Imperial College London

Intermittent Preventive Treatment in Infants (IPTi): An intervention's journey from RCT to Policy

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Centre for Health Policy
Institute of Global Health Innovation

Outline

- What is IPTi?
- The IPTi consortium
- The research findings
  - Cost effectiveness
- The Policy Process

ipti CONSORTIUM
INTERMITTENT PREVENTIVE TREATMENT IN INFANTS

Malaria

The problem

- In 2008, malaria caused nearly one million deaths, mostly among African children

- Malaria can decrease gross domestic product by as much as 1.3% in countries with high disease rates.

The solutions?

At present, those recommended by the World Health Organization (WHO) and Roll Back Malaria (RBM) are:

- Indoor Residual Spraying (IRS) with insecticides, primarily with DDT

- Prompt treatment of clinical attacks of malaria with an effective drug

- Insecticide-treated nets and other materials (ITN)

- Intermittent preventive treatment with sulphadoxine-pyrimethamine (SP) for pregnant women (IPTp)

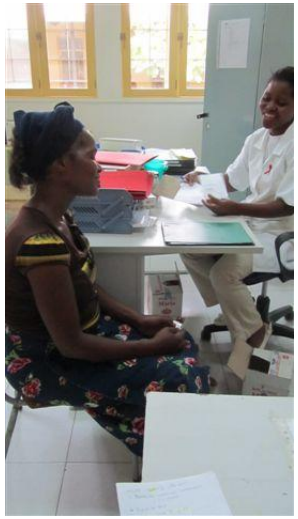
Source: WHO http://www.who.int/topics/malaria/en/

What is IPTi?

Intermittent preventive treatment involves administration of **a full therapeutic course of an anti-malarial drug** to the whole of a population at risk – **under one year olds - whether or not they are known to be infected**, at **specified times** with the aim of preventing mortality or morbidity.

IPT

IPT children



IPT pregnancy

http://www.mip-consortium.org/projects/phi.htm

IPT school children

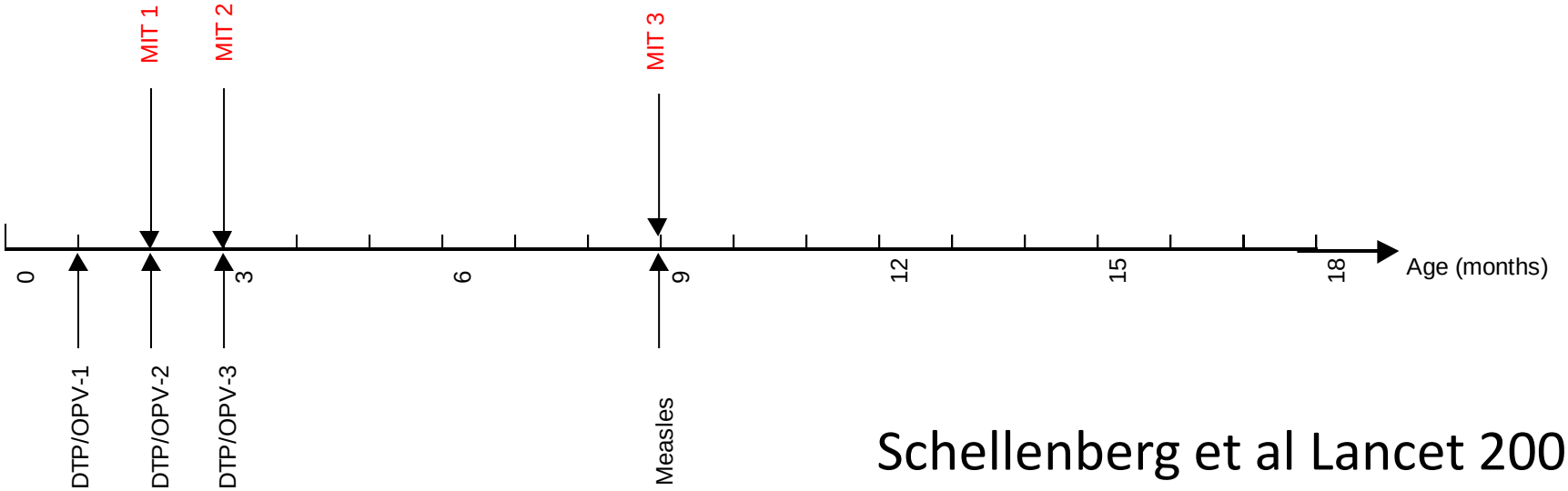
IPT infants

First IPTi Results

- 701 children recruited from Ifakara MCH clinic when attending for DTP/OPV dose 2
- Randomly assigned intermittent treatment (Fansidar*) or placebo

  * (1.25 mg pyrimethamine plus 25 mg sulfadoxine/kg)

- Doses received with DTP/OPV dose 2, DTP/OPV dose 3 & Measles



Schellenberg et al Lancet 2001

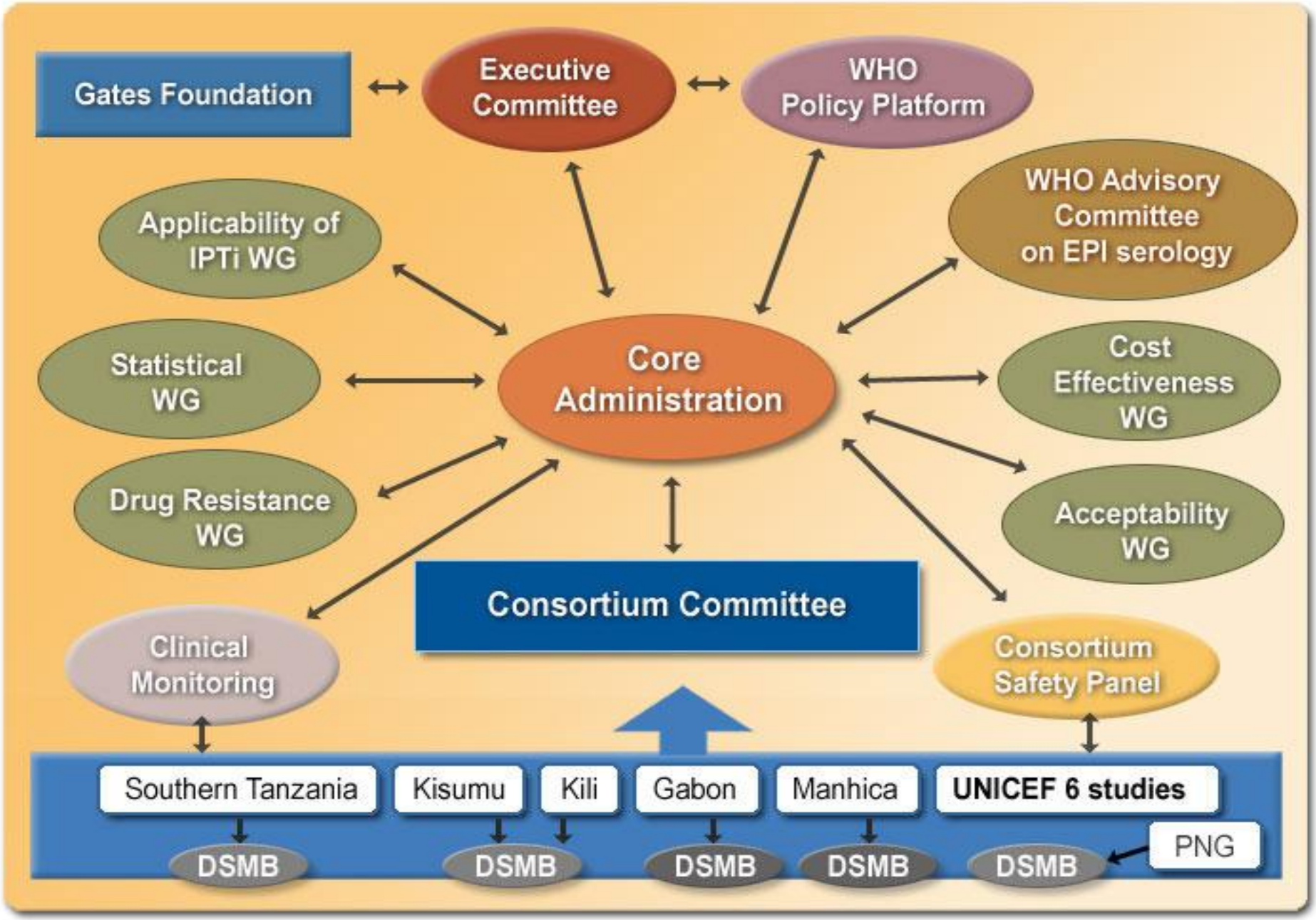
Summary Effects

- 59% (41,72) reduction in clinical malaria
- 50% (8,73) reduction in incidence of severe anaemia - PCV<25%
- No ‘rebound’ effect
- And persistence of efficacy…

What next?

