

Community Effectiveness of Intermittent Preventive Treatment for Infants (IPTi) in Rural Southern Tanzania

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Abstract. Intermittent preventive treatment of malaria in infants (IPTi) with sulphadoxine-pyrimethamine shows evidence of efficacy in individually randomized, controlled trials. In a large-scale effectiveness study, IPTi was introduced in April 2005 by existing health staff through routine contacts in 12 randomly selected divisions out of 24 in 6 districts of rural southern Tanzania. Coverage and effects on malaria and anemia were estimated through a representative survey in 2006 with 600 children aged 2–11 months. Coverage of IPTi was 47–76% depending on the definition. Using an intention to treat analysis, parasitemia prevalence was 31% in intervention and 38% in comparison areas ($P = 0.06$). In a “per protocol” analysis of children who had recently received IPTi, parasite prevalence was 22%, 19 percentage points lower than comparison children ($P = 0.01$). IPTi can be implemented on a large scale by existing health service staff, with a measurable population effect on malaria, within 1 year of launch.

INTRODUCTION

Malaria caused by *Plasmodium falciparum* continues to be a leading cause of death in young African children. In Tanzania, as in most of tropical Africa, children less than 5 years of age and pregnant women are at highest risk of severe malaria and death. The risks and consequences of severe disease vary over the first 5 years of life, and in high transmission settings infants aged 1–11 months appear to have the highest malaria mortality rates. Recent analyses suggest that even in moderate and low transmission settings, malaria causes a disproportionate number of deaths in infants.^{1,2}

In Tanzania there is evidence of a recent positive trend in infant and child survival, which is likely to be due in part to better malaria control.³ However, transmission remains high in most of the country and coverage of existing malaria control tools is both inadequate and inequitable. For example, in a recent national survey, 34% of those less than 5 years of age, and only 16% of the poorest children, slept under an insecticide-treated net (ITN) in 2007.⁴ Despite increases in both funding and action for malaria control in recent years, elimination will remain an unreachable goal without stronger health systems to deliver both new and existing interventions.

Intermittent preventive treatment of malaria in infants (IPTi) is defined here as giving a single curative dose of an antimalarial drug to children at routine vaccination clinic contacts in the first year of life, regardless of the presence of symptoms or parasitemia. After two efficacy studies in Tanzania reported 59%⁵ and 65%⁶ reductions in clinical malaria episodes, a group of researchers, funders, and policy makers agreed a research agenda to generate the evidence needed for this intervention to be considered for policy and practice. The group was partly motivated by delays of many years between first evidence of impact and decisions on policy and scale-up: for ITNs, this was 10 years. The resulting “IPTi Consortium” (www.ipti-malaria.org), has supported efficacy trials of IPTi in five countries, and together with other groups has generated information on safety, effi-

cacy, potential interactions with the Expanded Program on Immunization (EPI) vaccines, resistance, acceptability, immunology, cost, and cost-effectiveness.^{7–16} A recent independent review of IPTi concluded that “the evidence makes IPTi with sulphadoxine-pyrimethamine a promising public health strategy.”¹⁷

Efficacy is defined as the impact achieved by interventions when given in research settings. In contrast, effectiveness is the impact achieved in real-life health system settings. Effectiveness is almost inevitably much lower than efficacy, because coverage and compliance tend to be lower with real-life delivery systems than in more tightly controlled research studies. The overwhelming majority of research funding for child survival is for new technology, rather than better use of existing technology.¹⁸ The IPTi intervention takes advantage of an existing and successful delivery strategy, the EPI, which has been running since 1974 and reaches 83% of children in 49 countries in sub-Saharan Africa over their first year of life.¹⁹

Here, we describe results from a large-scale community-randomized intervention study of IPTi in rural southern Tanzania, including the coverage achieved by the routine health system and effects on malaria and anemia. The trial is registered on clinical trials.gov, no. NCT00152204.

METHODS

Study area. The study area is described in detail elsewhere.^{20,21} Briefly, the five districts of Nachingwea, Lindi Rural, Ruangwa, Tandahimba, and Newala are in Lindi and Mtwara regions of southern Tanzania. Districts are sub-divided into administrative areas called divisions, with 3–10 divisions in each district, and a total of 24 divisions in the study area. The total population in the study area was about 900,000 people in 2002, and infant and child mortality rates were reportedly the highest in the country (<http://www.tanzania.go.tz/census/>). Ethnic groups include the Makonde, Mwera, and Yao: Swahili is widely spoken. The most common occupations are subsistence farming and small-scale trading. Cashew nuts are the primary cash crop, whereas food crops include cassava, maize, sorghum, and rice. Most people live in mud-walled and thatched-roof houses: few houses have corrugated iron roofs. Common water supplies are hand-dug wells, communal boreholes, natural springs, and river water.

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Most rural roads are unpaved. There are two main rainy seasons, but rain is not uncommon in any month.

The public health system comprises a network of more than 130 dispensaries, health centers, and hospitals offering a varying quality of care. Not all health facilities have a qualified prescriber (Medical Officer, Assistant Medical Officer, Clinical Officer, or Assistant Clinical Officer) and sick children are not infrequently managed by nursing cadres (Nursing Officers, Nurse Midwives, Public Health Nurse B, or Maternal and Child Health Aides) even though these staff are, strictly speaking, not supposed to prescribe. Nursing cadres are responsible for preventive services such as antenatal care and well-child visits for weighing and vaccination. Some villages have volunteer village health workers. Children less than 5 years of age are exempt from paying fees at any government health facility. Malaria is endemic and transmission occurs all year round. The first-line antimalarial drug was sulphadoxine-pyrimethamine (SP) until the end of 2006, when this changed to artemether-lumefantrine (ALu).

A population-based survey in 2004²⁰ reported that parasite prevalence in children less than 2 years of age was 62%, and 31% of this age group had severe anemia (Hb < 8.0 g/dL). About one-third (30%) of those less than 2 years of age had slept under a net the night before the survey, with 9% having slept under a recently treated net (treated in the previous year). A total of 81% of children aged 12–23 months had received the third dose of DPT-Hb vaccine before they were 12 months old, and 69% received the measles vaccine. Infant mortality in the period 2001–2004 was 74 per 1,000 live births, with neonatal (first month) deaths at 43 per 1,000 live births.

