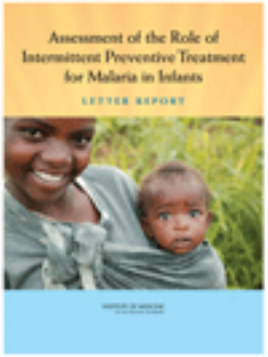

Assessment of the Role of Intermittent Preventive Treatment for Malaria in Infants: Letter Report

Committee on the Perspectives on the Role of Intermittent Preventive Treatment for Malaria in Infants

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Dear Dr. Brandling-Bennett:

At the request of the Bill and Melinda Gates Foundation, the Institute of Medicine (IOM) convened an expert committee to evaluate the evidence concerning intermittent preventive treatment for malaria in infants with sulfadoxine-pyrimethamine (IPTi-SP) and provide guidance on the value of continued investment in IPTi-SP. As this letter report describes in detail, the committee finds sufficient evidence to conclude that IPTi-SP is a valuable strategy for decreasing morbidity from malaria infections among infants who are at high risk because they reside in malaria-endemic areas in sub-Saharan Africa.

The committee greatly appreciated the briefing you provided on behalf of the Bill and Melinda Gates Foundation. The committee was also pleased with the comprehensiveness and clarity of the presentations made by the principal investigators of several of these IPTi studies, as well as with the lucid, inclusive, and extremely informative presentation made by a representative of the World Health Organization (WHO). We also appreciated the presentations given by others who have conducted related research or who have been involved in global policy deliberations related to IPTi. I am pleased to report the findings and recommendations of the committee, which reflect committee deliberations based on these presentations, additional analyses from the IPTi Consortium and the committee, and other relevant scientific literature.

This report begins with a summary of the committee's key messages, followed by background information on malaria, intermittent preventive treatment, the possibility of a rebound effect, and the Expanded Program on Immunization. The remaining sections present the committee's findings and recommendations, organized by the following topics:

- Efficacy of IPTi with Sulfadoxine-Pyrimethamine (based on review of individual and combined clinical trial results during treatment and follow-up periods)
- Potential collateral effects of IPTi-SP (resistance to SP, drug safety, relationship with childhood immunization programs, programmatic management, cost effectiveness)
- The potential value of continued investment in IPTi-SP

A complete list of the committee's conclusions and recommendations is compiled in Boxes 2 and 3 before the Appendixes.

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SUMMARY OF KEY MESSAGES

The Institute of Medicine (IOM) convened a committee with the following charge: (1) to review clinical trial methods and data analyses used in the studies conducted by the Intermittent Preventive Treatment in Infants (IPTi) Consortium (the Consortium); (2) to formulate consensus conclusions as to the advisability of further investment in IPTi using sulfadoxine-pyrimethamine (SP), on the basis of the results of six efficacy studies conducted over the last decade (or, if the evidence is sufficient, to consider investment with alternative drugs more recently studied); and (3) to consider drug safety (of prophylactic antimalarial drug use in infants in general and of treatment with SP in particular) and drug resistance; dosage regimens; potential collateral effects on other childhood healthcare programs (e.g., immunization); cost-effectiveness; and program management. As time and resources did not allow independent audits of trial conduct, data management, or analysis, the charge to the committee required it to assume, for the studies presented, that data collection and management were consistent with quality practices and that the analyses presented were correctly performed. The exception to this was the committee's undertaking to conduct limited analyses to confirm some of the results of unpublished data from the Consortium.

The purpose of the IOM review is to provide guidance to the Bill and Melinda Gates Foundation on a number of scientific, clinical, and programmatic issues related to IPTi, including whether the efficacy data from these studies support continued investment in IPTi-SP as a potentially useful tool to reduce morbidity from malaria in infants in some regions of sub-Saharan Africa. The Consortium (a group of autonomous institutions involved with malaria research in Africa, Europe, and the United States) is funded by the Bill and Melinda Gates Foundation.

The committee reviewed the published results of six IPTi-SP Consortium field trials as well as unpublished pooled analyses by the Statistical Working Group (SWG) of the Consortium. Based on these analyses, the committee found substantial evidence indicating that IPTi-SP significantly diminished the incidence of clinical malaria in infants living in areas of high and moderate intensity of transmission. Reported data showed that IPTi-SP diminished the incidence of clinical malaria episodes by approximately 20–30 percent in infants who received IPTi-SP rather than a placebo and who were followed from the time of their first dose until a point 5 months and 5 weeks after receipt of their last dose.[1] Data for the same period showed suggestive trends but not substantive evidence that IPTi-SP reduces the incidence of hospitalizations of patients with malaria parasites, anemia, and all-cause hospitalizations. The committee found that the extent of rebound is small compared to the overall benefit of IPTi-SP.

A 20-30 percent reduction in incidence of clinical malaria in these epidemiologic settings is comparable to the levels of efficacy observed for the use of impregnated bed nets (Lengeler, 2004), which have translated to important improvements in child survival when bed nets were implemented en masse (Schellenberg et al., 2001). **The committee therefore concludes that an intervention with results of this magnitude is worthy of further investment as part of a public health strategy to decrease morbidity from malaria infections in infants.**

[1] The 5-month follow-up period began 5 weeks after receipt of the last dose in order to allow time for the protective effect to wear off. Inclusion of the follow-up period is necessary to look for a rebound effect—that is, an increase in morbidity or mortality after treatment ends compared to a control group that had not received continuous chemoprophylaxis or intermittent therapy.

The committee was satisfied that the pooled analyses were done appropriately but had no information about how the SWG or the individual study teams ensured quality control of the uniformly defined outcomes or of data provided for the pooled analysis. Thus, **the committee recommends that the SWG obtain an independent technical audit of the accuracy of the study-level data and analyses included in the pooled analysis.**

The committee was not asked whether, when, or where IPTi-SP should be implemented. However, if an independent technical audit confirms the results presented, the committee would support the notion that IPTi-SP is ready to move to a new level. **If the decision is made to begin programmatic implementation, the committee recommends that IPTi-SP first be implemented in perennial, high- or moderate-intensity transmission areas in sub-Saharan Africa where the disease burden in infancy is high and SP resistance is not high, in order to obtain the greatest public health impact**. In considering the current and future role of IPTi-SP, one must be cognizant that in many areas of sub-Saharan Africa there is a trend for the malaria disease burden to be diminishing and particularly among infants. This might ultimately lead to changes in the desirable schedule for IPT-SP for infants and children.

The committee recommends that public health authorities monitor evidence for possible increases or decreases of SP resistance in areas or regions of implementation. However, the decreasing use of SP for treatment of malaria in favor of artemisinin-based combination therapy will likely lessen the threat of dissemination of resistance to SP.

If public health authorities elect to implement IPTi-SP, the committee recommends that monitoring efforts be undertaken in conjunction with initial implementation in select districts and countries to assess safety, effectiveness, cost-effectiveness, acceptability and sustainability at the community level, and logistical practicality; such efforts will help develop guidelines for larger-scale implementation. One important gap in the information about IPTi-SP is that there are not yet data to show its impact on infant and young-child mortality. An important goal should therefore be to try and gather such information, perhaps in conjunction with focal implementations and large-scale pilot projects. Strengthening the evidence base related to programmatic implementation and management could assist country-level decision makers at key decision points with respect to the national initiation, expansion, maintenance, or discontinuation of IPTi-SP. This approach can generate additional information on a variety of programmatic and pragmatic issues when IPTi-SP is used under real-life conditions.

BACKGROUND INFORMATION

Committee Process

The committee held a 3-day meeting to gather data and information as well as to discuss (1) the implications of the data and the peer-reviewed literature presented by the Consortium, and (2) other relevant literature available in the public domain. After the meeting, discussions continued by means of two teleconferences involving all committee members, as well as by frequent and highly detailed e-mail communications. There were also email communications and conference calls between the committee and members of the Consortium after the meeting.

The primary focus of this review was a collection of work completed by members of the Consortium (a group of 17 leading, autonomous institutions involved with malaria research in

Africa, Europe, and the United States and funded by the Bill and Melinda Gates Foundation) as well as by two United Nations agencies—the World Health Organization and the United Nations Children's Fund (IPTi Consortium, 2007a). These organizations came together in 2003 to "generate rigorous and compelling evidence to guide policy on IPTi" (IPTi Consortium, 2007a). Most of the work under consideration came from six peer-reviewed published studies[2] that were initiated by independent researchers, in most cases prior to the establishment of the Consortium. These studies were conducted in six separate locations across sub-Saharan Africa between 1999 and 2005.

The Consortium has added value to the separate studies in a variety of ways: It has conducted pooled analyses and has made those analyses available to the IOM committee. Because some of the work has not yet gone through the usual peer-review process that occurs prior to publication in a reputable journal, the IOM committee performed a careful assessment that included a multidisciplinary review of not only the results of the studies and of their interpretation by the Consortium researchers, but also of the relevant protocols and (where available) of safety monitoring reports. During the meeting, the committee also received an extensive briefing by the WHO on its latest technical and programmatic deliberations concerning the potential use of IPTi-SP in WHO's Global Malaria Program.

The committee's conclusions and recommendations relied upon currently available study reports and analyses that the Consortium provided, on discussions of unpublished data of the Consortium, on further analyses of the unpublished data by the committee, and on other publicly available literature. Because time and resources did not allow independent audits of trial conduct, data management, or statistical analyses, the committee was charged to assume that the data collection and management methods for the studies presented were consistent with high-quality practices and that the analyses presented were performed correctly. We requested and received limited additional analyses by the Consortium of some efficacy and safety data. Within this report the committee has identified which analyses come from the published papers, which analyses come from unpublished material from the Consortium, and which analyses the

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[2] Schellenberg, D., C. Menendez, E. Kahigwa, J. Aponte, J. Vidal, M. Tanner, H. Mshinda, and P. Alonso. 2001. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: A randomised, placebo-controlled trial. *Lancet* 357(9267):1471-1477; Schellenberg, D., C. Menendez, J. J. Aponte, E. Kahigwa, M. Tanner, H. Mshinda, and P. Alonso. 2005. Intermittent preventive antimalarial treatment for Tanzanian infants: Follow-up to age 2 years of a randomised, placebo-controlled trial. *Lancet* 365(9469):1481-1483.

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committee itself performed. A list of all materials reviewed by the committee is available to the general public through the National Academies' Public Access and Records Office (to contact by phone, 202-334-3543; by e-mail, PARO@nas.edu).

Malaria Epidemiology and the Burden of Malaria in Infants

Malaria is a leading cause of death among children in the developing world. According to WHO's estimates, 350–500 million cases of malaria occur each year worldwide; of the more than 1 million people who die of malaria each year, over 80 percent are young children in sub-Saharan Africa (Global Partnership to Roll Back Malaria and UNICEF, 2005). In Africa, malaria is estimated to cause 18 percent of childhood deaths (Rowe et al., 2006). Global public health initiatives to control malaria include WHO's Partnership to Roll Back Malaria, with its goal of decreasing the malaria burden by half by 2010 through a focus on treatment, prevention, and response. Goal six of the United Nation's Millennium Development Goals is to halt the spread of malaria and to begin the reversal of the incidence of malaria and other major diseases by 2015 (United Nations, 2008).

This report discusses clinical manifestations and consequences of malaria only in infants. The committee does not offer perspectives on other strategies for malaria prevention and control, such as the use of insecticide-treated bed nets or indoor residual insecticide spraying. Those interested may find a more detailed discussion of the history of malaria, of its clinical description, of the options for its treatment, and of the strategies and initiatives used to control it in a previous IOM report entitled *Saving Lives, Buying Time* (IOM, 2004) available at www.nap.edu.

Human malaria is caused by infection with one of four *Plasmodium* species transmitted by the bites of female *Anopheles* mosquitoes. Of the four human *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. malariae,* and *P. ovale)* known to cause infections in humans, *P. falciparum* is the most common species found in sub-Saharan Africa; it is associated with severe disease and high case fatality. In malaria-naïve individuals, infection frequently leads to clinical illness and is associated with a high risk of death. As children in malaria-endemic areas experience repeated episodes of malaria infection, they progressively acquire increasing degrees of immunity. Having acquired some degree of immunity, individuals may still become infected (i.e., may have asexual parasites evident in their erythrocytes) after being bitten by infected anophelines; in such partially immune people, however, overt clinical disease is less common, and severe disease is rare.

The age at which children living in malaria-endemic areas achieve partial immune status is determined by the intensity and seasonality of malaria transmission. The intensity of malaria transmission is classified as low, moderate, or high on the basis of either entomological inoculation rates (EIRs) or measures of parasite prevalence (e.g., cross-sectional surveys with examination of blood smears). Transmission patterns are further classified as either perennial (conditions that favor year-round exposure and infection) or seasonal (conditions that favor only periodic exposure and infection). Immunity is acquired most rapidly in perennial and high-intensity transmission settings. In areas of highest exposure, children younger than 2 years of age are at the highest risk for severe disease and death. For example, in areas of high malaria transmission in Tanzania, 70–80 percent of hospitalizations among infants younger than 1 year of age are due to severe malaria. As transmission decreases and seasonality increases, the burden

of clinical disease is spread over a wider age distribution. Thus, in moderate-transmission settings approximately 70 percent of hospitalizations for severe malaria occur during the first 5 years of life. In low-transmission venues the severe malaria burden is distributed over an even wider age range, as approximately 65 percent of hospitalizations for severe malaria occur among children 0–14 years of age (Reyburn et al., 2005). In sub-Saharan Africa, where the malaria burden is highest, most deaths due to malaria occur in children under 5 years of age.

The two common clinical presentations of severe malaria in children are severe anemia and cerebral malaria. These forms of severe disease are associated with a case-fatality rate of up to 20 percent. Severe anemia, defined as a hemoglobin concentration less than 5 g/dL, occurs in the first or second year of life, while cerebral malaria is more commonly diagnosed in older children. As exposure to malaria decreases in childhood, the age at which children develop cerebral malaria increases (Reyburn et al., 2005).

The relative but evident protection observed among infants during the first few months of life, even in areas of high transmission intensity, is believed to be mediated by several factors including transplacentally acquired maternal antibodies and the relatively high hemoglobin F content of the very young infant's erythrocytes (Riley et al., 2001). In areas of high transmission, however, even infants younger than 6 months of age can become infected. For example, one study showed that during the wet (malaria) season in Navrongo, Ghana, nearly half of the children younger than 6 months of age had parasitemia; the study did not report the incidence of clinical malaria illness (Chandramohan et al., 2007). Interventions to decrease exposure to malaria infection can lead to an increase in the age at which infants and young children acquire their first infections (Greenwood, 2006).

Intermittent Preventive Treatment

Intermittent preventive treatment (IPT) is the administration of a full therapeutic course of an antimalarial drug at defined intervals to at-risk individuals, regardless of the presence or absence of malaria infection (parasitemia) or symptoms. This treatment may provide benefit by completely or partially clearing any existing asexual erythrocytic stage parasites in the bloodstream at the time of administration or by subsequently preventing or reducing the biomass of new malaria infections until the drug level decays below inhibitory levels (O'Meara et al., 2005).

Intermittent Preventive Treatment in Pregnancy

Intermittent preventive treatment of malaria in pregnancy (IPTp), which is administered at the time of antenatal clinic visits, is recommended by WHO for preventing malaria during pregnancy. For IPTp, WHO currently recommends the use of SP (WHO, 2004a). A review conducted by ter Kuile et al. (2007) examined the effects of SP resistance on the efficacy of IPTp-SP. In this systematic review, nine randomized controlled trials of IPTp-SP in Africa were matched on the basis of country and time of trial with treatment studies of SP in symptomatic children. Protective efficacy of ITPp-SP was determined by comparing the different control groups (chloroquine prophylaxis, placebo (case management), or monthly IPT regimen) with a treatment group defined as receiving 2 doses of SP during pregnancy. Treatment failures of SP in

symptomatic children from the matched pediatric treatment studies were used to determine the protective efficacy of IPTp-SP vis-à-vis different levels of SP resistance. In these studies, the "assessment of the treatment response of children to SP was based on standard WHO criteria and defined as the proportion of total treatment failures by day 14, which combines clinical and parasitologic failure" (ter Kuile et al., 2007, p. 2605). Interestingly, the authors found that even given poor SP curative efficacy for the treatment of symptomatic disease in children (i.e., SP treatment failures as high as 30 percent in some areas), there was no strong decline in the protective efficacy of IPTp-SP (ter Kuile et al., 2007).

Intermittent Preventive Treatment in Infants

As indicated in this report, IPTi involves the administration of full therapeutic doses of an antimalarial to asymptomatic infants in conjunction with some of the infant's healthcare visits to receive immunizations; IPTi-SP is IPTi with SP as the antimalarial. The infant immunization schedule followed in almost all countries in sub-Saharan Africa is shown in Table 1 (Aylward et al., 2004). The recommended schedule of IPTi generally proposed by the Consortium (in particular for settings of high and perennial transmission where the disease burden is high in infants) is to administer doses in conjunction with the 10-week, 14-week, and ~9-month Expanded Program on Immunization (EPI) visits (see Table 1). Some studies have assessed IPT-SP doses given up to age 15 months (Grobusch et al., 2007a; Kobbe et al., 2007; Mockenhaupt et al., 2007). Administering a dose of SP in the second year of life, at 15 months of age in some of the studies, is relevant to areas where malaria transmission is highly seasonal. In the one Consortium trial site where malaria is highly seasonal, the last dose of SP or placebo was administered at 12 months of age. Targeting administration of doses of IPTi beyond 12 months of age in sub-Saharan Africa, however, is not currently practical: Regular EPI contacts are not scheduled beyond 9 to 12 months of age, although occasional mass campaigns (which include toddlers) with the measles vaccine or with the oral polio vaccine are carried out. In the future, an immunization contact may be added to the second year of life (e.g., to administer an additional dose of certain conjugate vaccines and a second dose of measles vaccine). Should such a change in the EPI schedule occur, information on IPTi-SP administered during the second year of life becomes of practical importance. Taking these points into consideration, the committee primarily focused its review on IPTi-SP in infants up to 1 year of age, a focus that is both consistent with the proposed IPTi-SP schedule in Table 1 and compatible with current EPI practices in most of sub-Saharan Africa.

TABLE 1 World Health Organization—Recommended EPI Schedule

EPI Contact	Age of Infant	Intervention	Proposed contacts for IPTi-SP
1	Birth	BCG, OPV (monovalent HBVat birth is recommended in areas where HBV seroprevalence is high and maternal-infant vertical transmission represents a public health problem)	
2	6 weeks	DPT, HBV[a], Hib conjugate, OPV	
3	10 weeks	DPT, HBV[a], Hib conjugate, OPV	+
4	14 weeks	DPT, HBV[a], Hib conjugate, OPV	+
5	9 months [b]	Measles and vitamin A (yellow fever vaccine is recommended for infants living in highly endemic areas)	+

NOTE: BCG = Bacille Calmette Guerin vaccine against tuberculosis; DPT = diphtheria toxoid, whole-cell pertussis, and tetanus toxoid vaccine combination; HBV = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; OPV = oral polio vaccine. Currently, many countries in sub-Saharan Africa are using a "pentavalent vaccine" at 6, 10, and 14 weeks (contacts 2–4) that delivers DPT, HBV, and Hib in a single inoculation.

[a] An acceptable alternative regimen for HBV is to give monovalent HBV at birth and at 6 and 14 weeks. However, this somewhat logistically complicated schedule (because of the skipped HBV dose at 10 weeks of age) is becoming less common as tetravalent (DPT, HBV) and pentavalent (DPT, HBV, Hib) combination vaccines (which require only a single injection) are becoming ever more popular.

[b] 9–12 months in areas where measles in infants has become uncommon.

SOURCE: Aylward et al., 2004; WHO, 2004b.

Intermittent Preventive Treatment in Children and Seasonal Intermittent Preventive Treatment

Intermittent preventive treatment in children (IPTc) refers to the use of IPT in children up to 5 years of age (Chandramohan et al., 2007). Seasonal IPT (sIPT) is defined as the administration of IPT to infants or children for a limited calendar period that coincides with the intense but highly seasonal transmission of malaria in certain ecologies, as in parts of West Africa. In practical terms, IPTc and sIPT often coincide, as seen in several studies that have investigated the relatively short-term use of IPT in children up to 5 to10 years of age during periods of marked seasonal transmission (Cisse et al., 2006; Dicko et al., 2004).

Concern About a Possible Rebound Effect

Theoretically, by delaying the acquisition of natural immunity, administering anti-malarial drugs either continuously or intermittently might lead to a "rebound"—an increase in morbidity or mortality after treatment ends compared to a control group that had not received continuous chemoprophylaxis or intermittent therapy. The committee carefully addressed concerns about continuous chemoprophylaxis by reviewing pertinent literature. For intermittent therapy, we considered in detail, both published and unpublished evidence provided by the IPTi Consortium.