- Despite the promising results from this trial, more scientific evidence was needed before WHO could recommend IPTi for the control of malaria.

- Evidence was needed on the **efficacy** of IPTi in **more malaria transmission settings**, and more **safety data** was needed as IPTi gives an anti-malarial drug to a healthy infant who does not have symptoms of clinical malaria



DSMB – Data and Safety Monitoring Board

IPTi
in southern Tanzania

ipti CONSORTIUM
INTERMITTENT PREVENTIVE TREATMENT IN INFANTS

01. Albert Schweitzer Hospital, Lambaréné, Gabon
02. Barcelona Centre for International Health Research, Barcelona, Spain
03. Case Western Reserve University, Cleveland, USA
04. Centers for Disease Control and Prevention, Atlanta, USA
05. Ifakara Health Research and Development Centre, Ifakara, Tanzania
06. Institut de Recherche pour le Développement, Dakar, Sénégal
07. Kenya Medical Research Institute, Kisumu, Kenya
08. Kilimanjaro Christian Medical Centre, Moshi, Tanzania
09. London School of Hygiene and Tropical Medicine, London, UK
10. Manhiça Health Research Centre, Manhiça, Mozambique
11. National Institute for Medical Research, Amani, Tanzania
12. PNG Institute of Medical Research, Goroka, Papua New Guinea
13. Swiss Tropical Institute, Basel, Switzerland
14. United Nations Children's Fund (UNICEF)
15. Université Cheikh Anta Diop de Dakar, Dakar, Sénégal
16. University of Copenhagen, Copenhagen, Denmark
17. University of Tübingen, Tübingen, Germany
18. Walter and Eliza Hall Institute of Medical Research, University of Melbourne, Australia
19. World Health Organization (WHO)

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FUNDACIÓ CLÍNIC BARCELONA

IPTi Consortium research portfolio

Efficacy studies

RCT trials

SP: Manhica, Lambaréné

Alternative drugs & combinations:

Kisumu – SP+Art, AQ+Art, Lapdap

Kilimanjaro – SP, MQ, Lapdap

PNG – SP+ Art, SP+AQ

IPTi-SP implementation studies

data on going-to-scale "real world data" on operational issues (implementation & monitoring ADRs by the health system)

Southern Tanzania

UNICEF Benin, Ghana, Madagascar, Senegal, Mali, Malawi

Sothern Tanzania
Developing an IPTi Strategy

- Implementation should not depend on a research team
  - Routine health services / MoH actively involved in strategy development
  - Broad group of stakeholders at National, Regional, District & facility levels
- IPTi management integrated into existing systems
- Training curriculum, guidelines, job aid developed
- Strategy development took ~1 year

Slide from Prof Schellenberg

The Projects

1) Pooled analysis of the efficacy of IPTi with SP

2) Pooled analysis of the safety of IPTi with SP

3) Effect of IPTi-SP on immune responses to EPI vaccines

The Projects

4) Effect of IPTi-SP on the development of naturally-acquired immunity to malaria

5) Effect of SP drug resistance on efficacy of IPTi-SP

6) Alternative drugs and combinations for IPTi

The Projects (continued)

7) Effectiveness of IPTi delivered through the existing health system

8) UNICEF pilot implementation of IPTi in six African countries

9) Cost effectiveness of IPTi

The Projects (continued)

10)Acceptability of IPTi

11)The age pattern of malaria and the applicability of IPTi & Web-based decision-support tool of where to implement IPTi

http://ipti.lshtm.ac.uk/

12)Modelling the impact of IPTi

1) Pooled analysis of the efficacy of IPTi with SP

All Consortium trials conducted to GCP levels

All non-Consortium trials audited

approx. 8,000 infants – 4,000 received SP, 4,000 received placebo

approx. 12,000 doses of SP were given

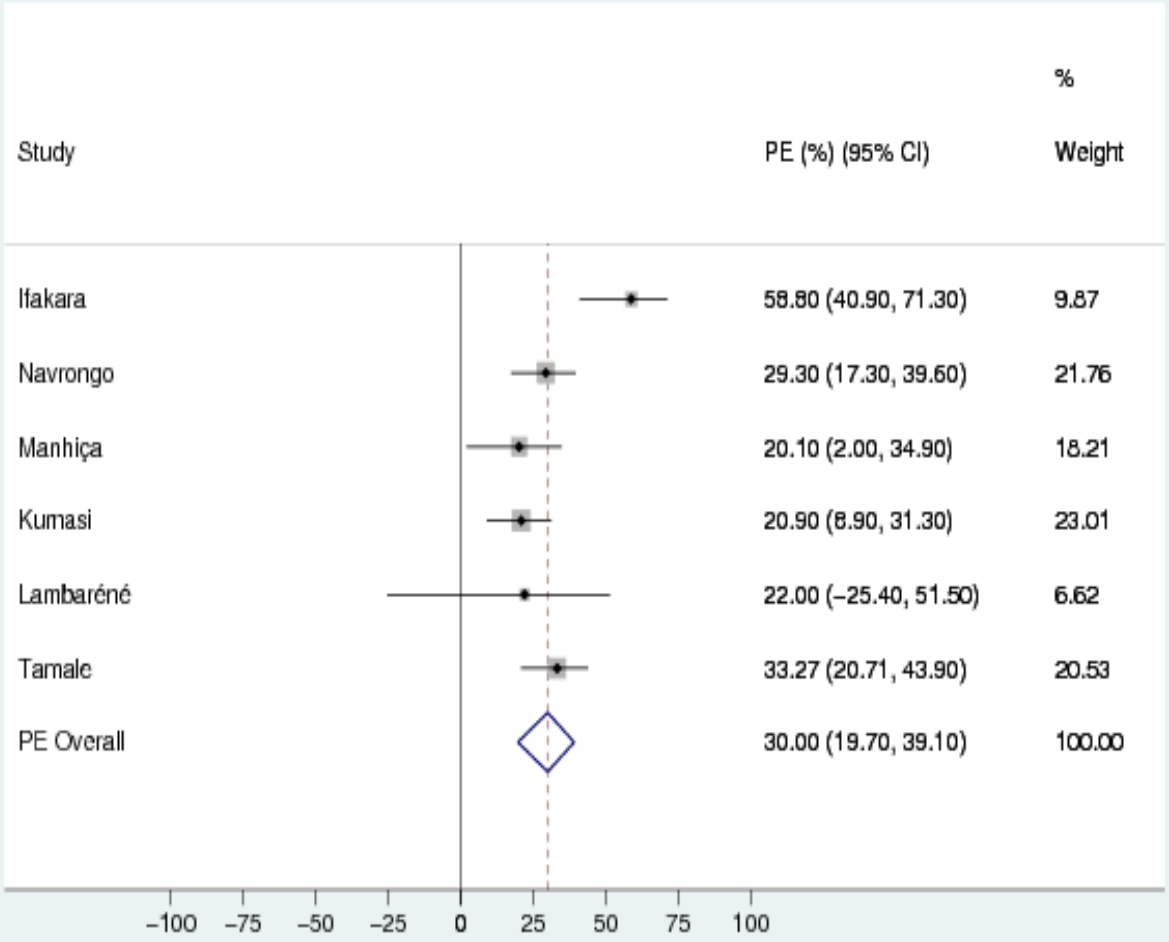
6 trials: Manhica, Gabon & Ifakara, Navrongo, Kumasi, Tamale