Study design. We randomized 12 of the 24 divisions to receive IPTi through the existing government health system

from April 2005 (Figure 1: map). Division populations and baseline mortality rates in children aged 2–11 months varied widely (9,838–101,039 population, and 12.4–81.1 deaths/1,000/year). The 24 divisions were first allocated into three strata on the basis of mortality in children aged 2–11 months between July 2001 and June 2004, as measured in the baseline household survey.²⁰ We allocated the 24 divisions to the two study arms using restricted randomization²² to assure adequate balance in terms of baseline mortality, overall population size, and geographic area (and hence district health management team). There were 70 ways of allocating half of the 8 divisions in each stratum to the intervention arm ($70! = 8!/[4! \times 4!]$), and 343,000 ways of allocating half the divisions to the intervention arm ($343,000 = 70 \times 70 \times 70$). We used a program in Stata version 8.0 (Stata Corp., College Station, TX) to test whether each of these possibilities satisfied balance criteria, including: 1) a mortality ratio between the two study arms of 0.9 to 1.1; 2) a population ratio between the two study arms of 0.7 to 1.3; and 3) an even distribution of intervention communities over the five project districts. A total of 11,014 allocations satisfied these criteria and one was chosen at random using a program written in Stata. This resulted in IPTi being allocated to 5 of the 10 divisions in Lindi Rural district; 3 of the 5 divisions in Nachingwea district; 2 of the 3 divisions in Ruangwa district, and 1 of the 3 divisions in each of Newala and Tandahimba districts.

The IPTi strategy. The IPTi intervention strategy was designed to be easily integrated into the routine Government health system, to maximize the potential for the intervention to be scaled-up and sustained by the Tanzanian Ministry of Health in the longer term, in the event of a national policy to implement IPTi. The strategy had the full support of district,

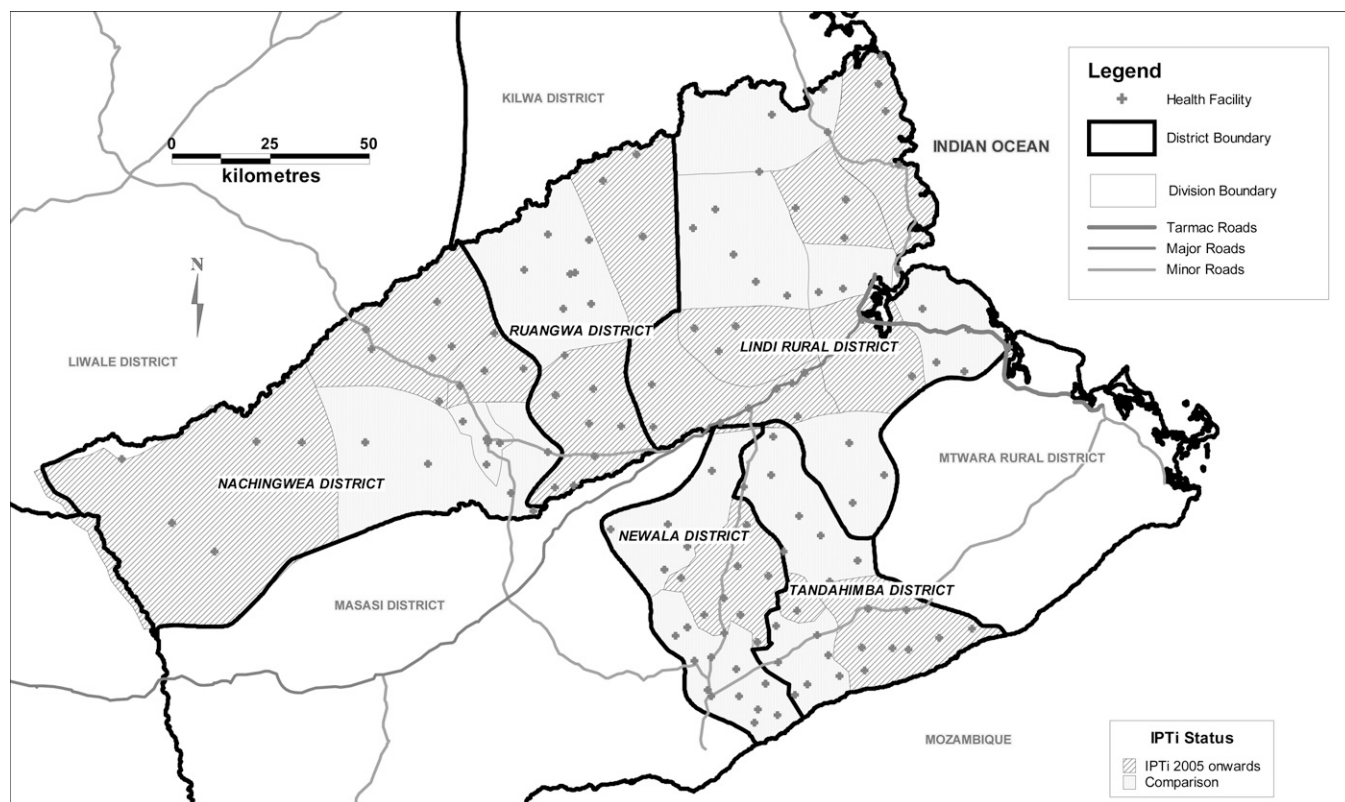


FIGURE 1. Map of the study area, showing divisions randomized to receive IPTi (shaded).

regional, and national health program staff and was tailored to their needs. The development of the IPTi strategy is described elsewhere.²³ Briefly, starting in April–May 2005, a single dose of SP was given at 2, 3, and 9 months of age, when children came to vaccination clinics for their routine EPI vaccine doses of DPT-Hb (given at 1, 2, and 3 months), and measles (given at 9 months). Tablets of 500 mg sulphadoxine and 25 mg pyrimethamine were donated by Hoffman-LaRoche, Basel, Switzerland. Children weighing 5 kg and over were given half a tablet, and those under 5 kg were given a quarter tablet. Health cards in intervention divisions were adapted to give space to document IPTi doses. Standard unadapted cards were used in comparison districts.