Greenwood (2006, p. 983) has defined (continuous) chemoprophylaxis as "the administration of a drug in such a way that its blood concentration is maintained above the level that inhibits parasite growth, at the pre-erythrocytic or erythrocytic stage of the parasite's life cycle, for the duration of the period at risk." Experts in malaria (Greenwood, 2006; White, 2005) unequivocally conclude that chemoprophylaxis provides benefits to children living in malaria-endemic areas during the period of prophylaxis, in particular citing the diminution of episodes of clinical malaria. In contrast, experts are uncertain as to what happens after cessation of continuous chemoprophylaxis of children. In particular, given the limited data, there is not a consensus on whether interference with attainment of immunity during the period of continuous prophylaxis will lead to an increase in clinical malaria infections after cessation of chemoprophylaxis. If there is such an increase, malariologists do not agree on whether the overall burden of clinical malaria assessed from initiation of prophylaxis to completion of extended follow-up post-cessation of drug will be less than in a placebo group followed for the same time period. Surprisingly, very few well-designed and executed studies are available to address this important question.

Three recent comprehensive reviews on continuous chemoprophylaxis have been published (Geerligs et al., 2003; Meremikwu et al., 2005, 2008). All three reviews identified just a few controlled trials of continuous chemoprophylaxis that were considered to be of sufficient rigor of design and description as to shed light on the question of rebound. The IOM committee only considered trials that (1) had a control group, (2) looked at clinical events as well as parasitemia, and (3) compared the treatment group during pre- and post-chemoprophylaxis to an appropriate control group. These reports are inconsistent as to whether continuous chemoprophylaxis renders infants or children more vulnerable to develop clinical malaria than children in the control group after the prophylaxis period has ended (Greenwood et al., 1995; Menendez et al., 1997; Otoo et al., 1988).

A "worst-case" situation with respect to the impedance of acquisition of immunity and to the potential for rebound occurring would be chemoprophylaxis of infants in an area of perennial moderate or high intensity transmission. The IOM committee concluded that the one modern well-designed and -executed study that illustrates this worst-case situation was carried out by Menendez et al. (1997) in Ifakara, Tanzania, which at the time of the study was a perennial, high-intensity transmission area; IPTi-SP was subsequently tested at this site (Schellenberg et al., 2001, 2005).

At 8 weeks of age, 832 infants were randomly allocated to one of four groups (i.e., 204–213 infants per group) to receive: (1) 2.5 ml of pyrimethamine-dapsone syrup (3.13 mg pyrimethamine and 25 mg dapsone per 5 ml) plus oral placebo (the DP group), (2) 2.5 ml of pyrimethamine-dapsone syrup plus oral iron syrup (the DI group), (3) oral iron syrup plus oral placebo (the IP group), and (4) two types of placebo syrup, (the PP group). The oral iron or similar-appearing placebo was given daily, whereas the anti-malarial or its placebo was given weekly from 8 weeks of age though 52 weeks of age. Episodes of malaria during that period of follow-up were considered to have occurred during the intervention period. A second period of follow-up proceeded for all groups from 53 weeks of age through 92 weeks of age.

During the intervention period, pyrimethamine-dapsone prevented 60.5 percent (95 percent CI, 48.2–69.9; $p<0.001$) of first or only episodes and 64.4 percent (95 percent CI, 53.3–73.0; $p<0.001$) of multiple episodes of clinical malaria compared with results in the placebo group. However, children who had received pyrimethamine-dapsone during the intervention period had significantly higher rates of first or only malaria episodes during the post-therapy

follow-up period (relative risk, 1.8; 95 percent CI, 1.3–2.6; $p<0.001$). The effect for multiple (two or more) malaria episodes was nearly the same: with a relative risk of two or more post-therapy malaria episodes of 1.8 (95 percent CI, 1.3–2.5, and $p<0.001$) in the chemoprophylaxis group. In the analysis of all subjects in the cohort, including the analysis of those children who had been withdrawn during the intervention follow-up period, there remained a significantly higher clinical malaria rate among recipients of pyrimethamine-dapsone compared with the rate among the controls (relative risk, 1.4; 95 percent CI, 1.1–1.7; $p=0.02$). The study investigators concluded that "the moderate efficacy against clinical malaria afforded by chemoprophylaxis during the first year of life was sufficient to impair the development of naturally acquired immunity" (Menendez, 1997, p. 848).

Menendez et al. (1997) also pointed out that the rebound effect appeared within a few weeks of the cessation of therapy. Indeed, "the frequency of clinical malaria in the 8 weeks after prophylaxis stopped was about twice as high as that seen in the placebo group at any time during the intervention period" (Menendez, 1997, p. 848). The authors attributed this increase to delaying risk of exposure in the absence of drug until an age when the protective effect of maternal antibodies had completely disappeared and little or no immunity had been acquired from malaria infections during infancy. They also concluded that continuous malaria prophylaxis during infancy just delayed the risk of malaria to an older age. This clear (albeit worst-case) example, of rebound with continuous chemoprophylaxis, has led some stakeholders to question whether IPTi may also lead to rebound, and if so, its relative importance with respect to the overall net benefit of IPTi.

Expanded Program on Immunization

Because IPTi-SP programs use the Expanded Program on Immunization (EPI) to distribute SP, this letter report comments on the status of the global EPI, which WHO initiated in 1974 after the success of the Smallpox Eradication Program. An estimate produced by WHO found that only about 5 percent of children were receiving three doses of the diphtheria, pertussis, and tetanus combination vaccine (DPT) and the oral polio vaccine (OPV) in 1974; a decade later, the coverage had increased to approximately 40 percent. As a result of the efforts made to strengthen immunization services in developing countries in the early 1980s, an estimated 70 percent of infants were receiving three doses of DPT (DPT3 coverage) by the late 1980s; however, DPT3 coverage did not increase further over the next decade. With the launch of the Global Alliance for Vaccines and Immunization or GAVI in 2000, unprecedented financial resources, political will, and managerial expertise became available to strengthen immunization services in the world's poorest countries. Consequently, DPT3 coverage by 2005 reached 79 percent globally—67 percent among the countries of sub-Saharan Africa (Arevshatian et al., 2007)— with greater homogeneity of coverage than previously within most developing countries.

In the early 1980s, a detailed review of numerous published studies of optional immunization schedules (Halsey and Galazka, 1985) led to the recommendation of a standard immunization schedule for EPI (Henderson et al., 1988). The selected schedule of 6, 10, and 14 weeks for DPT administration was based on starting at the earliest age at which no detrimental effect of early immunization had been observed; the second and third doses would then be administered at the shortest interval that would achieve close to 100 percent protection against

diphtheria and tetanus. Each country selects the immunization schedule to use for its children. Although several different schedules are used throughout the world, almost all countries in the areas of high and moderate malaria transmission in Africa have adopted the immunization schedule shown in Table 1 (WHO, 2008a).

Supplemental immunization activities, first introduced through the polio eradication program, were subsequently also adopted for control of measles mortality. For measles, an initial campaign to provide an extra dose to all children regardless of past immunization status targets children from 9 months to 14 years of age. Subsequent campaigns, held approximately every four years, target children from 1 to 4 years of age to provide a second dose to children born after the initial campaign. After these campaigns have reached 95–98 percent of eligible children in many districts, dramatic declines in the transmission of measles have occurred in many African countries (CDC, 2007).

A recent review estimates that immunizations save more than 3 million lives each year (Brenzel et al., 2006). A number of non-vaccine interventions have been added for programmatic administration through the EPI infrastructure. These include vitamin A supplementation, iodine supplementation, and distribution of insecticide-treated bed nets for control of malaria (Grabowsky et al., 2005, 2007). The administration of vitamin A through use of the EPI infrastructure has had variable success (Arevshatian et al., 2007; Dalmiya et al., 2006; WHO/CHD, 1998). Further analysis of factors associated with successful supplementation with vitamin A would be useful for assessing the potential of the proposed IPTi-SP program.

EFFICACY OF IPTi WITH SULFADOXINE-PYRIMETHAMINE

Framing the Discussion

To help frame the discussion about the efficacy of IPTi-SP, the committee considered as a benchmark the above-mentioned experience of a randomized, placebo-controlled trial of continuous chemoprophylaxis of infants (albeit with drugs other than SP) that was carried out in Ifakara, Tanzania (Menendez et al., 1997). Some of the same investigators who would become leaders in the Consortium subsequently tested IPTi-SP at this Tanzanian site. In that trial of continuous chemoprophylaxis in infants, the frequency of clinical malaria was significantly reduced compared with the frequency of clinical malaria in the control group during the treatment period. During the continuing follow-up after cessation of prophylaxis, however, the situation reversed: Children who had received continuous chemoprophylaxis experienced significantly higher rates of clinical malaria than did the control group of children who had previously received placebo. Much of the excess risk of malaria occurred within the first two months after chemoprophylaxis was stopped. The authors concluded that continuous chemoprophylaxis of infants in a site of perennial malaria transmission prevented the acquisition of immunity. Thus, the risk of developing malaria was delayed until the time when drug was no longer being administered (Menendez et al., 1997).

The fundamental tenet of IPTi-SP is that the administration to infants of a few (three) full therapeutic doses of SP (administered concomitantly when the infants receive routine EPI vaccines) will significantly diminish the incidence of malaria morbidity but will not substantially reduce the acquisition of immunity. In practical terms, this means that IPTi-SP must significantly protect infants from malaria when the doses of IPTi are administered but that this intervention

should not leave the child at increased risk of rebound episodes of malaria after the last dose of IPTi-SP (compared with those in a control group who had not received SP but who were followed for the same time period). Rebound episodes of malaria should be minor relative to the protective benefit during the treatment period.

Statistically, the effect of IPTi-SP should be assessed by comparing the SP group and the placebo group from randomization through several months after cessation of the intervention. There is, however, much to be learned by comparing the IPTi-SP and placebo groups during the intervention period and during the various follow-up periods for the biological reasons to be mentioned. After administration of a single dose, SP provides a relatively long period of antimalarial activity (Coulibaly et al., 2002; Greenwood, 2006; White, 2005). Several factors determine the duration of drug efficacy in killing asexual-stage erythrocytic parasites already in the subject's blood or in killing new parasites after exposure to infected anophelines during the period after a dose (Watkins and Mosobo, 1993). These include the drug pharmacokinetics that represent the composite of an individual's physiological and biochemical clearance processes by which blood and tissue levels of the drug progressively fall, the degree of drug sensitivity of the parasites within the individual, and the intensity of exposure to infected mosquitoes. When administered in areas where *Plasmodium* parasites are quite sensitive, the "drug effect" (i.e., the ability to reliably kill parasites or to suppress them below a clinically critical threshold) generally lasts approximately 1–2 months, with up to two months of protection only being achieved in settings with highly SP-sensitive parasites (Coulibaly et al., 2002; Watkins and Mosobo, 1993).

One illustrative example of data comes from the field study of Coulibaly et al. (2002); Just before the onset of the malaria season in Bandiagara, Mali, where malaria transmission is highly seasonal but intense, 400 subjects 3 months of age to 20 years of age were randomly allocated to receive a single dose of SP (adjusted by age) or to receive no treatment. The subjects were actively followed, with weekly clinical evaluations performed and blood smears made to detect cases of clinical malaria. Treatment with SP exhibited a clear but time-limited protective effect against clinical episodes of malaria (Figure 1). SP delayed the median time to the first episode of clinical malaria from 38.5 days to 68 days but, similar to the chemoprophylaxis trial by Mendendez et al. (1997), a sharp increase in malaria episodes was seen in the third month after SP treatment, just after protective SP levels would be expected to have waned. The overall incidence of clinical malaria throughout the study period was similar in the two groups.

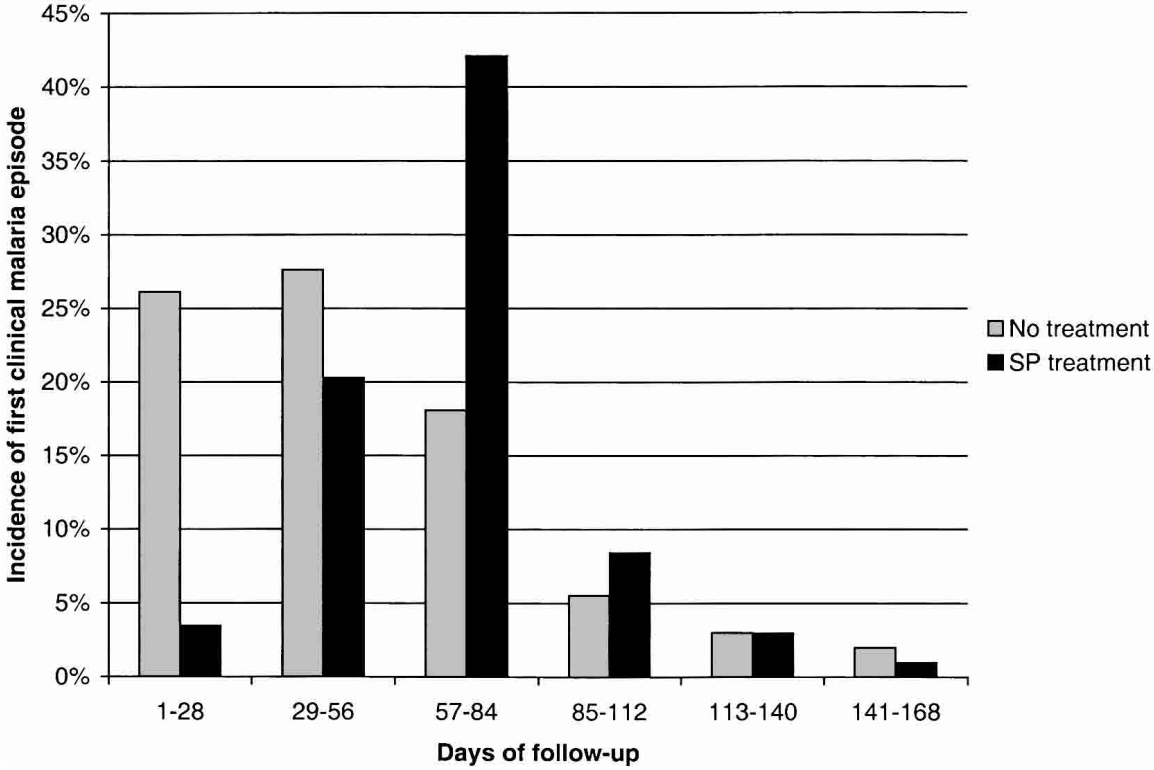

FIGURE 1 Incidence of first clinical malaria episodes over the course of the malaria season among subjects who received curative sulfadoxine-pyrimethamine.
SOURCE: Coulibaly et al., 2002. Reprinted with permission from the *American Journal of Tropical Medicine and Hygiene*. Copyright 2002 by the American Society of Tropical Medicine and Hygiene.

In the six IPTi-SP studies, all infants received a dose of SP or of placebo at 9 months of age, as either the second or the third SP (or placebo) dose. Notably, the previous dose of SP or of placebo had been administered at either 3 or 4 months of age, depending on the study (Table 2). In each study, therefore, the infants had 5–6 months of follow-up between doses, a follow-up time that is considerably longer than the 1–2 months during which drug levels of SP would be expected to remain protective and including early post-therapy period when rebound would be most likely to manifest (Coulibaly et al., 2002; White, 2005). Similarly, in the three studies in which children received their SP or placebo doses at 3, 9 and 15 months of age, the period between 9 and 15 months is far longer than one would expect the drug's protective effect to have lasted and to have been the only factor responsible for providing protection against the disease. Stated in another way, whatever the protective effect of SP during the intervention period, because of the long periods of time between the last two doses (either the time between the ages of 4 and 9 months or the time between the ages 9 and 15 months), one would expect the children to have considerable exposure to infected mosquitoes during periods when they do not have protective blood levels of the drug, and therefore they presumably will have repetitive immunologic stimulation by *Plasmodium*.

The ideal approach to assessing the efficacy of IPTi-SP would have been to have reviewed an array of large, randomized clinical trials conducted under several geographic and epidemiologic scenarios. These trials would have studied various clinical outcomes, including total burden of morbidity both during the period of SP use and for a subsequent period during which rebound could occur. The data available to the IOM committee were not ideal in all these

aspects. In particular, the six studies were limited to areas of high and moderate intensity of transmission. Nonetheless, the totality of the data did allow the committee to draw substantial conclusions about the potential of IPTi-SP in areas of high transmission. A more specific discussion of pertinent methodological issues follows.

Methods Used to Detect Clinical Outcomes of Interest in the IPTi-SP studies

Local conditions and logistical considerations led to differences among the six studies with respect to the active and passive follow-up methods used to detect relevant outcomes such as cases of malaria, anemia, hospitalizations of children with malaria parasites and all-cause hospitalization. As a convenience for the reader, Box 1 summarizes the different methods used in the six trials.

BOX 1
A Summary of the Methods Used in Each IPTi-SP Study to Detect Critical Outcomes Including Clinical Malaria and (Depending on the Specific Study) Anemia, Hospitalization of Patients with Malaria Parasites, and All Cause Hospitalizations

Study	Surveillance Methods
Ifakara Schellenberg 2001	Passive and active (three-monthly cross-sectional surveys including blood smears): "A round-the-clock hospital-based clinical surveillance system has been operating since 1994 and is described in detail elsewhere. In brief, at each consultation, and after identification of the patient, a detailed standardized questionnaire was completed documenting signs and symptoms. Blood films were prepared for malaria parasite examination, and the packed-cell volume was measured if there was a history of fever in the preceding 24 h, if the axillary temperature was at least 37..5ºC, or if the child appeared pale. Costs of treatment for children in the study were covered by the project. Blood samples were collected to assess seroconversion to EPI vaccines (DTP/OPV at 9 months, measles at 12 months), haemoglobin genotype (12 months), packed cell volume, and *P falciparum* parasitaemia (12 and 18 months). Because follow-up was based on passive case detection and cross-sectional surveys, we checked the vital status of each child by home visits at 12, 15, and 18 months of age."
Navrongo Chandramohan 2005	Passive and active (cross-sectional surveys including blood smears at 3, 9, 12 and 18 months and visit to detect illness at 23 months): "All study infants were given a photo identity card, and their guardians were asked to bring the card whenever they visited an EPI clinic or other health facility. A field worker visited the households of study infants one or two days before the date when DPT-2 (IPT-1), DPT-3 (IPT-2), and measles (IPT-3) vaccinations were due to remind caretakers to attend an EPI clinic. A similar visit was made shortly before the IPT-4 administration at the age of 12 months was due. Finger prick blood samples for assessing packed cell volume, malaria parasitaemia, and the immune response to EPI vaccines were taken when infants received IPT-1, IPT-3, and IPT-4…Study children were visited at home at 18 months of age to collect finger prick blood samples for assessing packed cell volume and the presence of malaria parasitaemia and again at 23 months of age to assess their health…A fieldworker visited a random 20% sample of study children at home within four weeks after administration of IPT dose 1 or dose 2 to assess adherence to administration of iron at home and to inquire about adverse events."
Manhiça Macete 2006	Passive and active (cross-sectional serological surveys at months 3, 4, 5, 9, 12; blood smears only at 12 months or if ill or febrile): "Parents were encouraged to attend the outpatient clinic at the Manhiça Health Center and the Maragra Health Post whenever the child became ill. An around-the-clock hospital-based clinical surveillance system has been operating in the area since 1997 and has been described in detail elsewhere. In brief, at each consultation, a detailed standardized questionnaire was completed that documented signs and symptoms. Blood films were prepared for malaria-parasite examination, and the packed cell volume (PCV) was measured if there was a history of fever during the preceding 24 h or if the infant's axillary temperature was greater or equal than 37.5 ºC. Episodes of uncomplicated malaria in study infants were treated with 7 days of oral quinine if the IPTi intervention had been administered within the preceding 2 weeks. Besides the

BOX 1 Continued

	passive case detection surveillance, the assessment of safety was conducted through home visits to assess morbidity 1 week after each dose, through specific registration of dermatological complaints of children attending the hospital, and through blood tests performed 1 month after receipt of the second IPTi dose."
Kumasi Kobbe 2007	Passive and active (monthly cross-sectional surveys including blood smears): "Episodes of clinical malaria, anemia, and adverse events were monitored monthly through active follow-up visits (20,733 visits in total). Blood films were obtained and hemoglobin levels were measured at each scheduled contact (active visit) or when patients presented independently from regular visits (passive case detection). Relevant events occurring between active visits and hospital attendances were documented on weighing charts. In addition to follow-up visits, trained field workers conducted house visits to improve compliance, foster information exchange, and encourage self-reporting of medical conditions."
Lambaréné Grobusch 2007	Passive and active (monthly visits to detect illness, blood smears only if ill or febrile): "Safety and tolerability of treatment was assessed on 2 visits on days 7 and 28 after treatment. Field-workers conducted monthly home visits for health status assessment. In the case of an acute febrile disease, a fingerprick blood sample was obtained and a thick blood film examined. The active follow-up continued until 30 months of age was reached. Parents were encouraged to present at the research unit if the child experienced health problems between the active follow-ups. On days 0 (before) and on days 7 and 28 after each drug administration, clinical chemistry, full blood count, and thick blood smears were performed."
Tamale Mockenhaupt 2007	Passive and active (monthly visits to detect illness, blood smears only if ill or febrile): "The individual follow-up schedule consisted of the three treatment visits at 3, 9, and 15 months of age and regular review visits at 6, 12, 18, 21, and 24 months of age (± 4 weeks each). Field workers visited the participants' home 2 days preceding a regular visit to remind parents. For passive case detection, parents were instructed to bring their children to the health center in case of any health problem. In addition, field workers performed monthly checkup visits at the participants' homes. Passive case detection was affected by a civil conflict which involved a state of emergency and changing curfews during the follow-up period (until August 2004). Consequently, children occasionally could not attend the health center or hospital after late afternoon hours. At each scheduled visit, children were clinically examined, a standardized medical history was obtained, and a venous blood sample was collected. A history of fever within the past 48 h was recorded when voluntarily reported. Blood samples were collected at unscheduled visits in the case of fever or a history of fever or when requested by the clinician."