Pooled Efficacy Analysis – Statistical Working Group (SWG)

Pooled Analysis of Adverse Events – Consortium Safety Panel (CSP)

Pooled Analysis of the Effect of IPTi on EPI serology – WHO Advisory Committee (2 trials: Manhica, Navrongo)

Malaria incidence up to age 12m



Combined estimate

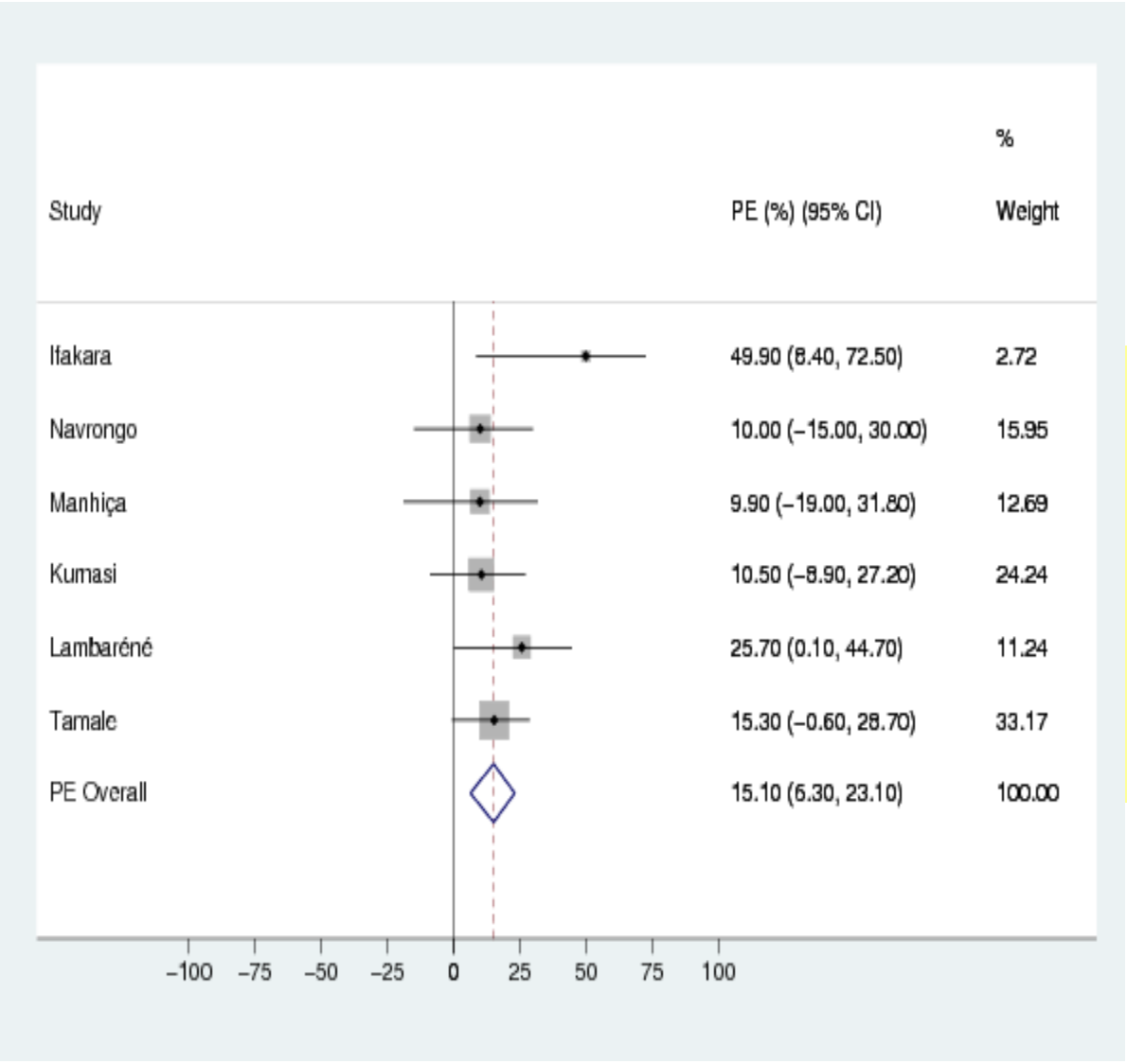
(random effects meta-analysis)

30%

p-value < 0.001

Reduction

Anaemia risk up to age 12m



Combined estimate

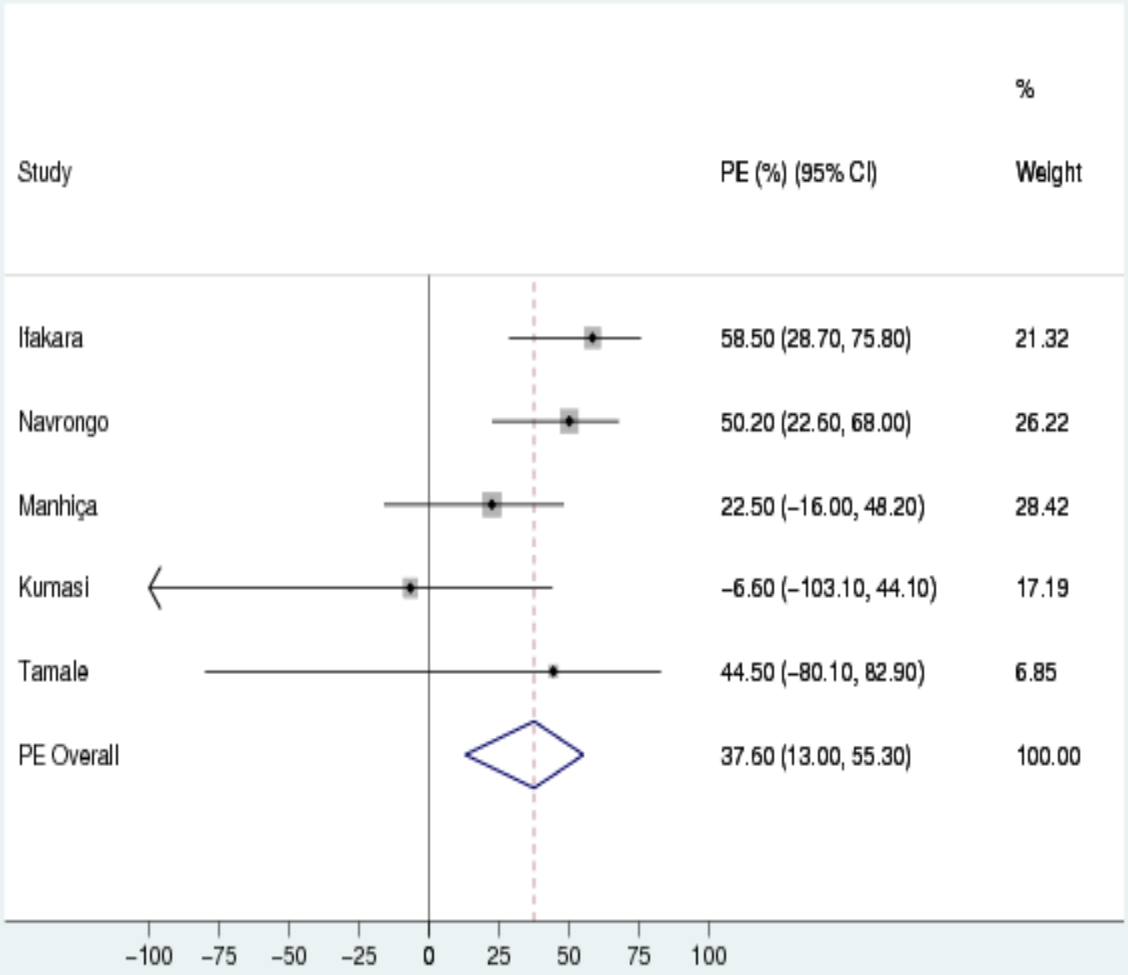
(random effects meta-analysis)