The IPTi was branded *MKINGE*, a Swahili term meaning “protect” and linked to posters carrying the line “*MKINGE mtoto wako dhidi ya malaria*” meaning “Protect your child from malaria.”²⁴ A training guideline and laminated A3 job aid for health workers contained step-by-step instructions for administration of IPTi, and included information on how to document the doses on the child’s health card, and in the routine reporting system. Before administering IPTi, health workers were trained to ask whether the child had ever had any adverse reactions to sulphur-containing drugs and whether the child had received SP for malaria treatment in the previous 2 weeks—both contraindications for IPTi. At the same facilities, health workers responsible for treatment of sick children were trained to check whether a child had received a dose of SP as IPTi in the previous 2 weeks, before they prescribed SP for malaria treatment.

From each health facility, the person in charge of the Reproductive and Child Health (RCH) section and the overall person in charge of the facility were given one day of training on ordering, storing, administering, and documenting IPTi. They were trained by their own District Health Management Teams, who in turn had been trained by the regional RCH coordinators, supported by the IPTi research team. A single follow-up visit to each health facility focused on IPTi: all subsequent visits were in the context of routine supervision visits by Council Health Management Team staff. A single member of the IPTi research team was designated as “implementation coordinator” and accompanied each District Health Management Team on a small proportion of their routine supervisory visits to health facilities in both intervention and comparison areas. Supervision of IPTi focused on stocks, use and recording of IPTi, and not on case management. Systems for the delivery and distribution of SP for IPTi mimicked those for vaccines, with supplies kept at the Regional and District Vaccine Stores. Supervision and management systems also shadowed that of the EPI program.

Health facility survey. We completed a survey in all vaccinating health facilities in the study area in May–June 2006, including the RCH section of hospitals, health centers, and dispensaries of the public health care delivery system, and non-governmental not-for-profit organizations. The overall focus of the survey was the availability and accessibility of IPTi and IPT in pregnancy. We also documented the availability of vaccines, drugs, supplies, and services essential for child health. We interviewed health workers, checked availability and functioning of equipment, and checked drug and vaccine stocks. The survey was conducted using an adapted World Health Organization (WHO) health facility survey tool, without case-management observation or exit interviews

(http://www.who.int/child_adolescent_health/documents/9241545860/en/). The tool included modules on health services, equipment, and supplies.

The survey was carried out by 16 experienced interviewers working in pairs, with one supervisor acting as the overall survey coordinator. Specific training took 3 days and included interview techniques, group work, role-play, practical fieldwork, and a pilot-test of the survey instruments. All data were collected using handheld computers (personal digital assistants or PDAs).²⁵ Each team visited an average of two facilities every day. Facilities that were closed were revisited at the end of the field work. A letter of introduction from each Council Health Management Team, signed by the District Medical Officer and the District Executive Director, was given out at the facility before the interviews. To help assure the quality of data, the supervisor repeated part of the interview at two or more facilities each day, and any discrepancies from the initial data were discussed and reconciled.

Household survey. We carried out a cross-sectional survey in a representative cluster sample of households from the five districts in July–August 2006. Eight clusters of 30 households were sampled from each of the 24 divisions, giving a total of 192 clusters and 5,760 households. The number of clusters selected from each ward (an administrative sub-unit of a division) was determined by probability proportional to the population of the ward, on the basis of the 2002 National Census population (<http://www.tanzania.go.tz/census/>). The required number of clusters was then selected at random from a list of all sub-villages (*vitongoji*, singular *kitongoji*), as supplied by the district council. Within each sub-village, 30 households were selected at random using a modified EPI-type sampling scheme that ensured an equal chance of any household being selected. For this purpose a household is defined as a group of people who eat from the same cooking pot.

Because there was no list of all households in the *kitongoji*, a team member dedicated to sampling of households went to the center of the *kitongoji* and threw a pen to choose a random direction. The “sampler” then walked in the direction indicated until the edge of the *kitongoji* was reached, sketching a map of all the households passed, and numbering them as they went. One of these houses was selected at random as the starting point, or “house 1” of the cluster. At this house, a pen was thrown to choose a random direction, and the sampler walked in that direction until they came to another household, which was the second house of the cluster, and so on. If there was a junction in the path, a pen was thrown again to select from the choices available. This procedure was repeated until 30 households were counted. All households were selected for an interview regardless of whether there were any women or children.

Villages were visited one day before the survey interviewers arrived, and an invitation letter left in each of the selected households. Both village and *kitongoji* leaders were briefed about the visit. Interviewers went from house to house, and if there was nobody at home an interviewer returned later in the day. No substitute household was included if the owner was repeatedly absent or did not wish to participate. The supervisor visited all households where people were reportedly absent or did not wish to take part, as a quality control measure.

We administered a modular questionnaire using handheld computers.²⁵ A household module included information on who lived in the household, dates of birth, education, and occupation

and ethnic group of the household head. We collected information on proxy markers of household socioeconomic status including ownership of a radio, bicycle, phone, animals, and poultry; whether the house had a corrugated iron roof, was owner-occupied or rented, and whether it was connected to the mains electricity supply. We also recorded household location using a handheld Global Positioning System (GPS).

The health module of the questionnaire was administered for all children less than one year of age. Mothers or carers (here we use the term “mother” to denote the main carer) were interviewed about whether the child was currently breastfed, and if so what other food or drink the child had received over the previous 24 hours. Information on IPTi and routine vaccinations was documented directly from health cards or other written records. Where no such record was available we asked about the number, but not dates of doses received. It should be noted that primary estimates of IPTi and vaccine coverage reported here are based on written information alone and are likely to be conservative.²⁶ Mothers were then asked about use of mosquito nets and net treatment, the name and location of their nearest health facility, and about any illness each child had during the 2 weeks before the survey, and what action had been taken. For children who had been sick, we asked about use of appropriate (non-traditional) health care providers including village health workers, dispensaries, health centers, hospitals, or private doctors. A finger-prick sample of blood was collected and hemoglobin (Hb) concentration measured using a battery-powered Hemocue photometer (HemoCue AB, Angelholm, Sweden). We tested for *P. falciparum* malaria parasitemia using the Paracheck rapid HRP2 antigen detection test (Orchid Biomedical Systems, Goa, India). Our assessments of parasitemia are therefore of antigenemia, and we use the expression “parasitemia (antigenemia)” below as a reminder. Children found to be anemic (Hb < 11 g/dL) or parasitemic were offered treatment according to Tanzanian national guidelines (14-day course of ferrous sulphate, SP, or both). Children with Hb < 5 g/dL were also encouraged to attend a hospital urgently and their transportation facilitated.