SOURCE: Chandramohan et al., 2005, pp. 728-729;Grobousch et al., 2007, p.1596;Kobbe et al., 2007, p.17;Macete et al., 2006, pp.278-279;Mockenhaupt et al., 2007, p. 3274;Schellenberg et al., 2001, p.1472.

Time Periods and Method of Analysis Taken into Consideration in Assessing Efficacy

In the view of the committee**,** estimates of the efficacy of IPTi-SP should take into account both the period spanning the dosings with SP and a further follow-up extending for months after the last dose of SP, the latter period representing when rebound might be expected to occur. The ideal length of follow-up after cessation of treatment with SP or placebo to detect rebound can be debated: Too short a period might exclude true cases of rebound. On the other hand, if the total burden of disease is measured from randomization to end of follow-up, too long a period might mask a beneficial effect (by diluting the impact of preventive SP) or make it harder to detect a rebound effect (since rebound is most prominent within 1–3 months after stopping chemoprophylaxis [Menendez et al., 1997] and following a single curative dose of SP [Coulibaly et al., 2002]). The optimal situation would therefore be to include a relatively long follow-up period and to analyze the data in a way that accounts for potential time-varying effectiveness of IPTi-SP.

To address the choice of follow-up period and considering what is known about the pharmacokinetics and pharmacodynamics of SP, the committee proposes that a period of time similar to the amount of time directly under the influence of SP would be a reasonable average target follow-up period. For example, if the time from first to last dose of IPTi-SP is approximately 7.5 months—between 10 weeks and 10 months of age—then a reasonable follow-up period to detect rebound would be 7.5 months from the age of the last dose of SP (i.e., until age 17.5 months). This target could vary depending on the intensity of transmission, and thus on the potential for a rebound infection to occur. In two of the six IPTi-SP trials (Ifakara and Manhiça) the last dose of SP was administered at nine months of age, whereas in Navrongo the last dose was given at 12 months of age. In the three other studies (Kumasi, Lambaréné, and Tamale) the last dose was administered at 15 months of age (Table 2).

TABLE 2 Characteristics of the Six IPTi-SP Trials

Location, Country	**Ifakara, Tanzania**	**Navrongo, Ghana**	**Manhiça, Mozambique**	**Kumasi, Ghana**	**Lambaréné, Gabon**	**Tamale, Ghana**
Reference	***Schellenberg et al.*** *Lancet 2001, 2005*	***Chandramohan et al.*** *BMJ 2005*	***Macete et al.*** *JID 2006*	***Kobbe et al.*** *CID 2007*	***Grobusch et al.*** *JID 2007*	***Mockenhaupt et al.*** *AAC 2007*
Recruitment (years)	1999–2000	2000–2002	2002–2004	2003–2005	2004–2005	2003
Entire study period	8/1999–4/2001	9/2000–6/2004	9/2002–2/2004	1/2003–9/2005	12/2002–8/2006	3/2003–7/2005
EIR/year	29	418	38	400	50	Not available
Transmission	Perennial	Highly seasonal	Perennial with seasonal peaks	Perennial	Perennial with seasonal peaks	Perennial with seasonal peaks
Predicted annual incidence of clinical malaria in placebo group (all episodes)	0.43	1.0	0.55	1.29	0.22	0.88
In vivo SP treatment resistance by day 14 %	31 (1999–2000)	22 (2004)	17 (2001)	NA	21 (2004)	14 (2002)
Use of bed nets (treated or untreated), % placebo/SP	67/68	17/19	0/0 (14/15)	20/20[a] (39/38)	5/5 (80/80)	<1%
Iron supplementation	Daily unsupervised from 2 to 6 mo of age (2mg/kg/day)	Twice weekly unsupervised for 1 mo after each IPTi dose, (2.5ml, 15mg elemental iron)	None	None	None	None
Ages at dosing (months)	2, 3, 9 (at time of DPT2, DPT3, & measles)	3, 4, 9, 12 (at time of DPT2, DPT3, measles + extra at 12 months)	3, 4, 9 (at time of DPT2, DPT3 & measles)	3, 9, 15 (at time of DPT3 & measles + extra at 15 months)	3, 9, 15 (at time of DPT3 & measles + extra at 15 months)	3, 9, 15 (at time of DPT3 & measles + extra at 15 months)
Method & duration of follow-up	PCD to age 24 mo (CSS at age 12 & 18 mo)	PCD to age 24 mo (CSS at age 2, 9, 12 & 18 mo)	PCD to age 24 mo (CSS at age 12 & 24 mo)	ACD monthly to age 21 mo & PCD	ACD monthly to age 30 mo & PCD	ACD every 3 mo to age 24 mo & PCD
No. of children enrolled, placebo/active	351/350 = 701	1,242/1,243 = 2,485	755/748 = 1,503	535/535 = 1,070	595/594 = 1,189	600/600 = 1,200
Follow-up	332/329 = 661 (94%) followed for 1 year; 278/277 = 555 (79%) followed for 2 years	1103/1088=2191 (88%) followed for 2 years	687/688 = 1375 (91%) followed for 1 year	439/448 = 887 (83%) followed for 2 years	315/287 = 602 (51%) followed for 18 months	527/520 = 1047 (87%) followed for 24 months
Type of randomization	Individual	Cluster	Individual	Individual	Individual	Individual
EPI serology analysis		Measles and yellow fever	DTP, polio, hep B, and measles			
Vitamin A supplementation	100,000 IU at time of measles vaccination	100,000 IU at 6 mo of age, then every 6 mo	100,000 IU starting at 6 mo of age, once every 6 mo up to 5 years of age	Every 6 mo, and for treatment of measles (6–11 mo = 100,000 IU; 12–59 mo = 200,000 IU)	None	None

NOTES: ACD = active case detection; CSS = Cross-sectional surveys; EIR = Entomological inoculation rate; mo = month; PCD = passive case detection; SAE = severe adverse event.
[a]Estimate.
SOURCE: Grobusch et al., 2007b; data on lines labeled "Entire study period" and percent follow-up from papers for the individual trials.

Measures of Efficacy

To address the time-varying effectiveness of IPTi-SP, the committee considered several different analyses. Some of the publications describing the individual IPTi-SP trials reported efficacy based on time to first (or only) episode of clinical malaria and first (or only) hospitalization with malaria parasites in the treatment and placebo groups. Analyses of time-to-first-event or probability of at least one event provide a measure of the ability of IPTi-SP, relative to placebo, to delay disease; however, because such analyses do not reflect the total number of cases of malaria during a period of observation, the committee also reviewed an unpublished report with data analyses performed by the Consortium's Statistical Working Group (SWG). These additional analyses examined the incidence of all episodes of clinical malaria, hospitalizations with malaria parasites and other outcomes over various time periods with person-years at risk as the denominators for the treatment and control groups.

Efficacy of IPTi-SP

Members of the Consortium conducted six randomized placebo-controlled trials of IPTi-SP between 1999 and 2005. Five of the six IPTi-SP studies were randomized, placebo-controlled, parallel group trials, with random allocation to SP or placebo at the level of individual infants; the sixth study (Navrongo) used a cluster design, randomizing clusters to either placebo or SP. As indicated in Table 2, which shows the characteristics of the study populations in the six IPTi-SP trials as well as the important features of the trials, the study designs and settings differed with respect to such features as the intensity and seasonal patterns of malaria transmission; the extent of insecticide-treated bed net coverage; the prevalence of SP resistance; the ages at which SP was administered; the period of treatment; the type of case detection (active or passive); and the length of follow-up after the last dose of SP. Two sites (Ifakara and Kumasi) manifest perennial transmission, three sites exhibit perennial transmission with seasonal peaks (Manhiça, Lambaréné and Tamale) and one site has highly seasonal transmission of malaria (Navrongo). The committee considered two sites to be indicative of high-intensity transmission venues at the time of the IPTi-SP trials (Navrongo and Kumasi) and the remaining four sites to be examples of moderate-intensity transmission venues.

The five parallel group trials selected their sample sizes to give 80 percent power to detect a 20–30 percent reduction from placebo to SP group in the outcome of interest. This projected 20–30 percent reduction is of the same general magnitude as is found with insecticide-treated bed nets and some other new tools in the malaria-prevention armamentarium that have been determined to be of public health value (Lengeler, 2006). The Navrongo trial had a power of 95 percent to detect a 25 percent reduction in the episodes of clinical malaria. The primary outcomes differed somewhat among the studies: Some used clinical malaria; some used a level of anemia (moderate or severe); and some used a combined endpoint (e.g., clinical malaria or moderate to severe anemia). For malaria, all but one study used time-to-first event as the measure of primary outcome; one study used the total number of episodes over the treatment period (see Table 3). For anemia, all studies used the diagnosis of anemia (yes or no) during the treatment period.

A seventh randomized, placebo-controlled trial, conducted in Kisumu, Kenya, between 2004 and 2007, studied IPTi with medications other than SP or in addition to SP. This trial

randomly allocated 1,365 infants into four roughly equal groups to receive placebo; SP+artesunate (SP-AS3); amodiaquine+artesunate (AQ-AS3); or chlorproguanil+dapsone (DC3). The primary outcome was "prevention of clinical malaria in the first year of life" (IPTi Consortium, 2008a). The results of this trial have not been published; however, the Principal Investigator of this trial presented a summary of the study design and preliminary results to the committee. Results of this unpublished study were of keen interest to the committee. Because of the very high prevalence of the use of insecticide-treated bed nets (>90 percent) in the households of the population of infants participating in the trial, this study can offer insights into the contributions of IPTi where other forms of malaria prophylaxis are already reducing the incidence of malaria.

TABLE 3 Primary Outcome and Power of the Six IPTi-SP Trials

Location, Country	**Ifakara, Tanzania**	**Navrongo, Ghana**	**Manhiça, Mozambique**	**Kumasi, Ghana**	**Lambaréné, Gabon**	**Tamale, Ghana**
Reference	***Schellenberg et al.*** *Lancet 2001, 2005*	***Chandramohan et al.*** *BMJ 2005*	***Macete et al.*** *JID 2006*	***Kobbe et al.*** *CID 2007*	***Grobusch et al.*** *JID 2007*	***Mockenhaupt et al.*** *AAC 2007*
Primary outcome-protocol	Incidence of clinical malaria and severe anaemia episodes in each group by 12 months of age. The word "incidence" is not defined in the protocol	N/A	Incidence of first or only malaria episodes [sic] in each study cohort by 12 months of age	Rate of episodes of malaria and/or severe anaemia	Proportion of children between 3 and 18 months of age with at least one episode of (1) anemia (Hb < 9g/dL) and (2) malaria (parasitemia with fever)	Incidence of clinical malaria, severe malaria, and hospital visits
Primary outcome-manuscript	First or only episode of clinical malaria and severe anaemia in the period from recruitment to 1 year of age	Incidence of all episodes of malaria associated fevers…and the incidence of anaemia during the intermittent treatment phase (2–15 months) and after the effect of the intervention had ceased (16–23 months)	Same as protocol	Not clear whether the primary outcome was "first or single malaria episodes" or "cumulative episodes" or malaria	(1) The proportion of children with at least 1 episode of mild anemia and (2) the proportion of children with at least 1 episode of malaria between 3 and 18 months of age. Anemia was defined as Hb<8.0g/dL. Malaria was parasitemia with fever.	Incidences of all and of first or only episodes of malaria and severe anemia during the intervention period
Assumptions – protocol	Control group: 0.63 incidence clinical malaria/PYAR; 0.42 incidence severe malaria/PYAR; 30% reduction in SP	N/A	Placebo incidence rate = 0.33 case/yr	Assumptions not presented	Placebo proportions—anemia: 0.28; malaria: 0.60	Assumptions not presented
Assumptions-manuscript	Control group: 0.36 clinical malaria/PYAR; 0.28 episodes of severe malaria/PYAR	Incidence in placebo group 25%	Same as protocol	Assumptions not presented	Same as protocol for anemia; no mention of malaria	Assumptions not presented
Power-protocol	Protocol says "adequate"	N/A	80% power to detect a protective efficacy of 30% against having at least one episode of malaria	Power not in protocol. Method of analysis not clearly defined	80% to detect a protective efficacy of 30% against having at least one episode of anemia and 16% for malaria	No power calculation
Power-manuscript	80%	95% power to detect a 25% reduction (cluster randomization)	Same as protocol	Study designed with 80% power to detect 20% reduction in "hazards of developing malaria in the SP group, compared with the placebo group"	Same as protocol for anemia; no mention of malaria	Sample size adequate to detect 25% reduction in malaria and severe anemia

NOTES: N/A = not available to the committee; PYAR = person years at risk.
SOURCE: Compiled from the trial protocols provided by the IPTi Consortium and the published manuscripts of the studies.

Protective efficacy is defined as [1 – (Incidence in the IPTi-SP group/Incidence in the control group)] x 100, which is analogous to the standard definition for vaccine efficacy. To compare results across the six trials, the committee used the estimates of 12-month protective efficacy whenever the data were available in the publications. As Table 4 shows, all the studies except the Lambaréné trial demonstrate a statistically significant reduction in the probability of contracting clinical malaria; for two of those five trials (Ifakara and Tamale), the lower limit of the 95 percent CI around the point estimate of efficacy is above 20 percent. The trials that report the effect of IPTi-SP on severe malaria all show a statistically significant benefit of IPTi; similarly, in three trials (Ifakara, Kumasi, and Navrongo), the lower limit of the 95 percent CI around the point estimate of efficacy is above 10 percent. For all trials, the estimated protective efficacy for anemia and all-cause hospitalization was in the direction of benefit, but only four trials showed a statistically significant benefit for anemia (Ifakara, Navrongo, Lambaréné, and Kisumu). Only three trials showed statistically significant benefit for all-cause hospitalizations (Ifakara, Manhiça, and Tamale). Because malaria is an episodic disease in the countries where IPTi-SP would be used, as mentioned above, *the committee was most interested in assessing the effect of IPTi on the total burden of disease, not only in decreasing the probability of having one or more episodes.* The next section of this letter report describes the data relevant to assessing the effect of IPTi-SP on the total burden of malaria in the first year of life.

TABLE 4 Summary of Outcomes of the Six IPTi-SP Studies and the Kisumu Trial During the First Year of Life

	At Least One Episode of Malaria				At Least One Episode of Anemia [b]		Episodes of All-Cause Hospitalizations	
	Clinical Malaria		Severe Malaria [a]					
Study	% PE (95% CI)	*P*	% PE (95% CI)	*P*	% PE (95% CI)	*P*	% PE (95% CI)	*P*
Ifakara	59 (41, 72)	<0.0001	68 (49, 80)	<0.0001	50 (8, 73)	0.023	30 (8, 47)	0.01
Kumasi	18 (4, 31)	0.01	20 [c] (11, 29)	<0.001	13 (–5, 28)	0.16	8.7 (–23, 32)	0.6
Lambaréné	13 (–32, 43)	0.50	NR	NR	26 (0, 45)	0.05	NR	NR
Manhiça	22 (4, 37)	0.020	24 (5, 39)	0.017	13 (–17, 35)	0.37	19 (4, 31)	0.014
Navrongo	25 [c] (14, 34)	<0.001	24 [c] (11, 34)	NR	36 [c] (11, 53)	NR	13 [c] (–5, 27)	NR
Tamale	33 [c] (21, 44)	<0.0001	28 [c] (6, 45)	<0.05	21 (–10, 43)	Not significant	38 (7, 59)	<0.05
Kisumu [d]	26 (6, 41)	0.01	42 (4, 65)	0.04	32 (–0.1, 53)	0.05	7.2 (–20, 28)	0.6

NOTES: NR = not reported; *P* = *p*-value; PCV = packed cell volume; PE = protective efficacy. Where available, table shows protective efficacy through 12 months of age even for studies where the primary outcome was after 12 months. The data for the outcomes of the Navrongo study, which come from the publication, are for 15 months. The columns labeled *P* give *p*-values where available. For the Kisumu study, the data come from unpublished information provided by the IPTi Consortium.

[a] Kumasi and Manhiça: >500 parasites/μL; Ifakara, Kisumu, Navrongo, and Tamale: >5,000 parasites/μL.

[b] Ifakara (PCV<25%): Kisumu (Hb<8.0 g/dL); Kumasi (Hb<7.5 g/dL); Lambaréné (Hb<9.0 g/dL); Manhiça (PCV<25%); Navrongo (PCV<24%); Tamale (Hb<7 g/dL).

[c] All episodes are in the first year of life.

[d] Results for sulfadoxine-pyrimethamine once plus artesunate 3 days (SP-AS3) vs. placebo.

SOURCE: Compiled from published articles of the trials and from documents provided by the IPTi Consortium for the Kisumu trial.

Biostatistical Analysis of the Combined Data During the First Year of Life

As described above, the six IPTi-SP trials studied different outcomes and defined the outcomes somewhat differently. As a result, comparing the results across trials directly from the publications is difficult. However, in assessing the totality of the evidence with regard to the effect of IPTi, the committee had access to "Pooled analysis of the IPTi trials with SP" (IPTi Consortium, 2007b), a report prepared by the SWG of the Consortium. Composed of one statistician from each trial, the SWG created uniform definitions of outcome variables across trials. The statisticians from each trial then used these uniform definitions to analyze their own data. To ensure that comparisons between the IPTi-SP and the placebo groups were protected by the randomization in each trial, the SWG used study-level meta-analysis of these patient-level data. In the words of the SWG (IPTi Consortium, 2007, p. 8):

> Incidence of all episodes (malaria, hospital admissions, all-cause mortality. . .) was analyzed with a negative binomial regression to allow for potential clustering of episodes within individuals. Robust standard errors were used to account for intra-cluster correlation at the community level for the Navrongo trial. For each endpoint, the time at risk was defined according to [definitions presented in the report]. For malaria, a lag of 21 days after an episode or after a malaria treatment was introduce[d] to prevent double-counting of the same episode or to account for any prophylactic effect for antimalarial given as treatment but not as IPTi, respectively. For hospital admissions, a lag of 21 days after an episode was introduce[d] to prevent double-counting of the same episode. During the lag period, subjects do not contribute to the person-time at risk. . . .
>
> Risk of at least one episode (malaria, anemia) and prevalence at 12 months (malaria, anemia) were analyzed using a Poisson regression model with log-link and a robust error variance to estimate the [r]elative risk [Zou, 2004].
>
> Combined estimates were obtained using meta-analysis with random effects. To evaluate how influen[t]ial an individual trial could be in the meta-analysis, a sensitivity analysis for all trials was conducted repeating the meta-analysis but removing from the analysis one trial at each time. To asses[s] the consistency of the results of the studies in [the] meta-analysis the I^2 quantity was calculated [Higgins, et al., 2003].

The re-analyses of the study data allowed the SWG to define "incidence of malaria" and "incidence of severe malaria" as the number of episodes over the period of interest. The methods the SWG used accounted for the intra-subject variance as well as for the cluster randomization in the Navrongo trial. The IOM committee found the methodology employed by the SWG, both in terms of the SWG's use of individual participant data and its approach to sensitivity analysis, consistent with modern statistical approaches for combining data across trials that ask similar questions but use somewhat different designs and different outcome variables (Berlin et al., 2002; Schünemann et al., 2008). In the analyses reported throughout the remainder of this report, we do not include the I^2 values, but we note here that no I^2 showed statistically significant evidence of heterogeneity of effect of IPTi-SP.

