IPTc BIBLIOGRAPHY

PUBLICATIONS ON IPTc IN CHILDREN IN THE COMMUNITY UNDER FIVE YEARS OF AGE

Published

2006


This randomised, controlled, double-blind study assessed the impact of IPTc using artesunate + sulphadoxine-pyrimethamine (SP) on the incidence of clinical malaria in over 1000 children aged 2-59 months in Senegal. IPTc led to an 86% reduction in the incidence of clinical malaria during the 13 weeks of follow up. No significant difference in the prevalence of anaemia was observed between the two study arms at the end of the intervention. The prevalence of SP resistance mutations was higher in the IPTc arm than in the placebo arm but the prevalence of drug resistant parasitaemia was lower in the IPTc arm due to a lower parasitaemia prevalence in these children. Children who received IPTc were more likely to vomit than children who received placebo but generally the intervention was well tolerated.


This review discusses the definitions of IPT, chemoprophylaxis and mass drug administration and the potential for overlap between these forms of chemoprevention. The paper also summarises experience with IPTc and highlights future challenges and research priorities.

2007


This study assesses the impact of IPTc on growth and nutritional status in children aged 2-59 months who participated in a randomised, double-blind, placebo-controlled trial of IPTc conducted in Senegal (Cisse at al, Lancet, 2006) Children who received IPTc gained three times as much weight as children in the placebo arm. Triceps and subcapsular skinfold thickness fell in both arms but the loss was greater in the placebo rather than the IPTc arm. IPTc did not have any effect on wasting or stunting. The study indicated that malaria prevention using IPTc in areas of seasonal transmission has the potential to improve nutritional status in children.

2008


This study assessed the effect of IPT using sulphadoxine-pyrimethamine (SP) on the incidence of clinical malaria and anaemia in children aged 6 months - 10 years in Mali. 262 children were individually randomised to receive either IPT with two doses of SP 8 weeks apart or no IPT during the peak malaria transmission season. Children
were followed up until the end of the subsequent transmission season. IPTc with SP bimonthly had an age adjusted protective efficacy against clinical malaria of 67.5% during the 16 week intervention period, which fell to 42.5% during the 12 month follow up period. The incidence of clinical malaria during the subsequent malaria transmission season was similar among both groups of children.


2451 children aged 3-59 months were enrolled in this study conducted in an area of perennial transmission with seasonal peaks in Ghana. Children were individually randomised to receive artesunate + amodiaquine (AS + AQ) either monthly or bimonthly, sulfadoxine-pyrimethamine (SP) bimonthly or placebo delivered by community volunteers over a period of 6 months of intense transmission. All regimens significantly reduced the incidence of malaria and anaemia compared to placebo. Monthly AS + AQ was found to be the most effective regimen, reducing the incidence of malaria by 69% and anaemia by 45%. Monthly administration of AS+AQ was more effective than bimonthly administration. No significant reductions in all-cause or malaria related hospital admissions were observed among children who received IPTc compared to those who received placebo.


This study compared the safety and efficacy of four different IPTc regimens [sulfadoxine-pyrimethamine (SP) +1 dose of artesunate (AS), SP + 3 doses of AS, SP + 3 doses of amodiaquine (AQ) or 3 doses of AQ + 3 doses of AS]. IPTc was delivered once a month on 3 occasions during the peak transmission period to a total of 2020 children. All children showed an improvement in haemoglobin concentrations and a reduction in parasite prevalence at the end of the intervention period. Children who received SP + 3 doses of AQ had the lowest incidence of clinical malaria and a lower parasite prevalence at the end of the intervention period than children who received the other regimens. Adverse events were more common among children who received AQ-containing regimens than AS-containing regimens. Markers of resistance to SP were found in virtually all samples tested at the end of the intervention, although the parasite prevalence was low.