One-third of each cluster of 30 households was chosen at random for malaria testing of all residents and the detailed interviews in infants described previously. This was carried out to evaluate the effects of IPTi on parasitological resistance, and findings will be reported in detail elsewhere. Among samples collected, overall frequency of dihydrofolate reductase (*dhfr*) triple mutant was 46–57% and of the dihydropteroate synthase (*dhps*) double mutant was 52–62%.

The survey was carried out by 35 people in five teams of seven, each consisting of four interviewers, a supervisor, a sampler, a driver, and a car. Interviewers were trained for 2 weeks. All teams worked in all divisions. The training included interview technique. A detailed field manual was prepared, piloted during the training sessions, and carried in the field by all interviewers. The trainees included participants from all study districts. At the end of the training period a pilot survey was carried out in part of Mtwara Rural district.

Five main quality control measures were taken during the survey. First, quality control of the sampling procedure was done by the supervisor through review of the sketch maps, discussion with village leaders, accompanied sampling, and checking a computer-generated report summary, which included the time taken on sampling each day and the dis-

tance from the center to the reported edge of the sampled *kitongoji* using GPS information. Second, at least one interview was accompanied by each supervisor each day and he/she also repeated key aspects of a random selection of a further four interviews per team per day. Any discrepancies between the initial and repeat interviews were discussed with the interviewer and appropriate action taken. Third, weighing scales and Hemocue machines were calibrated before, during, and after the survey work. Fourth, blood slides were taken alongside rapid diagnostic tests for one of the five survey teams. Detailed results from this substudy will be reported elsewhere. Fifth, data from each interviewer were synchronized with a laptop before leaving the *kitongoji* each day, from which automated reports were produced summarizing the work, and any internal inconsistencies were resolved before leaving the *kitongoji*.

Baseline data were collected using a similar approach in 2004, before randomization. Survey methods and summary findings from 2004 are reported elsewhere.²⁰

Data processing and analytical methods. All data were entered into PDAs at the point of data collection and standard range, consistency, and completeness checks were carried out at that time. Analysis was done in Stata version 8.0 according to a pre-agreed analytical plan and in accordance with the design of the survey, using “svy” commands, such as `svytab`, to summarize and adjust for the clustered nature of the household survey data.

We created an index of household wealth based on ownership of assets. The household wealth index was the weighted sum of household characteristics including whether they owned the house they occupied, whether they owned consumer durables such as a bicycle, radio, or corrugated iron roof, whether they owned animals or poultry, whether they used wood for cooking, and whether they had mains electricity. The weights for the assets in the index were generated by Principal Components Analysis.²⁷ Households were categorized into one of five equal-sized groups from the poorest to the least poor.

Standard vaccine coverage indicators generally apply to children aged 12–23 months, and were thus not readily applicable to IPTi in our survey of children aged 2–11 months. Therefore, we developed two definitions of IPTi coverage. First, we used a relatively conservative definition in children aged 6–11 months, of two doses of IPTi before they were 6 months of age, using information written on their health cards and assuming that those without a health card had not received the intervention. Second, we used a far less conservative approach in children aged 2–11 months, of one or more doses of IPTi as reported by the mother and written on the health card.

We carried out both “intention to treat” and “per protocol” analyses. For the intention to treat analysis, all children identified in the selected households located in a division randomized to receive IPTi were included in the intervention group, and compared with all children identified in the selected households in comparison divisions.

For the per protocol analysis of malaria and anemia, we restricted the analysis to children in implementing divisions whose records suggested they had received IPTi, and children from comparison divisions who had received a corresponding vaccine, in a defined period of 2 to 6 weeks before the survey. This period was chosen because of our use of the rapid antigen detection test for malaria parasitemia: this HRP2-based test

is known to remain positive for 2 weeks after parasites have been cleared.

Statistical testing of household survey data was based on the *t* test, using a summary measure of the data from each of the 12 intervention and 12 comparison divisions. This adjusts both for the survey design and for the study design, which was randomized by division.²² For health facility survey data, statistical testing was based on the χ^2 test.

Ethical approval and community consent. The study was undertaken within the framework of the assessment of the community effectiveness of IPTi, part of the IPTi Consortium (www.ipti-malaria.org). We received ethical approval from local and national institutional review boards (Ifakara Health Institute, formerly Ifakara Health Research and Development Center, Ifakara, and the National Tanzania Medical Research Co-coordinating Committee) through the Tanzania Commission for Science and Technology. Ethical and research clearance was also obtained from the institutional review board of the London School of Hygiene and Tropical Medicine, UK, and from the Ethics Commission of the Cantons of Basel-Stadt and Basel-Land, Switzerland. During field work, information sheets in Swahili about the study were given out, explaining why it was being done, by whom, and what it would involve. In the household survey, written consent of all household heads was sought. All possible steps were taken to minimize breaches of confidentiality.

In Tanzania, councilors are the elected representatives of the community at ward and division level. At the start of the project we held meetings in each district with the health, water, and education committee of the local councilors. The research team explained the project to these committees, and that they were free to decide whether to participate. All the groups agreed to participate. Carers were free to decline the

intervention at the health facility, and this was noted to occur even during piloting of the intervention.

