know at what level of resistance an alternative antimalarial should be used for IPTi. Although SP may remain useful for IPTi after it has failed as a curative agent, it will be important to evaluate other antimalarial drugs that could be used instead of SP. By increasing the use of antimalarial drugs, IPTi may increase the rate at which drug resistance develops, although this increased drug pressure is likely to be ameliorated by fewer infants requiring treatment for clinical malaria. The extent of the change in drug pressure is unknown, as are the consequent effects on parasitological and clinical efficacy of the drug in question.

The prevalence of parasitaemia was low in the southern Tanzanian study, suggesting that the mode of action of IPTi with SP was primarily prophylactic. If true, the long half-life of SP is likely to have been essential for the efficacy of IPTi, although it is uncertain whether drugs with shorter half-lives would also confer benefit. A better understanding of the optimal characteristics of the antimalarials used for IPTi in settings with differing transmission intensities will facilitate rational drug choice. The IPTi Consortium's research portfolio includes studies that will generate information on the safety and efficacy of alternative antimalarial drugs for IPTi. In addition, the Consortium is working with industrial partners to develop an antimalarial drug formulation that will facilitate the safe administration of an infant dose at the time of routine vaccination.

Malaria immunology

If SP given as IPTi works only by providing pharmacological protection, a 25% decrease in the incidence of clinical malaria in the first year of life would be expected, assuming that each dose of SP protects the infant for approximately 1 month. Hence the studies in Tanzania suggest that IPTi may also enhance the development of immunological protection against malaria. These observations raise

important questions about the development of protective immune responses to *P. falciparum* infection and disease, and the Consortium's research portfolio includes studies to investigate this further. Despite the lack of a rebound in malaria incidence among IPTi recipients in the Tanzanian trials, the implications of a rebound are sufficiently serious to merit further investigation in other settings.

Acceptability

Before IPTi can be promoted on a large scale, acceptance of the intervention by health staff and the community has to be assessed, as this is likely to have a direct impact on implementation and may also influence EPI coverage. New preventive health interventions such as IPTi can only be considered completely effective if they are socially and culturally acceptable, which will determine whether they are widely adhered to in the longer term. It is also crucial to ensure that new additions to EPI do not negatively influence people's attitudes to, and uptake of, immunization. On-going studies will lead to a comprehensive understanding of the role of socio-cultural factors involved in the acceptability of IPTi across a range of geographical and cultural settings and transmission areas, and involving a range of drugs and drug regimens.

Costing

It is likely that IPTi delivered through the EPI will be relatively cost-effective, as the incremental costs of any EPI-linked intervention will be low, and SP and amodiaquine, used in the Tanzanian studies, are inexpensive drugs. The Consortium is generating cost and cost-effectiveness data for a number of African countries, which will facilitate decision-making and provide a basis for predicting the budgetary and resource requirements of large-scale implementation of IPTi.

Platform for policy discussions

A WHO Study Group of leading scientists and policy makers will assess all available evidence for IPTi. Should this lead to a positive policy recommendation, the evidence for IPTi already shared with Ministries of Health in sub-Saharan Africa, international organizations and funding agencies is likely to facilitate subsequent national policy change.

Summary and timelines

By late 2006, the IPTi Consortium would have generated a comprehensive body of evidence for the safety, efficacy

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and impact of IPTi on serological responses to EPI vaccines in a variety of epidemiological settings. This will be used to inform a possible WHO policy recommendation on IPTi for national malaria control programmes in Africa.

By 2008, the Consortium would have generated additional key evidence for the choice of antimalarial drugs for IPTi, the relationship between IPTi and the development of drug resistance, the development of immunity, the possibility of a rebound effect, and the cost-effectiveness and acceptability of IPTi. This information will form the basis for the subsequent introduction of IPTi into routine child health programmes, while the experience gained from community effectiveness studies will facilitate rapid, widespread implementation.

References

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Appendix**Institutions currently participating in the IPTi Consortium**

Albert Schweitzer Hospital, Lambaréné, Gabon
 Centers for Disease Control and Prevention, Atlanta, USA
 Cheikh Anta Diop University of Dakar, Dakar, Senegal
 Hospital Clinic, University of Barcelona, Barcelona, Spain
 Ifakara Health Research and Development Centre, Ifakara, Tanzania
 Institut de Recherche pour le Développement, Dakar, Senegal and Montpellier, France
 Kenya Medical Research Institute, Kisumu, Kenya
 Kilimanjaro Christian Medical Centre, Moshi, Tanzania
 London School of Hygiene and Tropical Medicine, London, UK
 Manhiça Health Research Centre, Manhiça, Mozambique
 National Institute for Medical Research, Amani, Tanzania
 Swiss Tropical Institute, Basel, Switzerland
 Université Cheikh Anta Diop de Dakar, Dakar, Sénégal
 University of Copenhagen, Copenhagen, Denmark
 University of Tübingen, Tübingen, Germany
 United Nations Children's Fund (UNICEF)
 World Health Organization (WHO)
 Trials are collaborating with the local malaria control programmes and ministries of health.

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