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Title

Summary of intermittent preventive treatment in infants (IPTi) contextual factors

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Summary of IPTi contextual factors

This document summarizes the main findings from published studies with data on contextual factors related to IPTi implementation, including costs/cost-effectiveness, feasibility, equity, and acceptability.

Cost

IPTi generally considered to be cost-effective or highly cost-effective due to using the EPI delivery platform and the inexpensive drug SP. The cost per dose delivered in nearly all studies was found to be less than $0.25 for IPTi with SP and was more expensive with alternative drugs. The cost-effectiveness, however, depends on the impact on malaria reduction, and IPTi becomes less cost-effectives in settings with lower impact on malaria burden. Thus, cost-effectiveness is predicted to decrease with lower transmission.

Feasibility and equity

Several studies have assessed feasibility of IPTi delivery through the expanded program on immunization (EPI) platform, as well as coverage of IPTi and adherence to IPTi (if a non-SP drug is used). Despite logistical challenges such as accessing clean water, crushing the tablets, and occasional drug shortages, IPTi appears relatively feasible to implement through the EPI platform. One time-and-motion study in Tanzania found that the time used for IPTi implementation is acceptable and was estimated to be a median of 12.4 minutes ranging from 1.6-28.9 minutes per nurse per vaccination session.[1] Other studies have estimated that IPTi administration represents about 11% of health workers' time.[2] In one study undertaken to help address concerns that addition of IPTi would result in increased work burden that might disrupt routine EPI services, pre- and post-IPTi households surveys indicated a significant increase in immunization after implementation of IPTi; authors speculate that increased community sensitization might be responsible for this increase in EPI coverage in both arms, with an even greater draw from IPTi in the intervention arm.[3]

Two studies[4,5] have looked at IPTi coverage after pilot implementation in Tanzania and Sierra Leone and have found some 'missed opportunities' of IPTi whereby children received an EPI vaccine but not IPTi (e.g., 67% for IPTi-1 versus 80% for pentavalent dose 2 at 10 weeks; 36% for IPTi-3 versus 50% for measles at 9 months)[5]; reasons for this were unclear, and possibilities include dedicated outreach campaigns (e.g., for measles) that did not include IPTi, SP stockouts, or other reasons.

Little evidence was available on adherence, which might be relevant for future IPTi implementation using different drugs that require follow-up dosing at home. Several qualitative studies indicated that mothers forgot to give remaining doses (for 3-day drugs) sometimes or keeping them for later use.[6] One pharmacokinetic study of children in Papua New Guinea receiving SP plus three daily doses of amodiaquine indicated that only 39–50% of children received the three scheduled doses of AQ as prescribed, and that 33–37% received two doses.[7] The authors speculated that low medication adherence in the ideal trial research setting might translate into even lower adherence under routine circumstances.

A 2010 commentary by de Sousa *et al* on implementation of IPTi still rings very true today. They authors raised three key points: 1) the need for pediatric formulations of SP; 2) the need for alternative long-

lasting drugs for IPTi; 3) and a better understanding about malaria transmission thresholds below which IPTi is no longer cost-effective.[2]

Little information on equity of IPTi is available. One study found no association between wealth quintile and child's receipt of IPTi.[5]

Acceptability

Information on IPTi acceptability to caregivers and health providers has been collected prior to and during implementation of both trials and pilots across a variety of countries in sub-Saharan Africa as well as in Papua New Guinea. There is generally widespread acceptance of IPTi by caregivers, especially when delivered alongside vaccinations using the Expanded Program on Immunization (EPI) platform. EPI was also generally well accepted and perceived as beneficial and because it fits into to local health culture; particularly in Kenya and Tanzania, attending vaccination was seen as "the law" and one's civic duty[6,8], thus benefitting interventions delivered alongside it. Most caregivers did not confuse IPTi with a fully protective vaccine; in most assessments mothers comprehended the partially protective nature of IPTi. Thus IPTi did not appear to negatively affect care-seeking for febrile infants or malaria prevention behaviors (e.g., sleeping under a bednet).[6,8-11]

Caregivers generally did not like the way IPTi was administered, with some seeing sharing of spoons and cups as unhygienic.[6,8] Health workers also did not like having to crush SP and administer with spoons.[6] A pediatric formulation of SP would be very beneficial for reducing preparation time and palatability of SP for infants. Despite some health workers not liking the preparation mode for IPTi and some complaints that it increased workload[9], most had very positive perceptions of IPTi[5,9,12], with some noting that it improved EPI attendance[9] and reduced malaria cases.[12]

The following tables provide additional details on each study included for the IPTi contextual factors synthesis.