Pooled analysis of the data from the first year of life in the six IPTi-SP trials showed a 30 percent reduction (95 percent CI, 20–39) in the number of episodes of clinical malaria; in the number of children who experienced anemia, a 15 percent reduction (95 percent CI, 6–23), a 38 percent reduction (95 percent CI, 13–55) in the incidence of hospitalization of children with parasitemia, and in the incidence of all-cause hospitalization, a 23 percent reduction (95 percent CI, 10–34) (see Table 5).

The IOM committee had no information about the quality control of the analyses in the six individual studies. In the committee's experience, counting of outcomes within specific time periods is very difficult, because databases often have incomplete data on dates as well as on the lengths of episodes of malaria and of hospitalizations. Thus, the committee cannot judge the accuracy of data from the individual studies. In addition, the report of the SWG had two types of summaries. Some of the data came directly from the software program Stata (Stata, 2007), the program used to perform the meta-analysis. If the study-specific analyses are correct and the entry of data into Stata is correct, these analyses are reliable. Other information presented in the report of the SWG appears to have been transcribed by typing into tables rather than by being transferred directly by a computer program. In reviewing some of the tables presented by the SWG, the committee identified some errors that presumably were caused by faulty transcription. Because the committee did not have access to raw data, we could not confirm the analyses.

On the other hand, *if the analyses are corroborated by an independent audit, they provide very instructive information with respect to the ability of IPTi-SP to exert a protective effect against all episodes of clinical malaria through 11 months of age.* This is biologically important because this period includes the long interval from 3 or 4 months of age until 9 months of age in every study during which one would expect most of the life experience of infants in the treatment group to be without protective drug levels in the blood (which one would expect to endure for only about 4–5 weeks post-dose). It also includes the 3-month period for all infants after receipt of the dose of SP or of placebo at 9 months of age.

TABLE 5 Summary of Outcomes of the Six IPTi-SP Trials Through 12 Months of Age

	Episodes of Clinical Malaria								Episodes of Hospitalization			
	Any Parasites		Local Specific Density Cut-off [a]		High Density Cut-off		Risk of Anemia [b]		with Malaria Parasites		All Cause	
Study	% PE	95% CI	% PE	95% CI	% PE	95% CI	% PE	95% CI	% PE	95% CI	% PE	95% CI
Ifakara	59	(41, 71)	61	(43, 74)	56	(26, 75)	50	(8, 72)	58	(29, 76)	29	(7, 46)
Navrongo	29	(17, 40)	32	(16, 44)	34	(15, 48)	10	(–15, 30)	50	(23, 68)	18	(0, 32)
Manhiça	20	(2, 35)	31	(14, 45)	28	(8, 44)	10	(–19, 32)	22	(–16, 48)	25	(7, 39)
Kumasi	21	(9, 31)	23	(9, 34)	18	(–15, 42)	10	(–9, 27)	–7	(–103, 44)	18	(–22, 45)
Lambaréné	22	(–25, 52)	29	(–16, 56)	26	(–49, 64)	26	(0, 45)	NA	NA	–36	(–142, 24)
Tamale	33	(21, 44)	28	(6, 45)	30	(–15, 57)	15	(–1, 29)	44	(–80, 83)	50	(18, 69)
Combined [c]	30	(20, 39)	NA		NA		15	(6, 23)	38	(13, 55)	23	(10, 34)
Range[d]	(26, 33)		NA		NA		(14, 17)		(31, 44)		(20, 24)	

NOTES: NA = not provided; PE = protective efficacy. Incidence of episodes (malaria and hospitalizations) analyzed "with a negative binomial regression to account for potential clustering within individuals. Robust standard errors were used to account for intra-cluster correlation at the community level for the Navrongo trial." Clinical malaria: history of fever with any *P. falciparum* parasitemia. Risk of anemia (at least one episode) was analyzed using a Poisson regression model with a log-link and a robust error variance. To assess the sensitivity of the results to any single study, the SWG analyzed each outcome omitting one trial at a time. Estimates rounded to the nearest whole percentage.

[a]Locally cut-offs: >500µ/l for Ifakara, Manhiça, and Kumasi; >600µ/l for Lambaréné; >5000µ/l for Tamale; >8000µ/l for Navrongo.

[b]Anemia: PCV<25% for Ifakara, Manhiça, and Kumasi; Hb<8g/dl for Kumasi, Lambaréné, and Tamale.

[c]Combined estimates are based on random-effects meta-analyses.

[d]Range: lowest and highest estimated protective efficacy for the sensitivity analyses.

SOURCE: Compiled from data in the Report of the Statistical Working Group (IPTi Consortium, 2007b).

Mortality

Of the children in the six IPTi-SP trials, 104 died before their first birthdays: 55 in the SP group and 49 in the placebo group (p= 0.54 from a random-effects meta-analysis). Because of the importance of total mortality to the assessment of the safety and efficacy of interventions, the committee is presenting the complete data on mortality (Table 6). As the table shows, no statistically significant difference in mortality was observed between the IPTi-SP and the placebo groups within the first year of life in any of these clinical trials or in the combined data; however, neither any individual trial nor the combined data from the six trials had adequate power to detect plausible differences in mortality. The committee believes that a trial to assess the effect on mortality would have to be very large and therefore logistically challenging and also noted that the Consortium studies, individually and pooled, were not large enough to assess an effect of IPTi-SP in preventing mortality.

TABLE 6 Mortality in the First Year of Life for the Six IPTi-SP Trials

Study	SP n/N	Placebo n/N	Relative Risk (SP: Placebo)	95% CI
Ifakara	3/350	6/351	0.5	(0.1, 2.0)
Navrongo	23/1221	11/1225	2.1	(1.0, 4.3)
Manhiça	20/748	22/755	0.9	(0.5, 1.7)
Kumasi	3/535	3/535	1.0	(0.2, 4.9)
Lambaréné	0/504	0/507	Not estimable	Not estimable
Tamale	6/600	7/599	0.9	(0.3, 2.5)
Overall	55/3958	49/3972	1.1	(0.8, 1.6)

SOURCE: Data and estimates from IPTi Consortium 2008b,c.

Rebound Effect Following Cessation of IPTi-SP Dosing

Rebound would occur if intermittent administration of SP prevented or delayed the acquisition of a sufficient degree of naturally acquired immunity that would prevent severe and complicated malaria and death. As a consequence of the lack of acquisition of immunity in this theoretical scenario, when children who are no longer receiving intermittent SP therapy are subsequently exposed to the bites of infected mosquitoes, they would develop symptomatic **malaria** illness and **more severe clinical malaria** illness at a higher rate than would children of the same age who had not received IPTi-SP during the first year of life.

On the other hand, some researchers contend that the intermittent nature of IPTi-SP dosing may allow infants to acquire immunity despite the three spaced doses of SP administered during infancy (Schreiber et al., 2007). In order for infants to acquire immunity while on an IPTi-SP regimen, they must be exposed to several blood-stage infections during the period of IPTi-SP. Because of its intermittent nature, which consists of periods of up to 5.5 months between dosings (e.g., from the age 14 weeks to the age of 9 months), IPTi-SP would not be expected to prevent infection or asymptomatic parasitemia completely; hence, infants receiving IPTi-SP may still be able to acquire some measure of immunity.

Serum antibodies against certain surface antigens of asexual-stage erythrocytic parasites (and also against antigens of the sporozoite stage injected by anophelines) play a role in protection against symptomatic malaria. Although most malariologists believe some asexual-stage antigens (e.g., merozoite surface protein-1[MSP-1], apical membrane antigen-1[AMA-1],

etc.) provide protection, the relative contribution of antibodies against these and other known and unknown antigens to acquired clinical immunity is unclear. Moreover, the recognized malarial surface antigens (such as MSP-1 and AMA-1) are subject to extensive antigenic diversity. For these reasons, it is currently not technically possible to measure antibodies to the full panoply of relevant specific protective antigens of asexual-stage erythrocytic parasites or to identify markers of immune protection. Indeed, the lack of clear correlates of protection is recognized as a major gap in the understanding of malaria immunity and is an obstacle to vaccine development. Nevertheless, the prevalence and magnitude of titers of antibody can provide a rough estimate of the degree of relatively recent, prior antigenic contact with malarial parasites. Toward this end, in the Kumasi, Ghana, IPTi-SP trial, titers of IgG antibody against a *P. falciparum* lysate were measured as evidence of the degree of contact with *P. falciparum* in infants 9 months of age who had received a single dose of either SP or placebo at 12 weeks of age. The monthly follow-up visits allowed assessment of whether the infants had experienced clinical malaria or sub-clinical *P. falciparum* infection in the period between 3 and 9 months of age. The anti–*P. falciparum* antibody levels were significantly higher in placebo recipients than in SP recipients, even when stratified by whether prior malaria infection or disease had been observed (Schreiber et al., 2007). Even though malaria antibodies were lower in the IPTi-SP recipients (because the relations between the antibodies to various antigens and the threshold titers required to achieve clinical immunity are unclear), IPTi recipients may not be more susceptible even though they have lower antibody levels.

Rebound in Association with IPTi-SP

Initial Analysis of Events in the Months Following the Last Dose of IPTi-SP

The question of rebound occurring during the period after cessation of treatment in the Consortium's trials is difficult to address in isolation in a statistically rigorous manner, because at the end of the treatment period the two groups of children (those randomized to placebo and those randomized to SP) are now presumably different: The long period of the intervention has rendered them different with respect to the incidence of malaria disease in preceding months and in their degree of immune stimulation by malaria parasites. Clinical trials use randomization to provide balance, between the study groups at baseline. The longer that the study groups are followed after randomization the greater the chance that important— perhaps unknown or unmeasured—differences will develop in their composition. Hence, inferences involving a comparison of behavior of the two groups in which the baseline is reset to later in the study (in the case of IPTi-SP, to the end of the treatment period) necessarily become less certain and the use of the usual statistical methods become less valid for assigning causal relationships. The most rigorous methods for analyzing data from the IPTi-SP trials would start at randomization and would continue through the end of follow-up, with a long enough follow-up after cessation of therapy to account for potential rebound. Nonetheless, examining the incidence of various outcomes during the treatment and post-treatment periods separately provides useful insights into the time course of malaria transmission in the IPTi-SP and placebo groups.

In the six randomized, controlled trials of IPTi-SP, the Consortium found variable evidence of a rebound effect starting 1 month (35 days) after the last dose of SP was administered. The Consortium presented, in detail, a trial of IPTi (the Ifakara trial) that looked

carefully for rebound out to a point (24 months of age) that was 15 months after the last dose of SP (which was given at age 9 months); no evidence of rebound was observed (Schellenberg et al., 2005). Among the six trials, the most favorable outcome was seen in the initial IPTi studies in Ifakara, which showed a protective efficacy of 36 percent against the first or only episode of clinical malaria and of 23 percent for all episodes of malaria after the last dose of IPTi-SP in children aged 10 months (1 month after the last dose) to 2 years (Schellenberg et al., 2005). The least favorable outcome was seen in Tamale, where the risk and incidence of severe malaria and severe anemia (hemoglobin concentration<5.0 g/dl) were approximately doubled in children who received IPTi-SP during the 8 months starting 1 month after the last IPTi-SP dose (i.e., at 16 to 24 months of age). Specifically, 25 episodes of severe malaria and 24 episodes of severe malarial anemia occurred in 338 person-years at risk in infants given IPTi-SP compared with 13 severe malaria episodes and 11 severe malarial anemia episodes per 344 person-years at risk in infants given a placebo (Mockenhaupt et al., 2007). With respect to anemia (i.e., 7.5 g/dl) overall, 208 cases per 327 person-years of follow-up occurred in the SP group versus 220 cases per 331 person-years of follow-up in the placebo group. Because not all studies used severe anemia as an outcome and because definitions of anemia and of severe anemia differed in various IPTi trials, it was difficult to compare protection against anemia across studies.

Analysis of Events from Randomization Through the End of Follow-Up

Recognizing the methodological issue cited above, the committee addressed the question of rebound in several ways. First, the committee extracted relevant data from the six published IPTi-SP manuscripts on the incidence of malaria during the treatment period, during the follow-up period, and from randomization through the end of follow-up. This information afforded the longest follow-up time. In the five studies that reported efficacy from randomization through the end of the follow-up period, the point estimate of protective efficacy against the first or only case of malaria ranged from 5–42 percent; however, only three studies presented confidence intervals for the estimate and two of those intervals did not exclude zero. The analyses of Table 7 are limited by the fact that they measure time-to-first case of malaria rather than the total number of cases of malaria.

TABLE 7 Effect of SP During Treatment Period, Rebound Period, and Time from Randomization to End of Follow-Up

	Incidence of First Case of Clinical Malaria					
	Randomization Through End of Treatment Period		**Potential Rebound Period: End of Treatment Period Through End of Follow-Up Period**		**Randomization Through End of Follow-Up**	
Study	% PE	95% CI	% PE	95% CI	% PE	95% CI
Ifakara	59	(41, 72)	36	(11, 53)	*42*	NR
Kumasi	18	(4, 31)	–1.5	(–22, 15)	*5*	NR
Lambaréné	13	(–32, 43)	*–12*	NR	28	(–22, 58)
Manhiça	22	(4, 37)	NR	NR	NR	NR
Navrongo	25	(14, 34)	–5	(-21, 9)	16	(7, 25)
Tamale	30[a]	(20, 40)[a]	1.8[b]	(-9, 11)[b]	8[b]	(–5, 19)[b]

NOTE: CI: confidence interval; NR: not reported; Pbo: placebo; PE: protective efficacy. Values in italics were not reported in the papers and represent the Committee's rough calculation of protective efficacy given the published data.
[a] Data for the first 12 months of life, which does not include the last three months of treatment.
[b] Data for all cases of malaria.
SOURCE: Compiled from published manuscripts of the six efficacy trials.

Analysis of All Clinical Events in the Period During 35 Days After an IPTi Dose at Varying Ages

In this report, we have alluded several times to the long period between the dose of IPTi administered at 3 or 4 months and the next dose given at 9 months of age and has raised questions about what occurs during that long period. In its unpublished report, the SWG estimated protective efficacies during several specific follow-up intervals to shed light on this issue. First, they assessed the level of efficacy of IPTi against all episodes of malaria in the 35-day period after a dose of SP or of placebo was given to infants 3 months of age ("prophylactic effect 1"). In infants who received SP, one would expect the levels of drug present in most infants to be protective against sensitive and moderately sensitive parasites during this 35-day period. The results are shown in the Table 8 below.

Every trial showed that a moderate or high level of protection was observed at every trial site during this 35-day period. In five of the six trials, the difference in incidence between SP and placebo groups was significant—sometimes highly significant—and the lower limit of the 95 percent CI was well above zero. Very similar results were observed in the 35 days after an IPTi dose administered at 9 months of age ("prophylactic effect 2"), as shown below in Table 9.

Of the four sites that administered IPTi doses in the second year of life, the point estimates of efficacy in the 35 days after the dose ("prophylactic effect 3") were 92 percent (95 percent CI, 80, 95) for Tamale; 72 percent (95 percent CI, 57, 82) for Navrongo; 31 percent (95 percent CI, –3.6, 54) for Kumasi; and 29 percent (95 percent CI, –210, 84) for Lambaréné.

TABLE 8 Incidence of Malaria During Prophylactic Effect 1 (Period of 35 Days After Dose at 3 Months)

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana
Placebo						
Episodes	10	45	41	44	5	17
PYAR	30	98	55	48	48	53
Incidence	0.33	0.46	0.75	0.92	0.10	0.32
IPTi with SP						
Episodes	2	10	17	8	2	6
PYAR	30	98	57	49	48	55
Incidence	0.07	0.10	0.30	0.16	0.04	0.11
Efficacy (95% CI)	80 (9, 96)	78 (52, 90)	60 (29, 77)	82 (62, 92)	75 (–240, 98)	83 (13, 97)
p-value	0.038	<0.001	0.002	<0.001	0.29	0.034

NOTE: PYAR: Person-years at risk.
SOURCE: Reprinted with permission from the Statistical Working Group (IPTi Consortium, 2007b).

TABLE 9 Incidence of Malaria During Prophylactic Effect 2 (Period of 35 Days After Dose at 9 Months)

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana
Placebo						
Episodes	23	147	33	53	10	30
PYAR	25	107	49	40	40	51
Incidence	0.92	1.4	0.67	1.3	0.25	0.58
IPTi with SP						
Episodes	2	33	10	25	6	5
PYAR	26	107	51	41	40	53
Incidence	0.08	0.31	0.20	0.61	0.15	0.09
Efficacy (95% CI)	92 (64, 98)	78 (67, 84)	71 (41, 86)	54 (27, 72)	42 (–78, 82)	96 (85, 99)
p-value	0.001	<0.001	0.001	0.001	0.34	<0.001

NOTE: PYAR: Person-years at risk.
SOURCE: Reprinted with permission from the Statistical Working Group (IPTi Consortium, 2007b).

Analysis of All Clinical Events in the Period from 35 Days After (a) Dose 2 (Age 3 Months) in Ifakara; (b) Dose 2 (Age 4 Months) in Navrongo and Manhiça; (c) Dose 1 (Age 3 Months) in Kumasi, Lambaréné, and Tamale Until the Next Dose of IPTi Administered at 9 Months of Age

The SWG assessed the level of protection in the long period beginning 35 days after the SP dose given at age 3 or 4 months until the next dose was administered at age 9 months ("inter-dose 1 effect"). By excluding the period of 35 days immediately after the SP dose at age 3 or 4 months, the level of protection could be assessed over a period when drug concentrations would presumably have fallen to non-protective levels or would be entirely absent in the vast majority of SP recipients. The unpublished results, shown in Table 10 below, suggest much reduced efficacy compared with the efficacy during the first 35 days post-dosing (see Table 8). Nevertheless, it is interesting that in five of the six studies the effect was still positive, and in two sites (Ifakara and Tamale), the point estimates of protective effect (42 percent and 19 percent, respectively) had lower limits of the 95 percent CI that were just slightly below zero (–1.2 percent and –1.3 percent, respectively).

TABLE 10 Incidence of Malaria During the Inter-Dose 1 Period[a]

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana
Placebo						
Episodes	47	464	142	248	32	241
PYAR	99	580	184	184	173	200
Incidence	0.47	0.80	0.77	1.4	0.19	1.0
IPTi with SP						
Episodes	29	412	154	219	28	166
PYAR	102	578	194	184	173	201
Incidence	0.28	0.71	0.80	1.2	0.16	0.83
Efficacy (95% CI)	42 (–1, 67)	11 (–8, 26)	–2 (–37, 24)	11 (–6, 26)	14 (–56, 53)	19 (–1, 35)
p-value	0.055	0.23	0.88	0.19	0.61	0.064

NOTE: PYAR: Person-years at risk.

[a] The Inter-dose 1 period extends from 35 days after (a) dose 2 (age 3 months) in Ifakara; (b) dose 2 (age 4 months) in Navrongo and Manhiça; (c) dose 1 (age 3 months) in Kumasi, Lambaréné, and Tamale until the next dose of IPTi administered at 9 months of age.

SOURCE: Reprinted with permission from the Statistical Working Group (IPTi Consortium, 2007b).

Analysis of All Clinical Events in the Period of 5 Months from the Last Dose of IPTi-SP

To address the question of rebound more fully (i.e., with outcomes other than "time to first case of malaria"), the SWG of the Consortium presented estimates of protective efficacy for several outcomes. They provided uniform definitions of outcomes and defined the potential rebound period to last 5 months after the last dose of SP or placebo. The unpublished report of the SWG defines this as a period "during 5 months starting 35 days after actual last dose received." The purpose of excluding the 35 days after the dose was to look for possible rebound during the period when the protective blood levels of drug are no longer present. As shown in Table 11, most of the study-specific point estimates during this 5-month period show rebound, that is, higher rates in the IPTi-SP group than in the placebo groups, for episodes of clinical malaria, for episodes of hospitalization with malaria parasites, for episodes of all-cause hospital admissions, and for the number of subjects with anemia. As described above, these analyses redefine the baseline as the time of the last dose of SP or of placebo, so the two treatment groups are no longer directly comparable. Nonetheless, with respect to the 5-month period beginning 35 days after the last dose of SP or of placebo, the pooled data show no difference between the SP and placebo groups in the number of episodes of malaria (protective efficacy 0.0 percent; 95 percent CI, –10, 9; $p>0.99$). The combined data showed an approximately 20 percent increased risk of being hospitalized with malaria for children who had received SP compared with placebo during the 5-month period after the last dose, an approximate 11 percent increased risk of being hospitalized for any reason, and an approximate 2 percent decreased risk of contracting anemia. (All estimates are based on random effects meta-analysis; see Table 11). Although none of these overall effects is statistically significant, the overall data from the six studies show confidence limits that do not exclude a rebound effect in any of the four outcomes.

