Intermittent screening and treatment or intermittent preventive therapy for the control of malaria in pregnancy in Indonesia: an open label randomised control trial

Rukhsana Ahmed, Feiko ter Kuile, Jayne Webster & Jenny Hill

Liverpool School of Tropical Medicine

- Background to the clinical trial
- Part 1: Results of the clinical trial on IST, IPT or SST in Indonesia
- Part 2: sub-studies on acceptability, feasibility and cost effectiveness of the three strategies

Study Background

- **MIP Prevention in Asia-Pacific region:**
  - *P.falciparum* and *P.vivax* infections in pregnancy are associated with maternal anaemia, and low birthweight (preterm or intrauterine growth retardation)
  - Lacks a strategic MiP prevention framework like that exists in the African region
  - Mostly provision of LLITN and passive case detection (PCD)

- **Challenges for MIP prevention in Asia-Pacific region**
  - Diverse exposure risks: very low to intense transmission
  - Needs to target both *P.falciparum* and *P.vivax*
  - Sub microscopic infections are common; important?
  - P. Vivax relapse,
    - Primaquine not an option
    - Suppress the 'next' relapse for as long as possible
    - Prevent new infections
  - Multi-drug resistance, including to SP, the only antimalarial currently recommended for IPT

Indonesia

- Diverse exposure risks
  - ‘full spectrum’ (very low to intense transmission)

- MiP prevention policy since 2012
  - Single screening and treatment (SST) at 1st ANC visit
    - Screen all by microscopy or RDT at first ANC visit
    - Treat test-positive cases with DP in 2nd & 3rd trimester, quinine in 1st trimester
  - LLINs first ANC visit followed by passive case detection

STOPMIP-Trial Design

- Open-label 3-arm parallel-group matched cluster-randomised controlled superiority trial
- All gravidae
- Unit of randomisation: antenatal clinics
- Two sites in Eastern Indonesia:
  - South west Sumba (‘low’ transmission)
  - Timika in Papua (‘moderate’ transmission)
- Malaria diagnosis
  - RDT at point of care for IST and SST and clinical cases in all arms
    - First Response Malaria Ag pLDH/HRP2 Combo
  - Microscopy and placental histology
  - LAMP, confirmed by qPCR and nested PCR
- Study drug: dihydroartesiminin-piperaquine (DP) Eurartesim (Sigma Tau)
- All arms used monthly visits, enrolled 16-30 weeks gestation

Trial Objectives

- To compare the efficacy and safety of
  - IPTp-DP or ISTp-DP in the 2nd and 3rd trimester vs current strategy SSTp-DP