Summary of cost data on IPTi

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Country-wide annual start-up and operating costs	Cost per dose delivered	Cost per case averted	Cost per DALY averted	Other cost/cost-effectiveness information
Manzi 2008[13]	Tanzania	Large-scale community randomized trial of IPTi in half of Southern Tanzania (5 districts in 2 regions), population of ~900,000	SP at 3, 4, and 9 months	• Costing template used to track costs and extrapolate to national scale-up • Distinguished between IPTi development (national level) and IPTi implementation (district level and below) • Health system perspective used	• National start up and running cost in first year: $1,480,000 ○ Training was 51% start-up costs • ~$459,000 (about one-third start-up cost) annual operating cost thereafter, plus $170 per district for BCC materials • No incremental expenditure for delivery at health facility level (delivered without working overtime)	• $0.23 per IPTi dose (78% financial expenditure, 22% opportunity cost) • Cost per full course (3 doses): $0.69 • 56% of cost was purchase and distribution of SP	-	-	-
Hutton 2009[14]	Tanzania and Mozambique		SP at 3, 4, and 9 months	• Intervention costs from large-scale pilot in Mtwara and Lindi regions of Tanzania (excluding research) • Effectiveness based on trial data	-	• $0.13 in Tanzania • $0.15 in Mozambique	• $1.57 (range: $0.80 - $4.0) in Tanzania • $4.73 in Mozambique	-	• Cost per death averted was $100.2 (range: $43.0 - $330.9) in Tanzania • Cost per death averted was $301.1 (range: $95.6- $2,498.4) in Tanzania
Conteh 2010[15]	Tanzania, Mozambique, Gabon, Kenya Ghana	5 different drug regimens analyzed: SP, mefloquine,	Clinical trial study sites in sub-Saharan	• Cost data collected alongside trials • Pooled efficacy of 30% (6 trials) for	-	• SP=$0.13 (0.09,0.17) • SP+AS3=$0.60 (0.42,0.78)	• $1.36–$4.03 for IPTi-SP using trial-specific data	• <$36 per DALY averted	• Highly cost-effective in settings where it has a significant impact on malaria

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Country-wide annual start-up and operating costs	Cost per dose delivered	Cost per case averted	Cost per DALY averted	Other cost/cost-effectiveness information
		CD, SP+AS3, and AS-AQ.	African (9 sites in 5 countries with 5 different drug regimens)	clinical malaria used for SP • Efficacy of other drugs from relevant trial • Incidence of malaria was that in trial placebo arms			• $0.68–$2.27 for IPTi-SP using pooled data • Costs for alternative IPTi drug regimens higher ○ $4.62 for ASAQ to $18.56 for mefloquine		(majority of studies) • Within cost-effective range if using WHO threshold of <1*GDP *per capita* • In places where IPTi did not impact malaria (typically low-transmission areas) not cost-effective
Sicuri 2011[16]	Gabon	Clinical trial in Lambaréné, Gabon	SP at 3, 9, and 15 months	• Intervention costs used from the large-scale pilot in southern Tanzania (excluding research costs)	-	-	Cost per case of anemia averted: • $12.8 for ITT pop'n • $11.3 for ATP pop'n		Impact on malaria not statistically significant in trial, but impact on anemia was
Ross 2011[17]	[None]	Modeling study	SP and ASAQ	• Dynamic, individual-based simulation model of *Pf* malaria, drug actions, and case management • Costs taken from previous trial and pilot data	-	-	$0.42 - $7.71	Predicted number of DALYs averted is low at low transmission intensities and increases up to a plateau at	-

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Country-wide annual start-up and operating costs	Cost per dose delivered	Cost per case averted	Cost per DALY averted	Other cost/cost-effectiveness information
								moderate levels	
Abotsi 2012[18]	Ghana	IPTi implementation research study in Ghana (Upper East Region, UER, since 2007)	SP	• Effectiveness based on pooled estimated of 30% (Aponte 2009) • Financial information gathered at each cost level in Ghana	-	• $2.0 per complete course of 3 doses in start-up year • $0.87 per course in routine year	-	• $3.49 (not exceeding $4.50 in sensitivity analyses)	• Net cost of IPTi for 1,000 infants = $3,416 in routine years • Time spent administering one dose of IPTi estimated at 3.15 minutes (3 minutes to crush and dissolve SP)

