Effect of IPTp-SP on malaria and sexually transmitted and reproductive tract infections in pregnancy

Roll Back Malaria
Working Group on Malaria in Pregnancy
Annual Meeting

19 September 2017

Matthew Chico
Assistant Professor
London School of Hygiene & Tropical Medicine
Keppel Street, London, WC1E 7HT, United Kingdom
Email: matthew.chico@lshtm.ac.uk
Mobile: +44 794 844 4456 l Office: +44 207 927 2841

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Outline

Burden of curable STIs/RTIs in pregnancy

- **Adverse birth outcomes associated with curable STIs/RTIs.**
- **Prevalence of malaria and curable STIs/RTIs in pregnancy in sub-Saharan Africa.**
- **Prevalence of malaria and curable STI/RTI co-infection in pregnancy in Zambia.**

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Outline

Protective effects of SP and azithromycin

- **Protective effect of IPTp-SP against malaria and curable STIs/RTIs in pregnancy in Zambia.**
- **Protective effect of azithromycin against curable STIs/RTIs.**

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Adverse birth outcomes associated with STIs/RTIs

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

Adverse birth outcomes associated with STIs/RTIs

Reference	Stillbirth	IUGR	Preterm birth	Low birthweight
Syphilis				
Watson-Jones (2002)	RR = 18 (95% CI: 5.5, 59.6)	RR = 2.1 (95% CI: 1.0, 4.2)	RR = 6.1 (95% CI: 2.5, 15.3)	OR = 3.3 (95% CI: 2.0, 5.4)
Temmerman (1995)	RR = 3.34	Not reported	Not reported	OR = 4.01 (<32 weeks)
McDermott (1993)	OR = 10.98	Not reported	Not reported	Not reported
Donders (1993)	Not reported	Not reported	33%; 5 of 15 cases	Not reported
Elliott (1990)	Not reported	Not reported	OR = 1.4 (95% CI: 0.5, 4.1)	Not reported

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

STIs/RTIs and adverse birth outcomes

Reference	Stillbirth	IUGR	Preterm birth	Low birthweight
Neisseria gonorrhoeae				
Johnson (2011)	Not reported	Not reported	OR = 2.0 (95% CI: 1.0, 4.0)	OR = 0.8 (95% CI: 0.3, 2.3)
Donders (1993)	Not reported	Not reported	56%; 5 of 9 cases	*P*<0.005
Elliott (1990)	Not reported	Not reported	OR = 3.2 (95% CI: 1.3, 8.4)	Not reported

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

STIs/RTIs and adverse birth outcomes

Reference	Stillbirth	IUGR	Preterm birth	Low birthweight
Chlamydia trachomatis				
Rours (2011)	Not reported	Not reported	OR = 4.4 (95% CI: 1.3, 15.2) < week 32 OR = 2.7 (95% CI: 1.1, 6.5) < week 35 OR = 1.17 (95% CI: 0.6, 2.4) < week 37	OR = 1.0 (95% CI: 0.4, 2.2)
Silveira (2009)	Not reported	Not reported	OR = 0.7 (95% CI: 0.4, 1.4)	Not reported`
Wilkowska-Trojniel (2009)	Not reported	Not reported	Not reported	Not reported
Blas (2007)	Not reported	Not reported	RR = 1.5 (95% CI: 1.1 to 2.0)	OR = 1.1 (95% CI: 0.7, 1.7)
Odendaal (2006)	Not reported	Not reported	22.2%; 8 of 36 cases vs. 10.4% 32 of 307 cases; *P*=0.037	Not reported
Johnson (2011)	Not reported	Not reported	OR = 1.0 (95% CI: 0.6, 2.0)	OR = 2.1 (95% CI: 1.0, 4.2)
Kovacs (1998)	Not reported	7.3 v 5.8% *P*>0.05	Not reported	15.5% vs. 13.2% *P*>0.05
Donders (1993)	Not reported	Not reported	27%; 6 of 22 cases	Not reported
Elliott (1990)	Not reported	Not reported	OR = 0.7 (95% CI: 0.4, 1.4)	Not reported
Johns Hopkins (1989)	Not reported	OR = 2.4 (95% CI: 1.3, 4.2)	OR = 1.6 (95% CI: 1.0, 4.2)	Not reported
Gravett (1986)	Not reported	Not reported	OR = 4.0 (95% CI: 1.7, 9.2)	OR = 2.7 (95% CI: 1.3, 5.7)

