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REVIEW ARTICLE

Review of intermittent preventive treatment for malaria in infants and children

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Abstract: Malaria is one of the greatest killers of children in the world. Treatment is available, but there are problems with affordability, availability, accessibility and increasing drug resistance. A new regime, intermittent preventive treatment in infants (IPTi) shows promise. It involves giving a treatment course of antimalarial drugs, regardless of parasitaemia, at intervals over the first year of life. The aim is to decrease the frequency of malarial illness while allowing the development of natural immunity. Its strength is that it can be linked with the childhood immunisation schedule. Early studies are encouraging, but much remains to be learned before its potential place in the prevention of malaria in children can be determined and it can safely be introduced as public policy. A review of the literature was performed in July 2006 for references relating to IPTi and other forms of personal prevention of malaria in infants and children.

Key words: child; infant; international child health; malaria; prevention and control.

An estimated one million people die from malaria each year,[1] mostly children under 5 years old, and mostly in sub-Saharan Africa.[2] The number of childhood and infant deaths is even higher if malaria's indirect contributions to immunosuppression, anaemia, prematurity, low birthweight and poverty are taken into account.[1,2] Malaria is caused by a parasite known as *Plasmodium*, and is transmitted by the female Anopheles mosquito. *Plasmodium falciparum* is the most dangerous subtype, and the type most common in sub-Saharan Africa. In young children the symptoms and signs of malaria including anaemia commonly pass unrecognised and untreated, so a preventive rather than a curative approach is attractive and may also decrease pressure on curative resources.[1] In the past, regular chemoprophylaxis was used to prevent malaria, but problems with its large-scale use preclude it from current practice in most instances. Preventive measures now focus on sleeping under insecticide-impregnated bed nets (ITNs), prompt case management to decrease the infective pool, and vector control in some circumstances. Intermittent preventive treatment of infants (IPTi) is a new way to protect the highest risk population (infants) with some of the benefits of chemoprophylaxis and fewer drawbacks.

Key Points

1 Intermittent preventive treatment of malaria in infants (IPTi) is a new concept of malaria prevention in infants. It involves giving a treatment dose of antimalarial drugs to vulnerable infants at the time of immunisation, regardless of parasitaemia.
2 Its aim is to decrease the frequency of malarial morbidity and mortality in infants, while allowing the development of protective immunity.
3 An IPTi Consortium has been developed to quickly research this concept, with the aim of rapidly introducing it as policy if it is found to be safe and effective.

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Objectives

The purpose of this review was to examine the historical context for IPTi, its rationale, safety, efficacy, risks, logistics and role in the prevention of malaria morbidity and mortality in young children.

Method

A search of electronic databases was performed, including Google, Google Scholar, X-base and PubMed for combinations of the terms 'malaria', 'prevention and control', 'infant', 'child', 'preschool child', 'intermittent preventive treatment' and 'malaria vaccine'. The Cochrane database of system reviews was searched for the terms 'malaria' and 'preventive therapy'. Bibliographies and reference lists were scanned for additional references. All articles relating to IPTi were selected. Articles relating to alternative personal protective measures were scanned, and the most representative article was selected. The literature search was originally performed in October 2005 and updated in July 2006.

Discussion

Chemoprophylaxis

Regular chemoprophylaxis is effective in reducing the mortality and morbidity from malaria.[2] It is used successfully in travellers to malarious areas, and it has also been used effectively in endemic areas for prophylaxis-reduced transmission. Quinine was used in Italy in the 1920s and 30s and was associated with a marked decrease in the incidence of malaria.[3] In the 1950s, trials of chemoprophylaxis for children under 2 years showed that treated children grew better, had higher mean haemoglobins and fewer episodes of malaria than those given placebo.[3,4] In 1995 a clinical trial of chemoprophylaxis involving infants born in a malaria hyperendemic area of Tanzania had encouraging results.[5] Weekly pyrimethamine-dapsone was safe and effective in decreasing malaria by 61% and severe anaemia by 60% in the first year of life, but there was a significant rebound effect during the 8 weeks after chemoprophylaxis was stopped, with an increase in the frequencies of both malaria and severe anaemia. A similar rebound was described in a trial of children in The Gambia.[6] It was postulated that the chemoprophylaxis had been sufficient to impair the development of naturally acquired immunity.[5] This rebound effect, together with the cost, drug side effects, practicalities of weekly delivery and fears of increasing resistance made chemoprophylaxis an unattractive option for the widespread control of malaria.[2]

This prompted the idea of using occasional treatment doses of chemotherapy, allowing the development of natural immunity between courses. This is known as intermittent preventive treatment (IPT) and was initially used during pregnancy (IPTp).

