

## Viewpoint

# Intermittent preventive treatment of malaria in infants: how does it work and where will it work?

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### Summary

We discuss the potential public health impact of IPTi by estimating the cases of malaria, anaemia and hospital admissions likely to be averted in different transmission settings; and we review the mechanism of action, choice of drugs regimens, and the effect on immunity of IPTi. IPTi using an efficacious drug is likely to substantially reduce cases of clinical malaria in moderate to high transmission settings. However, geographical heterogeneity in malaria transmission could hamper rolling out IPTi as a national policy.

**keywords** IPTi, public health impact, malaria, anaemia, review

### Introduction

Intermittent Preventive Treatment of malaria (IPT) is a form of chemoprevention achieved by giving therapeutic doses of antimalarials at pre-defined time points (Greenwood 2007). IPT during pregnancy (IPTp) is now widely adopted in Africa to reduce low birth weight and maternal anaemia, the main consequences of malaria in pregnancy. Randomised placebo controlled trials of IPT in infants (IPTi) (Schellenberg *et al.* 2001; Massaga *et al.* 2003; Chandramohan *et al.* 2005; Macete *et al.* 2006; Grobusch *et al.* 2007; Kobbe *et al.* 2007; Mockenhaupt *et al.* 2007), in <5-year-old children (IPTc) (Cisse *et al.* 2006; Dicko *et al.* 2008; Sokhna *et al.* 2008) and in primary school children (ITPsc) (Clarke *et al.* 2008) have shown that IPT can reduce the incidence of malaria among these target groups. Both pregnant women and older children are mostly semi-immune and when infected are more likely to develop asymptomatic parasitaemia than to develop acute clinical malaria in moderate and high transmission areas. In these groups, where asymptomatic parasitaemia is common, clearing existing parasitaemia and preventing new infections would be important. By contrast, the prevalence of asymptomatic parasitaemia in infants is very low in areas of low and moderate transmission (Gosling *et al.* 2009) and varies remarkably between dry and rainy seasons in areas of highly seasonal transmission (Chandramohan *et al.* 2007). Thus the effects of IPTi will depend on the endemicity of malaria. We review the evidence of the mechanism of action of IPTi, and its efficacy and potential public health impact.

### The mechanism of IPTi

An effective antimalarial given to an asymptomatic child will clear existing parasites (treatment effect) and prevent new blood stage infections (prophylactic effect) (White 2005). Two separate mathematical models based on this simple mechanism of action of IPTi were able to predict protective efficacies against malaria within the 95% confidence intervals in published IPTi trials in all but one study (Gosling *et al.* 2008b; Ross *et al.* 2008). Secondary analyses of three IPTi trials showed that the length of protection against malaria provided by IPTi is approximately equal to the likely period of prophylaxis given by the drugs used (Cairns *et al.* 2008; May *et al.* 2008). In a recent study, comparing long-acting and short-acting drugs for IPTi (Gosling *et al.* 2009) the long-acting drug, mefloquine was efficacious in preventing clinical episodes of malaria up to 12 months of age (PE 38%; 95% CI 12%, 57%) whereas the short-acting drug combination, chlorproguanil-dapsone was not (PE 11%, 95% CI -25%, 36%).

The first published IPTi trial (Schellenberg *et al.* 2001) showed a high protective efficacy of IPTi against malaria (62%; 95% CI 44%, 75%) and prolonged protection into the second year of life (Schellenberg *et al.* 2005). Some investigators hypothesise that the extended period of protection was a 'vaccination effect' caused by persistence of low levels of parasitaemia, providing prolonged stimulation of the immune system (Sutherland *et al.* 2007). Others argue that this high estimate of protective efficacy was a function of the fast decline in malaria incidence during the study period, and would not be seen in areas of