2009


This modelling study assessed the impact of IPT in infants (IPTi), children (IPTc) and school children (IPTsc) on clinical malaria. Models were used to simulate the effects of IPTi, IPTc and IPTsc under different transmission settings, while varying the assumptions for acquisition of immunity. Data from the study conducted by Cisse et al in Senegal (Lancet, 2006) was used to parameterise one of the models. The study suggests that IPTc has a significant potential to reduce transmission, particularly in areas of low to moderate transmission, as evidenced by the reduction in clinical cases and asymptomatic infections.


This study was conducted in Ghana in an area with perennial malaria transmission with a seasonal peak during the rainy season. Community assistants delivered IPTc using artesunate (AS) + amodiaquine (AQ) every 4 months during a 12 month period to children aged 6-60 months and presumptively treated all episodes of febrile illness also using AS + AQ. All children received both interventions and a pre-post design was used with baseline and follow-up surveys for parasite prevalence and haemoglobin concentration. These surveys demonstrated a significant, beneficial effect of combining IPTc and community case management (CCMm) on both outcome
measures. The study demonstrated the feasibility of training community assistants to deliver both IPTc and CCMm.


This study, conducted in Senegal, compared the tolerability and efficacy of three different IPTc regimens: sulfadoxine-pyrimethamine (SP) + amodiaquine (AQ), dihydroartemisinin (DHA) + piperaquine (PQ) or SP+PQ. IPTc drug regimens were given by community health workers three times during the high transmission period. A total of 1893 children were enrolled. PQ combinations were found to be better tolerated than SP + AQ with a significantly lower risk of common, mild adverse events. The risk of clinical malaria in children who received each regimen was very similar and PQ combinations were found to be non-inferior to SP + AQ. The proportion of children who carried parasites with markers of resistance to SP was low in all groups at the end of the transmission season.


This cluster randomised study compared coverage with IPTc using sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ) that could be achieved through either community based delivery using community volunteers or facility based delivery (static health facility or expanded programme on immunisation outreach teams) in Ghana. High levels of coverage were achieved with both delivery mechanisms, although the proportion of children that received at least the first dose of at least 3 courses of IPTc was slightly higher in the community delivery arm than in the facility based arm. Doses of AQ on days 2 and 3 were given to caregivers to administer at home and surveys found that over 90% of children in both arms received these doses.

2010


This study, which was conducted in The Gambia, compared the safety, tolerability and efficacy of alternative drug regimens for IPTc: sulfadoxine-pyrimethamine (SP) + amodiaquine (AQ), SP + piperaquine (PQ) and dihydroartemisinin (DHA) + PQ. A total of 1008 children were individually randomised to receive IPTc delivered by nurses in the local health centre. No drug related severe adverse events were observed and the total percentage of children who reported any adverse event was higher among a group of control children who received no medication than among study children. Comparison of the incidence of clinical malaria in an age matched group of control children from nearby villages allowed estimation of the protective efficacy of each of the drug regimens. The protective efficacy against clinical malaria was 87% for DHA+PQ and 93% for both SP + AQ and SP + PQ.


This study assessed whether IPTc increases children’s susceptibility to subsequent malaria infection by altering their anti-Plasmodium acquired immunity. IgG antibody responses to P. falciparum schizont extract were measured in Senegalese children who had received IPTc using artesunate + sulfadoxine-pyrimethamine or placebo eight months earlier. Anti-schizont antibody responses were slightly lower among children who had received IPTc. In a multivariate model, parasitaemia, past malaria morbidity and increasing age were strongly associated with a higher specific IgG response. Carriage of Plasmodium appeared to be the key factor
influencing anti-schizont IgG responses, irrespective of the preventive treatment received, although the possibility of some contributory effect from the anti-malarial drugs used for IPT could not be completely excluded.


This paper reviews three IPT strategies, namely IPT in pregnancy (IPTp), IPT in infants (IPTi) and IPT in children (IPTc), focusing on the mechanism of action, choice of drugs available, controversies and future research.