IPTp

Immunity against malaria does not appear to prevent infection, rather it diminishes parasite burdens and suppresses the inflammatory response which causes illness. In pregnancy, immunity does not protect the placenta which acts as a 'privileged site' for parasite multiplication, leaving pregnant women at increased risk of severe malaria, severe anaemia and death, and the fetus vulnerable to miscarriage, growth retardation, prematurity and neonatal death.[7,8] Regular chemoprophylaxis in pregnancy has been used in the past leading to improved maternal haemoglobin and birthweights, but the logistics of giving regular chemoprophylaxis to pregnant women are difficult. IPTp involves giving a treatment dose of an antimalarial drug, usually sulphadoxine-pyrimethamine (SP) at specified intervals in the second and third trimesters, regardless of parasitaemia.[3,9] Trials in Malawi[10] and Kenya[11] showed improved birthweights and reduced prevalence of severe anaemia in first and second pregnancies and IPTp is now recommended by the World Health Organisation (WHO).[12,13]

IPTi

Following the introduction of IPTp, Schellenberg *et al*. published the results of the first randomised, placebo-controlled trial of intermittent preventive treatment of infants in 2001.[14] A total of 701 infants in a high *Plasmodium falciparum* transmission intensity region of Tanzania were randomly assigned a dose of either SP or placebo at 2, 3 and 9 months of age at the time of routine vaccinations delivered through WHO's Expanded Program on Immunisations (EPI). The treatment was well tolerated and effective, and interestingly the protection continued into the 12 months following the treatment.[15] Massaga *et al*. published a smaller randomised double-blind placebo-controlled trial using amodiaquine at 3, 5 and 7 months in a holoendemic area of Tanzania with high resistance to other antimalarials.[16] Results were similarly encouraging. Four further studies of IPTi have been published and they all showed benefit in reducing malaria.[17–20]

Efficacy

Reports of efficacy vary. Schellenberg reported a 59% protective efficacy against malaria and a 50% efficacy against severe anaemia in a high transmission perennial situation.[14] Massaga also reported a reduction of malarial fevers of 63.4% and in the prevalence of anaemia by 71%.[16] Results obtained by Chandramohan[18] in an area of intense seasonal transmission in Ghana were less striking, with a reduction in clinical malaria of 24.8% and anaemia of 35%. In this study more children died in the malaria treatment arm than in the placebo arm (70 vs. 58) but the deaths were considered to be unrelated to the treatment. Macete *et al*. obtained similar results in a region of moderate perennial transmission in Mozambique with a protective efficacy of 22.6% for clinical malaria.[20] Most studies have been in areas of high endemicity. It is possible that in low transmission areas or areas with high insecticide-treated bed net (ITN) coverage IPTi would be less effective, because of fewer opportunities for the development of natural immunity.

IPT in children (IPTc)

In areas of high transmission the main burden of malaria is borne by infants under 12 months of age, but in much of Africa, particularly where malaria is intense and seasonal, the burden shifts to older children.[21] Therefore, if IPTi is timed to coincide with infant immunisations, it is unlikely to have a major impact on malaria morbidity. A clinical trial of seasonal IPT in children (sIPTc) in Senegal using SP and artesunate given at monthly intervals for 3 months during the peak transmission season resulted in a protective efficacy of 86%.[22]

Choice of drug, safety and resistance

Any drug proposed for mass use particularly in infants and children requires an excellent safety profile. Amodiaquine has been associated with agranulocytosis (1 in 2000) and SP with Stevens Johnson syndrome (1 in 7000). These side effects precluded their use as prophylaxis in Western travellers.[8] No IPTi study has yet reported either condition, but numbers of children included are limited. White raises concerns about the use of IPT in infants and pregnant women.[8] First, rapidly increasing resistance to SP in Africa makes it unlikely that intermittent SP prophylaxis is as effective now as it was when it was evaluated in pregnancy 5–10 years ago, and second SP and amodiaquine pharmacokinetics have not until now been well studied in infants, though new studies are emerging. Macete *et al*. studied the effect of SP during a trial of IPTi in Mozambique, and found no attributable severe skin reactions or abnormal haematological or biochemical parameters.[20] The main attraction of SP is that it can be given as a single dose at the time of immunisation under direct observation whereas amodiaquine requires additional doses to be given at home. Current trials are looking at mefloquine, chlorproguanil/dapsone, and various combinations of amodiaquine, SP and artesunate.[23] Alternatives include artemether-lumafantrine and dihydroartemesinin-piperaquine, but both would require further evaluation of safety, pharmacokinetics and efficacy, and both require more than a single dose.[8]

One of the greatest problems with malaria treatment worldwide has been the development of drug resistance. Given the long acting nature of SP, during IPTi there is a considerable amount of time when the drug can suppress fully sensitive strains of Plasmodium, leaving the opportunity for the selection of resistant strains.[8] Shorter acting drugs or combinations leave a smaller opportunity for the development of resistance in theory and in models[8,24,25] but would not give as long a period of intermittent prophylaxis between treating doses. Schellenberg postulated that IPTi would have only a marginal effect on resistance as intermittent treatment would constitute only a small proportion of a country's total malarial treatment doses.[14] He also suggested that by reducing the incidence of clinical malaria fewer treatment doses would need to be given. However, in areas of high transmission, infants make up a high proportion of the infected population at any time. They also carry Plasmodium blood stage densities that are typically orders of magnitude higher than adolescents or adults,[26] and are therefore an important reservoir for infection, including infection with resistant organisms.