Analysis of All Clinical Events in the Period from Randomization up to 5 Months After the Actual Last Dose of SP or Placebo Received

A more favorable estimate of protective efficacy is seen in the full period from randomization through 5 months after the last dose of IPTi-SP (see Tables 11–15). For outcomes for which the SWG did not provide pooled estimates of protective efficacy, the committee used Stata to calculate pooled estimates of protective efficacy from random-effects meta-analyses from unpublished data of the Consortium. The table notes identify the analyses performed by the committee.

The estimated protective efficacy against episodes of malaria from randomization up to 5 months after the last dose of SP, calculated from a random-effects meta-analysis, was 21 percent with a 95 percent CI of (11, 29) (Table 12). Similarly, when analyzed from randomization through month 5 after the last dose of SP, the risk of anemia was lower in the IPTi groups in all six studies (Table 13); however, in no individual study was the difference statistically significant. The pooled estimate of protective efficacy was 10 percent with a 95 percent CI of (4, 17). The incidence of hospital admissions with malaria parasites was lower in the IPTi groups in four of the studies (Table 14), including two in which the difference was statistically significant. The pooled estimate of protective efficacy was 21 percent with a 95 percent CI of (–2, 38). The number of all-cause hospital admissions was lower in the IPTi groups in all five of the studies that reported on this outcome (Table 15); in two studies, the difference was statistically

significant. The pooled estimate of protective efficacy was 18 percent with a 95 percent CI of (9, 27).

TABLE 11 Protective Efficacy (PE) and Reported 95% Confidence Intervals (CI) for Outcomes During the 5 Months After Last Dose of SP or Placebo

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana	Overall
Number of Subjects							
Placebo	344	1216	755	159	446	561	
IPTi-SP	344	1197	748	162	459	556	
Episodes of Clinical Malaria							
Placebo	87	443	191	298	24	436	
IPTi-SP	62	436	192	301	34	442	
% PE	30	0	–6	–3	–36	0	0
95 CI (%)	(1, 51)	(–19, 16)	(–39, 19)	(–21, 12)	(–146, 25)	(–19, 15)	(–10, 9)
Episodes of Hospitalization with Malaria Parasites							
Placebo	21	32	32	8	NR	4	
IPTi-SP	18	36	42	12	NR	7	
% PE	15	–14	–32	–46	NR	–74	–20
95 CI (%)	(–65, 56)	(–96, 33)	(–114, 18)	(–258, 40)	NR	(–496, 49)	(–60, 10)
Episodes of All-Cause Hospital Admissions							
Placebo	68	117	146	17	13	13	
IPTi-SP	71	134	138	28	14	22	
% PE	–5	–16	8	–61	–1	–74	–11
95 CI (%)	(–47, 25)	(–53, 12)	(–26, 33)	(–194, 12)	(–116, 52)	(–264, 16)	(–30, 6)
Subjects with Anemia							
Placebo	26	60	43	191	13	259	
IPTi-SP	15	68	39	204	15	248	
% PE	42	–15	8	–4	–12	3	2
95 CI (%)	(–7, 69)	(–69, 21)	(–40, 40)	(–27, 14)	(–133, 46)	(–10, 15)	(–8, 11)

NOTE: NR: Not reported.
SOURCE: Compiled from data in the report of the Consortium's Statistical Working Group (IPTi Consortium, 2007b).

TABLE 12 Incidence of Malaria from Randomization Up to 5 Months After the Last Dose of SP

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana	Overall
Placebo							
Episodes	158	1419	380	910	93	891	
PYAR	288	1398	540	614	558	667	
Incidence	0.55	1.01	0.70	1.48	0.17	1.34	
IPTi with SP							
Episodes	75	1068	269	770	82	711	
PYAR	291	1403	546	620	577	668	
Incidence	0.26	0.76	0.68	1.24	0.14	1.06	
Efficacy (95% CI)	55 (27, 68)	25 (14, 35)	5 (–18, 24)	16 (8, 24)	13 (–26, 40)	21 (10, 30)	21 (11, 29)
p-value	<0.001	<0.001	0.64	<0.001	0.46	<0.001	<0.001

NOTE: PYAR: Person-years at risk
SOURCE: Compiled from data in the Report of the Statistical Working Group (IPTi Consortium, 2007b).

TABLE 13 Risk of Anemia from Randomization Up to 5 Months After the Last Dose of SP

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana	Overall
Placebo							
Episodes	31	234	87	316	110	347	
Subjects	351	1225	748	535	507	599	
Risk (%)	9	19	12	59	22	58	
IPTi with SP							
Episodes	22	215	103	291	86	319	
Subjects	350	1221	755	535	504	600	
Risk (%)	6	18	14	54	17	53	
Efficacy (95% CI)	29 (–29, 58)	8 (–15, 26)	15 (–11, 35)	9 (–8, 22)	21 (–1, 39)	8 (–2, 17)	10 (4, 17)
p-value	0.21	0.47	0.24	0.31	0.06	0.10	0.003

NOTE: The committee used Stata to calculate the overall efficacy and its 95 percent confidence limit.
SOURCE: Data from the Report of the Statistical Working Group (IPTi Consortium, 2007b).

TABLE 14 Incidence of Hospital Admission with Malaria Parasites from Randomization Up to 5 Months After the Last Dose of SP

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana	Overall
Placebo							
Episodes	52	91	79	35	38	16	
PYAR	310	1401	628	710	561	717	
Incidence	0.17	0.06	0.13	0.05	0.07	0.02	
IPTi with SP							
Episodes	27	58	69	38	44	10	
PYAR	309	1405	634	709	580	709	
Incidence	0.09	0.04	0.11	0.05	0.08	0.01	
Efficacy (95% CI)	49 (15, 70)	36 (10, 55)	15 (–21, 40)	–9 (–72, 31)	–12 (–75, 28)	37 (–43, 72)	21 (–2, 38)
p-value	0.009	0.011	0.37	0.73	0.61	0.27	0.066

NOTE: PYAR: Person-years at risk. The committee used Stata to calculate the overall efficacy and its 95 percent confidence limit.
SOURCE: Data from the Report of the Statistical Working Group (IPTi Consortium, 2007b).

TABLE 15 Incidence of All-Cause Hospital Admissions from Randomization Up to 5 Months After the Last Dose of SP

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana	Overall
Placebo							
Episodes	172	445	359	94	NA	73	
PYAR	303	1400	632	710	NA	714	
Incidence	0.57	0.32	0.57	0.13	NA	0.10	
IPTi with SP							
Episodes	138	397	298	92	NA	49	
PYAR	303	1405	637	709	NA	707	
Incidence	0.46	0.25	0.47	0.13	NA	0.07	
Efficacy (95% CI)	20 (–3, 38)	11 (–6, 26)	24 (7, 38)	2 (–30, 27)	NA	33 (0, 55)	18 (9, 27)
p-value	0.09	0.20	0.01	0.89	NA	0.05	0.001

NOTE: NA: Not available; PYAR: Person-years at risk. The committee used Stata to calculate the overall efficacy and its 95 percent confidence limit.
SOURCE: Data from the Report of the Statistical Working Group (IPTi Consortium, 2007b).

Analysis of Events from Cessation of the Intervention (IPTi or Placebo) for a Period of 11 Months Thereafter

The data summarized in Table 7 from publication of the six IPTi-SP studies are limited because they address not the total number of cases of malaria but rather the occurrence of at least one case. The data from Tables 11 through 15 address all cases in the 5 month period after the last dose of SP, a period of time the committee judges as adequate for assessing the impact of IPTi-SP. The committee also reviewed unpublished data presented by the SWG on outcomes in the 11-month period beginning 35 days after the last dose. The Ifakara, Navrongo, and Manhiça trials collected relevant data; these indicate no clear impact on the risk in either direction in that follow-up period (Table 16). The SWG did not originally provide analyses from randomization through 11 months plus 35 days after the last SP dose; however, because of the importance of those data for assessing the impact of IPTi-SP, the committee requested that the SWG perform these analyses. As seen in Table 17, three of the sites had relevant data. For each outcome, the combined estimate of protective efficacy was in the direction of benefit; the 95 percent confidence intervals, however, showed lower limits that were either just above zero (0.8 percent for episodes of malaria and 0.2 percent for all-cause hospitalizations) or slightly below zero (–0.9 percent for hospitalizations with malaria parasites and –6 percent for incidence of anemia). In summary, the SWG of the Consortium presented several unpublished analyses for the individual studies and pooled data focusing on the 5-month and 11-month periods after the end of treatment; in none of those analyses was the rebound statistically significant. Moreover, all combined analyses presented from randomization to 5 months after the end of treatment and from randomization to 12 months after the end of treatment showed positive estimates of protective efficacy for the outcomes measured. Some of these estimates were statistically significant.

TABLE 16 Protective Efficacy (PE) and Reported 95% Confidence Intervals (CI) for Outcomes During the 11 Months After Last Dose of SP or Placebo

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique
Number of Subjects			
Placebo	344	1216	755
IPTi-SP	344	1197	748
Episodes of Clinical Malaria			
Placebo	166	826	336
IPTi-SP	146	854	344
% PE	14	–5	–16
95 CI (%)	(–11,33)	(–22, 9)	(–51, 11)
p-value	0.25	0.49	0.29
Episodes of Hospitalization with Malaria Parasites			
Placebo	34	54	58
IPTi-SP	30	52	74
% PE	12	2	–39
95 CI (%)	(–45, 47)	(–57, 39)	(–130, 15)
p-value	0.61	0.94	0.19
Episodes of All-Cause Hospital Admissions			
Placebo	108	203	205
IPTi-SP	111	224	202
% PE	–1	–12	4
95 CI (%)	(–38, 25)	(–43, 11)	(–34, 32)
p-value	0.94	0.34	0.79
Subjects with Anemia			
Placebo	40	102	64
IPTi-SP	35	117	61
% PE	12	–17	4
95 CI (%)	(–34, 43)	(–59, 15)	(–35, 31)
p-value	0.54	0.34	0.82

SOURCE: Compiled from data in the report of the Consortium's Statistical Working Group (IPTi Consortium, 2007b).

TABLE 17 Protective Efficacy (PE) and Reported 95% Confidence Intervals (CI) for Outcomes from Randomization Through 11 Months After Last Dose of SP or Placebo

Location, Country	Ifakara, Tanzania	Navrongo, Ghana	Manhiça, Mozambique	Overall
Number of Subjects				
Placebo	351	1225	748	
IPTi-SP	350	1221	755	
Episodes of Clinical Malaria				
Placebo	259	1871	576	
IPTi-SP	180	1570	564	
% PE	32	16	2	17
95 CI (%)	(14, 47)	(4, 26)	(–20, 20)	(0.8, 30)
p-value	0.002	0.007	0.84	0.04
Episodes of Hospitalization with Malaria Parasites				
Placebo	71	122	102	
IPTi-SP	42	83	108	
% PE	42	32	–3	26
95 CI (%)	(12, 62)	(5, 51)	(–56, 32)	(–0.9, 46)
p-value	0.011	0.023	0.89	0.057
Episodes of All-Cause Hospital Admissions				
Placebo	226	561	402	
IPTi-SP	191	513	379	
% PE	16	8	13	12
95 CI (%)	(–6, 34)	(–10, 23)	(–10, 31)	(0.2, 22)
p-value	0.14	0.36	0.25	0.046
Subjects with Anemia				
Placebo	52	274	108	
IPTi-SP	42	263	119	
% PE	23	4	8	9
95 CI (%)	(–11, 47)	(–19, 22)	(–16, 28)	(–6, 21)
p-value	0.16	0.73	0.47	0.22

SOURCE: Compiled from data in the report of the Consortium's Statistical Working Group (IPTi Consortium, 2008f).

The IOM committee was aware that it had available for deliberations more data and analyses than had been available to other independent committees that had previously assumed the task of reviewing and assessing the efficacy of IPTi-SP. Nevertheless, we were sensitive to the fact that some of the most important analyses we reviewed were from reports that had not yet been published.

Finding about heterogeneity of IPTi-SP studies: The committee found that the six IPTi-SP studies differed in their settings, intensity and seasonality of malaria transmission, use of insecticide-treated bed net coverage, prevalence of SP resistance and age at administration of doses of SP (or of placebo). The committee viewed this heterogeneity as a positive feature of the set of trials, concluding that IPTi-SP has been evaluated in several venues within sub-Saharan Africa that have different conditions, which allows generalizability to other sites in sub-Saharan Africa that have high or moderate intensity of transmission. Analysis of results from the different sites both shows the generalizability of IPTi-SP and identifies limitations that might not be detected if the conditions were more homogeneous.

Conclusion about efficacy data: The committee concluded that the trials had adequate power to assess the effect of IPTi-SP on the number of episodes of clinical malaria.

Assuming the analyses of the data from the individual trials are correct, the substantial amount of data on this outcome provides convincing evidence of an overall net benefit of IPTi-SP. With respect to the incidence of malaria from randomization up to 5 months after the last dose, the combined estimate of protective efficacy using a random-effects meta-analysis was 21 percent with a 95 percent CI of (11, 29; $p < 0.001$). The committee also concluded that an intervention with an efficacy of approximately 20 percent in diminishing the incidence of clinical malaria in infancy is a potentially useful adjunctive tool to control morbidity from malaria in areas in sub-Saharan Africa **where the incidence of malaria in infants is high** and where a well-functioning EPI infrastructure with reasonable immunization coverage exists (e.g., DPT3 coverage >50 percent, the GAVI cut-off for new vaccine eligibility).

Conclusion about overall efficacy of IPTi-SP: The committee concluded that the overall estimate of efficacy of IPTi-SP compared with placebo represents a composite of events that occurs during a number of distinct time periods. For example, in the long lag from the time a dose is given at 3 or 4 months of age until the next dose at 9 months of age, a high level of protection is observed during the first 35 days after the dose of SP. Although the efficacy falls considerably over the next few months, a modest level of protection appears to persist. Exposure to infected mosquitoes in the few months just before the dose at age 9 months may result in infections that stimulate the immune system before the dose at 9 months eliminates or suppresses the circulating parasites. After the last dose of IPTi and the drop in drug blood levels roughly 5 weeks later, a period of potential rebound occurs in which more cases may occur among children who previously received SP than among children who received placebo. The cumulative efficacy during these distinct periods results in an overall net benefit from IPTi-SP.

Finding for measured outcome events other than clinical malaria: The committee found that the cumulative data supporting an effect on hospitalization with malaria parasites, anemia and all-cause hospitalization were more modest and less consistent across the trials than the effect on episodes of clinical malaria. For hospitalizations of children with malaria parasites, analyses from randomization up to 5 months after the last dose of IPTi showed a net benefit in four of the six studies (estimated efficacies of 49, 37, 36 and 15 percent), with two being statistically significant. The other two sites showed an increased risk for this outcome with efficacies of –9 percent and –12 percent. The pooled estimate of protective efficacy was 21 percent with a 95 percent CI of (–2, 38). For all-cause hospitalizations, five studies had analyses from randomization through 5 months after the last dose; all showed a positive net effect with efficacies of 33, 24, 20, 11, and 2 percent; in two instances, these were statistically significant. The pooled estimate of efficacy in preventing all-cause hospitalizations was 18 percent with a 95 percent CI of (9, 27). Analyses from randomization up to 5 months of age after the last dose suggested a modest effect on preventing anemia. The efficacy estimate was positive for each of the six sites but in no single site was the result statistically significant. The pooled estimate of efficacy was 10 percent with a 95 percent CI of (4, 17). The committee found the estimated efficacy for these additional outcomes to be encouraging but less robust than the cumulative data for efficacy against clinical malaria. Accordingly, the committee remained cautious in drawing conclusions concerning the effect of IPTi-SP in preventing

these other outcomes. The analyses from randomization through 5 months after the last dose of IPTi-SP leave open the possibility that studies with much larger sample sizes might have demonstrated a statistically more convincing protective effect.

Finding about Consortium's rebound data and analyses: Several analyses provided by the SWG of the Consortium were very useful in evaluating whether IPTi-SP leads to rebound malaria. In particular, for each study and for the combined studies using random-effects meta-analyses, the analyses of malaria episodes in the period 5 months after the last dose of IPTi-SP (beginning 5 weeks after the dose) were very helpful. The overall combined estimates of efficacy against various outcomes are summarized in Table 18. With respect to clinical malaria, the primary outcome of interest, the combined estimate of protective efficacy using random-effects meta-analysis was 0 percent with a 95 percent CI of (–10, 9; $p>0.99$). For hospitalizations with malaria parasites the combined estimate of protective efficacy (using fixed-effects meta-analysis) was –20 percent with a 95 percent CI of (–60, 10; $p=0.23$). Similarly, for all-cause hospitalizations the combined estimate of protective efficacy was –11 percent (–30, 6; $p=0.22$). The combined estimate of protective effect against anemia using random effects meta-analysis was 2 percent with a 95 percent CI of (–8, 11; $p=0.74$).

These analyses focus only on the period of risk for rebound, comparing the SP and placebo groups. A statistically more rigorous and clinically more relevant approach is to perform analyses from randomization through 5 months after the last dose of IPTi-SP. For convenience and comparison, those analyses, which provide the net balance of effect between the treatment period and the potential rebound period, are also shown in Table 18 below.

Summary of conclusions about IPTi-SP efficacy and rebound:

- The six IPTi studies differed in their settings, intensity and seasonality of malaria transmission, use of insecticide-treated bed net coverage, prevalence of SP resistance and age at administration of doses of SP (or of placebo). The committee considered this heterogeneity a positive feature that allows generalizability of the findings to a variety of other sites in sub-Saharan Africa that have high or moderate intensity of transmission.

- The data and analyses available to the committee were deemed sufficient to detect efficacy of 20–30 percent, which is an adequate basis for judging the intervention worthwhile.

- Protective efficacy for clinical malaria was high during the treatment periods, mixed during the rebound period (see table 18) and moderate (21 percent combined estimate of efficacy against clinical malaria [95 percent CI, 11, 29]) during the full period from randomization through 5 months after the last dose of SP or placebo.

- The committee found that the cumulative data supporting an effect on hospitalization with malaria parasites, anemia and all-cause hospitalization were more modest and less consistent across the trials than the effect on episodes of clinical malaria (Table 18). The committee found the efficacy estimates for these additional outcomes to be encouraging but less robust than the cumulative data for efficacy against clinical malaria. Accordingly, the committee remained cautious in drawing conclusions concerning the effect of IPTi-SP in preventing these other outcomes. The analyses from randomization through 5 months after the last dose of IPTi-SP leave open the possibility that studies with much larger sample sizes might have demonstrated a statistically more convincing protective effect.

- Depending on the specific outcome event measured, the committee found mixed evidence regarding the existence of a rebound. In no case was the rebound sufficiently large to negate the overall benefit of IPTi-SP. Based on its review of all the data and the analyses presented, the committee concluded that the extent of rebound is small and that the benefits of IPTi-SP outweigh this negative effect.

TABLE 18 Overall Pooled Estimates of Efficacy Against Clinical Malaria and Other Relevant Outcomes During Two Periods of Follow-Up

	Period of Observation	
Outcome	**During the 5 months Starting 35 days After the Last Dose of SP or Placebo (Rebound Period)**	**From Randomization Up to 5 Months After the Last Dose of SP or Placebo**
Clinical malaria		
% PE	0	21
95 CI (%)	(–10, 9)	(11, 29)
p-value	0.99	<0.001
Hospitalizations of children with malaria parasites		
% PE	–20	21 [a]
95 CI (%)	(–60, 10)	(–2, 38) [a]
p-value	0.23	0.066 [a]
All-cause hospitalizations		
% PE	–11	18 [a]
95 CI (%)	(–30, 6)	(9, 27) [a]
p-value	0.22	0.001 [a]
Subjects with Anemia		
% PE	2	10 [a]
95 CI (%)	(–8, 11)	(4, 17) [a]
p-value	0.74	0.003 [a]

[a] The committee used Stata to calculate the overall efficacy and its 95 percent confidence limit.
SOURCE: Data from the Report of the Statistical Working Group (IPTi Consortium, 2007b).