15%

p-value = 0.001

Reduction

Malaria admissions up to age 12m



Combined estimate

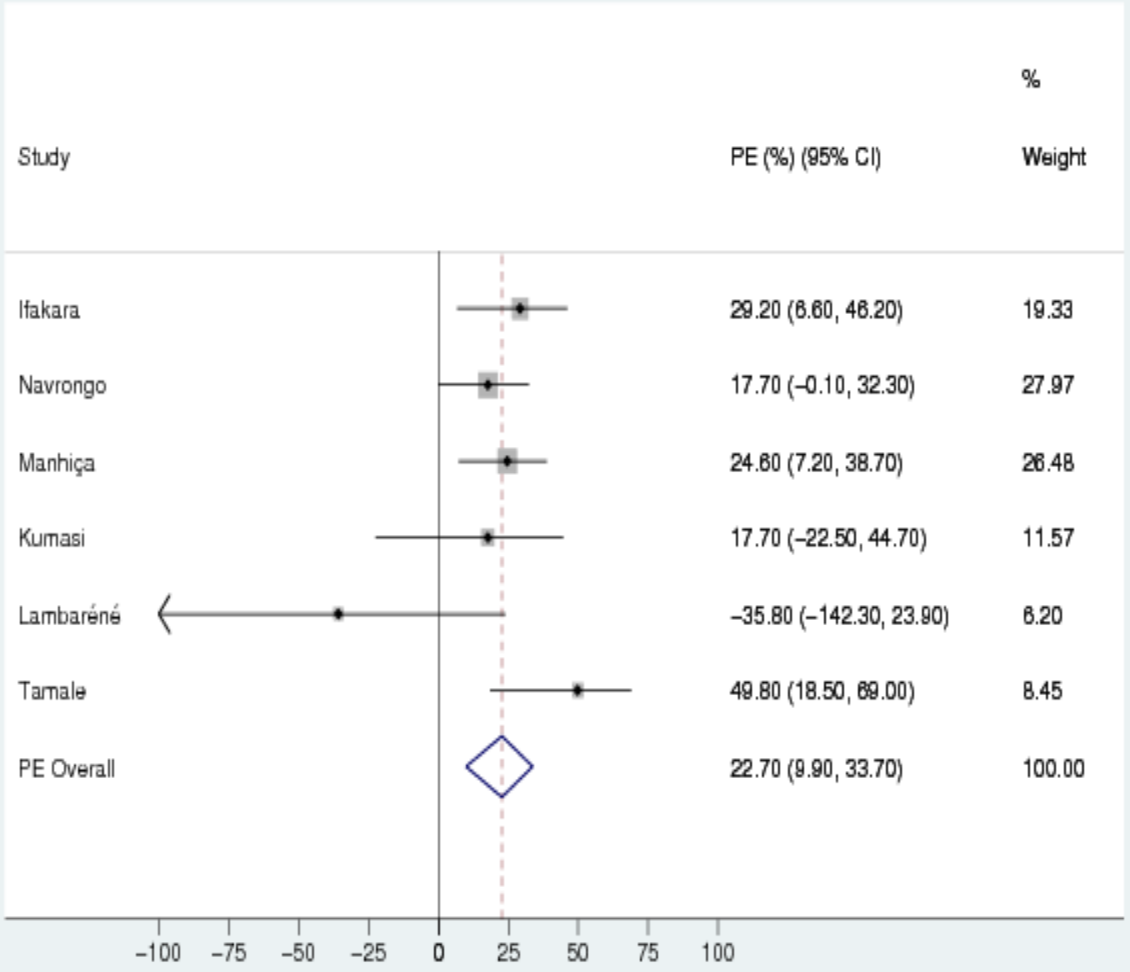
(random effects meta-analysis)

38%

p-value = 0.005

Reduction

All-cause admissions up to age 12m



Combined estimate

(random effects meta-analysis)

23%

p-value = 0.001

Reduction

9) Cost effectiveness of IPTi

CEWG Main Aims

- Economic studies conducted alongside clinical and implementation trials will provide key information on the economic costs and cost-effectiveness of the IPTi interventions to reduce malaria morbidity and mortality.

- Information generated by the studies will be used at both national and international level to as to the evidence base for policy changes, priority setting, resource allocation and budgeting.

Data Collected

- Intervention Costs
- Provider Costs
- Patient/Household Costs
- Time and Motion
- Interviews with Key Informants
- Provider Choice/Demand Analysis

Outputs

Cost Effectiveness Analyses

Cost Analysis of Malaria Treatment

Treatment Seeking Behaviour

IPTi Intervention Costs

Estimated unit cost of IPTi per dose delivered in Mtwara, Southern Tanzania (US Cents 2005)

Activity Component	Health System level	Financial costs	Opportunity costs	Total costs
Policy change	National	0.01	0.02	0.03
Sensitization	District	0.76	1.12	1.88
BCC	National	0.03	0.05	0.08
SP purchase and distribution	National	12.56	0.26	12.82
Training	District	3.06	2.30	5.36
Administration of intervention in health facilities	District	0.00	1.25	1.25
Strategy management	National	0.65	0.10	0.75
	District	0.62	0.00	0.62
Sub-Total	***National***	***13.25***	***0.43***	***13.68***
	District	***4.44***	***4.67***	***9.11***
Overall total (in US Cents)		**17.68**	**5.11**	**22.79**

Manzi et. al., BCM Health Service Research (2008)

Economic evaluation: formulas

- Cost-effectiveness ratio (Malaria episodes averted):
  - **Intervention costs** (1000 infants) / Malaria episodes averted
    - Malaria episodes averted=PE*Malaria incidence*1000
- Savings for the health system (thanks to fewer cases of malaria):
  - **Malaria treatment cost** *Number of visits averted (considers **treatment seeking behaviour** and proportion of severe cases)

CEA Model: Effectiveness Inputs

Best Estimates and (Ranges used in the sensitivity analysis)