This study determined the association between amodiaquine (AQ) dosage by body weight and the incidence of mild adverse events using data from two trials of IPTc using sulphadoxine-pyrimethamine (SP) + AQ in Senegal. In one of these trials the dose of AQ was determined by age and in the other the dose was determined by body weight. Both dosage strategies resulted in some children receiving AQ doses above the recommended therapeutic range. The odds of vomiting increased with increasing AQ dosage and, in one study, the incidence of fever also increased with increasing dosage. Simple amendments to the age based dosing schedule could increase the tolerability of IPTc using SP +AQ in situations where weighing the child is impractical.


This study assessed the cost effectiveness of IPTc using either artesunate (AS) + amodiaquine (AQ) administered monthly or bimonthly, sulphadoxine-pyrimethamine (SP) administered bimonthly or placebo delivered by community volunteers in Hohoe, Ghana (Kweku et al, PLoS ONE, 2008). Economic costs per child who received at least the first dose of each course were lowest for SP bimonthly, followed by AS + AQ bimonthly and then AS + AQ monthly. In this study, AS + AQ administered monthly was the most cost effective regimen due to its substantially higher protective efficacy against clinical malaria. The cost per child enrolled fell substantially when scale up to district level was modelled.


This study used samples collected during an IPTc trial conducted in Hohoe, Ghana (Kweku et al, PLoS ONE, 2008) to assess how IPTc effects the genetic diversity of P. falciparum infections and the risk of clinical malaria in the 12 months following the intervention. Effective seasonal IPT temporarily reduced the prevalence and genetic diversity of P. falciparum infections as measured by genotyping of the merozoite surface protein 2 gene. The reduced risk of malaria in children with multiclonal infections seen only in untreated children suggests that persistence of antigenically diverse P. falciparum infections is important for the maintenance of protective malaria immunity in high transmission settings.


This study, conducted in the middle belt of Ghana, randomised 13 communities to receive home management of malaria with artesunate (AS) + amodiaquine (AQ) with or without the addition of three courses of IPTc with AS + AQ delivered at two monthly intervals during the peak transmission period. Malaria experience in approximately 700 children in each group was compared during the six month period peak transmission period.
IPTc resulted in a 62% reduction in presumptive cases of malaria but had no effect on anaemia. Malaria diagnosis was presumptive and not confirmed by malaria microscopy or a rapid diagnostic test.

2011


A commentary which discusses new evidence published in *PLoS Medicine* on potential delivery mechanisms for IPTc (Bojang et al), as well as on integration of IPTc with other malaria control interventions such as ITNs (Dicko et al and Konaté et al).


This cluster-randomised study assessed the effectiveness of IPTc using sulphadoxine-pyrimethamine + amodiaquine in children aged up to five years when delivered by village health workers (VHWs) or reproductive and child health trekking teams in The Gambia. Delivery by village health workers showed a substantially higher level of coverage with three courses of IPTc than delivery by the trekking team (74% versus 48%) primarily because the VHWs could more easily follow up children who missed doses due to their presence in the community. Delivery of IPTc by VHWs was less costly in both economic and financial terms compared to delivery by the trekking team. A nested case control study indicated a substantial protective efficacy of IPTc against clinical malaria of 87%.


This study, conducted in over 3000 children aged up to five years in Mali, assessed whether IPTc provides additional protection to children sleeping under an ITN. Children were individually randomised to receive an ITN plus either three rounds of IPTc using sulphadoxine-pyrimethamine + amodiaquine or placebo during the high transmission season. A highly significant protective efficacy of 82% against clinical episodes of malaria was observed in the IPTc + ITN arm compared to ITN alone group. Beneficial effects on severe malaria, as well as parasitaemia and moderately severe anaemia at the end of the transmission season were also observed. No serious adverse events were observed and adverse events were similar between arms.


This individually randomised, placebo controlled study assessed the additive benefit of providing IPTc with sulphadoxine-pyrimethamine + amodiaquine to children aged up to five years sleeping under an ITN in Burkina Faso. A total of over 3000 children were enrolled in the study. IPTc had a protective efficacy of 70% against clinical malaria, a protective efficacy of 69% against severe malaria and reduced all-cause hospital admissions by 46% compared to the ITN + placebo arm. Beneficial effects on the prevalence of parasitaemia and moderately severe anaemia at the end of the transmission season were also observed.