Recommendation: In view of the importance of the unpublished analyses by the SWG in showing a net benefit for IPTI-SP, and whereas the committee had no information about how the SWG or the individual study teams ensured quality control of the individual study data and hence the uniformly defined outcomes, the committee recommends that the SWG obtain an independent technical audit of the accuracy of the study-level data and analyses included in the pooled analysis. If this

audit confirms the results presented, the committee would support the notion that IPTi-SP is ready to move to a new level. The committee's confidence in the efficacy of IPTi-SP in preventing cases of clinical malaria is sufficient to encourage larger-scale pilot implementations and evaluations in areas where the incidence of malaria in infants is high (often areas of perennial, high- and moderate-level transmission areas) to assess the impact of the intervention under real-life conditions. The provision of stronger evidence on these issues would be invaluable; the committee, however, recognizes that trying to estimate these parameters may involve an ethical challenge. If the evidence of IPTi-SP in preventing clinical malaria is deemed sufficient to propose instituting pilot implementations, there may not be sufficient equipoise to justify large controlled trials of IPTi-SP to evaluate its ability to prevent anemia, hospitalizations with malaria, or all-cause hospitalizations. One possible solution might be to nest case-control studies within large-scale, population-based pilot implementations of IPTi-SP. Nested studies of various designs may allow assessment of the effectiveness of IPTi in preventing malaria hospitalizations, anemia, and infant deaths.

None of the committee's conclusions related to efficacy for the different outcome events measured or rebound effect are meant to encourage the premature cessation of any currently ongoing IPTi trial or to discourage the initiation of previously planned trials intended to address specific questions of IPTi in particular settings. The committee recognizes several important gaps remain in what is known about IPTi-SP including the lack of data upon which to draw conclusions about the impact of IPTi-SP on infant and young-child mortality; filling those gaps, although very difficult in practice, is important. For example, the evidence supporting the efficacy of IPTi in preventing hospitalizations of patients with malaria parasites, anemia, and all-cause hospitalizations is suggestive but not conclusive. Indeed, further insight on the potential for rebound and on the relative morbidity associated with such cases in diverse operational settings would be desirable. For example, randomized controlled trials of IPTi-SP in geographic areas where the incidence of malaria illness in infants is known to be relatively low compared to older children (including some areas of highly seasonal transmission) would be of value. If additional randomized, controlled assessments of IPTi go forward to assess its utility in other settings, follow-up after the last dose of IPTi should be long enough to allow estimation of the overall benefit of the intervention not only for the treatment period but also for a reasonable period thereafter to take into account a possible rebound that might counterbalance a protective effect evident during the treatment period.

CONSIDERATION OF POTENTIAL COLLATERAL EFFECTS OF IPTi PRIOR TO IMPLEMENTATION

Drug Resistance and Sulfadoxine-Pyrimethamine

The committee considered the implications for IPTi-SP of *P. falciparum* resistance to SP, focusing on three questions: (1) Do SP resistance and efficacy for treating acute clinical malaria in children predict the efficacy of IPTi-SP? (2) Are there levels of resistance or treatment failure above which IPTi should not be recommended? (3) Will IPTi-SP result in increases in SP resistance that could compromise the use of SP or other antifolate antimalarials for IPTi or other indications?

Sulfadoxine-Pyrimethamine Resistance and Treatment Efficacy

The October 2006 WHO technical consultation on IPTi concluded that the six IPTi trials demonstrated a general trend toward decreasing estimated efficacy over time (WHO, 2008b). The IOM committee noted that most of this effect is attributable to the high efficacy in the first trial in Ifakara, Tanzania (Schellenberg, 2001). The subsequent trials all reported approximately 20–30 percent protective efficacy against clinical malaria. To address the concern that any trend toward declining efficacy was caused by increasing resistance of *P. falciparum* to SP (as manifest by the declining efficacy of SP for treating uncomplicated falciparum malaria in children), the Consortium presented an analysis showing no apparent relationship between SP treatment efficacy and IPTi efficacy at the clinical trial sites (Grobusch et al., 2007b; unpublished IPTi Consortium data). Resistance to SP can vary substantially across small distances and can change rapidly from year to year (Mugittu et al., 2004; Raman et al., 2008). Some of the studies of the efficacy of SP treatment were performed at times and places different from those of the IPTi trials; the committee therefore judged that the data do not rule out a relationship between the efficacy of SP treatment and the efficacy of IPTi-SP. Many treatment failures occur between 14 and 28 days after SP treatment; therefore, 14-day efficacy estimates can be associated with a wide range of 28-day efficacy levels (Plowe et al., 2004). When studied systematically, malaria drug resistance is ideally assessed by blood examination not only during the immediate post-treatment period but also from 14 to at least 28 days after treatment, because at lower levels of resistance the malaria parasites can appear to have been eliminated after parasitemia falls below the threshold of microscopic detection. A recrudescence can occur, however, when the effect of the drug is removed.

The Consortium also presented an unpublished analysis of the relationship between IPTi-SP efficacy and the contemporaneous prevalence of molecular markers for SP resistance. The data suggested a relationship between increasing prevalence of the *P. falciparum* dihydrofolate reductase (*dhfr*) "triple mutant" resistance marker and lower IPTi-SP protective efficacy. The apparent closer association between molecular resistance markers and IPTi-SP efficacy than between SP treatment efficacy and IPTi-SP efficacy suggests that, as might be expected, increasing SP resistance is likely to compromise IPTi efficacy. Whereas intrinsic resistance of *P. falciparum* to SP would be expected to affect the efficacy of both SP treatment and IPTi-SP, other factors that contribute to the rates of SP treatment failure in children (e.g., age and immune

status, drug quality, nutritional factors) are likely to vary across trial sites, obscuring the relationship between SP efficacy for treating malaria in children and parasite drug resistance. At present, WHO recommends that many countries in sub-Saharan Africa no longer use SP for the treatment of malaria; hence, SP drug pressure is likely to decrease soon, which may limit the spread of SP-resistant parasites (WHO, 2003).

The dihydrofolate reductase (*dhfr)* triple mutant is associated with high levels of pyrimethamine resistance in vitro (Peterson, 1990) and is strongly associated with clinical treatment failure of SP (Kublin, 2002). A further *dhfr* mutation (Leu-164) is associated with very high rates of SP treatment failure in Asia (100 percent resistance in Thailand) and in South America (94 percent in vivo resistance in Bolivia), but to date this further mutation has been reported only rarely and at low frequency in Africa (Nzila et al., 2005; Plowe et al., 1997). The Consortium presented unpublished data on the prevalence of the *dhfr* triple mutant from five IPTi-SP trial sites. The prevalence of the *dhfr* triple mutant was 44 percent in Navrongo, 47 percent in Tamale, 64 percent in Manhiça, 73 percent in Lambaréné and 77 percent in Kumasi. Data on the prevalence of the *dhfr* triple mutant prevalence are not available from Ifakara. In addition, data are not available for IPTi-SP efficacy where SP resistance exceeds 77 percent, and are also not available where the *dhfr* Leu-164 mutation associated with very high-level SP resistance is prevalent. The efficacy of IPTi-SP may be compromised if the prevalence of SP-resistant parasites increases beyond 80 percent or if very high-level resistance emerges and spreads, as found with the *dhfr* Leu-164 mutation. If the very high-level SP resistance common in Asia and South America appears in Africa, the effectiveness of IPTi-SP may be threatened. Evidence for the emergence and spread of such resistant parasites is likely to be available from resistance monitoring groups and networks.

> **Finding about IPTi-SP effectiveness, efficacy, and SP parasite resistance:** On the basis of the evidence presented, the committee found that the clinical effectiveness of SP for treating acute malaria in children is not an accurate indicator of IPTi-SP effectiveness, and that IPTi-SP has measurable efficacy in the face of moderate to high prevalence of SP resistant parasites that are common in much of sub-Saharan Africa (40 to 80 percent prevalence of dhfr triple mutant).

IPTi-SP and the Promotion of Resistance

The long clearance times of SP give it potential value as a practical intermittent preventive treatment for malaria in infants; however, the long clearance times also establish potentially selective levels of SP-resistant parasites in the bloodstream. In IPTi-SP, therefore, the malarial parasites are exposed to selective concentrations in an immunologically naïve infant with a potential for growth and transmission of resistant parasites.

Unpublished data from Manhiça, Mozambique, provided by the Consortium suggest that *P. falciparum* infections occurring within two months after the third dose of IPTi-SP had higher rates of some SP resistance markers than did infections occurring in infants who had received placebo. During this immediate post-treatment period the prevalence of the dihydrofolate reductase/dihydropteroate synthase (*dhfr/dhps)* quintuple mutant was 82 percent in IPTi-SP recipients compared with 44 percent in placebo recipients; the difference was not statistically

significant (owing perhaps to the small sample sizes and the consequent low power for the comparison). The observed difference reflected mainly a higher prevalence of the *dhps* double mutant in the IPTi group (91 percent) than in the placebo group (56 percent), because the *dhfr* triple mutant was high in both groups (91 percent in IPTi recipients and 81 percent in the placebo group). If prevalence in the placebo group represented the baseline prevalence of these resistance markers, these data suggest a selection by IPTi-SP of SP-resistant parasites, although none of these changes in prevalence reached statistical significance. These observations are consistent with a large body of published data describing rapid selection of antifolate-resistant parasites by SP and by pyrimethamine, whether given as treatment or as prophylaxis or whether resistance is measured by parasitological or molecular methods (Clyde and Shute, 1957; Diourte, 1999; Doumbo, 2000; Staedke et al., 2004). During the period between 2 months after the third dose of IPTi-SP and the end of the follow-up period in the Manhiça, Mozambique, trial, however, the prevalences of *dhfr* and *dhps* mutations in the IPTi-SP and placebo groups were again similar and close to baseline levels, suggesting that the selective effect was transient.

The preliminary data provided by the Consortium showed no evidence of increasing prevalence of SP resistance markers at the population level as a result of IPTi-SP. Prevalences of the *dhfr* triple mutant and the *dhps* double mutant were measured in 2004 and in 2006 in 12 subdistricts in southern Tanzania where IPTi-SP had been implemented in 2005 and also in 12 adjacent subdistricts where it had not been implemented. Although the data showed an overall increase in the prevalence of the resistance markers across the district, there was no suggestion that prevalence had increased more in subdistricts where IPTi-SP had been implemented than in subdistricts where it had not: The prevalence of the *dhfr* triple mutant and the *dhps* double mutant increased, respectively, by 7.2 and 18.1 percent in the IPTi-SP implementation subdistricts and by 7.6 and 17.8 percent in the control subdistricts. A non-Consortium researcher presented a mathematical model that suggested that the contribution of IPTi-SP to the dissemination of drug resistance would be modest, but might increase as malaria transmission decreases (O'Meara et al., 2006).

Conclusion about SP and drug resistance: Some selection for SP-resistant parasites is likely to occur in infections in infants who have recently received SP; however, the committee noted that IPTi did not result in increasing SP resistance at the population level in one setting. The committee concluded that concerns about accelerating the spread of SP resistance do not provide justifications for delay or limitation of IPTi implementation.

Recommendation: **The committee recommends that if programmatic implementation of IPTi-SP were to ensue, public health authorities should monitor evidence of possible increases or decreases of SP resistance in the areas or regions of implementation.**

Safety of Intermittent Preventive Treatment in Infants with Sulfadoxine-Pyrimethamine

Use of SP is known to cause hypersensitivity reactions including nonspecific rashes, urticaria (hives), and other adverse effects. In Africa, hypersensitivity reactions are less common

in children than in adults (Gimnig et al., 2006). Continuous use of SP is known to cause hematological disorders.

In rare cases, SP causes severe cutaneous reactions (SCR), namely Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Although SJS and TEN have similar clinical characteristics, these reactions differ in their pattern of distribution and the extent of macule formation and epidermal detachment (Emberger et al., 2003; García-Doval et al., 2000). The clinical manifestations of SJS include an erythematous rash with macules of irregular shape and size (Auquier-Dunant et al., 2002; Emberger et al., 2003) and, occasionally, vesicles and bullae that may coalesce and erode, in addition to lesions in the oral mucous membranes, anogenital regions, and conjunctivae (Emberger et al., 2003; Segal et al., 2007). In TEN, cutaneous eruption is generally preceded by 1 to 3 days of fever, sore throat, cough, and burning eyes (García-Doval et al., 2000). Rates of SCR of 10–40 per 100,000 were associated with the use of SP by travelers when SP was being used for malaria prophylaxis (Miller et al., 1986). Note that these rates of SCR were observed in people who received repetitive doses of SP as chemoprophylaxis. Treatment of malaria with SP has been associated with SCR at a rate of 0.3 per 100,000 in children younger than 15 years of age in Malawi and at a rate of 1.7 per 100,000 in adults. The rates of all adverse cutaneous reactions are higher in HIV-infected persons (Gimnig et al., 2006).

The evidence presented from the IPTi trial for safety monitoring was based primarily on passive reports in the six efficacy trials and in the additional trial in Kisumu, but the surveillance methods varied as noted in Table 19 (and Box 1).

TABLE 19 Safety Monitoring for IPTi Surveillance Methods of the Six IPTi-SP Studies and the Kisumu Trial

Trial Site	Surveillance Method(s)
Ifakara	Passive system reports; no cases SCR (trial protocol)
Kumasi	Treatment visit, questions, and monthly home visits
Lambaréné	Day 7 and day 28 visits, monthly home visits; sickness during clinic visits monitored
Manhiça	Home visit 1 week post-dose
Navrongo	20% sample visited <4 weeks post-dose
Tamale	Passive reports and monthly home visits
Kisumu	Passive case detection

SOURCE: Compiled from literature and data presented by the IPTi Consortium, 2008.

The approximately 4,000 children in the six IPTi-SP Consortium studies received an average of 2.8 doses of SP. The incidence of hospitalizations from all causes was reduced in the treatment arm in three of the trials during IPTi. There was no reported evidence of an increased rate of other severe adverse events in SP recipients compared with placebo recipients. Two SP recipients were reported to have developed SJS after the third dose in the Kumasi, Ghana, trial: Both of these children were seen at home by a general physician who noted bullous skin lesions, but did not recommend hospitalization. The children were examined approximately 2 weeks later and were found to be well. As SJS is a severe disorder requiring intensive care and is associated with a high case-fatality rate, the committee questions the validity of the diagnosis of SJS in these two children. Moreover, whatever type of skin reactions these were, they occurred in toddlers who received a dose of SP at 15 months of age. This dosing age, as used in the Kumasi, Ghana, study, is not one that would be part of IPTi-SP implementation through the EPI as

currently recommended by the Consortium (wherein doses are administered at 10 and 14 weeks and ~ 9 months of age in conjunction with EPI visits).

The rate of all-cause hospitalizations in the Consortium studies showed statistically significant 20–30 percent decreases in the first year of life among SP recipients compared with placebo recipients. Data provided to the committee included an analysis that suggested a higher rate of hospitalization following the second and third doses of IPTi compared with hospitalizations after the first dose, but it is unclear whether the reported rates were adjusted for the time at risk. The pooled data showed similar all-cause mortality rates in the placebo and SP groups; however, not all the published reports provided clear summaries of the total number of deaths, the malaria-related deaths, and the times of death.

No information was presented on the risks or benefits of IPTi-SP in infants who are receiving trimethoprim-sulfamethoxazole (TS, also known as cotrimoxazole) prophylaxis to prevent HIV-related opportunistic infections; however, numerous previous studies in a variety of settings in Africa have shown that cotrimoxazole is highly effective in preventing malaria (Anglaret et al., 1999; Mermin et al., 2004; Thera et al., 2005). With increased acceptance of voluntary HIV testing of pregnant women, most HIV-exposed children are expected to receive TS prophylaxis beginning at 6 weeks of age and are not expected to benefit from IPTi-SP. Some HIV-infected children will not be identified until later in infancy or childhood and thus will begin TS prophylaxis after having received IPTi-SP doses. Monitoring such infants for evidence of increased risk of hypersensitivity reactions to antifolates would be valuable.

> **Finding and Conclusion about SP safety with antifolate medications:** The committee found no evidence of additional benefit of IPT with SP among children receiving TS prophylaxis. No information is available on the risk of adverse events associated with coadministration of these antifolate medications. Because of this lack of information, the committee concluded that IPTi-SP should not be offered to infants or young children who are taking long-term, daily cotrimoxazole to prevent HIV-associated infections**.**

> **Recommendation: Post-implementation monitoring should include pharmacovigilance with longer-term follow-up for children (e.g., 24 months) to detect adverse reactions that may arise when recipients of IPTi-SP in infancy subsequently receive cotrimoxazole or other sulfa drugs.**

Pharmacokinetics of Sulfadoxine-Pyrimethamine

Ideally, data on the pharmacokinetics of SP in healthy African infants would be useful; however, little information is available on the pharmacokinetics of antimalarial drugs, including SP, in the first year of life. Moreover, even if such data existed for healthy aparasitemic and parasitemic African infants, the relevance of these data is uncertain for infants with malnutrition or HIV infection.

Despite decades of widespread use, little information is available to inform choice of dosage for IPTi (Barnes et al., 2006). Most IPTi studies have chosen drugs with long half-lives such as amodiaquine and SP, to maximize the prophylactic window of each dose. The first two doses are given only 1 month apart (e.g., at 10 and 14 weeks of age); an interval of 5–6 months separates the second dose of SP (at 14 weeks) and the third (at 9 months of age) doses of SP. The

committee noted that some ongoing studies are evaluating alternative drugs (e.g., amodiaquine, mefloquine, and chlorproguanil-dapsone) given either alone or in combination with artemesinins.

Finding and Conclusion about SP and other antimalarial pharmokinetics: The committee found that although the pharmacokinetics of SP in infants and toddlers 3–15 months of age in IPTi have not been well studied, a wealth of data supports the benefits and safety of SP dosages currently recommended for these age groups as used in therapeutic and preventive regimens. The committee concluded that studying other drugs would be a reasonable avenue for further research as the evidence base for IPTi with drugs other than SP is still limited. Further, if trials are undertaken to study the efficacy of IPTi with antimalarial drugs other than SP, and if pharmacokinetic data in infants are not available for those drugs, nesting pharmacokinetic studies within the clinical trials could yield valuable information**.** Generating pharmacokinetic data on the new drugs in infants may provide information with which to design improved and more effective treatment schedules and dosage regimens.

Impact of IPTi on Response to Expanded Program on Immunization Vaccines

The report on IPTi produced by the WHO Technical Expert Group (which was convened in Geneva October 8-10, 2007) states that there is "sound evidence that IPTi has no adverse impact on serological responses to DPT, polio, hepatitis B, *Haemophilus influenzae* type b (Hib), yellow fever and measles vaccines" (WHO, 2008b, p. 7). To support this statement, this Technical Expert Group cited an internal WHO report from 2006, "Interim Report on IPTi with SP," prepared by the WHO Advisory Committee on serological responses to EPI vaccines in infants receiving IPT.

This advisory committee was comprised of two pediatricians with extensive experience in laboratory assessment of serological responses, an expert in vaccine safety, a clinician with expertise in clinical trials of antimalarial drugs, and a biostatistician with extensive experience in statistical design of clinical trials and in analysis of serological data. This group first analyzed all of the data from the serological IPTi studies with SP alone or in combination with other antimalarial drugs and then advised WHO accordingly.

The serological study, with guidance from the WHO Advisory Committee, was designed as a set of non-inferiority studies nested into five IPTi, randomized-controlled trials that were already underway to assess the protective efficacy of IPTi against clinical malaria and anemia. The sites included three Consortium IPTi sites (Navrongo, Ghana; Manhiça, Mozambique; and Kisumu, Kenya) and two additional sites in Bungoma, Kenya and Kilimanjaro, Tanzania. The purpose of the non-inferiority design was to demonstrate that IPTi-SP does not reduce serological responses to EPI vaccines by a clinically important amount. The primary outcome was serological responses to measles vaccine and the sample sizes were selected to give 80 percent power to exclude more than a 5 percent difference in the proportion of infants attaining protective levels of antibody post-vaccination from the IPTi group compared with the placebo group. For the secondary endpoint, serological responses to all other EPI vaccines, the sample sizes were selected to give 80 percent power to exclude a 10 percent difference in the proportion of infants attaining protective levels of antibody post-vaccination in the IPTi group compared with the placebo group (WHO, 2006).

The Health Agency in the United Kingdom performed all serological assays in duplicate by using standardized reagents or validated test kits; they performed the assays in accordance with the principles of Good Laboratory Practice. Where sufficient blood samples were available to carry out all of the assessment assays, there was a specified, ranked order based on the relative immunogenicity of each antigen. The London School of Tropical Medicine and Hygiene Tropical Epidemiology group conducted the statistical analyses by using all results of the laboratory serology, the relevant clinical data from each study sites, and the randomization codes to compare the post-vaccination geometric mean antibody concentrations and the proportion of infants attaining the protective level for each EPI antigen in the IPTi and placebo groups. Reverse cumulative curves were plotted for each antigen (WHO, 2006).