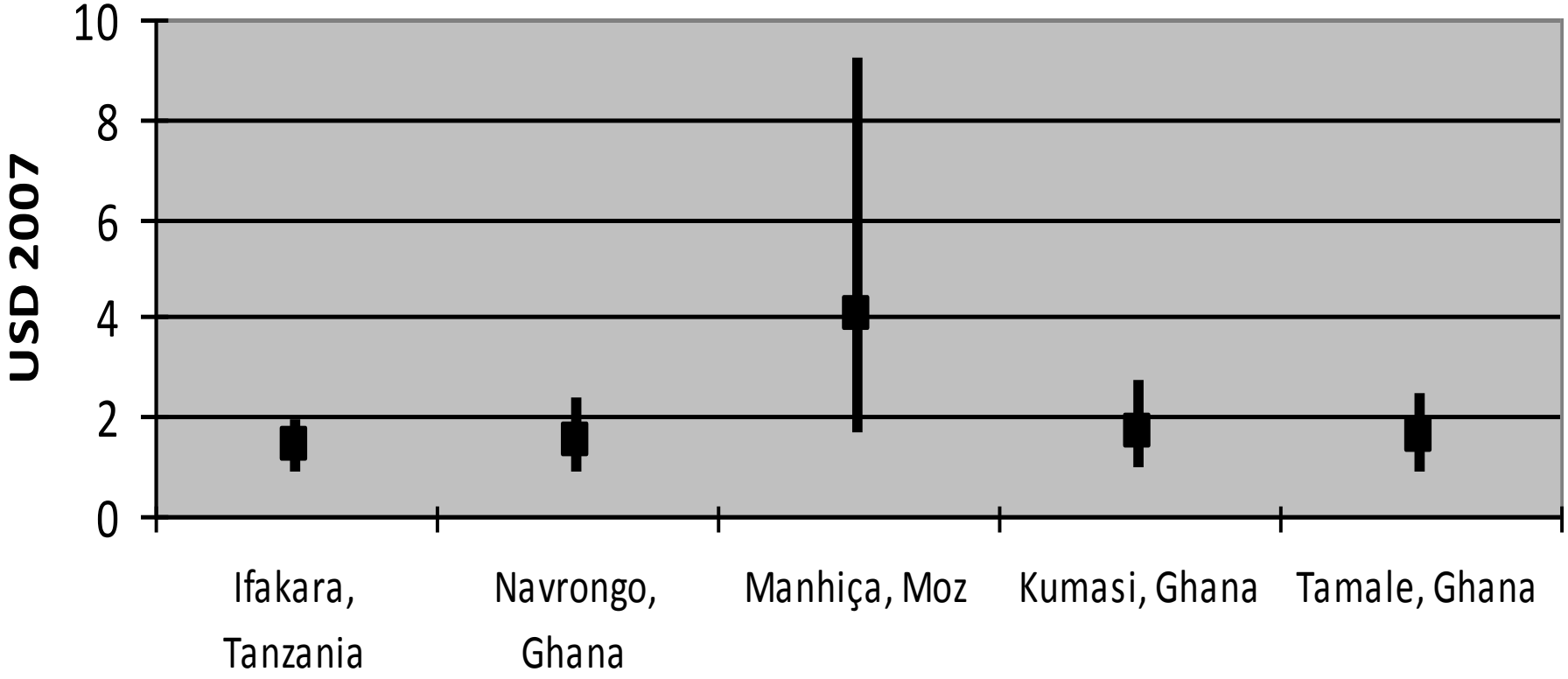
Study Site	*IPTi Efficacy against episodes of clinical malaria (%)*	*Malaria incidence (Episodes/PYAR) taken from placebo group)*	*Case Fatality Rate= Number of deaths in placebo group (%)*	*% of under five years children with malaria symptoms taken to a government facility (%)*	*Incidence (episodes/PYAR) of Hospital Admission with Malaria Parasites*
Ifakara, Tanzania	59 (41, 71)	0.55 (0.41, 0.69)	1.57 (1, 3)	55 (41, 69)	0.17 (0.13, 0.21)
Manhiça, Mozambique	20 (2, 35)	0.70 (0.53, 0.88)		51 (38, 64)	0.13 (0.10, 0.16)
Navrongo, Ghana	29 (17, 40)	1.01 (0.76, 1.26)		28 (21, 35)	0.02 (0.15, 0.25)
Kumasi, Ghana	21 (9, 31)	1.48 (1.11, 1.85)		28 (21, 35)	0.05 (0.04, 0.06)
Tamale, Ghana	33 (21, 44)	0.93 (0.70, 1.16)		28 (21, 35)	0.06 (0.05, 0.07)
Kisumu, Kenya	22 (3 , 38) 28 (6 , 40)	0.98 (0.74, 1.23)		37 (28, 46)	0.22 (0.17, 0.28)
Korogwe, Tanzania	38 (12, 57)	0.31 (0.23, 0.39)		55 (41, 69)	0.14 (0.11, 0.18)

CEA Model: Cost Inputs (USD 2007)

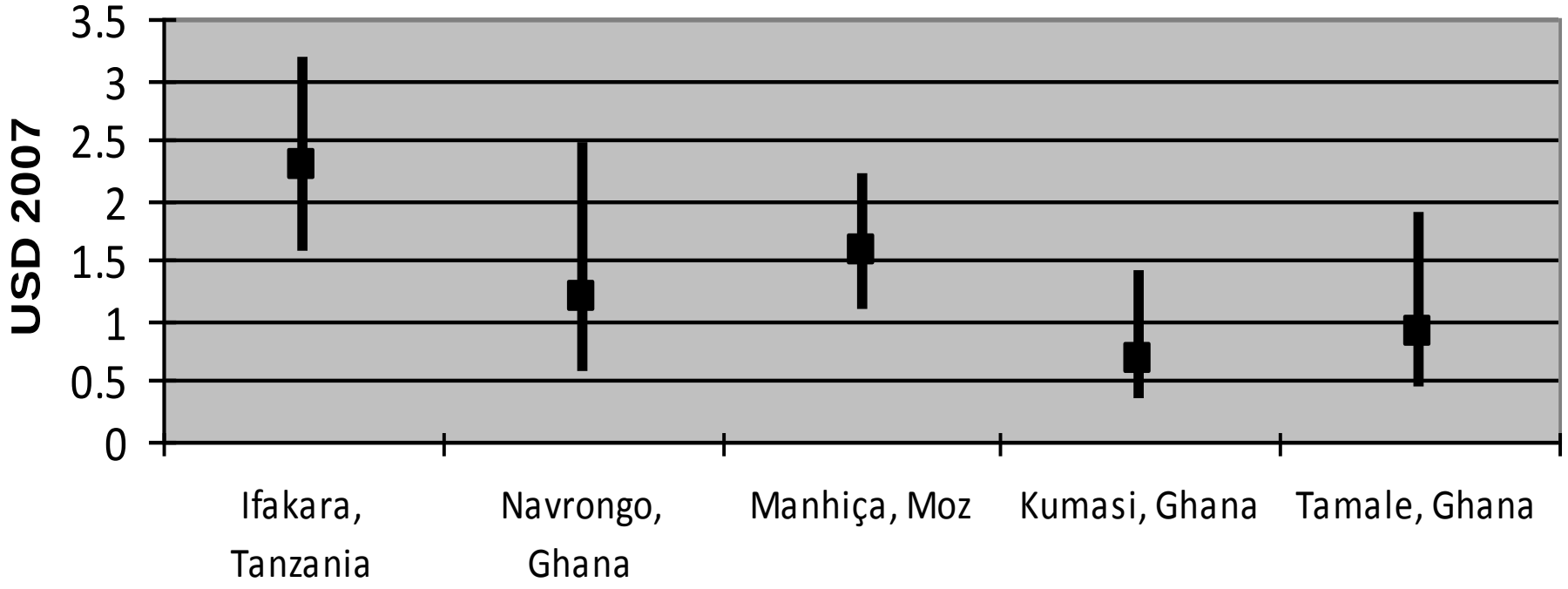
Best Estimates and (Ranges used in the sensitivity analysis)