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

STIs/RTIs and adverse birth outcomes

Reference	Stillbirth	IUGR	Preterm birth	Low birthweight
Trichomonas vaginalis				
Johnson (2011)	Not reported	Not reported	OR = 1.4 (95% CI: 0.7 to 2.8)	OR = 1.5 (95% CI: 0.9 to 2.6)
Meis (1995)	Not reported	Not reported	OR = 1.5 (95% CI: 0.1, 8.1) < week 24 OR = 0.9 (95% CI: 0.2, 3.6) < week 28	Not reported
Sutton (1999)	Not reported	Not reported	Not reported	OR = 2.1 (95% CI: 1.0 to 4.7)
Minkoff (1984)	Not reported	Not reported	Not reported	Not reported
Cotch (1997)	Not reported	Not reported	OR = 1.3 (95% CI: 1.1, 1.4)	OR = 1.3 (95% CI: 1.1 to 1.5)

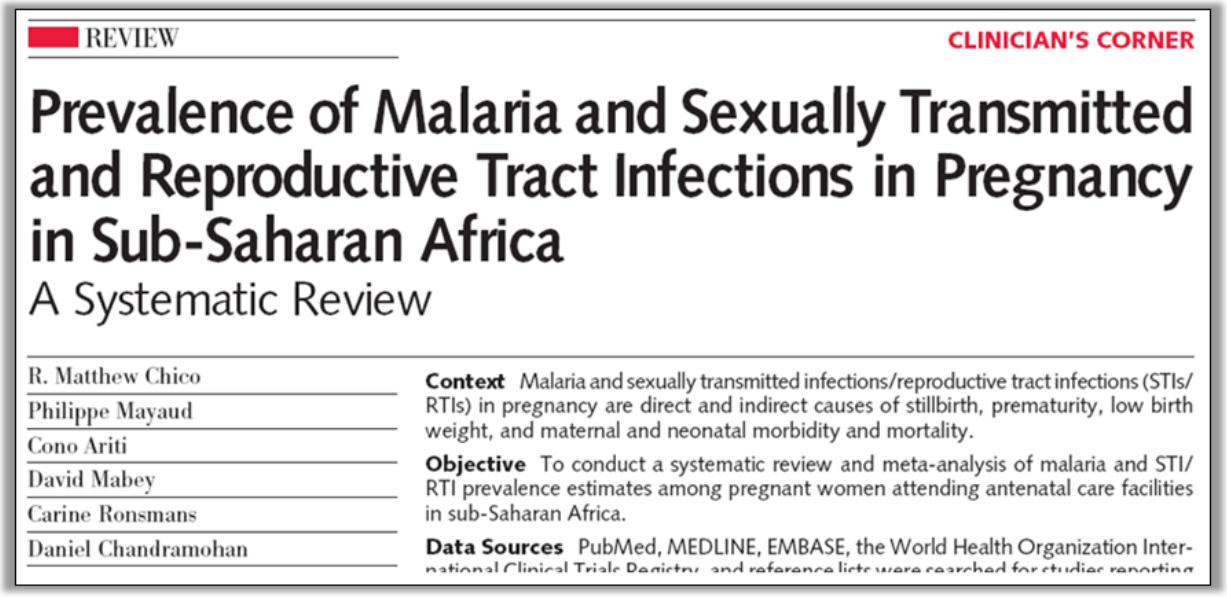
Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

STIs/RTIs and adverse birth outcomes

Reference	Stillbirth	IUGR	Preterm birth	Low birthweight
Bacterial vaginosis				
Johnson (2011)	Not reported	Not reported	OR = 1.3 (95% CI: 0.9 to 2.1)	OR = 1.1 (95% CI: 0.6 to 1.8)
Svare (2006)	Not reported	Not reported	OR = 2.5 (95% CI: 1.6 to 3.9)	OR = 2.0 (95% CI: 1.3 to 2.9)
Watson-Jones (2007)	Not reported	Not reported	OR = 3.0 (95% CI: 1.3 to 6.6)	Not reported
Leitich (2003)	Not reported	Not reported	OR = 2.2 (95% CI: 1.5 to 3.1)	Not reported
Meis (1995)	Not reported	Not reported	OR = 1.4 (95% CI: 0.9 to 2.05) < week 24 OR = 1.8 (95% CI: 1.2 to 3.0) < week 28	Not reported
McGregor (1995)	Not reported	Not reported	OR = 1.9 (95% CI: 1.2 to 3.0) RR = 1.5 (95% CI: 0.7 to 3.0) diagnosed 28-32 weeks	Not reported
Hillier (1995)	Not reported	Not reported	OR = 1.4 (95% CI: 1.1 to 1.8)	OR = 1.5 (95% CI: 1.2 to 1.7)
Hay (1994)	Not reported	Not reported	OR = 13.1 (95% CI: 4.0 to 42.6) diagnosed with intermediate flora (Nugent 4-7)	Not reported
Elliott (1990)	Not reported	Not reported	OR = 1.0 (95% CI: 0.6 to 1.8)	Not reported
Gravett (1986)	Not reported	Not reported	Not reported	OR = 1.5 (95% CI: 0.8 to 2.0)