This study assessed whether there is an additive effect of administering IPTc with sulphadoxine-pyrimethamine + amodiaquine to children aged under five years on top of an existing home management programme using artemether-lumefantrine treatment for clinical episodes of malaria delivered by village health workers in The Gambia. A protective efficacy against clinical malaria of IPTc of 66% was observed, but this result was not significant as a result of the extremely low incidence of clinical malaria in the study area. The study found that village health workers were able to deliver both interventions successfully with 94% of study children receiving at least the first dose of all three IPTc courses.


This paper describes a systematic review and meta-analysis of IPTc studies. Twelve relevant studies were identified. Meta-analysis showed an overall protective efficacy of monthly administered IPTc against clinical malaria of 82% during the transmission season. IPTc reduced all-cause mortality during the transmission season by over a half, although the number of deaths was relatively small. No serious adverse events attributable to IPTc were observed in any of the twelve studies. Meta-analysis of data from three studies indicated a slight increase in the incidence of clinical malaria in the transmission season in the year following IPTc administration.


A comprehensive individual-based model fitted to data from sites across sub-Saharan Africa was used to simulate the epidemiological impact and cost-effectiveness of IPTi and IPTc varying characteristics of the setting, drug or implementation. Cost components were taken from economic evaluations of published trials. The numbers of DALYs averted by IPTc were driven mainly by the predicted effect on deaths. IPTc was cost-effective, defined using the threshold suggested by the World Bank of US$2009$223 per DALY, in most of the simulated scenarios. Cost-effectiveness was predicted to decrease with low transmission, badly timed seasonal delivery in a seasonal setting, shorter-acting and more expensive drugs, higher frequencies of drug resistance and high levels of treatment of malaria fevers. The number of DALYs averted was predicted to decrease if the five-year age band for IPTc was shifted from children under five into older children, except in settings with very low transmission intensities.

**In Press**

**Under Review**


This paper describes a modelling study in which the protective efficacy of IPT in infants (IPTi) and children (IPTc) using alternative delivery strategies was estimated for a range of epidemiological scenarios. The model was parameterised with data from Navrongo, Ghana where, although transmission is seasonal, there is some transmission all year round. In Navrongo, the predicted protective efficacy against clinical attacks of malaria at 24 months of age was 26.1% with 4 courses of seasonal IPTc compared to 15.6% with 4 courses of IPTi linked to EPI. Post treatment prophylaxis following the use of long acting artemisinin combination therapies (ACT) for case management may provide a similar level of protection to IPTi. Both IPT strategies will be more protective if combined with long acting ACTs.

This paper reviews the current evidence on community case management of malaria (CCMm) and IPTc and discusses the potential for combining these two interventions. Evidence from three studies which combined IPTc and CCMm are reviewed. In areas of seasonal transmission where IPT is an appropriate intervention, community health workers could deliver IPTc during the peak transmission season and also provide CCMm during this period and throughout the year when occasional cases of malaria may occur.


The study aimed to evaluate the safety and effectiveness of IPTc using sulphadoxine-pyrimethamine (SP) + amodiaquine (AQ) in children aged below ten years when delivered by district health staff on a large scale in three rural districts in Senegal. A surveillance system was set up in order to record all deaths, malaria cases diagnosed in health facilities and adverse events. No severe adverse events attributable to IPTc have been observed during a two-year period in which 313,000 courses of IPTc have been administered. The study demonstrates that IPTc using SP + AQ is safe and well tolerated when delivered on a large scale.

28. Pitt C; Conteih L; Diawara H; Ouédraogo D J; Diarra S; Kaboré H; KouélaK; Traoré A; Dicko A; Konaté A; Chandramohan D; Diallo D; Greenwood B. Intermittent preventive treatment of malaria in children (IPTc): a qualitative study of Community Perceptions and Recommendations in Burkina Faso and Mali. PLoS ONE.