**Table 1** Summary of published IPTi trials

Years of study	Site & Country <sup>ref</sup>	Drug tested	Age at dosing (months)	Resistance levels to study drug at day 28	Incidence in placebo group (PYAR)	Protective efficacy (PE) % (95% Confidence intervals)			
						Clinical malaria (fever or history of fever plus parasites)	Moderate anaemia	All cause hospital admissions	
1999–2001	Ifakara, Tanzania (Scellenberg <i>et al.</i> 2001)	SP	2, 3 & 9	40%	0.43	62.3 (44.2, 74.6)	50.3 (7.6, 73.2) <sup>a</sup>	30.0 (8.1, 46.6)	12 months
2000–2004	Navrongo, Ghana (Chandramohan <i>et al.</i> 2005)	SP	3, 4, 9 & 12	22%*	1	24.9 (14.5, 34.1)	35.5 (11.2, 53.1) <sup>b</sup>	12.7 (-4.8, 27.3)	15 months
2002–2005	Mahnica, Mozambique (Maccete <i>et al.</i> 2006)	SP	3, 4 & 9	21%*	0.55	22.6 (1.6, 39.2)	12.7 (-17.3, 35.1) <sup>a</sup>	19.0 (4.0, 31.0)	12 months
2003–2004	Tamale, Ghana (Mockenhaupt <i>et al.</i> 2007)	SP	3, 9 & 15	14%*	1.16	22.5 (11.8, 31.9)	31.3 (2.9, 51.4) <sup>c</sup>	23.6 (4.1, 39.1)	18 months
2003–2005	Ashanti, Ghana (Kobbe <i>et al.</i> 2007)	SP	3, 9 & 15	NA	1.2	20.3 (10.6, 28.9) <sup>e</sup>	7.2 (-7.7, 20.1) <sup>d</sup>	8.7 (-23.4, 32.4)	18 months
2004–2006	Lambarene, Gabon (Grobusch <i>et al.</i> 2007)	SP	3, 9 & 15	31%	0.16	17 (-24, 44)	22 (-1, 40) <sup>c</sup>	NA	18 months
2004–2008	Korogwe, Tanzania (Gosling <i>et al.</i> 2009)	SP	2, 3 & 9	80%	0.31	-6.7 (-45.9, 22.0)	-15.9 (-56.9, 14.3) <sup>f</sup>	-14.7 (-51.7, 13.2)	12 months
2004–2008	Korogwe, Tanzania (Gosling <i>et al.</i> 2009)	MQ	2, 3 & 9	NA	0.31	38.1 (11.8, 56.5)	-6.0 (-44.0, 22.0) <sup>f</sup>	2.3 (-30.6, 26.9)	12 months
2004–2008	Same, Tanzania (Gosling <i>et al.</i> 2009)	SP	2, 3 & 9	80%	0.018	-77.2 (-505.4, 48.1)	20.7 (-26.7, 50.4) <sup>f</sup>	13.8 (-15.1, 35.5)	12 months
2004–2008	Same, Tanzania (Gosling <i>et al.</i> 2009)	MQ	2, 3 & 9	NA	0.018	50.2 (-171.9, 90.9)	24.7 (-20.9, 53.1) <sup>f</sup>	-9.2 (-43.3, 16.7)	12 months

SP, Sulphadoxine–Pyrimethamine, MQ, Mefloquine, \*Resistance at Day 14 post treatment (no data available for day 28), Anaemia measured as <sup>a</sup>PCV <25%, <sup>b</sup>PCV <24%, <sup>c</sup>Hb <7 g/dl, <sup>d</sup>Hb <7.5 g/dl, <sup>e</sup>Hb <9 g/dl and <sup>f</sup>Hb <8 g/dl. <sup>g</sup>Parasite density >500 per microlitre.

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stable or slowly declining incidence (Gosling *et al.* 2008b) as found in two separate modelling exercises (Gosling *et al.* 2008b; Ross *et al.* 2008). This argument is supported by evidence of a decline in the incidence of malaria in the study area during the time of the study (Schellenberg *et al.* 2004) and by a reduction in malaria incidence in the placebo group from a peak of 0.92 cases per year at the age of 9 months (Institute of Medicine 2008) to a mean of 0.41 cases per year between 10 and 24 months of age (Schellenberg *et al.* 2005), which is unlikely to be explained by the age-distribution of malaria cases alone.

### The efficacy of IPTi

Results from eight IPTi trials have been published – seven trials tested the protective efficacy of sulphadoxine–pyrimethamine (SP-IPTi) (Chandramohan *et al.* 2005; Schellenberg *et al.* 2001; Macete *et al.* 2006; Kobbe *et al.* 2007; Grobusch *et al.* 2007; Mockenhaupt *et al.* 2007; Gosling *et al.* 2009). The protective efficacies of chlorproguanil–dapson (CD-IPTi) and mefloquine (MQ-IPTi) were compared with SP in one study (Gosling *et al.* 2009) and amodiaquine was tested (AQ-IPTi) (Massaga *et al.* 2003) in another. We excluded the trial of AQ-IPTi from this analysis as: (i) it was carried out during the 6-month high transmission season only with a 2-month follow-up after the last IPTi dose, (ii) the doses of IPTi were given only 2 months apart and (iii) the doses were not given at times of immunisation. This is akin to seasonal administration of IPTi with short intervals effectively providing chemoprophylaxis and a short follow-up time, and this would lead to a higher estimate of the protective effect of AQ-IPTi in comparison to the protective effect of IPTi administered along with EPI vaccination as was estimated over an 11-month period for the other trials.