RESULTS

Comparability at baseline. The trial profile is shown in Figure 2. The baseline household survey²⁰ included 599 children aged 2–11 months, of whom 340 were from intervention and 259 from comparison divisions. There was no evidence of any difference between intervention and comparison divisions with regard to age, sex, or socio-economic status (Table 1). With regard to preventive health measures, exclusive breastfeeding in children aged 2–6 months was reported by 11% of mothers from intervention and 15% of mothers from comparison divisions ($P = 0.62$). Mosquito net use the night before the survey in children aged 2–11 months was reported by 31% of mothers in both intervention and comparison divisions ($P = 0.93$). Vaccine coverage was slightly lower in intervention than comparison divisions, but this difference did not reach statistical significance (59% and 69%, $P = 0.16$). Weight-for-age in children aged 2–11 months was also comparable in the two groups, with 20% in both areas having a z-score of -2 or less ($P = 0.81$).

With regard to infection, illness, and health-seeking behavior in children aged 2–11 months, the two groups were also broadly comparable. Malaria parasitemia (antigenemia) was detected in 59% of children in intervention divisions and 57% of children in comparison divisions ($P = 0.69$). Prevalence of severe anemia ($Hb < 8/dL$) was 33% in children from intervention areas and 29% in those from comparison areas ($P = 0.48$). Fever in the 2 weeks preceding the survey was reported in 34% of children from intervention areas and 30% of those from comparison areas ($P = 0.30$). There was no evidence of

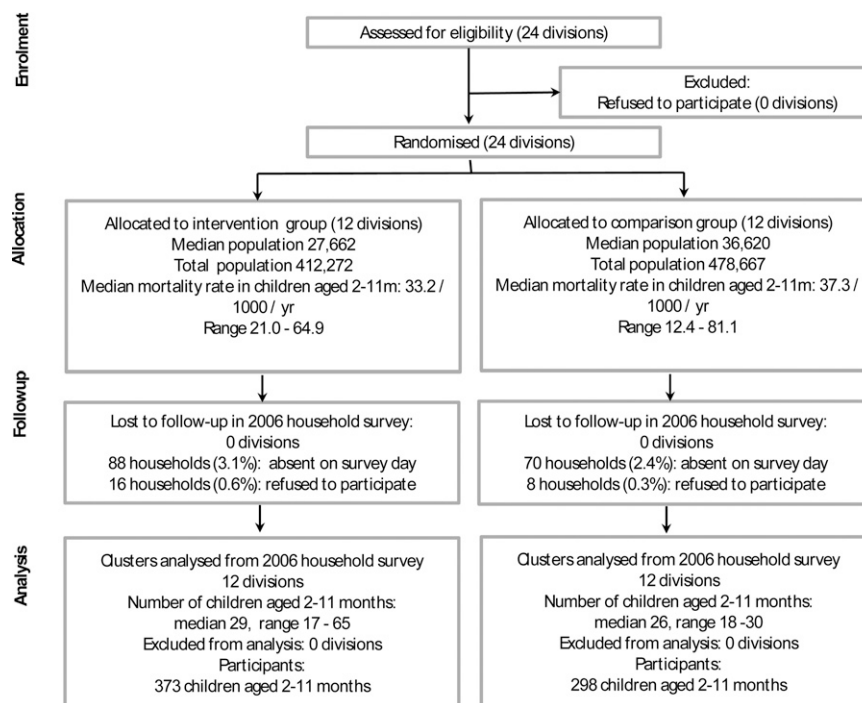


FIGURE 2. Trial profile.

TABLE 1
Baseline (2004) household survey: comparability of a sample of children from intervention and comparison areas*

	Intervention divisions (IPTi) n/N (%)	Comparison divisions n/N (%)	P†
Age			
2–4 months	109 (32%)	72 (28%)	0.42
5–8 months	133 (39%)	108 (42%)	
9–11 months	98 (29%)	79 (30%)	
All children (2–11 months)	340	259	
Sex			
Girls	160 (47%)	130 (50%)	0.39
Boys	180 (53%)	129 (50%)	
Socioeconomic status (quintiles)			
Q5 (Poorest)	64 (19%)	38 (15%)	0.69
Q4	70 (21%)	53 (21%)	
Q3	49 (14%)	46 (18%)	
Q2	72 (21%)	54 (21%)	
Q1 (Least poor)	85 (25%)	65 (25%)	
Total	340	256	
Preventive health measures			
Child aged 2–6 months is exclusively breastfed	15/140 (11%)	15/97 (15%)	0.62
Child 2–11 months sleeps under a mosquito net	104/336 (31%)	80/258 (31%)	0.93
Child 6–11 months received 3 doses of DPT vaccine	118/200 (59%)	111/162 (69%)	0.16
Low weight for age z-score (< -2) in 2–11 months	59/298 (20%)	47/237 (20%)	0.81
Infection, illness, and health-seeking behavior in 2–11 m olds			
Prevalence of malaria parasites	176/300 (59%)	135/236 (57%)	0.69
Severe anemia prevalence (Hb < 8 g/dL)	100/300 (33%)	69/238 (29%)	0.48
Fever in 2 weeks preceding survey	114/337 (34%)	78/259 (30%)	0.30
Distance (km) to the nearest health facility 6 km or over	83/298 (28%)	50/221 (23%)	0.45
Sought care for sick baby from non-traditional type provider	79/173 (46%)	57/117 (49%)	0.30
Proportion admitted since birth	35/337 (10%)	32/259 (12%)	0.28

*IPTi = intermittent preventive treatment of malaria in infants; DPT = diphtheria pertussis tetanus.
†Using *t* tests that adjust for the survey design and study design (randomized by division).

a disparity with regard to care seeking, with 46% of sick children from intervention areas reportedly taken to an appropriate (non-traditional) health care provider, compared with 49% in comparison areas ($P = 0.30$). Reported hospital admissions since birth were also similar in the two groups, with 10% of children in intervention and 12% in comparison divisions having been admitted to the hospital ($P = 0.28$).

Availability of IPTi: Health facility survey findings. The health facility survey included interviews and reviews of health facility records in 135 facilities between May 25 and June 7, 2006, 65 in the intervention and 70 in comparison areas. Materials to support IPTi were widely available in intervention areas: 86% of facilities had IPTi-adapted RCH cards in stock (Table 2) and 79% had IPTi job aids. A total of 94% had SP for IPTi in stock on the day of the survey. However, 24% of health facilities had experienced one or more IPTi stock-out at some point during the preceding 6 months. Neither materials to support IPTi, nor IPTi itself, were found in any health facilities in the comparison areas.