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

Prevalence of malaria and STIs/RTIs



REVIEW

CLINICIAN'S CORNER

Prevalence of Malaria and Sexually Transmitted and Reproductive Tract Infections in Pregnancy in Sub-Saharan Africa

A Systematic Review

R. Matthew Chico
Philippe Mayaud
Cono Ariti
David Mabey
Carine Ronsmans
Daniel Chandramohan

Context Malaria and sexually transmitted infections/reproductive tract infections (STIs/RTIs) in pregnancy are direct and indirect causes of stillbirth, prematurity, low birth weight, and maternal and neonatal morbidity and mortality.

Objective To conduct a systematic review and meta-analysis of malaria and STI/RTI prevalence estimates among pregnant women attending antenatal care facilities in sub-Saharan Africa.

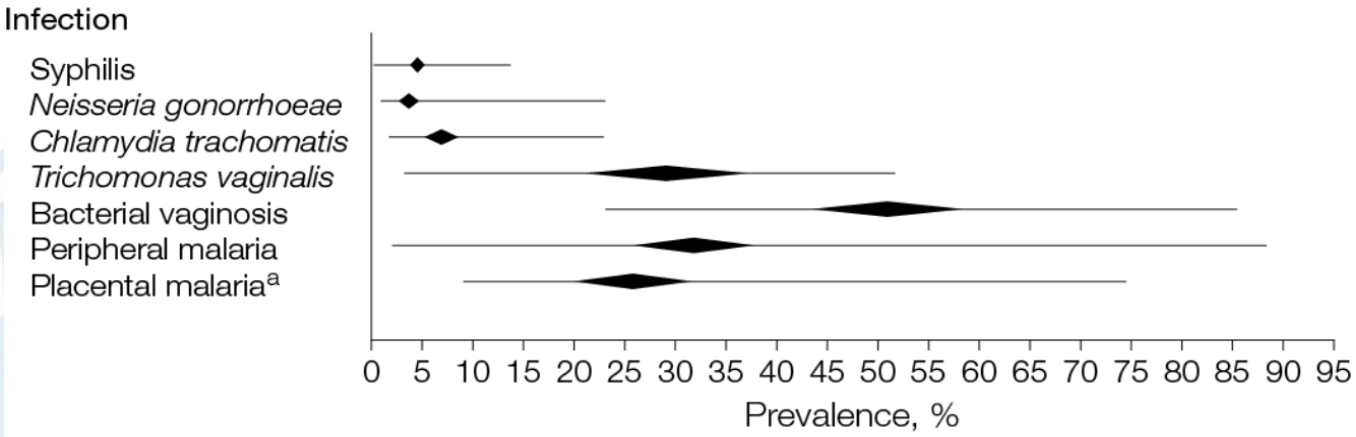
Data Sources PubMed, MEDLINE, EMBASE, the World Health Organization International Clinical Trials Registry, and reference lists were searched for studies reporting

Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in Sub-Saharan Africa: a systematic review. *JAMA: Journal of the American Medical Association.* 2012; Volume 307, Issue 19, pp. 2079-2086

East and Southern Africa

Pooled prevalence of malaria and STIs/RTIs in pregnancy with highest and lowest point estimates

Infection	No. of Women: Positive Diagnosis	No. of Women: Tested	Pooled Prevalence Estimates, % (95% CI)	Lowest to Highest Point Estimates, Range, %
Syphilis	8346	136 686	4.50 (3.90-5.10)	0.10-13.70
Neisseria gonorrhoeae	626	17 220	3.70 (2.80-4.60)	1.40-23.30
Chlamydia trachomatis	350	5159	6.90 (5.10-8.60)	2.00-23.20
Trichomonas vaginalis	5502	28 189	29.10 (21.00-37.20)	3.90-51.70
Bacterial vaginosis	4280	14 112	50.80 (43.30-58.40)	23.50-85.50
Peripheral malaria	11 688	47 443	32.00 (25.90-38.00)	2.10-87.90
Placental malaria[a]	1388	6649	25.80 (19.70-31.90)	8.50-74.70