The protective efficacies against clinical malaria, moderate anaemia and all cause hospital admissions observed in the trials included in this review are shown in Table 1. SP-IPTi had a protective efficacy against malaria ranging from 14% to 62% (95% CI 1.6%, 74.6%) in five sites where day 28 parasitological failure of SP ranged from 14% to 40%. In an area with high SP resistance [day 28 failure rates >80% (Gesase *et al.* 2009)], SP-IPTi had no effect on malaria but MQ-IPTi had a high protective efficacy (38%; 95% CI 12%, 57%) (Gosling *et al.* 2009).

The effect of IPTi on anaemia varied substantially between studies. The first IPTi trial in Ifakara showed a 50% protective efficacy and two subsequent studies in northern Ghana showed protective efficacies of 35% and 31% respectively. However, none of the other studies, including the MQ-IPTi trial, showed a significant effect on anaemia. Similarly the Ifakara trial showed a protective

efficacy of 30% against all cause hospital admissions supported by two further studies in Ghana that showed protective efficacies of 24% and 19% against this end-point. However, none of four other studies including MQ-IPTi showed a protective effect against all cause admissions.

An analysis of pooled data of the first six of the SP-IPTi trials (Schellenberg *et al.* 2001; Chandramohan *et al.* 2005; Macete *et al.* 2006; Grobusch *et al.* 2007; Kobbe *et al.* 2007; Mockenhaupt *et al.* 2007) showed a combined protective efficacy of 30% (95% CI 20%, 39%) against clinical malaria, 15% (95% CI 6%, 23%) against anaemia (Hb <8 g/dl) and 23% (95% CI 10%, 34%) against hospital admissions (Institute of Medicine 2008).

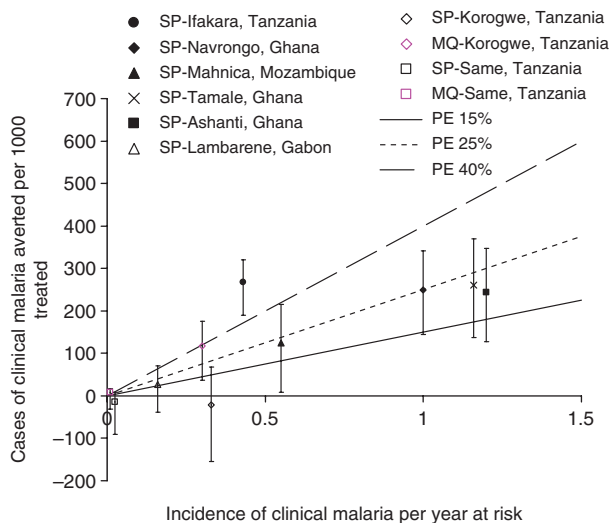
No study showed an effect on mortality but none had adequate power to detect this outcome. Furthermore, in trial settings early diagnosis and prompt treatment of most malaria cases could have prevented the development of severe disease and death. A large study on effectiveness of IPTi conducted in southern Tanzania (clinicaltrial.gov NCT00152204) that was completed recently would provide evidence on the effect of IPTi on mortality.