Study Site *(Malaria treatment cost sources)*	***IPTi Cost Per Dose Delivered***	***Provider Malaria Treatment Costs***		***Household Malaria Treatment Cost (Direct)***		***Household Malaria Treatment Cost (Indirect)***	
		Uncomplicated/ Outpatient	Severe/ Inpatient	Uncomplicated/ Outpatient	Severe/ Inpatient	Uncomplicated/ Outpatient	Severe/ Inpatient
	Economic						
Ifakara, Tanzania	SP = 0.24 (0.18, 0.30)	4.35 (3.79, 4.84)	17.60 (13.20, 22.00)	1.12 (0.68, 1.74)	5.32 (3.99, 6.65)	3.05 (1.87, 4.20)	13.94 (10.46, 17.45)
Manhiça, Mozambique	SP = 0.27 (0.20, 0.34)	3.89 (2.92, 4.89)	9.23 (6.92, 11.54)	0.71 (0.53, 0.89)	3.49 (2.62, 4.36)	1.59 (1.19, 1.99)	4.94(3.71, 6.18)
Navrongo, Ghana	SP = 0.26 (0.18, 0.30)	2.64 (1.98, 3.30)	25.21 (18.91, 31.51)	4.41 (3.31, 5.51)	22.16 (16.62, 27.7)	0.92 (0.69, 1.15)	17.57 (13.18, 21.96)
Kumasi, Ghana	SP =0.26 (0.18, 0.30)	2.64 (1.98, 3.30)	25.21 (18.91, 31.51)	4.41 (3.31, 5.51)	22.16 (16.62, 27.7)	0.92 (0.69, 1.15)	17.57 (13.18, 21.96)
Tamale, Ghana	SP = 0.26 (0.18, 0.30)	2.64 (1.98, 3.30)	25.21 (18.91, 31.51)	4.41 (3.31, 5.51)	22.16 (16.62, 27.7)	0.92 (0.69, 1.15)	17.57 (13.18, 21.96)
Kisumu, Kenya	SP + Art3 = 0.60 (0.45, 0.75) AQ3 + Art3 = 0.44 (0.33, 0.55)	2.92 (1.66, 3.88)	21.07 (14.59, 29.76)	1.03 (0.49, 1.98)	8.65 (4.46, 12.28)	8.25 (3.74, 11.17)	29.32 (11.77, 49.57)
Korogwe, Tanzania	MQ = 0.63 (0.47, 0.79)	4.35 (3.79, 4.84)	17.60 (13.20, 22.00)	1.12 (0.68, 1.74)	5.32 (3.99, 6.65)	3.05 (1.87, 4.20)	13.94 (10.46, 17.45)

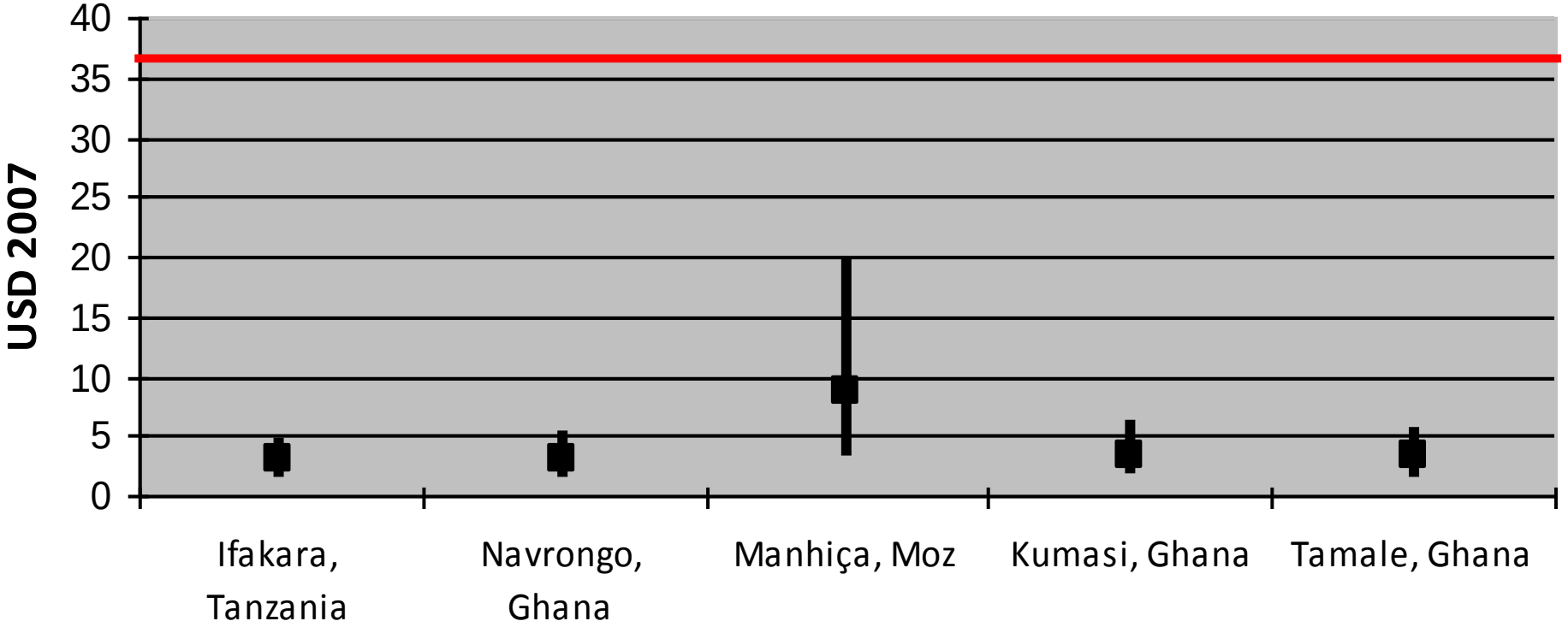
SP trials: Cost per malaria episodes averted (95% Confidence Intervals)



SP pooled analysis: Cost per malaria episode averted (95% Confidence Intervals)



SP trials: Cost per DALY averted
(95% Confidence Intervals)