The advisory committee's report focused on the Navrongo, Manhiça, and Bungoma sites because of their exclusive use of IPTi-SP. For the pooled analysis, data were pooled from the Navrongo and Manhiça sites only, and methods accounted for the cluster randomization in the Navrongo trial and for the individual randomization in Manhiça. The Bungoma trial was excluded after an audit revealed problems that, although ultimately corrected, raised doubts about the validity of its clinical and serological data. Results from the pooled analyses showed a highly significant formal test of non-inferiority ($p<0.001$) for the primary outcome. The advisory committee concluded from the pooled analysis that IPTi-SP does not have an adverse impact on the measles vaccine. "The reverse cumulative distribution [sic] curves for both the IPTi and placebo groups were closely aligned across the range of antibody concentrations, including the assigned protective level of 120mIu/ml" (WHO, 2006, p. 15). The advisory committee's overall conclusion (based on the individual serology studies from Navrongo, Manhiça, and Bungoma) was that the data strongly suggested that IPTi-SP has no adverse impact on serological responses to the DPT, polio, hepatitis B, and Hib vaccines.

In view of WHO's critical role in providing technical guidance and oversight to the EPI in sub-Saharan Africa, the IOM committee was pleased to be made aware of WHO's technical leadership on this important point relevant to EPI.

> **Finding and Conclusions about SP and EPI vaccines:** On the basis of the evidence presented, the committee found that the studies were adequately powered to assess non-inferiority or seroequivalence and that the studies used appropriate serologic assays. The pooled analysis showed no evidence suggesting that SP has a negative impact on the serologic response to the EPI vaccine antigens evaluated to date. Thus, the committee concluded that the administration of SP with scheduled EPI visits has been demonstrated to be an effective means for implementing IPTi. The committee also concluded that, as other vaccine antigens (e.g., the rotavirus, Haemophilus influenzae type b, pneumococcal-conjugate, and meningococcal-conjugate vaccines) are added to the EPI for infants in sub-Saharan Africa in the future, it will be prudent to document that IPTi does not negatively impact the immunogenicity of those vaccines. Similarly, if an evidence base with IPTi that uses other antimalarials accumulates and proves to be as robust as the data for IPTi-SP, it will have to be shown (as has been done for IPTi-SP) that these other antimalarials do not adversely impact immune responses to EPI vaccines.

Program Management of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine

Information on operational issues that must be addressed in implementing IPTi has been collected from pilot implementation in countries with high mortality rates for children younger than 5 years of age and from formative research studies associated with the efficacy trials detailed above. Final results from the largest pilot study conducted by the United Nations Children's Fund (UNICEF) and implemented December 2006–December 2007 in Benin, Ghana, Mali, Senegal, Madagascar, and Malawi are expected in June 2008.

Acceptability of Intervention

The committee reviewed the published results of studies of the community response to IPTi in Manhiça, Mozambique and the preliminary data from the southern Tanzania implementation study. The program was well accepted by the community in Mozambique after initial resistance due to misunderstanding of some of the study procedures (e.g., measuring infant height and weight were interpreted as measurements for coffins, and rumors spread about the purpose of drawing blood from the infants). The barriers to acceptability were identified; study procedures were changed when possible; and community education was emphasized. These changes led to improved acceptance in the population (Pool et al., 2006). No such suspicions developed in southern Tanzania. At both locations, IPTi-SP was perceived to be part of EPI, although most parents understood that SP was not a vaccine that prevented all malaria but was instead a measure to decrease its severity. At all sites, some surveyed caregivers mistook SP as an antipyretic that prevented fever after immunization.

Enrollment data for the UNICEF sites showed a large discrepancy between initial enrollment figures and actual participation in the trials. The Consortium spokesperson from UNICEF explained that this discrepancy resulted from successful, initial recruitment of women in clinics followed by withdrawal due to rejection of their participation by husbands when mothers and children returned home. Further exploration may elucidate the reasons for such withdrawal and whether these reasons are related to the acceptability of the intervention at the caregiver level or at the household level. Alternately, unpublished Consortium data from the acceptability trial in southern Tanzania indicate differences in the influence of men in a child's health decision-making. The findings show that even though men are involved in matters related to child health, mothers have relative freedom in health decision-making because the mothers are ultimately responsible for taking the children to health clinics. The southern Tanzanian investigators concluded that there is uncertainty regarding the level of male influence when the health intervention is provided at home and not at the health facility (IPTI Consortium, 2008d).

The need to dissolve the drug tablet in water was a major barrier to optimal implementation in southern Tanzania and at the UNICEF sites because of unclean and/or inconsistent water supplies and also because of suboptimal methods of cleaning the spoons and cups between patients. In Tanzania, this led to the practice of giving parents the SP to administer at home. At the UNICEF sites, several different strategies were adopted, all with significant drawbacks. For example, dissolving the drug in the mother's breastmilk was tried, but this technique led to the exclusion of children brought to the site by a family member other than a

mother. In another example, the water used for administration was boiled, which led to a significant increase in the time spent on IPTi activities. Other barriers identified from the preliminary data collected from the UNICEF sites include the requirement to cut the SP tablet, the need for intensive supervision of the program, the continuity of the drug supply, and the EPI shortages or cold-chain disruption that led to temporary cessation of child vaccinations (IPTi Consortium 2008e). Unique barriers to acceptability may arise in each location where IPTi-SP is implemented and locally applicable solutions will need to be developed.

Logistics for Mode of Delivery and Effect on EPI

Drawing on the lessons learned from the difficult introduction of vitamin A into EPI in Tanzania, UNICEF described a deliberate process to prepare for implementing IPTi: Adding an implementation coordinator and developing an integrated health information management system, issuing provider guidelines, and providing training curricula. Preliminary results from UNICEF's study indicate that more than 400,000 doses of SP were delivered across all of the sites to more than 300,000 children. UNICEF's IPTi-SP coverage dropped in Malawi to a range below the other participating countries. In Malawi, the shortage of quality SP for treatment of malaria (owing to concerns about counterfeit medication in the country's treatment supply) led to using UNICEF's supply of SP for treatment; as a result, SP was no longer available for IPTi-SP in the UNICEF sites in Malawi. This example illustrates the importance of adequate logistical planning for drug procurement and distribution in conjunction with the country entities responsible for drug forecasting and for the procurement of SP for treatment.

The UNICEF data on EPI coverage, which was collected from the first quarter of 2006 to the second quarter of 2007 in pre- and post-implementation surveys addressed whether and how much IPTi influenced either EPI coverage or other malaria-control strategies. In the project area, UNICEF found that EPI coverage rose from an average of less than 50–70 percent for all antigens during the course of the study. In IPTi areas, the DPT3 dropout rate was nearly 26 percent in control sites compared with 7 percent in new IPTi treatment sites.

Pharmacovigilance Monitoring of IPTi-SP

Before gaining ethical clearance to implement the pilot study in each country, UNICEF established a pharmacovigilance system to assess adverse events after the use of IPTi-SP. The UNICEF goals for pharmacovigilance surveillance of IPTi-SP were to learn best practices, to assess the costs of strengthening pharmacovigilance systems, and to collect accurate data for documentation and swift investigation of causality of adverse events that occurred after an infant received IPTi-SP. Five countries participated in UNICEF's passive surveillance monitoring efforts and two in active surveillance. Of the 5,000 doses administered to the approximately 4,600 infants actively followed in Ghana and Madagascar, UNICEF reported that a larger cohort of children received all three doses of IPTi-SP in Madagascar. Only three children in Ghana received all three doses; the majority of the Ghanaian children received only one or two doses of SP, but the reasons for this discrepancy were not explained. A range of adverse events—from crying to skin rashes—was successfully reported in the active system.

Finding and Conclusion about programmatic management of IPTI-SP: The committee found that many issues relevant to programmatic management of IPTi-SP were not well-explored in the studies presented. To enhance the acceptability and sustainability of IPTi-SP, the committee concluded that systematic capture of this information can help support continued improvement of a stepwise strategy for increasingly larger-scale implementation of IPTi-SP in relevant areas of sub-Saharan Africa if public health authorities implementing IPTi-SP are asked to regularly share information related to logistics, policy and program implementation, monitoring and evaluation, mode of delivery, and acceptability.

Cost-Effectiveness of IPTi-SP

Methodology

Using standard cost-effectiveness methodology based on a societal perspective, the Consortium presented incremental cost-effectiveness ratios (the change in costs of a therapeutic intervention to the change in effects of the intervention) based on the IPTi intervention compared with a "do-nothing" alternative. Health effects were estimated by using the efficacy results of the intervention and were combined with malaria incidence in the target population to estimate malaria cases averted for two sites—Ifakara, Tanzania and Manhiça, Mozambique. Cost-effectiveness ratios included cost per malaria episode averted, cost per malaria death averted and cost per Disability-Adjusted Life-Year (DALY) averted. Age-weighted DALYs were based on averted morbidity measured from the trials with mortality having an assumed case-fatality rate of 2 percent. Intervention costs included start-up and recurrent costs related to planning, delivery, and monitoring of IPTi. Treatment costs of inpatient and outpatient care (used to estimate resource savings) were collected from the study sites at the time of the trials.

Costing Data

The conditions of the Ifakara trial and the Manhiça trial did not reflect the actual practice of IPTi-SP delivery or the costs incurred. The researchers therefore also relied upon recently collected cost data from an effectiveness study being conducted in a community IPTi-SP trial in the Mtwara and Lindi regions of southern Tanzania. The Consortium reported using the same data for Mozambique because of the country's similarity to Tanzania in health systems, resources available, and pricing, with the only difference being the actual cost of SP. Investigators used 2006 Tanzanian prices to calculate intervention costs and excluded the costs associated with research and with operation of clinical trials. Cost-effectiveness ratios (using efficacy results from the 2 individual trials and excluding cost savings from less severe malaria cases) were reported in 2006 U.S.$: per DALY averted US$ 3.7 (1.61–12.20) in Ifakara (Tanzania) and US$ 11.2 (3.58–92.0) in Manhiça (Mozambique) when only gross intervention costs were considered. When savings due to treatment averted (with the assumption of uncomplicated treatment for outpatient malaria cases and complicated treatment for inpatient

cases) are included in the analysis, these will outweigh the costs of the intervention (cost per malaria episode averted was US$ 1.6 (0.8–4.0) and US$ 4.7 (1.7–30.3) for Ifakara and Manhiça, respectively). Costs per death averted were reported at US$ 100.0 (43.0–330.9) and US$ 301.0 (95.6–2498.4) for Ifakara and Manhiça, respectively. Sensitivity analyses were performed by the Consortium to explore the robustness of the results.

Cost-effectiveness of IPTi Relative to Other Malaria-Control Interventions

While costing methodologies vary significantly between the two sites, the study indicated that IPTi is cost-effective relative to many other malaria-control interventions in sub-Saharan Africa. Specifically, studies in sub-Saharan Africa, as reported in cost per DALY (all in U.S. dollars), include: $10 to $12 for reported case management with artemisinin-based combination therapy (Morel et al., 2005); $3 to $41 for chemoprophylaxis for children (Goodman et al., 1999); $4 to $29 for intermittent preventive treatment in pregnancy (Goodman et al., 1999); $32 to $41 for indoor residual insecticide spraying (Morel et al., 2005); and $29 to $40 for provision and treatment of bed nets (Goodman et al., 1999; Morel et al., 2005). The estimates of IPTi cost-effectiveness estimates reported by the Consortium also fall well below the benchmark of US$ 30 for the highly cost-effective interventions recommended by the World Health Organization (WHO, 1996). Benchmarks and thresholds of cost-effectiveness are only a guide for those who make the decisions about monetary resources. With most African governments devoting less than US$ 5 per person annually to public health, an IPTi program (no matter how cost-effective) could only be sustained through the continuing infusion of substantial international funds. The critical issue for consideration, therefore, is whether the financing of IPTi-SP can be sustained as an intervention competing for limited healthcare resources.

> **Finding and Conclusion about cost-effectiveness of IPTI-SP:** The committee found that, in one study, IPTi-SP delivered through a robust EPI system with high levels of coverage and acceptability appears to be relatively cost effective and compares well with other malaria-control interventions. The committee therefore concluded that this preliminary finding suggests that IPTi-SP delivered through EPI could be considered as a potential intervention to be included in the malaria control tool kit for sub-Saharan Africa.
>
> **Recommendation: If larger-scale implementation of IPTi-SP in a given country were to ensue, it should be accompanied by the collection of evidence under varying conditions that are likely to affect the cost-effectiveness of the intervention, including the extent to which there is excess capacity under EPI (e.g., staff time, equipment, and vehicle use) to implement IPTi-SP; malaria transmission intensities; the case-fatality rates; the unit prices of IPTi drugs; and the program start-up costs**.

THE POTENTIAL VALUE OF CONTINUED INVESTMENT IN IPTi-SP

In areas where malaria in infancy is an important health problem, IPTi-SP is likely to decrease morbidity from malaria. The most recently available data have indicated that regions with high and perennial malaria transmission have the greatest burden of malaria in infancy. As effective treatment and control measures (including widespread use of insecticide-treated bed nets, indoor residual insecticide spraying, and artemisinin-based combination therapies) become more widely implemented, more areas of Africa will be moving toward lower transmission intensities and may experience a resultant decrease in the burden of disease in the first year of life. Chandramohan and colleagues conducted a secondary analysis of data from an IPT trial in Ghana to explore whether EPI-linked IPT is the best option for maximizing the benefits of IPT for children younger than 5 years of age. They found that the highly seasonal transmission of malaria as in parts of West Africa differs from that in some sites for the initial IPTi trials and suggested that perhaps only 10 percent of malaria episodes in infants would be averted with current EPI coverage rates in such areas of extremely seasonal transmission (Chandramohan et al., 2007). For this reason, the burden of malaria in infancy in a particular country is likely to affect the potential value of IPTi if adoption is considered. Chandramohan and colleagues concluded that in areas of seasonal transmission or high disease rates in children above 1 year of age, IPT outside of the EPI system may be considered. However, in most areas of sub-Saharan Africa it is not clear how IPT could be delivered in a practical, cost-effective, sustainable way outside the EPI.

Conclusion about continued investment in IPTi: On the basis of the evidence presented, the committee concluded that a decrease in the malaria burden in infancy would be expected to ensue after programmatic implementation of IPTi-SP in areas with high incidence of clinical malaria. The greatest public health impact of IPTi-SP will almost certainly be observed in areas of sub-Saharan Africa with high- and moderate-intensity, perennial transmission. In areas of low or seasonal transmission, where the greatest burden of malaria occurs after the first year of life, the public health benefit of IPTi may be less. The committee further concluded that continued investment in the strategy appears warranted but cautions that drug supply and logistics, monitoring and resistance, and community acceptance and reaction to IPTi-SP could arise as problems in conjunction with large-scale implementation.

Recommendation: If large-scale implementation is to be pursued, the committee recommends that the first IPTi-SP programs should be used where the infant population is at high risk for malaria morbidity because of perennial, high- and moderate-intensity transmission. Support should be continued for current efforts to identify more precise parameters, such as transmission intensity, seasonality of transmission, DPT3 coverage, and severity of clinical disease for locations in which IPTi-SP is to be implemented. Additionally, if large-scale implementations proceed or wherever large pilot projects are carried out, the committee urges that attempts be made to evaluate the impact of IPTi-SP on mortality in infant and young children.

Recommendation: Because of the issues discussed in this document, plans for monitoring and evaluation should accompany the programmatic implementation of IPTi-SP. Indicators would include the burden of malaria in infancy, which is likely to change in response to ongoing and new interventions, SP resistance, side effects, and impact on EPI coverage. Post-implementation monitoring of IPTi-SP would benefit from a baseline assessment followed by regular measurements of the burden of malaria in infancy. This could be accomplished through surveillance at sentinel sites, including hospitals and primary-care centers; in different transmission settings; and in other inter-country networks with capacity for data collection.

Once the policy is well established and large-scale implementation is shown to be effective, notable changes may be detected in the age distribution of the pediatric malaria burden that may warrant modification of the policy. For example, if the frequency of infant malaria begins to increase, programmatic shortcomings and the emergence of drug resistance would require investigation. If IPTi, in conjunction with other measures, is highly effective and infant malaria is dramatically reduced or eliminated, the program may be modified to target the appropriate vulnerable age groups, possibly to include older children.

CONCLUSION

Now is a propitious moment for the control of malaria in sub-Saharan Africa. A tool box of preventive and therapeutic interventions has been assembled, with each tool offering the potential to reduce a portion of the burden of malaria disease and deaths. Among those tools already operational are insecticide-treated bed nets, indoor spraying with safer residual insecticides, IPTp, and artemisinin combination therapies. None of these tools by itself represents a magic bullet for control of malaria; if, however, these tools are used collectively, they may well achieve heretofore unparalleled results for sub-Saharan Africa. Early in its review of the trial designs and the data from those trials that constitute the evidence base addressing efficacy, the committee noted that the IPTi-SP studies were powered to assess an approximate 20–30 percent reduction for outcome events (e.g., clinical malaria) in the primary aim, comparing the IPTi-SP and the placebo groups. Where the incidence of malaria in infants is high, if there is a well-functioning EPI, an intervention that could achieve a 20–30 percent reduction in malaria morbidity events in the target group would be considered substantial. Thus, the committee finds the data supporting the efficacy and the safety of IPTi-SP against episodes of clinical malaria to be sufficiently persuasive to endorse continued investment in IPTi-SP and to believe that this intervention is ready to progress to another level. The committee is also acutely aware that the epidemiology of malaria in many areas of sub-Saharan Africa appears to be undergoing change, resulting in diminished exposure of local populations to infective mosquitoes and a diminished burden of clinical disease, particularly among infants.

Continued investment in IPTi-SP could take several forms. One might be additional large-scale pilot implementations like the few that have already been undertaken in southern Tanzania and in several other countries (Benin, Ghana, Madagascar, Malawi, Mali and Senegal) in sub-Saharan Africa. Many practical lessons can be learned from such pilot projects. For example, the overall impact of IPTi-SP will depend not only on the incidence of malaria among infants in a population but on their access to EPI services, on the EPI coverage, and on how well

SP drug therapy is integrated into the routine EPI at the local level. Investment might also take the form of generating evidence to fill remaining gaps. In the view of the committee, these would include having more extensive and robust data to quantify the impact of IPTi-SP on diminishing malaria hospitalizations, anemia, all-cause hospitalizations, and infant mortality. Additional evidence of this type would be invaluable to public health decision makers who must grapple with recommending where to implement IPTi-SP and under what set of conditions. The committee therefore envisions that IPTi-SP has great potential to serve as an additional tool to assist in the control of malaria **among infants at high risk who live in areas of perennial, high- and moderate-intensity malaria transmission in sub-Saharan Africa and in regions where EPI services achieve reasonable coverage (e.g., DPT3 >50 percent)**. Box 2 and 3 below summarize the Committee's Findings, Conclusions and Recommendations. The Findings and Conclusions are in order of appearance in the report, while the Recommendations are in order of significance. The basis for the recommendations is explained in the text.

As additional evidence is generated from pilot projects, step-wise implementations, and focused studies to fill knowledge gaps and to expand the existing knowledge base about IPTi, its relative value as a control measure will become more clear. The IOM Committee on the Perspectives on the Role of Intermittent Preventive Treatment for Malaria in Infants appreciates the opportunity to provide input into the global health initiatives of the Bill and Melinda Gates Foundation. We would be pleased to brief you and your staff regarding the findings and recommendations provided in this letter.

BOX 2
List of Committee Findings and Conclusions by Order of Appearance in the Letter Report

The committee's findings and conclusions are based on the evidence presented to and reviewed by the committee including publicly available literature.