Summary of feasibility data on IPTi

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Key feasibility findings	Coverage	Adherence
Manzi 2009[1]	Tanzania	Large-scale pilot in 5 southern districts	SP at 3, 4, and 9 months	• Time-and-motion study	• IPTi implementation took a median of 12.4 min (range 1.6—28.9) per nurse per vaccination clinic • IPTi nearly always distributed at the same time as routine vaccines • However, stockouts of IPTi remained relatively common (10% facilities) • Supervision visits for IPTi relatively infrequent	-	-
Armstrong-Schellenberg 2010[4]	Tanzania	Large-scale pilot in 5 southern districts	SP at 3, 4, and 9 months	• Household survey with 600 children aged 2–11 months • Health facility survey	• 94% facilities had SP in stock but one-quarter had an SP stockout in the past 6 months	• 47% children (health card only) – 76% (card and mother's recall) had received 2 doses IPTi by 6 months • Evidence of "Missed Opportunities" for IPTi at health facilities (children received DPT-Hb or measles vaccine but not IPTi) (~30% time)	-
de Sousa 2010[2]	Multiple (6 from UNICEF pilot)	Multiple (6 from UNICEF pilot)	SP at 3, 4, and 9 months	Various	• IPTi administration took 11% of health workers' time (60% time on preparing the drug)	-	-
Dicko 2011[3]	Mali	Randomized pilot in one district	SP at 3, 4, and 9 months	• Pre- and post-IPTi implementation household surveys	-	• Approximately 90% coverage ITPi-1 and IPTi-2 and 77% for IPTi-3 • Full vaccination status among 9–23-month-olds	-

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Key feasibility findings	Coverage	Adherence
						increased from 37% at baseline to 54% in control zone and 70% in intervention zone	
Sottas 2019[7]	Papua New Guinea	Trial	SP plus either AQ (3 days) or AS (3 days) at 3, 6, 9, and 12 months	• Blood samples on Day 3 (one day after last dose) for 64 patients receiving SP+AQ • Pharmacokinetic (PK) modeling based on amodiaquine half-life	-	-	Results suggest that only 39–50% of children received the three scheduled doses of AQ as prescribed, 33–37% two doses and 17–24% only the first dose administered by the study nurse

Lahuerta 2021[5]	Sierra Leone	Large-scale pilot (district of Kambia)	SP at 3, 4, and 9 months	• KAP survey with health workers
				• Health facility survey
				• Household survey (households with children 3–15 months) to assess coverage and IPTi perceptions
					• Good stocks of SP for IPTi at facilities	• IPTi coverage slightly lower than coverage of EPI vaccines given at the same time
						• Among children 3–15 months:
						  ○ 67% had received any IPTi
						  ○ 32% had received complete IPTi
						• Most common reasons for child not receiving IPTi: caregiver did not know it was required, it was not offered, child has not had any vaccines
						• Only factor related to IPTi coverage was whether the
							-

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Key feasibility findings	Coverage	Adherence
						caregiver had heard about it	
Audibert 2021[12]	Sierra Leone	National implementation		• IDIs with CHWs, health center managers, parents of children receiving IPTi, and national decision makers	• Largest challenges were logistical, including access to clean water, crushing the tablets, drug shortages and high staff turnover. • An addition challenge was poor attendance to EPI visits.	-	-

Summary of acceptability data on IPTi

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Community acceptability	Health worker perceptions	Other
Pool 2006[11]	Mozambique	Randomized, placebo-controlled trial	SP delivered at 3, 4, and 9 months (with EPI)	• In-depth interviews with trial participants and those refusing • Semi-structured interviews with child caregivers, community members, and traditional healers • Participant observation in both community and clinic settings	• IPTi generally acceptable, despite initial resistance • Perceived negative aspects of IPTi did not affect perceptions of EPI • Initial resistance related more to the trial than to IPTi *per se* • Widespread acceptance of vaccinations/EPI • IPTi not misinterpreted as immunization against malaria; thus preventive behaviors (e.g., LLIN use) and treatment seeking levels did not appear to change		

Pool 2008[8]	Tanzania	5-year pilot of IPTi in 5 rural districts (approximately 800,000 people)	SP at 3, 4, and 9 months	• In-depth interviews
				• Focus group discussions
				• Participant observation
					• Although some rumors about SP, it was generally acceptable as a drug for IPTi
					• Attending vaccination visits perceived as a civic duty
					  ○ Mothers saw benefits in knowing child's growth, liked social interactions at the clinic
					  ○ Main reasons for missing the EPI clinic were practical: heavy rain, farm work, distance, illness, (reported), absence of the doctor
					• Mothers did not like the way tablets were administered
					• Some mothers perceived sharing of cups to administer IPTi unhygienic
					• Caregivers did not think IPTi completely prevented malaria, but rather reduced illness frequency or severity		