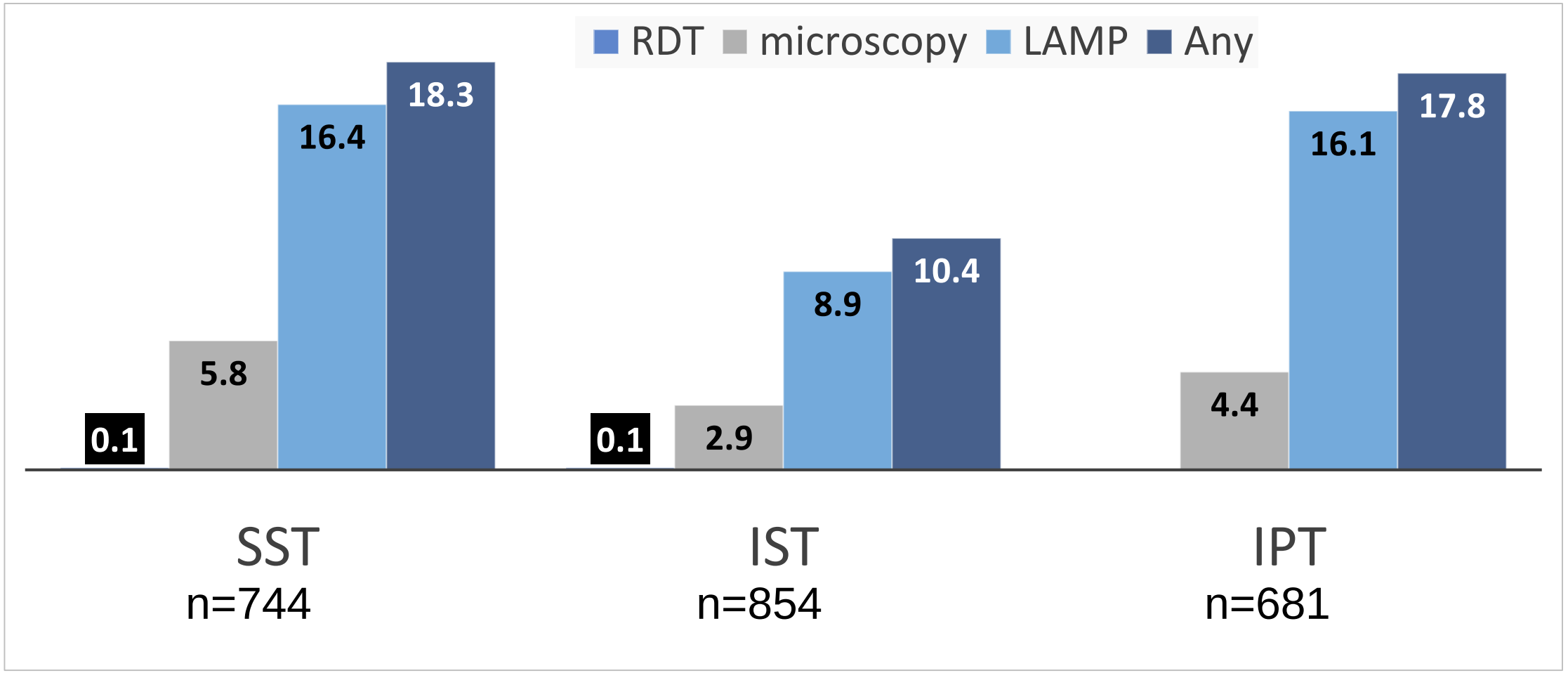
- To determine the acceptability, feasibility and cost effectiveness of SST, IST and IPT alongside the STOPMiP trial.

- Primary outcome

50% reduction of any malaria infection at delivery in women protected with LLITNs

Baseline malaria (at enrolment) N=2279

Less malaria in IST arm (in both sites)