This paper presents the results of a qualitative study of community perceptions of IPTc in the context of two clinical trials conducted in Mali and Burkina Faso assessing the added benefit of IPTc to children sleeping under an ITN. In-depth interviews and focus group discussions were held with caregivers and community health workers. Participants observed significant reductions in malaria in children, which they attributed to IPTc. Participants did not express any concerns about the specific drug combination used or about the concept of providing tablets to children without clinical symptoms of malaria. There was no evidence that IPTc was perceived as a substitute for bed net usage, nor did it inhibit care seeking. In these two clinical trials, IPTc (including doses of AQ on days 2 and 3) was delivered by the research team at the local health centre. However, many caregivers stated that they would prefer delivery from a fixed point in the village.

29. Dicko A et al. Morbidity from malaria in children in Mali in the year after receiving intermittent preventive treatment of malaria with sulphadoxine pyrimethamine plus amodiaquine. PloS ONE

This study determined whether administration of IPTc was associated with a subsequent increase in incidence of malaria by continuing surveillance for clinical malaria during the post-intervention malaria transmission season. In the intervention year, study children were randomised to receive and ITN and IPTc with either active drugs or placebo (Dicko et al, Plos Med, 2011). There was a small increase in risk of clinical malaria during the post-intervention malaria transmission season (Relative Risk 1.09) which was more marked in younger children but the benefit of IPTc was maintained over the 24 month period of follow-up.


This study determined whether administration of IPTc was associated with a subsequent increase in incidence of malaria by continuing surveillance for clinical malaria during the post-intervention malaria transmission season. In the intervention year, study children were randomised to receive and ITN and IPTc with either active drugs or placebo (Konate et al, Plos Med, 2011). Ninety-four percent of children enrolled were followed for a second year. A slight increase in clinical malaria was observed in the post-intervention period (Relative Risk 1.12) but this did not offset the beneficial effect of IPTc during the intervention period. Over the whole 16 month period following administration of the first IPTc dose there was still a significant protective effect of IPTc, which was
more marked in the younger children. At the end of the year 2 transmission season, there was no increase in the risk of moderately severe anaemia, wasting, stunting or underweight among children who had received IPTc.


This costing study is a component of a community randomized trial designed to assess the effectiveness of IPTc in terms of adherence obtained through 2 different delivery systems: a facility-based system, including health facility or EPI outreach team and a community-based system by volunteers (Kweku et al, PLoS ONE, 2009). For each of the delivery systems, economic and financial total costs were calculated from the perspective of the health care provider (Ministry of Health). Under the facility-based delivery system, the main economic cost categories were personnel cost for dispensing IPTc to children, supervision cost and cost for delivering IPTc to the distribution points; under the community-based delivery system, the main cost categories were supervision cost, transport cost for delivering IPTc drugs to the distribution points and personnel cost for dispensing IPTc to children. The following economic unit costs are presented and compared across delivery systems: the cost per child “fully” covered; the cost per child “acceptably” covered; the cost per “fully” adherent child; and finally the cost per “acceptably” adherent child.

In Preparation


The aim of this pilot study was to investigate the feasibility of delivering IPT to children in rural areas through the routine health service, and the acceptability of the intervention to communities, prior to a large-scale implementation study. Consultations with health staff at regional and local level were held to identify an appropriate method of delivery, which was then piloted during one transmission season. Costs of delivery, coverage, compliance, the incidence of adverse events, and the acceptability of IPTc by the community and health care providers, were assessed. The study showed that high coverage of the intervention, with good adherence to supervised doses and the doses administered unsupervised by the mother, could be achieved through monthly rounds delivered at home by local community health workers. 81% of eligible children received all 3 scheduled courses of treatment; the most common reason for not receiving IPT doses was being away from the village at the time of the treatment round. The main cost driver was the daily incentives paid to community health workers.