### Cases averted using IPTi in different transmission settings

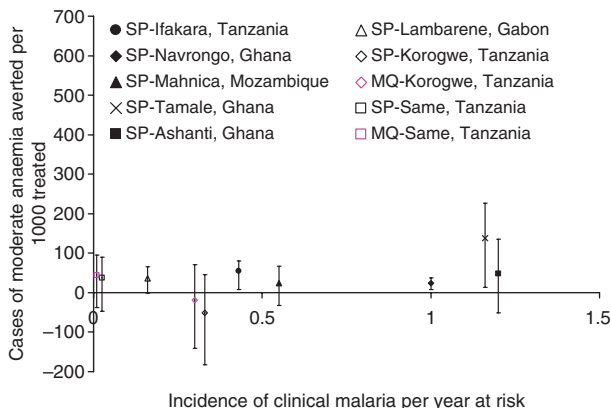
For any intervention to be acceptable for implementation the benefits must outweigh the risks and costs of the program. Cases of malaria, anaemia and all cause admissions averted per 1000 infants given IPTi estimated from the published studies are shown in Figures 1, 2 and 3 respectively. Cases averted were calculated by multiplying the incidence of malaria, anaemia and all cause hospital admissions in the placebo group by the protective efficacy of IPTi against each of these outcomes reported by the trials. A robust modelling of cases averted in non-trial settings has been undertaken previously (Ross *et al.* 2008), and here we present a more intuitive interpretation of the actual data available from the trial sites.

The relationship between the cases of malaria, anaemia and hospital admissions averted and the endemicity of malaria was explored by plotting these outcomes against the incidence of malaria in the placebo group in each trial as a proxy for transmission intensity. In addition, the expected number of cases averted based on fixed protective efficacies against clinical malaria are shown to indicate the range of potential benefits of IPTi and how this varies with transmission intensity.

As expected, the number of malaria cases averted by IPTi increased as the incidence of malaria increased, ranging from 125 to 275 per 1000 infants in moderate to high transmission settings with an average IPTi protective

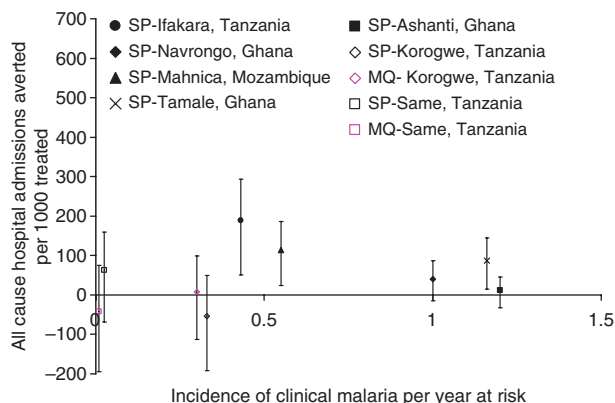


**Figure 1** Cases of clinical malaria averted per 1000 children receiving IPTi from seven trials by incidence rate of clinical malaria in the placebo group, Cases averted were calculated by multiplying the incidence of clinical malaria in the placebo group by the protective efficacy of IPTi against this outcome reported by the trials. Lines show fixed PE s of 15%, 25% and 40% by incidence of clinical malaria per year at risk.



**Figure 2** Cases of moderate anaemia per 1000 children receiving IPTi from seven trials by incidence rate of clinical malaria in the placebo group, Cases averted were calculated by multiplying the incidence of moderate anaemia in the placebo group by the protective efficacy of IPTi against this outcome reported by the trials.

efficacy of 25%. Neither numbers of cases of moderate anaemia nor all cause hospital admissions averted seem to be related to malaria incidence. Most studies showed small numbers of cases of anaemia and hospital admissions averted and the majority are not statistically significant.



**Figure 3** Cases of all cause hospital admission averted per 1000 children receiving IPTi from seven trials by incidence rate of clinical malaria in the placebo group, Cases averted were calculated by multiplying the incidence of all cause hospital admissions in the placebo group by the protective efficacy of IPTi against this outcome reported by the trials.

**Choice of drug regimen**

Factors that might influence the choice of drug for IPTi include its length of action, efficaciousness and safety. Drugs that have been used in trials and seem to have a suitable half life are SP, MQ and AQ. SP appears to have a good safety record. Only two serious adverse events (Steven-Johnsons syndrome) possibly linked to SP (Kobbe *et al.* 2007) (dose given at 15 months of age) were reported from approximately 4500 children involved in the seven trials. However, the declining efficacy of this drug means that it may not be useful in some regions. In the trial using MQ, the formulation used caused vomiting and irritability in 8% of children (Gosling *et al.* 2009). A bimonthly regimen of AQ-IPTi had a high protective efficacy against malaria in Tanzania (65%, CI 42%, 77%) (Massaga *et al.* 2003) and a monthly regimen of SP+AQ had higher protective efficacy than monthly SP+ single dose of artesunate in a seasonal IPTc study in Senegal (Sokhna *et al.* 2008). However, AQ has to be given over 3 days and the adherence to a 3 day IPTi regimen may not be optimal.