General supervision and services related to the corresponding vaccines with which IPTi is given were reasonably widely available and comparable in intervention and comparison areas. With regard to supervision, 72% of intervention area facilities had one or more supervisory visits in the 6 months before the survey, compared with 70% in comparison areas ($P = 0.81$). The DPT vaccination services were available on at least 1 day each week in 89% of health facilities in intervention areas and 91% of facilities in comparison areas ($P = 0.64$). In intervention areas, on the day of the survey, 82% of facilities had DPT-Hb and 89% had measles vaccine in stock. In comparison areas, on the day of the survey, 77% of facilities had DPT-Hb in stock and 86% had measles vaccine in stock ($P = 0.50$ and $P = 0.52$, respectively). During the preceding 6 months, stock-outs

of DTP-Hb, oral polio vaccine (OPV), and measles vaccine had occurred in 74%, 51%, and 34% facilities, respectively.

Follow-up: 2006 household survey findings. The household survey was carried out between July 3 and August 19, 2006, and included 5,734 households in 192 clusters of 30 households each. In 5,574 households (98%) someone was at home to be interviewed on the day of the survey. Over 99.5% of household heads agreed to take part (5,552/5,574). In these households, there were 671 children aged 2–11 months who took part in the survey, of whom 373 (56%) lived in divisions randomized to receive IPTi (Table 3). The two groups were similar with regard to age and sex distribution, but there was some evidence that children from intervention divisions were slightly poorer on average than those from comparison divisions. For example, 40% of children

TABLE 2
Provision of IPTi and related services in intervention and comparison areas, 2006 health facility survey*

	Intervention divisions	Comparison divisions	P†
IPTi-adapted child health card (or sticker) available	56/65 (86%)	0/69 (0%)	N/A
IPTi service available	61/65 (94%)	0/69 (0%)	< 0.0001
SP for IPTi available	61/65 (94%)	0/69 (0%)	< 0.0001
Stock-out of SP for IPTi in previous 6 months	13/55 (24%)	N/A	
Received ≥ 1 supervisory visit during previous 6m	46/64 (72%)	49/70 (70%)	0.81
DPT vaccination services available at least 1 day per week	57/64 (89%)	64/70 (91%)	0.64
DPT-Hb vaccine available	53/65 (82%)	53/69 (77%)	0.50

*IPTi = intermittent preventive treatment of malaria in infants; SP = sulphadoxine-pyrimethamine; DPT = diphtheria pertussis tetanus; N/A = not available.
†From χ^2 test.

TABLE 3
Findings from 2006 household survey: age, sex, socio-economic status, preventive health measures, IPTi coverage and timing*

	Intervention divisions	Comparison divisions	P†
Age group			
2–4 month	121 (32%)	95 (32%)	0.98
5–8 month	136 (36%)	115 (39%)	
9–11 month	117 (31%)	88 (30%)	
All children (2–11 month)	373	298	
Sex (% male)	183/374 (49%)	142/298 (48%)	0.69
Socioeconomic status (quintiles)			
Q5 (Poorest)	67 (18%)	45 (15%)	0.06
Q4	104 (28%)	62 (21%)	
Q3	52 (14%)	48 (16%)	
Q2	87 (23%)	67 (22%)	
Q1 (Least poor)	64 (17%)	76 (26%)	
Preventive health measures			
Child aged 2–11 months sleeps under mosquito net	195/364 (54%)	182/286 (64%)	0.31
Exclusive breast feeding in children 2–5 months old	25/155 (16%)	115/118 (13%)	0.25
Child 6–11 months old received 3 doses of DPT vaccine	162/219 (74%)	133/180 (74%)	0.38
Child 6–11 months old received 3 doses of polio vaccine	162/219 (74%)	134/180 (74%)	0.82
IPTi Coverage Measures			
Child 6–11 months received 2 doses of IPTi before 6 months of age, using information from health card alone	103/219 (47%) 95% CI (37,57)	4/180 (2%) 95% CI (1,6)	< 0.0001
Child 2–11 months received at least 1 one dose of IPTi, using information from health card or reported by the mother	272/359 (76%)	29/280 (10%)	< 0.0001
“Missed opportunities” for IPTi			
Child 2–11 months old with DPT dose 2 received IPTi at time of DPT-2	202/291 (69%)	9/229 (4%)	
Child 3–11 months old with DPT dose 3 received IPTi at time of DPT-3	151/212 (71%)	6/177 (3%)	
Median age at each dose of IPTi (months)			
Dose 1	2 m 27 d (IQR 2 m 7 d–3 m 18 d) (N = 226)		
Dose 2	4 m 7 d (IQR 3 m 18 d–5 m 4 d) (N = 164)		
Dose 3	9 m 8 d (IQR 9 m 3 d–10 m 3 d) (N = 33)		

* IPTi = intermittent preventive treatment of malaria in infants; DPT = diphtheria pertussis tetanus; IQR = interquartile range.

† Using *t* tests that adjust for the survey design and study design (randomized by division).

in the intervention area were in the top two quintiles of socio-economic status, whereas 48% of children in the comparison areas were ($P = 0.06$, based on mean SES score).

Preventive health measures including exclusive breastfeeding in children aged 2–5 months, mosquito net use, and coverage of DPT-Hb, polio, and measles vaccine were comparable in the two groups (Table 3). Mosquito net use had almost doubled, from 31% coverage reported in 2004 to 58% in 2006, but there was no evidence of a difference between the two groups (54% and 64% in intervention and comparison divisions, respectively, $P = 0.31$). Treated net use (treated in the last year) was also similar in the two groups (29% [107/364] and 35% [101/285], $P = 0.50$). The DPT-Hb and polio vaccine coverage were identical (74%) in both intervention and comparison divisions ($P = 0.38$ for DPT-Hb and $P = 0.82$ for polio).