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Community acceptability	Health worker perceptions	Other
					• No evidence that IPTi had negative effect on adherence to EPI • No evidence that IPTi had negative effect on treatment seeking or malaria prevention		
Mushi 2008[19]	Tanzania	Large-scale pilot in 5 districts of southern TZ	SP at 3, 4, and 9 months	• Mixed methods to assess communities' and providers' knowledge/ practices re: malaria, EPI, SP ○ Focus group discussions ○ In-depth interviews ○ Quantitative provider survey • Results used to develop appropriate communication strategy for IPTi	• Vaccination services well accepted • Babies usually taken for vaccination • SP widely used and accepted for malaria treatment and IPTp • Mothers expressed high willingness to give IPTi to children	• 96% providers ready to take/give spouse SP in pregnancy or for treatment	
Manzi 2009[1]	Tanzania	Large-scale pilot in 5 southern districts	SP at 3, 4, and 9 months	• In-depth interviews with nurses about expectations and actual experiences with IPTi • Time-and-motion studies	-	• Nurses reported no major difficulties implementing IPTi • No reports of changes to the work schedules	
Gysels 2009[6]	5 countries : Gabon, Kenya, Tanzania, Ghana, Malawi	3 efficacy trials (Gabon, Kenya and north-eastern Tanzania) 2 implementation pilots	Various (mostly SP, but also mefloquine, CD, AS, AQ)	• Structured questionnaires, semi-structured interviews, in-depth interviews, and focus group discussions with mothers, fathers, health workers, community members,	• IPTi widely acceptable (resonated with existing preventive practices and concern about infant health) • IPTi fit within already widely accepted routine vaccination ○ Vaccine clinic seen as social outlet • Newer drugs seen as more efficacious but also more dangerous	Health workers did not like crushing of tablets and administration with cups and spoons	IPTi generally acceptable across a wide range of settings in Africa and involving

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Community acceptability	Health worker perceptions	Other
		(Malawi and Ghana)		opinion leaders, and traditional healers. • Participant observation in clinics	• Strong preference for single dose formulation given at clinic • 88% mothers had positive experiences with IPTi • Mothers did not like crushing of tablets and administration with cups and spoons • No negative impact on EPI • Little evidence that IPTi had negative impact on health seeking for infants with febrile illness or existing preventive practices		different drugs and regimens
Pell 2010[10]	Papua New Guinea	Randomized placebo-controlled trial	SP plus 3 days of either artesunate or amodiaquine, given at 3, 6, 9, and 12 months	• Questionnaires for mothers of infants in RCT • Interviews with: o Mothers who refused infant participation o Health workers o Community reporters/opinion leaders • Focus group discussions with men and women from local community	• Respondents viewed IPTi as acceptable and beneficial for infant health • Mothers reported complying with at-home administration of IPTi due to perceived benefits of IPTi • Despite low knowledge, demand for and generally favorable views of infant vaccinations • Little evidence that IPTi negatively impacts attitudes to EPI, EPI adherence or existing malaria prevention practices	-	• Methods based on those used in IPTi trials in Africa • Similar findings of favorable caregiver perceptions as African settings
De Sousa 2012[9]	Benin, Madagascar and Senegal	Pilot implementation	SP at 3, 4, and 9 months	• Direct observation • IDIs and FGDs with caregivers and health workers	• Very positive perceptions and attitudes towards IPTi • No refusals or negative rumours related to IPTi coupling with immunizations • Misperception that IPTi decreases fever stemming from vaccinations	• Very positive perceptions of IPTi • Perceptions that IPTi improved EPI adherence • HWs noted that mothers came	Very similar responses across three countries

Article	Country	IPTi study/pilot	Drug regimen(s) used	Methodology/ data drawn from	Community acceptability	Health worker perceptions	Other
					• IPTi did not negatively influence attitudes towards other malaria control strategies	more frequently and earlier for EPI • Some HWs complained of additional (uncompensated) workload (preparing SP and weighing babies)	
Lahuerta 2021[5]	Sierra Leone	Large-scale pilot (district of Kambia)	SP at 3, 4, and 9 months	• KAP survey with health workers • Health facility survey • Household survey to assess coverage and IPTi perceptions	• Two-thirds of caregivers had heard about IPTi ○ Among these, 95% perceived it to be safe • Previous qualitative data collection indicated high community acceptance of IPTi	• HWs felt confident in ability to give IPTi • HWs noted that IPTi was well accepted by caregivers and community leaders	
Audibert 2021[12]	Sierra Leone	National implementation	SP at 3, 4, and 9 months	• IDIs with health center managers, parents of children receiving IPTi, and national decision makers	• IPTi widely accepted and perceived as efficacious and safe by parents	• HWs perceived IPTi as effective in reducing the number of malaria cases • Favorable IPTi perceptions also based on absence of side effects and the good supply of SP	

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