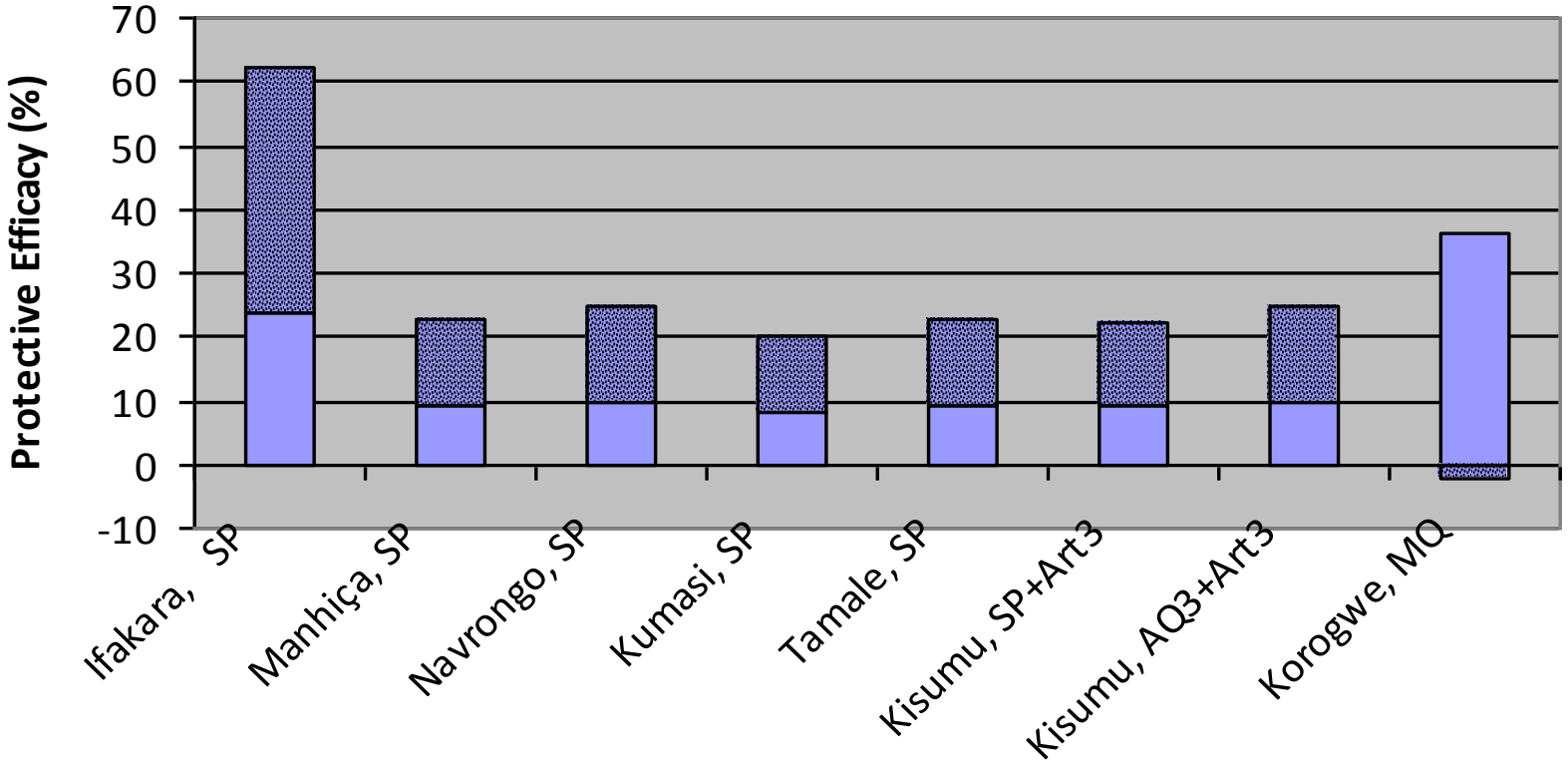


HIGHLY COST EFFECTIVE THRESHOLD (US$36 /DALY averted)

Cost-effectiveness threshold = US$220 /DALY averted

(World development report 1993)

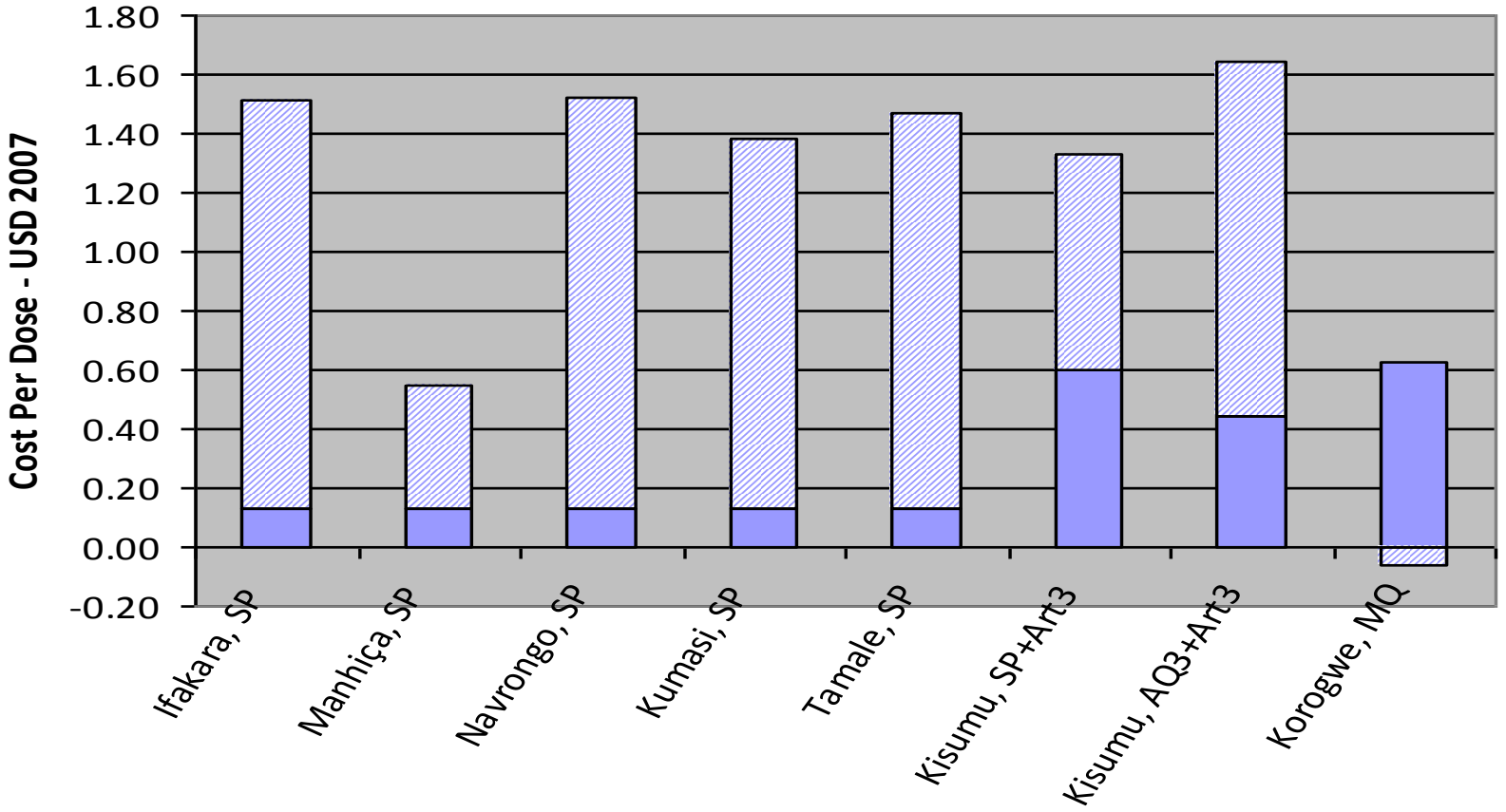
Highly Cost Effective Thresholds of Levels of PE against Clinical Malaria



Protective efficacy against 1st or only malaria episode

Threshold of highly cost effectiveness (36 US$/DALY averted)

Highly Cost Effective Thresholds of Unit Cost per Dose when Delivered through the EPI system



IPTi cost per dose of drug delivered through EPI

Threshold of highly cost effectiveness (36 US$/DALY averted)

CEWG Conclusions

In sites where IPTi was not efficacious is was not cost effective.
In sites where IPTi had a significant effect on reducing malaria:

- The cost per episode averted for IPTi-SP was very low, USD1.36-4.03 based on trial specific data and USD0.68-2.27 based on a pooled analysis.
- For IPTi using alternative antimalarials, the lowest cost per case averted was for AQ3-AS3 in Kisumu (USD4.62) and the highest was for MQ in Korowge (USD18.56).
- Where efficacious, IPTi was shown to be cost effective in all the sites and *highly* cost-effective in all but one of the sites, ranging from USD2.90 (Ifakara, SP) to USD39.63 (Korogwe, MQ) per DALY averted.
- IPTi also reduced health system costs and showed significant savings to households from malaria cases averted.