Coverage of IPTi. In the divisions randomly allocated to IPTi, 47% of surveyed children aged 6–11 months had received two doses of IPTi before they were 6 months of age, using information written on their health cards and assuming that those without a health card had not received the intervention (Table 3). This indicator is likely to be an underestimate of true coverage of two doses because children without a health card were assumed not to have received the intervention. In comparison areas, the same indicator was found in 2% of children ($P < 0.0001$). Using our alternative coverage indicator, using information on one or more doses reported by

the mother and that written on the health card, we found that 76% of children aged 2–11 months in intervention divisions had received at least one dose of IPTi, compared with 10% in comparison divisions ($P < 0.0001$).

We found evidence of “Missed Opportunities” for IPTi at health facilities, where children had attended the vaccine clinic and received DPT-Hb or measles vaccine but had not been given IPTi. A total of 69% of DPT-Hb2 recipients received IPTi alongside the routine vaccination, suggesting that 31% (=100–69) had a “missed opportunity” for IPTi. For DPT-Hb3 recipients, 71% received IPTi at the same time, suggesting that 29% had a “missed opportunity” for IPTi. For measles vaccine recipients, 66% received IPTi at the same time, suggesting that 34% had a “missed opportunity” for IPTi. Overall, therefore, roughly one-third of children eligible for IPTi at a routine vaccine clinic did not receive the intervention.

There was a tendency for both vaccines and IPTi to be given slightly later than scheduled: the median age at first dose of IPTi, given alongside DPT-Hb dose 2 was 2 months and 27 days (interquartile range [IQR] 2 m 7 d to 3 m 13 d, $N = 226$). The median age at second dose, given alongside DPT-Hb dose 3, was 4 m 7 d (IQR 3 m 18 d to 5 m 4 d, $N = 164$), and the median age at third dose, given alongside measles vaccine, 9 m 8 d (IQR 9 m 3 d to 10 m 3 d, $N = 33$).

Safety of IPTi. Hospital admissions were equally common in children aged 2–11 months in intervention and comparison

divisions: 9% in each group ($P = 0.91$). No children aged 2–11 months were admitted because of a rash associated with SP in either IPTi or comparison divisions. Fever in the 2 weeks before the survey was similar in the two groups, being reported for 38% children in the intervention areas and 41% children in comparison areas ($P = 0.24$).

Effects of IPTi on malaria: Intention-to-treat analysis. *Plasmodium falciparum* test results were available for 621 children aged 2–11 months (Table 4). Overall, the prevalence of parasitemia (antigenemia) had dropped from 58% in 2004 to 34% in 2006. Using an intention to treat analysis, there was some evidence that IPTi resulted in less malaria: parasitemia (antigenemia) was found in 31% of children living in areas where IPTi was available, and in 38% children living in comparison areas ($P = 0.06$). Figure 3 shows parasitemia (antigenemia) by age in months, with arrows to show the median age at each dose of IPTi.

Effects of IPTi on anemia, intention-to-treat analysis. Results for anemia were available for 620/671 (92%) children aged 2–11 months (Table 4). Overall, the prevalence of mild anemia ($Hb < 11$ g/dL) had dropped from 93% in 2004 to 84% in 2006, and the prevalence of severe anemia ($Hb < 8$ g/dL) had dropped from 31% in 2004 to 14% in 2006. Using an intention to treat analysis—i.e., including all children living in intervention divisions in the IPTi group, regardless of whether they had actually received the intervention—there was some evidence that IPTi reduced anemia: mild anemia ($Hb < 11$ g/dL) was found in 80% of children living in areas where IPTi was available, and in 88% children living in comparison areas, 8% points lower ($P = 0.02$). Differences for severe anemia ($Hb < 8$ g/dL: 12% and 16%, $P = 0.19$) and overall mean hemoglobin (9.66 and 9.39 g/dL, $P = 0.10$) did not reach statistical significance. Figure 4 shows mean hemoglobin by age in months, with arrows to show the median age at each dose of IPTi.

Effects of IPTi on malaria and anemia: “Per protocol” analysis. We compared parasitemia (antigenemia) and anemia in the 98 children from intervention divisions seen in the survey in the period from 2 to 6 weeks after a dose of IPTi with that in the 85 children from comparison divisions seen in the survey in the same period after the corresponding dose of DPT-Hb or measles vaccine. In children who had recently received IPTi, malaria parasite prevalence was reduced by 19 percentage points (22% versus 41%, 22/98 versus 35/85, $P = 0.01$); and mean hemoglobin was increased by 0.5 g/dL (9.3 versus 9.8 g/dL, $P = 0.05$).

TABLE 4

Findings from 2006 household survey: effect of IPTi on cross-sectional morbidity indicators, using intention-to-treat analysis*

	Intervention n/N (%)	Comparison n/N (%)	P†
Malaria parasitemia (antigenemia)	109/347 (31%)	103/274 (38%)	0.06
Mild anemia (Hb < 11 g/dL)	277/346 (80%)	241/274 (88%)	0.02
Severe anemia (Hb < 8 g/dL)	40/346 (12%)	44/274 (16%)	0.19
	Intervention (mean & 95% CI)	Comparison (mean & 95% CI)	P†
Hemoglobin	9.66 (9.5–9.8)	9.39 (9.2–9.6)	0.10

* IPTi = intermittent preventive treatment of malaria in infants; CI = confidence interval. † Using *t* tests that adjust for the survey design and study design (randomized by division).

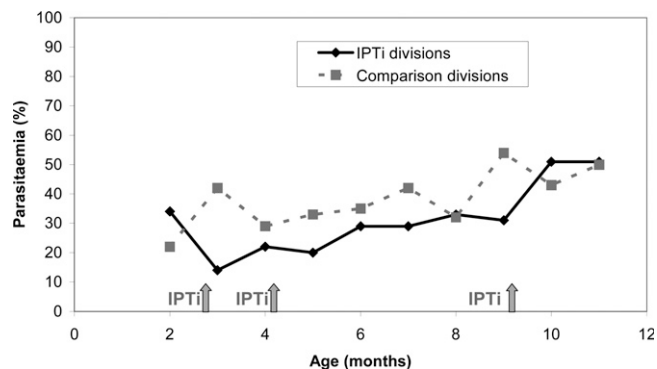


FIGURE 3. Malaria parasitemia (antigenemia) by age in months in children from IPTi and comparison areas, 2006 household survey, using intention-to-treat analysis.