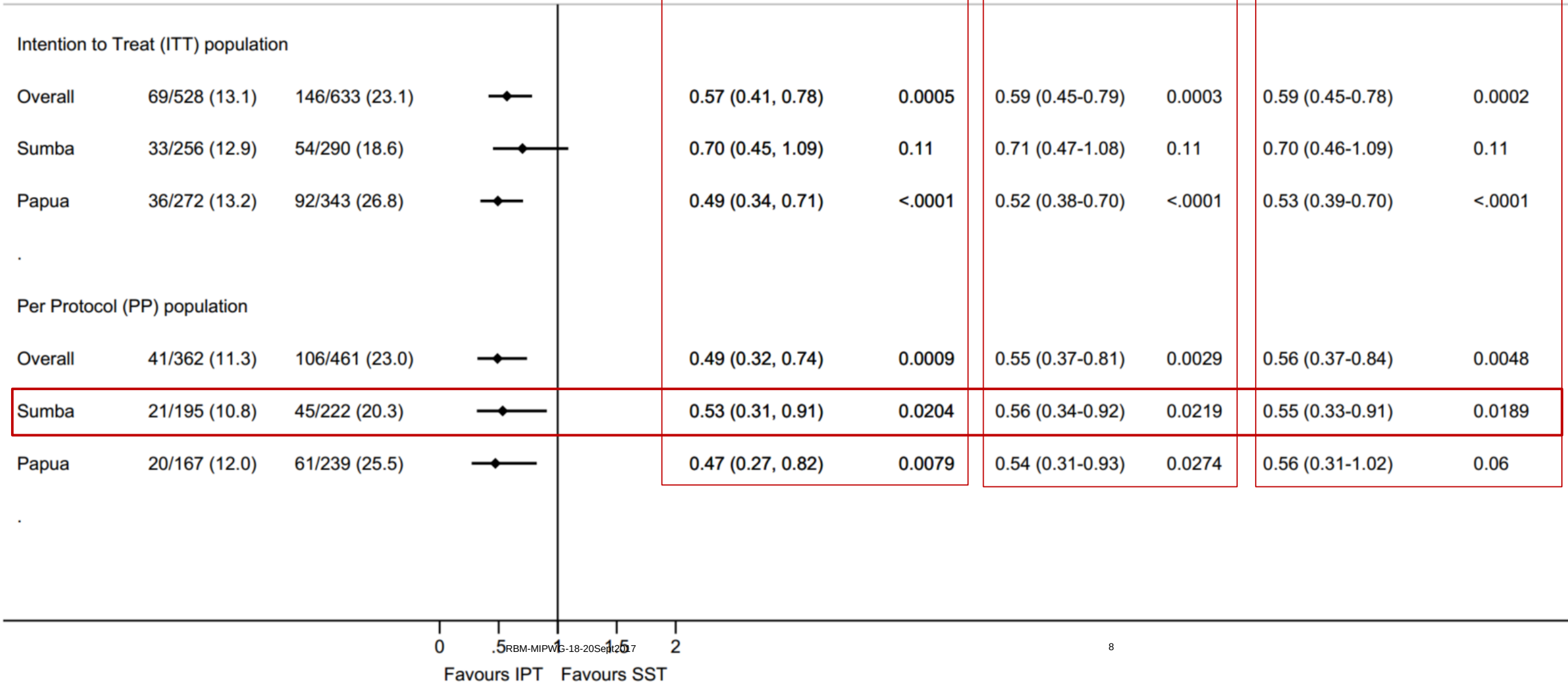


RESULTS IPT

Is IPT better than SST ?

Primary endpoint (malaria at delivery): IPT vs SST

IPT vs SST	IPT n/N (%)	SST n/N (%)	Crude RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value	Adjusted RR (post-hoc) (95% CI)	P-value
Intention to Treat (ITT) population								
Overall	69/528 (13.1)	146/633 (23.1)	0.57 (0.41, 0.78)	0.0005	0.59 (0.45-0.79)	0.0003	0.59 (0.45-0.78)	0.0002
Sumba	33/256 (12.9)	54/290 (18.6)	0.70 (0.45, 1.09)	0.11	0.71 (0.47-1.08)	0.11	0.70 (0.46-1.09)	0.11
Papua	36/272 (13.2)	92/343 (26.8)	0.49 (0.34, 0.71)	<.0001	0.52 (0.38-0.70)	<.0001	0.53 (0.39-0.70)	<.0001
Per Protocol (PP) population								
Overall	41/362 (11.3)	106/461 (23.0)	0.49 (0.32, 0.74)	0.0009	0.55 (0.37-0.81)	0.0029	0.56 (0.37-0.84)	0.0048
Sumba	21/195 (10.8)	45/222 (20.3)	0.53 (0.31, 0.91)	0.0204	0.56 (0.34-0.92)	0.0219	0.55 (0.33-0.91)	0.0189
Papua	20/167 (12.0)	61/239 (25.5)	0.47 (0.27, 0.82)	0.0079	0.54 (0.31-0.93)	0.0274	0.56 (0.31-1.02)	0.06



Summary: Safety and tolerance of IPT-DP

- Safety
  - No differences in foetal loss, neonatal mortality, congenital anomalies
  - QTc prolongation evident but not affected by the number of previous monthly courses taken
- Tolerance
  - Early vomiting rates similar to SP (<1%)
  - Within 7 days of drug intake: mild and self-limiting
    - Late vomiting: 10% of women at least once, 4% of courses
    - Nausea: 8% of women at least once, 3% of courses
    - Headache: 9% of women at least once, 3% of courses
    - AEs declined rapidly with advancing pregnancy (i.e. 2nd course better tolerated than 1st, 3rd better than 2nd etc)
- Adherence
  - 87% took all 3 doses and each scheduled course
  - Well tolerated, yet high drop out due to refusals (IPT 9%, vs IST 1% & SST 1%)
    - Mainly in Papua (14% vs 2% vs 0%), not Sumba (3% vs 3% vs 1%)
    - Papua: reputational, rumours: 30% refusals in 2 of 7 clusters
    - Society not used to taking drugs during pregnancy when not ill