IPTi Consortium - Research Portfolio

…developed with WHO

- Efficacy studies
  - SP & alternative anti-malarials, in different transmission settings
- Cross-cutting issues
  - Safety
  - EPI serology
  - Drug resistance
  - Development of immunity
  - Costing and cost-effectiveness
  - Acceptability
- Community effectiveness study
- Pilot implementation

ipti CONSORTIUM INTERMITTENT PREVENTIVE TREATMENT IN INFANTS

WHO Malaria Policy Process

1. Technical Expert Group (TEG)

Preventive Chemotherapy

Tasked with appraising the evidence and developing a draft recommendation

2. Technical Research Advisory Committee (TRAC)

Chairs of the 6 TEGs, including the Preventive Chemotherapy TEG

Review and endorse the TEG recommendation

3. Scientific Technical and Advisory Group (STAG)

TEG/TRAC recommendation presented to STAG - endorse TEG/TRAC recommendation

STAG meeting report goes to WHO Director General

4. WHO Director General – issue the recommendation

WHO Policy Review of IPTi with SP - 2006

1. Technical Expert Group (TEG)

Preventive Chemotherapy (Geneva, 25-27 October 2006)

Appraised evidence and developed draft recommendation

Data reviewed: Six randomised controlled trials of IPTi with SP

- **IPTi is safe & resulted in 19% reduction in SAEs (hospitalisations)**
- **Hospitalisations in SP & placebo group related to IPTi**
- **Does not interact with EPI vaccines**
- **2 Cases of SJS in SP group in 1 trial related to tx (after dose in 2nd yr of life) & 1 placebo group not related**

Pooled analysis, in 1st year of life, IPTi with SP reduces: Malaria by 30%, Anaemia (Hb<8g/dl) by 15%, Malaria hospital admissions by 38%

Individual trial analysis: 1 trial had sustained 36% protection in 2nd yr, 2 trials saw some minor evidence of rebound

IPTi-SP is acceptable and cost effective

Effectiveness study in Southern Tanzania – IPTi-SP rapidly implemented through routine health services, safe, acceptable, affordable

TEG Recommendation – 2006

In settings where SP remains effective, the benefits of implementing IPTi using SP appeared to outweigh the risks.

The panel concluded that IPTi is a promising new intervention to consider adding to the package of available interventions for malaria control where there is a malaria burden in infants, provided:

- Rigorous systems to monitor AEs and DR are put in place to continually review the risk-benefit profile
- Implementation of IPTi does not detract from current efforts to scale-up existing strategies for malaria control
- The effectiveness of IPTi is monitored within the context of optimized malaria control efforts with other existing interventions
- The medicines used for IPTi should not compromise current and future medicines for curative treatment of malaria

WHO Policy review of IPTi with SP 2007

1. Technical Expert Group (TEG)
   Preventive Chemotherapy (Geneva, 8-10 October 2007)
   Reconvened to review updated information

Updated data:

Individual trial analysis: 1 trial had double the level of severe malaria anaemia in IPTi-SP recipients in 2nd yr of life

Additional pooled analysis:
In 1st year of life, IPTi with SP reduces all-cause hospital admissions by 23%

In 5 month period after end of IPTi, no evidence of rebound of malaria, anaemia, malaria hospital admissions, all-cause hospital admissions

Effectiveness study of IPTi-SP in Southern Tanzania: 60,000 doses given to 20,000 infants – safe, acceptable, affordable, doesn't drive drug resistance

Conclusions of the TEG 2007

- **Prevention of malaria in infancy (and childhood) through intermittent preventive treatment (IPT) is a potentially valuable and cost-effective intervention**
- **The EPI programme provides an effective existing platform for delivery of IPT to infants (IPTi)**
- **IPTi (SP) provided protection from malaria for approximately 35 days after each dose**
- **The preventive effects on anaemia and hospital admission varied in magnitude between studies**
- **3 studies there was evidence of a rebound in malaria or anaemia**
- **There remain significant safety concerns, particularly regarding the risk of severe skin reactions**

TEG Recommendation – 2007

"Taking into account these safety concerns when IPTi would be administered to otherwise healthy children, the duration of protection against malaria, the uncertainty over the magnitude of the protective effect against anaemia and severe malaria, the uncertainty concerning the efficacy against highly SP resistant parasites and the optimal dose and timing of administration, the committee cannot recommend general deployment of SP-IPTi"

TEG Recommendation – 2007 cont

- **However, IPTi remains a promising intervention in areas of stable malaria with high transmission**
- **In order for the full potential of IPT to be realized, the development of other antimalarials that are suitable for preventive treatment both in infants and other risk groups, with adequately characterized pharmacokinetic – pharmacodynamic profiles (and ideally formulations suitable for infants) is a priority**

TEG Recommendation – 2007 cont

- **Since the established benefits of SP-IPTi might override the safety concerns in areas where there is a very large burden of malaria in infants, carefully monitored assessments of SP-IPTi may be considered in parallel with the development of alternative medicines to SP**
- **Anticipated that further information will be available in the near future on SP-IPTi and IPTi using alternative antimalarials, so this recommendation will be reviewed in 2008**

Debates in Academic Journals & Press

Controversial aspects

"..... the uncomfortable possibility that although IPT with sulfadoxine–pyrimethamine provides benefit, it is the wrong drug at the wrong dose at the wrong time".

".....WHO has clearly struggled with these issues, and currently considers that the benefits of IPT with sulfadoxine–pyrimethamine exceed the risks. But it seems a close call".

McGready Lancet 2009

Gates Foundation's Influence Criticized
New York Times, 16 February 2008

Dr. Kochi said the Gates Foundation "takes its vested interest to seeing the data it helped generate taken to policy" as an example, he cited IPTi.

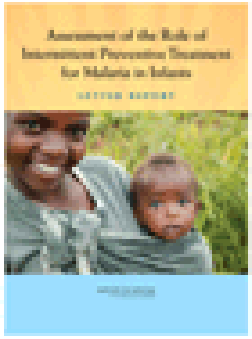
Other experts said IPTi involved giving babies doses of an older anti-malaria drug, Fansidar, when they got their shots at 2 months, 3 months and 9 months. In early studies, it was shown to decrease malaria cases about 25%. But each dose gave protection for only a month.

Since it is not safe or practical to give Fansidar constantly to babies because it is a sulfa drug that can cause rare but deadly reactions and because Fansidar-resistant malaria is growing, WHO scientists had doubts about it.

Dr. Kochi wrote, although it was "less and less straightforward" that the WHO should recommend it, the agency's objections were met with "intense and aggressive opposition" from Gates-backed scientists and the foundation. WHO, he wrote, needs to "stand up to such pressures and ensure that the review of evidence is rigorously independent of vested interests"

Institute of Medicine (IOM) Report

Overall, **IPTi-SP a promising public health strategy** to diminish the morbidity from malaria infections, especially for the incidence of clinical malaria, **among infants at high risk who reside in areas of high- or moderate-intensity transmission** and is **worthy of continued investment**.



The committee also **cautioned** that during **large-scale implementation problems** such as drug supply and logistics; monitoring and resistance; and community acceptance and reaction to IPTi-SP could arise

Political Timeline


World Health Organization

WHO Policy recommendation on Intermittent Preventive Treatment during Infancy with sulphadoxine-pyrimethamine (SP-IPTi) for *Plasmodium falciparum* malaria control in Africa

March 2010

Background

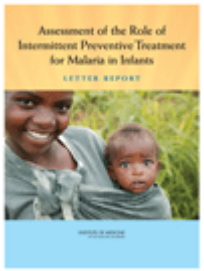
1st IPTI Trial 1999-2000 (Schellenberg et al Lancet 2001)

A WHO technical advisory group concluded that the available evidence was not sufficient to recommend the widespread introduction of IPTi –SP 2008

WHO Policy recommendation on (SP-IPTi) for *Plasmodium falciparum malaria control in Africa* *March 2010*

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

The IPTi Consortium received US$28m funding from the Bill and Melinda Gates Foundation in 2004



IOM Report 2008

IPTi publications in The Lancet in September 2009

IPTi Trials Running & Data Collection and Dissemination 1999 -2009

World Malaria Report 2011

- IPTi with SP is the administration of a full therapeutic course of SP delivered through immunization services at defined intervals corresponding to routine vaccination schedules – usually at 10 weeks, 14 weeks,and approximately 9 months of age – to infants at risk of malaria.

- WHO recommends IPTi in countries with moderate to high malaria transmission, where levels of parasite resistance to SP are low.

- **So far no country has adopted IPTi** as national policy since its recommendation in 2009; however, the IPTi implementation guidelines were released only in September 2011, and 8 countries recently met to discuss possible implementation.

http://www.who.int/malaria/world_malaria_report_2011/en/