DISCUSSION

In this large-scale implementation research study we have shown that IPTi can be administered and managed by the routine health system in a relatively under-resourced area of Tanzania, achieving coverage levels that approach those of the EPI vaccines within a year of launching the intervention.

Our study has several limitations. First, we could not adapt existing standard vaccine coverage indicators because we studied children aged 2–11 months, when a more conventional approach would have been to include children aged 12–23 months. Our study aimed to estimate coverage relatively soon after the launch of IPTi, and children over a year old could not have received the first dose of IPTi. We therefore developed two indicators, the first to represent a highly conservative estimate of two doses of IPTi, and the second to estimate coverage of at least one dose in a much less conservative way. Coverage figures should always be interpreted with care: while routine health information systems have a tendency to overestimate coverage,²⁶ household surveys may tend to under-estimate the true coverage, particularly those taking written information from health cards alone and assuming that children with no health card did not receive the intervention in question. In our second, less conservative, approach, we asked mothers whether their children had received IPTi and vaccines, as well as reviewing written information from health cards, which is likely to be an overestimate. The true coverage of one or more

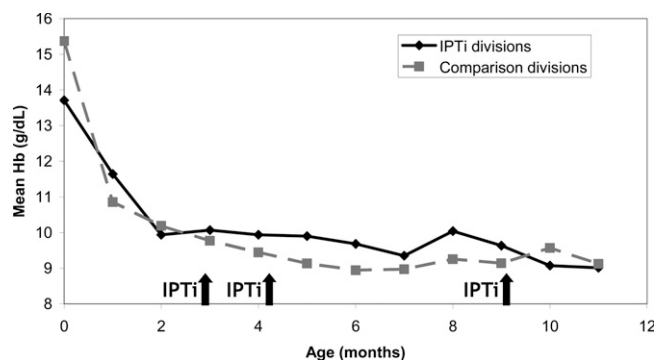


FIGURE 4. Hemoglobin levels by age in months in children from IPTi and comparison areas, 2006 household survey, using intention-to-treat analysis.

doses of IPTi is likely to lie between these two extremes of 47% and 76%.

A second limitation of our study is the use of a rapid diagnostic test for malaria, rather than to use thick blood films. Such tests are known to lack specificity²⁸⁻³⁰; ours is no exception, and detailed results will be presented elsewhere (Laurent and others, in preparation).

There was evidence of "missed opportunities" for IPTi, whereby between 29% and 34% of children attending health facilities and receiving routine immunizations did not receive the corresponding dose of IPTi. Acceptability of IPTi was good, and it is unlikely that these missed opportunities were because of mothers' refusal to accept the intervention.¹⁰ Informal enquiries among the IPTi field research team and a convenience sample of health facility, district, and national staff suggest that staff attitude may have had an important role to play. Despite the scale of implementation and the obvious support from senior Ministry of Health staff, facility staff was aware that IPTi implementation was part of a pilot project, not a formal recommendation of the Ministry of Health, and not being implemented in all facilities. There were anecdotal reports of facility staff not covering IPTi-related duties when colleagues who had been trained in IPTi were absent from work, mainly because IPTi was not a recognized policy. There were also minor deficiencies in knowledge, problems with stock-outs of SP for IPTi, and poor documentation. In addition, approximately 5% of children were treated with SP for malaria in the 2 weeks before attending vaccination clinic (data not shown), and these children were ineligible for IPTi. It was noteworthy that the frequency of stock-outs of SP for IPTi was lower than that for associated vaccines. Despite this, vaccine coverage in the area was relatively good, reflecting a tendency for children to reattend when vaccines came into stock.

The "per protocol" analysis was conducted to look for evidence of biological efficacy of IPTi in children known to have received the intervention. We found strong evidence of a protective effect of IPTi on immediate health outcomes. Recent IPTi administration was associated with an increase in mean hemoglobin of 0.5 g/dL and an approximate halving in the prevalence of parasitemia (antigenemia) (22% compared with 41%). This suggests that the contemporaneous levels of resistance to SP did not preclude a biological effect of the intervention.

Despite only modest IPTi coverage, an intention to treat analysis revealed some evidence of a measurable population effect of IPTi on hemoglobin and parasitemia, with malaria parasitemia being seven percentage points lower in the intervention group than in the comparison group, and mild anemia (Hb < 11 g/dL) being eight percentage points lower. Such effects on the prevalence of parasitemia and anemia have not previously been documented in randomized controlled trials of IPTi.¹¹

The median age at dosing was older than that intended by the EPI program. Doses 1 and 2 of IPTi should have been administered at age 2 and 3 months, but were actually administered roughly 1 month late on average. The timing of each dose is important because the risk of life-threatening malaria is particularly high in the first few months of life,¹ especially in areas of high and perennial malaria transmission (www.ipti-webtool.org). It is possible that better compliance with the timing of vaccinations will increase the impact of IPTi in routine practice.

We have presented evidence that routine health services in an impoverished, remote, and rural part of Tanzania were able to initiate and sustain implementation of IPTi with minimal specific additional inputs. Analysis of samples collected in the weeks after a dose of IPTi showed a reduction in the prevalence of *P. falciparum* infection and of anemia, suggesting that existing levels of drug resistance were not preventing a beneficial effect of IPTi. About a year after routine implementation of IPTi started, we found that IPTi coverage, though suboptimal, was sufficient to make anemia and malaria less prevalent among children living in areas where IPTi was implemented than in comparison areas. These encouraging results were generated in the context of a dramatic increase in the coverage of insecticide-treated nets and a general decline in the prevalence of parasitemia. Such changes in the coverage of malaria control tools and *P. falciparum* parasitemia are increasingly common.³¹⁻³³ The IPTi may be a useful addition to malaria control strategies in many parts of sub-Saharan Africa.

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