Summary: IPT

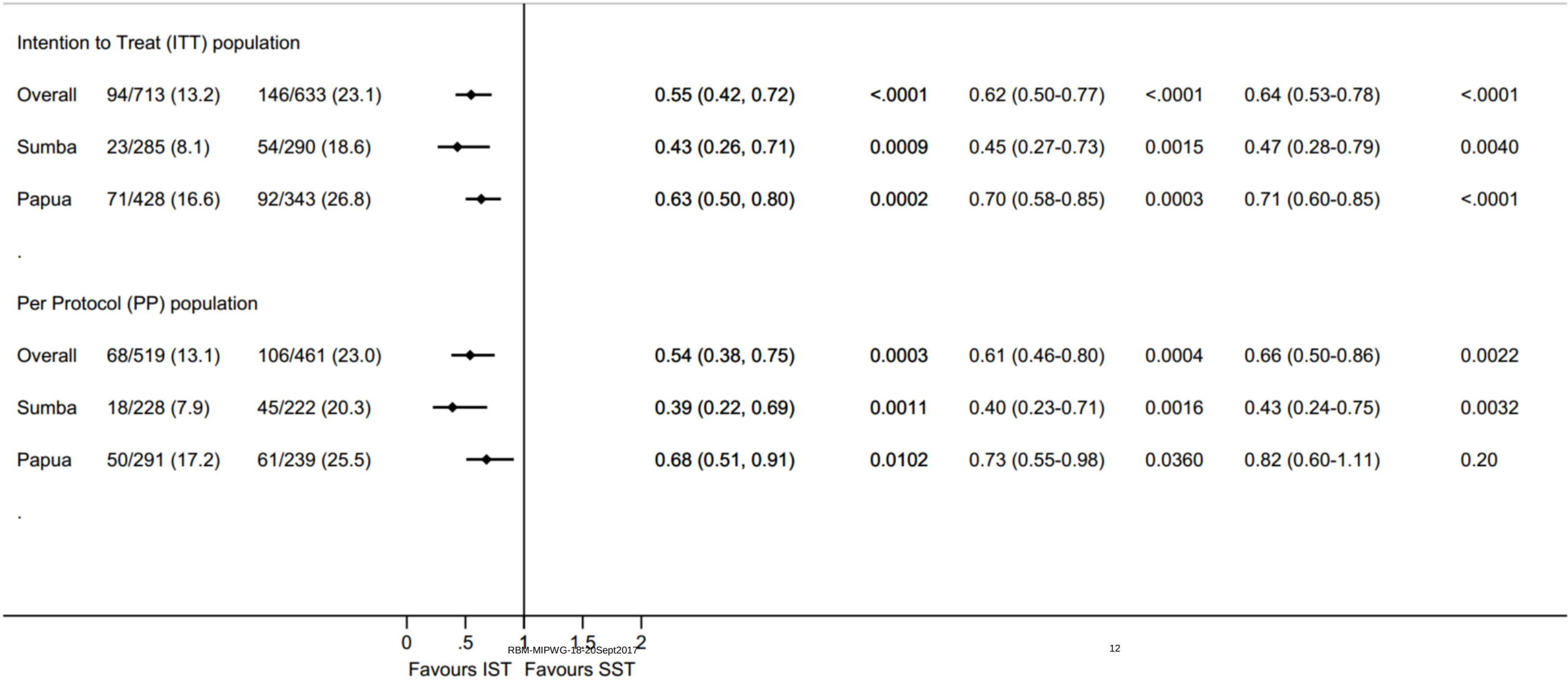
- First trial of IPT with DP for malaria in pregnancy in Asia-Pacific region
- Efficacy: Median of 4 courses of monthly IPT-DP superior to SST in Indonesia
  - Pregnancy
    - Malaria infection: Approximately halved incidence during pregnancy & prevalence at delivery
      - All gravidae, dry and rainy season, both Pf and Pv infections
    - Predominantly in Papua (Sumba significant only in PP analysis, and only at delivery)
      - Incident malaria infections: 78% reduction (similar to trials in Kenya & Uganda vs IPTp-SP)
        - »Patent vs sub-patent: reduction 95% vs 73%
      - Moderate-severe maternal anaemia (Hb<9 g/dL) delivery: 36% reduction
      - Clinical malaria was rare in SST arm (1.5%) and not found in IPT arm
    - Tolerance overall good, more AEs after 1st course, improves with subsequent courses
  - Infants
    - Hb: Higher cord Hb (+0.8 g/dL); Mod-severe anaemia by 12 months: 48% reduction
    - No improvement in birth outcomes, overall and in Papua

RESULTS IST

Is IST better than SST ?