Another drug under consideration for IPTi is piperiquine, which is long-acting and could be given as a single dose. The combination of SP plus piperiquine had a better protective efficacy against malaria than SP plus AQ in an IPTc trial in Senegal (Sokhna *et al.* 2008). However, the combination of SP plus piperiquine has not yet gone through the rigorous clinical development process required for registration. Furthermore dihydroartemisinin plus piperiquine is currently undergoing clinical development and this ACT is considered to be the next generation first

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line treatment for non-severe malaria. It is probably better to use a different drug combination for first line treatment of non-severe malaria and for IPT in order to minimise the risk of over dosing and to prolong the usefulness of the drugs reserved for treatment purposes. Thus dihydroartemisinin plus piperaquine may not be appropriate for IPT programs.

### Frequency of doses and age at administration

The number of doses in an IPTi programme and the optimum ages at which to administer them are debatable. So far, IPTi doses have been given in varying combinations at 2, 3, 9, 12 and 15 months of age. The time and frequency of IPTi will depend on the age-specific incidence of malaria which varies between settings and the age-specific protective efficacy of IPTi. In the published trials, the protective efficacies during the 35-day post IPTi period after each dose differ considerably. The protective efficacies generally decrease as age increases. This may be explained by a suboptimal dose regimen given by age instead of by weight and by the fact that the children in the placebo group gain immunity and become less susceptible compared with the IPTi groups. Predicted effects of single doses of IPTi at different ages have been modelled (Ross *et al.* 2008) and show greatest benefits between 5 and 10 months of age in high transmission settings.

### Timing of IPTi

As the number of cases averted is linked to incidence, IPTi should be administered at times when incidence is high. This is affected by the age of children, as discussed above, but also by seasonality (Chandramohan *et al.* 2007). Duration and seasonal pattern of transmission varies greatly over the African continent. Administration of IPTi at times of high malaria transmission would maximise the number of cases averted but it requires a delivery system other than the EPI programme as the doses of IPTi need to be linked to a calendar date and not to the EPI vaccination schedule. How this would affect effectiveness of IPTi is unknown. However, seasonal IPTc delivered by community-based volunteers in controlled study settings showed promising results (Cisse *et al.* 2006; Sokhna *et al.* 2008).

### Effects on immunity

There are few studies of the effects of IPTi on immunity. Quelhas *et al.* (2008) showed that there is no difference in IgG and IgM against erythrocyte antigens (MSP-1<sub>19</sub>, AMA-1 and EBA-175) between children who received SP-IPTi or placebo and that in some children IgG levels were increased

in the SP-IPTi group. By contrast, Schreiber *et al.* (2007) showed a decrease of antibodies to *Plasmodium falciparum* lysate after a single dose of SP in one of the IPTi studies. The first study was designed to look at correlates of immunity during an IPTi study with follow up to 24 months of age, whereas the second was designed to detect exposure to blood stage infection following a single dose of SP. In addition the first study took place in Mozambique (Mayor *et al.* 2008) where the frequency of resistant alleles to SP was higher than in the second study in Ghana (Marks *et al.* 2004).

It is assumed that children will be exposed to malaria in between doses of IPTi when the drug concentration falls below the required levels for effective prophylaxis and will thus develop immunity. This appears to be true as there has not been a significant increase in the overall number of cases of clinical malaria in any of the trials during the period after IPTi administration. However, in one trial, there was an increased incidence of high parasitaemia malaria (Chandramohan *et al.* 2005) and in another an increased risk of severe anaemia cases in the second year of life (Mockenhaupt *et al.* 2007).

There are methodological issues in measuring immunity or lack of it in these studies due to the focal nature of malaria (Mwangi *et al.* 2008). Control groups have to be carefully selected to represent children at similar risk of malaria. In one IPTi study (Gosling *et al.* 2009) more than 60% of participants never reported a case of malaria up to 24 months of age and in another only 17% had a recorded episode of clinical malaria (Schwarz *et al.* 2008). Thus, using the whole cohort to explore immunity could result in a dilution of true differences to an undetectable level. One might expect that the effect of IPTi on immunity would be less pronounced in areas of high transmission because children are exposed to malaria outside the protected time and develop immunity. Equally, at low levels of transmission the chance of exposure to malaria during the period protected by IPTi will be low and thus IPTi may have no effect on the development of immunity. Moderate transmission settings probably offer the best opportunity to detect an impact of IPTi on the development of immunity to malaria. Stratifying for risk of malaria infection by using entomological data and other risk factors such as house type, ITN use, maternal education, distance to health facility and more may allow for improved assessment of differences in immunity comparing children with similar exposure.