Efficacy of Sulfadoxine-Pyrimethamine for Use in Intermittent Preventive Treatment

- The committee found that the six IPTi-SP studies differed in their settings, intensity and seasonality of malaria transmission, use of insecticide-treated bed net coverage, prevalence of SP resistance and age at administration of doses of SP (or of placebo). The committee viewed this heterogeneity as a positive feature of the set of trials, concluding that IPTi-SP has been evaluated in several venues within sub-Saharan Africa that have different conditions, which allows generalizability to other sites in sub-Saharan Africa that have high or moderate intensity of transmission. Analysis of results from the different sites both shows the generalizability of IPTi-SP and identifies limitations that might not be detected if the conditions were more homogeneous.
- The committee concluded that the trials had adequate power to assess the effect of IPTi-SP on the number of episodes of clinical malaria. Assuming the analyses of the data from the individual trials are correct, the substantial amount of data on this outcome provides convincing evidence of an overall net benefit of IPTi-SP. With respect to the incidence of malaria from randomization up to 5 months after the last dose, the combined estimate of protective efficacy using a random-effects meta-analysis was 21 percent with a 95 percent CI of (11, 29; $p < 0.001$). The committee also concluded that an intervention with an efficacy of approximately 20 percent in diminishing the incidence of clinical malaria in infancy is a potentially useful adjunctive tool to control morbidity from malaria in areas in sub-Saharan Africa **where the incidence of malaria in infants is high** and where a well-functioning EPI infrastructure with reasonable immunization coverage exists (e.g., DPT3 coverage >50 percent, the GAVI cut-off for new vaccine eligibility).
- The committee concluded that the overall estimate of efficacy of IPTi-SP compared with placebo represents a composite of events that occurs during a number of distinct time periods. For example, in the long lag from the time a dose is given at 3 or 4 months of age until the next dose at 9 months of age, a high level of protection is observed during the first 35 days after the dose of SP. Although the efficacy falls considerably over the next few months, a modest level of protection appears to persist. Exposure to infected mosquitoes in the few months just before the dose at age 9 months may result in infections that stimulate the immune system before the dose at 9 months eliminates or suppresses the circulating parasites. After the last dose of IPTi and the drop in drug blood levels roughly 5 weeks later, a period of potential rebound occurs in which more cases may occur among children who previously received SP than among children who received placebo. The cumulative efficacy during these distinct periods results in an overall net benefit from IPTi-SP.
- The committee found that the cumulative data supporting an effect on hospitalization with malaria parasites, anemia and all-cause hospitalization were more modest and less consistent across the trials than the effect on episodes of clinical malaria. For hospitalizations of children with malaria parasites, analyses from randomization up to 5 months after the last dose of IPTi showed a net benefit in four of the six studies (estimated efficacies of 49, 37, 36 and 15 percent), with two being statistically significant. The other two sites showed an increased risk for this outcome with efficacies of –9 percent and –12 percent. The pooled estimate of protective efficacy was 21 percent with a 95 percent CI of (–2, 38). For all-cause hospitalizations, five studies had analyses from randomization through 5 months after the last dose; all showed a positive net effect with efficacies of 33, 24, 20, 11, and 2 percent; in two instances, these were statistically significant. The pooled estimate of efficacy in preventing all-cause hospitalizations was 18

BOX 2 Continued

percent with a 95 percent CI of (9, 27). Analyses from randomization up to 5 months of age after the last dose suggested a modest effect on preventing anemia. The efficacy estimate was positive for each of the six sites but in no single site was the result statistically significant. The pooled estimate of efficacy was 10 percent with a 95 percent CI of (4, 17). The committee found the estimated efficacy for these additional outcomes to be encouraging but less robust than the cumulative data for efficacy against clinical malaria. Accordingly, the committee remained cautious in drawing conclusions concerning the effect of IPTi-SP in preventing these other outcomes. The analyses from randomization through 5 months after the last dose of IPTi-SP leave open the possibility that studies with much larger sample sizes might have demonstrated a statistically more convincing protective effect.

- Several analyses provided by the SWG of the Consortium were very useful in evaluating whether IPTi-SP leads to rebound malaria. In particular, for each study and for the combined studies using random-effects meta-analyses, the analyses of malaria episodes in the period 5 months after the last dose of IPTi (beginning 5 weeks after the dose) were very helpful. The overall combined estimates of efficacy against various outcomes are summarized in the table below. With respect to clinical malaria, the primary outcome of interest, the combined estimate of protective efficacy using random-effects meta-analysis was 0 percent with a 95 percent CI of (–10, 9; $p>0.99$). For hospitalizations with malaria parasites the combined estimate of protective efficacy (using fixed-effects meta-analysis) was –20 percent with a 95 percent CI of (–60, 10; $p=0.23$). Similarly, for all-cause hospitalizations the combined estimate of protective efficacy was –11 percent (–30, 6; $p=0.22$). The combined estimate of protective effect against anemia using random effects meta-analysis was 2 percent with a 95 percent CI of (–8, 11; $p=0.74$). These analyses focus only on the period of risk for rebound, comparing the SP and placebo groups. A statistically more rigorous and clinically more relevant approach is to perform analyses from randomization through 5 months after the last dose of IPTi-SP. Those analyses (mentioned above) provide the net balance of effect between the treatment period and the potential rebound period.
- Depending on the specific outcome event measured, the committee found mixed evidence regarding the existence of a rebound. In no case was the rebound sufficiently large to negate the overall benefit of IPTi-SP. Based on its review of all the data and the analyses presented, the committee concluded that the extent of rebound is small and that the benefits of IPTi-SP outweigh this negative effect.

Drug Resistance and Sulfadoxine Pyrimethamine

- On the basis of the evidence presented, the committee found that the clinical effectiveness of SP for treating acute malaria in children is not an accurate indicator of IPTi-SP effectiveness, and that IPTi-SP has measurable efficacy in the face of moderate to high prevalence of SP resistant parasites that are common in much of sub-Saharan Africa (40 to 80 percent prevalence of dhfr triple mutant).
- Some selection for SP-resistant parasites is likely to occur in infections in infants who have recently received SP; however, the committee noted that IPTi did not result in increasing SP resistance at the population level in one setting. The committee concluded that concerns about accelerating the spread of SP resistance do not provide justifications for delay or limitation of IPTi implementation.

BOX 2 Continued

Safety of Intermittent Preventive Treatment in Infants and Sulfadoxine Pyrimethamine

- The committee found no evidence of additional benefit of IPT with SP among children receiving TS prophylaxis. No information is available on the risk of adverse events associated with coadministration of these antifolate medications. Because of this lack of information, the committee concluded that IPTi-SP should not be offered to infants or young children who are taking long-term, daily cotrimoxazole to prevent HIV-associated infections**.**
- The committee found that although the pharmacokinetics of SP in infants and toddlers 3–15 months of age in IPTi have not been well studied, a wealth of data supports the benefits and safety of SP dosages currently recommended for these age groups as used in therapeutic and preventive regimens. The committee concluded that studying other drugs would be a reasonable avenue for further research as the evidence base for IPTi with drugs other than SP is still limited. Further, if trials are undertaken to study the efficacy of IPTi with antimalarial drugs other than SP, and if pharmacokinetic data in infants are not available for those drugs, nesting pharmacokinetic studies within the clinical trials could yield valuable information**.** Generating pharmacokinetic data on the new drugs in infants may provide information with which to design improved and more effective treatment schedules and dosage regimens.

Impact of Expanded Program on Immunization Vaccines

- On the basis of the evidence presented, the committee found that the studies were adequately powered to assess non-inferiority or seroequivalence and that the studies used appropriate serologic assays. The pooled analysis showed no evidence suggesting that SP has a negative impact on the serologic response to the EPI vaccine antigens evaluated to date. Thus, the committee concluded that the administration of SP with scheduled EPI visits has been demonstrated to be an effective means for implementing IPTi. The committee also concluded that, as other vaccine antigens (e.g., the rotavirus, Haemophilus influenzae type b, pneumococcal-conjugate, and meningococcal-conjugate vaccines) are added to the EPI for infants in sub-Saharan Africa in the future, it will be prudent to document that IPTi does not negatively impact the immunogenicity of those vaccines. Similarly, if an evidence base with IPTi that uses other antimalarials accumulates and proves to be as robust as the data for IPTi-SP, it will have to be shown (as has been done for IPTi-SP) that these other antimalarials do not adversely impact immune responses to EPI vaccines.

Program Management of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine

- The committee found that many issues relevant to programmatic management of IPTi-SP were not well-explored in the studies presented. To enhance the acceptability and sustainability of IPTi-SP, the committee concluded that systematic capture of this information can help support continued improvement of a stepwise strategy for increasingly larger-scale implementation of IPTi-SP in relevant areas of sub-Saharan Africa if public health authorities implementing IPTi-SP are asked to regularly share information related to logistics, policy and program implementation, monitoring and evaluation, mode of delivery, and acceptability.
- The committee found that, in one study, IPTi-SP delivered through a robust EPI system with high levels of coverage and acceptability appears to be relatively cost effective and compares well with other malaria-control interventions. The committee therefore concluded that this preliminary finding suggests that IPTi-SP delivered through EPI could be considered as a potential intervention to be included in the malaria control tool kit for sub-Saharan Africa.

BOX 2 Continued

The Potential Value of Continued Investment in IPTi

- On the basis of the evidence presented, the committee concluded that a decrease in the malaria burden in infancy would be expected to ensue after programmatic implementation of IPTi-SP in areas with high incidence of clinical malaria. The greatest public health impact of IPTi-SP will almost certainly be observed in areas of sub-Saharan Africa with high- and moderate-intensity, perennial transmission. In areas of low or seasonal transmission, where the greatest burden of malaria occurs after the first year of life, the public health benefit of IPTi may be less. The committee further concluded that continued investment in the strategy appears warranted but cautions that drug supply and logistics, monitoring and resistance, and community acceptance and reaction to IPTi-SP could arise as problems in conjunction with large-scale implementation.

BOX 3
Committee Recommendations in Order of Significance

Recommendation: In view of the importance of the unpublished analyses by the SWG in showing a net benefit for IPTI-SP, and whereas the committee had no information about how the SWG or the individual study teams ensured quality control of the individual study data and hence the uniformly defined outcomes, the committee recommends that the SWG obtain an independent technical audit of the accuracy of the study-level data and analyses included in the pooled analysis. If this audit confirms the results presented, the committee would support the notion that IPTi-SP is ready to move to a new level. The committee's confidence in the efficacy of IPTi-SP in preventing cases of clinical malaria is sufficient to encourage larger-scale pilot implementations and evaluations in areas where the incidence of malaria in infants is high (often areas of perennial, high- and moderate-level transmission areas) to assess the impact of the intervention under real-life conditions. The provision of stronger evidence on these issues would be invaluable; the committee, however, recognizes that trying to estimate these parameters may involve an ethical challenge. If the evidence of IPTi-SP in preventing clinical malaria is deemed sufficient to propose instituting pilot implementations, there may not be sufficient equipoise to justify large controlled trials of IPTi-SP to evaluate its ability to prevent anemia, hospitalizations with malaria, or all-cause hospitalizations. One possible solution might be to nest case-control studies within large-scale, population-based pilot implementations of IPTi-SP. Nested studies of various designs may allow assessment of the effectiveness of IPTi in preventing malaria hospitalizations, anemia, and infant deaths.

Recommendation: If large-scale implementation is to be pursued, the committee recommends that the first IPTi-SP programs should be used where the infant population is at high risk for malaria morbidity because of perennial, high- and moderate-intensity transmission. Support should be continued for current efforts to identify more precise parameters, such as transmission intensity, seasonality of transmission, DPT3 coverage, and severity of clinical disease for locations in which IPTi-SP is to be implemented. Additionally, if large-scale implementations proceed or wherever large pilot projects are carried out, the committee urges that attempts be made to evaluate the impact of IPTi-SP on mortality in infant and young children

Recommendation: The committee recommends that if programmatic implementation of IPTi-SP were to ensue, public health authorities should monitor evidence of possible increases or decreases of SP resistance in the areas or regions of implementation.

Recommendation: Because of the issues discussed in this document, plans for monitoring and evaluation should accompany the programmatic implementation of IPTi-SP. Indicators would include the burden of malaria in infancy, which is likely to change in response to ongoing and new interventions, SP resistance, side effects, and impact on EPI coverage. Post-implementation monitoring of IPTi-SP would benefit from a baseline assessment followed by regular measurements of the burden of malaria in infancy. This could be accomplished through surveillance at sentinel sites, including hospitals and primary-care centers; in different transmission settings; and in other intercountry networks with capacity for data collection. Once the policy is well established and large-scale implementation is shown to be effective, notable changes may be detected in the age distribution of the pediatric malaria burden that may warrant modification of the policy. For example, if the frequency of infant malaria begins to increase, programmatic shortcomings and the emergence of drug resistance would require investigation. If IPTi, in conjunction with other measures, is highly effective and infant malaria is dramatically reduced or eliminated, the program may be modified to target the appropriate vulnerable age groups, possibly to include older children.

Recommendation: If larger-scale implementation of IPTi-SP in a given country were to ensue, it should be accompanied by the collection of evidence under varying conditions that are likely to affect the cost-effectiveness of the intervention, including the extent to which there is excess capacity under EPI (e.g., staff time, equipment, and vehicle use) to implement IPTi-SP; malaria transmission intensities; the case-fatality rates; the unit prices of IPTi drugs; and the program start-up costs.

Recommendation: Post-implementation monitoring should include pharmacovigilance with longer-term follow-up for children (e.g., 24 months) to detect adverse reactions that may arise when recipients of IPTi-SP in infancy subsequently receive cotrimoxazole or other sulfa drugs.

Sincerely,

Myron M. Levine, Chair
Committee on the Perspectives of the Role of Intermittent Preventive Treatment for Malaria in Infants

Attachments

Appendix A

Committee Members and Staff

COMMITTEE ON THE PERSPECTIVES ON THE ROLE OF INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA IN INFANTS

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Appendix B

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Appendix C

Glossary

Anopheline—Referring to *Anopheles* mosquito.

Chemoprophylaxis—Use of drugs to prevent infection or progression of infection to illness.

Disability-adjusted life-year (DALY)—Health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of "healthy" life lost by virtue of being in states of poor health or disability. The DALY combines in one measure the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of healthy life and the burden of disease.

DPT3—Three doses of a combined vaccine that protects against diphtheria, pertussis, and tetanus, given within the first 12 months of a child's life.

Entomological inoculation rate (EIR)—Measurement of the frequency with which a human is bitten by an infectious mosquito, or the average number of infective bites that a resident of a malarious area receives over a year or other time period.

Erythrocytic stage—A stage of the malaria parasite's life cycle of infecting, developing, or remaining latent in liver cells (hepatocytes).

Half-life—Time required for half of the amount of a substance (e.g., a drug or radioactive tracer) in a physiologic or ecologic system to be eliminated or to disintegrate by natural processes.

Hematocrit—Ratio of the volume of packed red blood cells to the volume of whole blood as determined by a centrifugation instrument: a measure of possible anemia.

Insecticide-treated bed net (ITN)—A fine-mesh net that has been either treated with a long-lasting insecticide or manufactured with insecticide directly incorporated into its fibers, hung over a bed to protect sleepers from insect bites.

Molecular markers—Genetic markers, usually proteins or DNA sequences, detected by biochemical methods.

Parasitemia—Condition in which parasites are present in the blood with or without clinical symptoms.

Pharmacokinetics—Interactions of drugs with people who take them—how the compounds are absorbed, metabolized, distributed, and excreted.

Pharmacovigilance—The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The aims of pharmacovigilance are to improve patient care and safety in relation to the use of

medicines and all medical and paramedical interventions; to improve public health and safety in relation to the use of medicines; and to contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational, and more effective (including cost-effective) use; and to effective communication to the public.

Splenomegaly—An enlarged spleen; a common finding in malaria patients that can sometimes be detected by physical examination of the abdomen.

Appendix D

Meeting Agenda

Meeting of the Committee on the Perspectives on the Role of Intermittent Preventive Treatment of Malaria in Infants

January 9, 2008–January 11, 2008
American Public Health Association (APHA)
800 I (Eye) Street, N.W.
Washington, DC 20001-3710
Main Floor, Conference Room A

Wednesday, January 9, 2008—APHA Conference Room A
OPEN SESSION

10:15am–10:45am Welcoming Remarks
Patrick Kelley, M.D., Dr.P.H.
Director, Board on Global Health, IOM
Myron M. Levine, M.D., D.T.P.H.
Director, Center for Vaccine Development,
University of Maryland School of Medicine, and IOM
Committee Chair

10:45am–11:15am Remarks from Sponsor (phone conference)
David Brandling-Bennett, M.D., D.T.P.H.
Project Officer, Bill & Melinda Gates Foundation

11:15am–11:45am Antimalarial Drugs and Drug Resistance
Christopher Plowe, M.D., M.P.H.
Professor of Medicine, Epidemiology and Preventive Medicine, and Microbiology and Immunology; Chief, Center for Vaccine Development's Malaria Section, University of Maryland, and IOM Committee Member

11:45am–12:15pm Malaria Overview and Burden of Malaria in Infancy
Miriam Laufer, M.D., M.P.H.
Assistant Professor of Pediatrics, Division of Infectious Diseases and Tropical Pediatrics, Center for Vaccine Development, University of Maryland School of Medicine, and IOM Committee Member

12:15pm–12:45pm Childhood Immunizations/EPI in Developing Country Context
Neal Halsey, M.D.
Professor, Department of International Health, Johns Hopkins Bloomberg School of Public Health, and IOM

Committee Member

12:45pm–1:30pm Lunch

1:30pm–1:45pm Overview of the IPTi Consortium
Pedro Alonso, M.D., Ph.D.
Director, Barcelona Centre for International Health Research at the Hospital Clinic and Professor at the University of Barcelona

1:45pm–2:15pm Pooled Efficacy of Intermittent Preventive Treatment for Malaria in Infants with Sulfadoxine-Pyrimethamine (IPTi-SP)
John Aponte, M.D., M.Sc.
Research Professor and Head, Statistics Unit of the Barcelona Centre for International Health Research (CRESIB)

2:15pm–2:30pm Break

2:30pm–4:30pm Acceptability, Cost-Effectiveness, Drug Resistance, Applicability of IPTi-SP, Effectiveness Study of IPTi-SP (five presentations)
David Schellenberg, M.B.B.S., D.T.M.H., M.R.C.P., Ph.D.
Professor, Malaria and International Health,
London School of Hygiene and Tropical Medicine

4:30pm–5:10pm United Nations Children's Fund (UNICEF) Pilot Implementation of IPTi-SP
Alexandra de Sousa, M.D., Ph.D.
Operational Research Coordinator,
Unit of Policy and Evidence, UNICEF

5:10pm–5:30pm IPTi Consortium Policy Process
Andrea Egan, Ph.D.
Coordinator, IPTi Consortium

5:30pm–5:40pm Concluding Remarks, Questions, Public Announcement of Change to Next Day's Schedule with WHO Speaker Starting at 8:15am.
Myron M. Levine, M.D., D.T.P.H.
IOM Committee Chair

Thursday, January 10, 2008—APHA Conference Room A
OPEN SESSION

8:15am–9:00am World Health Organization's Global Malaria Program: Considerations of IPTi-SP Within Context of Malaria Control Program
Dr. Peter Olumese, M.B., FMCPaed
Case Management and Research Team, Global

	Malaria Programme, World Health Organization
9:00am–10:10am	Pooled Safety of IPTi-SP *Sir Alasdair Breckenridge*, M.D., M.Sc. Chairman, UK Medicines and Healthcare Products Regulatory Agency
10:10am–10:20am	Break
10:20am–10:50am	Potential Impact of IPT on Spread of Drug-Resistant Malaria: Considerations from Mathematical Modeling *Wendy Prudhomme O'Meara*, Ph.D. Research Associate NIH/Fogarty Center, Centre for Geographic Medicine Research, KEMRI-Wellcome Trust Research Center, Kenya
10:50am–11:30am	Program Implementation Challenges in a Developing Country Context *Carol Medlin*, Ph.D., M.P.A. Professor, Anthropology and Social Medicine, University of California, San Francisco
11:30am–12:00pm	Kisumu—Results from First Trial of IPTi with Alternative Drugs to Sulfadoxine-Pyrimethamine *Larry Slutsker*, M.D., M.P.H. Chief, Malaria Branch of the U.S. Centers for Disease Control and Prevention
12:15pm–1:15pm	Lunch for Speakers and Registered Guests in Conference Room A CLOSED LUNCH SESSION FOR COMMITTEE, Conference Room C
1:15pm–2:15pm	Open Question-and-Answer Session
2:15pm–2:55pm	Considerations for the Implementation of IPTi (by phone) *Brian Greenwood*, M.D. Manson Professor of Clinical Tropical Medicine, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine
2:55pm–3:52pm	Public Comment and Question Session
3:52 pm	Concluding Remarks and Adjournment to Closed Sessions *Myron M. Levine*, M.D., D.T.P.H. IOM Committee Chair *Patrick Kelley*, M.D., Dr.P.H. Director, IOM Board on Global Health

Appendix E

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

PHILIP ADONGO, Navrongo Health Research Centre
PATRICK DUFFY, Seattle Biomedical Research Institute
STEPHEN L. HOFFMAN, Sanaria Inc.
PETER KAZEMBE, Lilongwe Central Hospital
MARK KLINE, Texas Children's Hospital
RAMANAN LAXMINARAYAN, Resources for the Future
MIKE SOTO, Georgetown University
ANDY STERGACHIS, University of Washington School of Public Health and Community Medicine
CATHERINE M. WILFERT, Elizabeth Glaser Pediatric AIDS Foundation

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by ELENA O. NIGHTINGALE, Scholar-in-Residence, Institute of Medicine, HAROLD C. SOX, Annals of Internal Medicine, and EDWARD B. PERRIN, University of Washington (emeritus). Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Appendix F

List of Tables, Figures, and Boxes

TABLES

FIGURES

BOXES