Primary endpoint (malaria at delivery): IST vs SST

Site	IST n/N (%)	SST n/N (%)	Crude RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value	Adjusted RR (post-hoc) (95% CI)	P-value
Intention to Treat (ITT) population								
Overall	94/713 (13.2)	146/633 (23.1)	0.55 (0.42, 0.72)	<.0001	0.62 (0.50-0.77)	<.0001	0.64 (0.53-0.78)	<.0001
Sumba	23/285 (8.1)	54/290 (18.6)	0.43 (0.26, 0.71)	0.0009	0.45 (0.27-0.73)	0.0015	0.47 (0.28-0.79)	0.0040
Papua	71/428 (16.6)	92/343 (26.8)	0.63 (0.50, 0.80)	0.0002	0.70 (0.58-0.85)	0.0003	0.71 (0.60-0.85)	<.0001
Per Protocol (PP) population								
Overall	68/519 (13.1)	106/461 (23.0)	0.54 (0.38, 0.75)	0.0003	0.61 (0.46-0.80)	0.0004	0.66 (0.50-0.86)	0.0022
Sumba	18/228 (7.9)	45/222 (20.3)	0.39 (0.22, 0.69)	0.0011	0.40 (0.23-0.71)	0.0016	0.43 (0.24-0.75)	0.0032
Papua	50/291 (17.2)	61/239 (25.5)	0.68 (0.51, 0.91)	0.0102	0.73 (0.55-0.98)	0.0360	0.82 (0.60-1.11)	0.20



IPT VS IST

Is IPT better than IST ?

Other clinical endpoints (mother)

- Clinical malaria during pregnancy
  - IPT=0 (0%)
  - IST=4 (0.5%)
  - SST=5 (0.7%)
- No differences in all-cause or non-malaria sick visits

- Moderate severe anaemia (Hb <9 g/dL) at delivery
  - IPT: 22% reduction (p=0.046) (36% in Papua, p=0.02)
  - IST: 10% reduction (p=0.44)

- Infants
  - No improvement in birth outcomes
  - No improvement in infant malaria at 6 weeks post-natal

Summary: IST

- Baseline prevalence 43% lower in IST than SST arm (10% vs 18%)
- Malaria infection
  - Results not consistent
    - Prevalence at delivery: crude 45% reduction, adjusted 36% reduction
    - Yet, no reduction in placental malaria or incidence during pregnancy
  - Only 5 RDT+ out of 2,886 screening visits in IST arm
  - Overall more infections detected and treatment in SST arm during follow-up (passive case detection), despite monthly screening with RDT in IST arm
  - Thus few women in IST can have benefitted from post-treatment prophylaxis
- Majority of infections were RDT+ subpatent (Pf 78%; Pv 89%)
- Difference observed in IST arm a reflection of:
  - Lower transmission intensity in IST clusters ?
  - Other unknown confounding effect ?

Evaluation of the Implementation of SST for the Control of Malaria in Pregnancy in Eastern Indonesia (quantitative study)

Jayne Webster, Ansariadi, Faustina Helena Burdam, Chandra Umbu Reku Landuwulang, Halasan Panggabean, Jane Bruce, Rini Poespoprodjo, Din Syafruddin, Rukhsana Ahmed, Jenny Hill

Overview

Objective

- To evaluate implementation of the current policy of single screening and treatment (SST) for malaria in pregnancy in two sites in Eastern Indonesia (West Sumba and Papua)

Study design

- Quantitative study – ANC observations and exit interviews
- Qualitative study – in-depth interviews with health providers; FGDs with ANC attendees

Sampling

-Hospitals,
-health centres (*Puskesmas*)
-health posts (*Posyandu*)

Results summary

- Adherence was better in **Papua** than Sumba
- Adherence to malaria screening at first ANC visits **varied by level of health facility**
- In each site, adherence was **highest at health centres** (Papua 94.8% [95% CI 81.1, 98.7]; Sumba 60.0% [95% CI 32.6, 82.3]) and **lowest in health posts** (3.8% [95% CI 1.6, 8.8] and 9.8% [95% CI 4.4, 20.5], respectively)
- Most screening conducted at first ANC visit was **by microscopy** - 1.1% (2/185) first ANC visits screened by RDT in Papua, and 1.2% (2/161) in West Sumba

Conclusions

In Timika screening at 1st ANC

- Successfully implemented in health centres (& hospital)
- Poorly implemented in health posts

In West Sumba testing at 1st ANC

- Not implemented in the hospital and poorly implemented in health posts

- *Post study note:* No RDT shipment to Sumba from Global Fund in 2015, MoH is now trying to shift RDT procurement to be funded by the national budget