### Role of IPTi for control of malaria

To understand the role of IPTi for malaria control, it is important to recognise that risk of malaria is heterogeneous

**Table 2** Proportions of Tanzanian population living in regions with different levels of prevalence of malaria parasite

	parasite prevalence in <5-year-old children				
	<2%	2–9%	10–19%	20–30%	>30%
Number of regions	6	4	5	3	5
% of population of Tanzania	23.9	18.8	22.2	13.5	23.0

Parasite prevalence figures are from the Tanzanian National HIV and Malaria Indicator Survey Preliminary Report 2007–2008. Population proportions calculated from the 2002 census <http://www.tanzania.go.tz/census/tables.htm>.

(Mwangi *et al.* 2008) and in some parts of sub-Saharan Africa malaria transmission has fallen substantially (Gosling *et al.* 2008a). This means that many parts of sub-Saharan Africa that were previously recognised as having moderate or high transmission may now have low transmission or contain pockets of low transmission (Guerra *et al.* 2008). For instance, endemicity of malaria in Tanzania is considered to be high (WHO 2008, MARA 2004). However, 40% of the population live in areas with a malaria parasite prevalence <10% in <5-year-old children (Table 2) (Tanzania Commission For Aids & Zanzibar Aids Commission, National Bureau Of Statistics & Measures 2008) Although the parasite prevalences are estimated from a small but representative sample in each region, the variation in transmission is remarkable and about one quarter of the population has a very low risk of malaria.

There is strong evidence that IPTi using an efficacious drug has a substantial impact on clinical cases of malaria and, in some settings, also has an effect on all cause hospital admissions. The public health impact i.e. cases of malaria averted, is proportional to the endemicity of malaria and thus IPTi will be most useful in highly endemic areas (Institute of Medicine 2008). IPTi using a drug with 25% protective efficacy would be expected to prevent approximately 100 cases of malaria per 1000 children receiving IPTi when the incidence of clinical malaria is 0.4 episodes per infant year of observation (Figure 1). What proportion of these 100 cases of clinical malaria prevented would have gone on to require hospital admission or have died is unknown. Assuming that 1% of these clinical cases die (Greenwood *et al.* 1991), 1000 children must be treated with three doses of IPTi to prevent one death. Clearly this calculation is crude, however the result is in agreement with a robust modelling exercise which suggests between 1 and 4 deaths averted per 1000 children treated, depending on the transmission setting (Ross *et al.* 2008) .. This compares to approximately five deaths prevented for 1000 children vaccinated with the nine valent

pneumococcal vaccine (Cutts *et al.* 2005) and 5.5 deaths per 1000 among those using insecticide treated bed-nets (Lengeler 2004). These estimates of deaths prevented by pneumococcal vaccination and ITNs are in children <5 years of age and thus are not directly comparable to the expected number of infant deaths prevented by IPTi. However these estimates are helpful to understand the relative role of IPTi in reducing child mortality in malaria endemic areas.

No malaria control strategy works in isolation and interventions should be tested in real life situations where a combination of strategies is in place. Strategies that are likely to interact are ITN distribution and Insecticide Residual Spraying (IRS) as they may reduce transmission and improving access to effective case management particularly through home management of malaria. The IPTi effectiveness trials in Southern Tanzania and UNICEF pilot implementation projects in Benin, Ghana, Mali, Senegal, Madagascar and Malawi (<http://www.ipti-malaria.org/>) will go some way in exploring how some of these strategies interact. However, unlike mass distribution of ITNs and improved access to treatment, IPTi is unlikely to affect transmission of malaria as only a small proportion of those at risk will be treated and given prophylaxis (Ghani *et al.* 2009).

## Conclusion

IPTi with an efficacious drug is likely to reduce cases of clinical malaria substantially in areas of moderate to high transmission. Although theoretically this should lead to a reduction in severe hospitalised cases and maybe deaths, there is inadequate evidence to support this. This may be due to the close follow up achieved in clinical trials. In addition, the impact of IPTi will probably be lower than expected due to decreasing malaria incidence in some parts of Africa. Thus, IPTi will be of benefit to malaria control primarily when it is applied to areas with moderate to high transmission with good EPI uptake.

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