Mechanism of action and timing

Infants appear to be relatively protected from malaria in the first 3 to 6 months of life. The mechanisms for this are not completely understood, but may involve fetal haemoglobin[27] and some sort of transplacental immunity.[28] This protection wanes by 6 months of age leaving the infant vulnerable to malaria until some protective immunity is acquired. The underlying means by which IPT prevents malaria is not understood. IPTi action probably differs from IPTp in that it is being used on naïve subjects, rather than in pregnancy, where it could be assumed that the woman already has a degree of protective immunity. Both may act by clearing parasites intermittently, or through a long acting prophylactic effect.[20,21] Paradoxically drugs which do not completely clear an infection may be more effective for IPTi, as effective truncation of an infection may impair the development of immunity.[21]

For convenience, the doses of intermittent preventive treatment are timed to coincide with immunisations at 2, 3 and 9 months. The long gap between the second and third doses leaves the infant vulnerable to malaria.[8] This may be both a strength and a weakness of the method. The fact that the baby has some exposure to malaria aids in the development of natural immunity, and the long acting nature of the drugs chosen thus far leaves considerable time when the parasite is attenuated, allowing the body to effectively overcome the infection and still develop immunity. However, the gap also leaves the infant vulnerable to severe infection at the time when natural immunity is at its nadir.

Effect on immunisations

Four studies of IPTi and have found no impairment of the serological conversion rate following vaccination.[14,16,18,20] This is important, as any mass IPTi programme would probably be part of the extended programme for immunisation. Chemoprophylaxis has been shown to improve the response to unconjugated polysaccharide vaccines.[29] IPTi may increase the immune responsiveness to vaccines by reducing episodes of malaria.[23] It may also increase the uptake rate of vaccination if it is perceived by the community to be beneficial.

What are the alternatives to IPTi?

Alternative large-scale preventive measures to decrease the burden of malaria in infants and young children rely on limiting contact with vectors. The two methods recommended by Roll Back Malaria are indoor residual spraying with agents such as DDT, and the use of ITNs. A recent review of ITNs found them to be extremely effective at preventing malaria and severe malaria, decreasing parasite prevalence and saving lives. They reduce deaths in children by one-fifth, and episodes of malaria by half.[30] Indoor residual spraying and ITNs are both cost-effective for large scale application.[31] Universal deployment as advocated by Roll Back Malaria requires major financial, operational, educational and technical inputs.[32] Increased funding for malaria through organisations such as the Global Fund to fight AIDS, TB and malaria and the Bill and Melinda Gates Foundation will help.[13] An effective vaccine is still believed to be at least 10 years away.[33] It would need to be more effective or more cost-effective than the alternative control methods in order to replace them, or it would need to add substantial value to be worth using alongside them.[34]

Implementation

A major attraction of IPTi is its potential to slip into the EPI already in place. It is vital that it does not add an additional burden or disrupt routine services.[35] It should be introduced with sufficient funding to adequately strengthen the health system to cope with the additional workload. The alternative of a separate vertical programme would compete with rather than strengthen the existing system.[36]

Where to from here?

In order to further evaluate the place of intermittent preventive treatment in infants, the IPTi Consortium, an alliance of the WHO, the United Nations Children's Fund and leading research centres in Africa, Europe and the United States has been developed. It has received a grant commitment of $28m from the Bill and Melinda Gates Foundation to rapidly resolve outstanding scientific questions, with the aim of moving IPTi quickly into policy and practice.[37] The key issues being addressed by the consortium are:

- Efficacy against malaria in different settings
- Safety and tolerability of drugs
- Immune responses to EPI vaccines
- Drug choice and resistance
- Malaria immunology
- Acceptability
- Cost-effectiveness[37]

Most of these answers will be available by the end of 2008.

The consortium also provides a platform for policy discussions.[37]

Following completion of the studies, WHO, the United Nations Children's Fund and the Global Alliance for Vaccines and Immunisations are willing to implement its recommendations.

Where does this fit into the overall scheme?

Greenwood states,

> There is no clear, single path to improve malaria control. Such an approach will probably come from a series of incremental steps involving better and more widespread use of the methods that have already been shown to be effective, as well as the stepwise introduction of new treatments and partly effective control measures shown to be effective.[1]

If IPTi is found to be safe and effective, it could be one arm of an overall plan to decrease the overwhelming burden of malaria on children. It could be used alongside ITNs,[18] but it probably has a more important role in areas where the implementation of ITNs has been slow.

Conclusion

The prospect of a simple, effective prophylactic regime to protect children from malaria warrants close scrutiny. It is too early to say whether it will be able to deliver on all it promises. Much remains to be learned about its safety and efficacy in regions of differing endemicity, and with different population characteristics. These questions should be answered by the studies currently underway. If it transpires that different drugs and different dosing schedules are required for different locations, it will certainly detract from its simplicity and ease of use. Yet the potential benefits are exciting indeed. If it does prove to be a useful addition to the current approaches to prevent malaria, there are structures already in place and organisations willing to implement it rapidly. Perhaps within the next 10 years we will at last experience a downturn in the dreadful toll of malaria.

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