Qualitative SST evaluation: Summary results

- Health providers of all cadres were accepting of SST as a preventive strategy, with a **strong preference for microscopy** over RDTs for screening
- Implementation of the policy was **inconsistent in both sites**, with least extensive implementation reported in West Sumba compared to Timika
- SST **predominantly implemented at health centre** level using microscopy, whereas implementation at community health posts was said to occur in less than half the selected health facilities
- **Lack of availability of RDTs** was cited as the major factor preventing provision of SST at health posts **village midwives cannot prescribe medicines so women who test positive in health posts are referred to health centres for antimalarials

Health Provider acceptability of IST or IPT-DP vs SST: Summary and Conclusions

- **ISTp**: High acceptance owing to existing SST policy - culture of screening women at ANC and providing treatment based on a positive diagnosis BUT….need more sensitive RDTs and reliable supplies

- **IPTp**: Requires a major shift in HP attitudes towards giving antimalarials presumptively SO… need further exploration to see if effective communication and training could change attitudes
- **In the context of this study ISTp appears to be more plausible strategy to control MiP compared to IPTp**

Cost effectiveness: Summary results

Different results found by site:

- In **Sumba**, the current strategy of **SSTp-DP** incurred lower costs (for intervention delivery and cost of consequences) and resulted in fewer DALYs compared to IPTp-DP or ISTp-DP.

- In contrast, in the **higher malaria transmission setting of Papua**, **IPTp-DP and ISTp-DP** were both incrementally more cost effective than the current strategy of SSTp-DP; although IPTp-DP and ISTp-DP incurred higher incremental costs than SSTp-DP, they resulted in incrementally fewer DALYs.

RBM-MIPWG-18-20Sept2017

Interpretation

- Although ISTp appears to have had an effect on the primary trial outcome of malaria infection at delivery in Papua, very few women were screened as positive and so treated with DP in either site.

- As current RDTs miss most infections which are subpatent and asymptomatic, IST is not effective and therefore cannot be cost effective

- Although cost per capita of delivering IPTp-DP is higher than the current strategy of SSTp-DP, it is possible that it may be an efficacious strategy for the prevention of adverse outcomes of malaria in pregnancy in the context of malaria transmission found in Papua.

RBM-MIPWG-18-20Sept2017

Conclusions

- **Majority of infections were below the level of RDT or microscopy detection and asymptomatic (clinical malaria was rare, also in SST arm [1.5%])**

- IST
  - Monthly screening with the current generation of RDTs unlikely to be ever cost-effective
  - **More studies are needed with highly sensitive RDTs/ (or field friendly molecular tests, eg. LAMP)**

- IPT
  - **Monthly IPT-DP potential alternative to the existing SST strategy in Papua Indonesia and other areas with moderate transmission in the Asia-Pacific region, like PNG**
  - However, implementation studies needed to determine feasibility of strategy as monthly prophylaxis to asymptomatic women is a new in concept in Indonesia and the region

Investigators and acknowledgments

STOPMIP Investigators

- Rukhsana Ahmed
- J Rini Poespoprodjo
- Din Syafruddin
- Carole Khairallah
- Cheryl Pace
- Theda Lukito
- Silvia Maratina
- Puji Asih
- Maria Santana-MoraLes
- Emily Adams
- Vera Unwin
- Chris Williams
- James Smedley
- Tao Chen
- Duolao Wang
- Brian Faragher
- Ric Price
- Feiko ter Kuile

- **DMEC members:**
  - Andy Stergachis
  - Tim Peto
  - Marcus Rijken
- **TSC members:**
  - Bill Hawley
  - Larry Slutsker
  - Julie Simpson,
  - Rosemary Keogh
  - Padma Murti

- **STOPMIP site teams:** Study nurses/midwives, Research Assistants, Lab staff, data clerks, administrative staff, drivers, home visitors
- **Officials:** DHO, Puskesmas & Posyandu staff, Village Heads and village community
- **LSTM Governance**
- **Prodia CRO**
- **Study participants** (pregnant women & babies)

Acknowledgments

- **Funder**: United Kingdom Joint Global Health Trials Scheme (JGHT: G100024) (MRC/DFID/Wellcome Trust)

MRC Medical Research Council

wellcome trust

UKaid from the Department for International Development

Cardiac monitoring

CARDIABASE BY BANOOK GROUP

LAMP kits

FIND Because diagnosis matters

Study drug

sigma-tau









Thank you