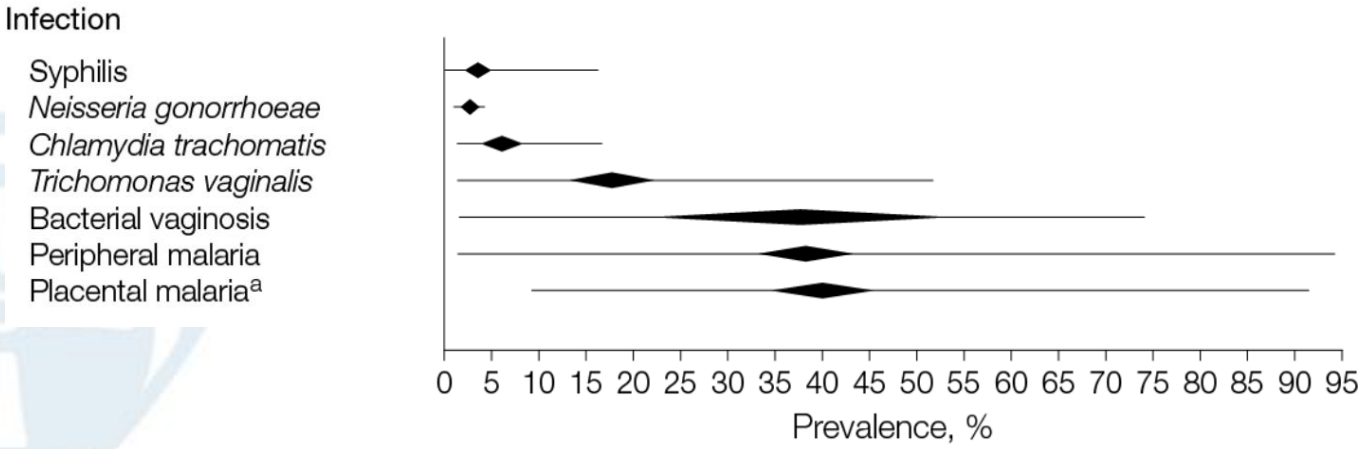


Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in Sub-Saharan Africa: a systematic review. *JAMA: Journal of the American Medical Association.* 2012; Volume 307, Issue 19, pp. 2079-2086

West and Central Africa

Pooled prevalence of malaria and STIs/RTIs in pregnancy with highest and lowest point estimates

Infection	No. of Women: Positive Diagnosis	No. of Women: Tested	Pooled Prevalence Estimates, % (95% CI)	Lowest to Highest Point Estimates, Range, %
Syphilis	851	10 797	3.50 (.80-5.20)	0.10-16.30
Neisseria gonorrhoeae	73	2737	2.70 (.70-3.70)	1.60-4.60
Chlamydia trachomatis	357	5414	6.10 (.00-8.30)	1.40-16.40
Trichomonas vaginalis	822	9806	17.80 (2.40-23.10)	1.60-52.00
Bacterial vaginosis	1208	7435	37.60 (8.00-57.20)	18.00-74.50
Peripheral malaria	12 242	43 312	38.20 (37.30-44.10)	0.90-94.50
Placental malaria[a]	4658	27 535	39.90 (34.20-45.70)	9.00-91.60



Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in Sub-Saharan Africa: a systematic review. *JAMA: Journal of the American Medical Association.* 2012; Volume 307, Issue 19, pp. 2079-2086

Prevalence of malaria and STI/RTI co-infection in pregnancy

Malarial Infection and Curable Sexually Transmitted and Reproductive Tract Infections among Pregnant Women in a Rural District of Zambia

Enesia Banda Chaponda,[1,2]* R. Matthew Chico,[2] Jane Bruce,[2] Charles Michelo,[3] Bellington Vwalika,[4] Sungano Mharakurwa,[5,6] Mike Chaponda,[7] James Chipeta,[8] and Daniel Chandramohan[2]

[1]*Department of Biological Sciences, University of Zambia, Lusaka, Zambia;* [2]*Department of Disease Control, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom;* [3]*Department of Public Health, University of Zambia School of Medicine, Lusaka, Zambia;* [4]*Department of Obstetrics and Gynaecology, University of Zambia School of Medicine, Lusaka, Zambia;* [5]*Faculty of Health Sciences, Africa University, Mutare, Zimbabwe;* [6]*Department of Medical Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland;* [7]*Department of Clinical Sciences, Tropical Diseases Research Centre, Ndola, Zambia;* [8]*Department of Paediatrics and Child Health, University of Zambia School of Medicine, Lusaka, Zambia*

- Nchelenge District of north-east Zambia
- 1,086 pregnant women recruited at first ANC visit as part of standard antenatal care
- Biological samples for malaria and curable STIs/RTIs were collected at enrolment analysed retrospectively at reference laboratory
- Care for curable STIs/RTIs was provided throughout pregnancy using the syndromic management algorithms that are national policy in Zambia and recommended by WHO

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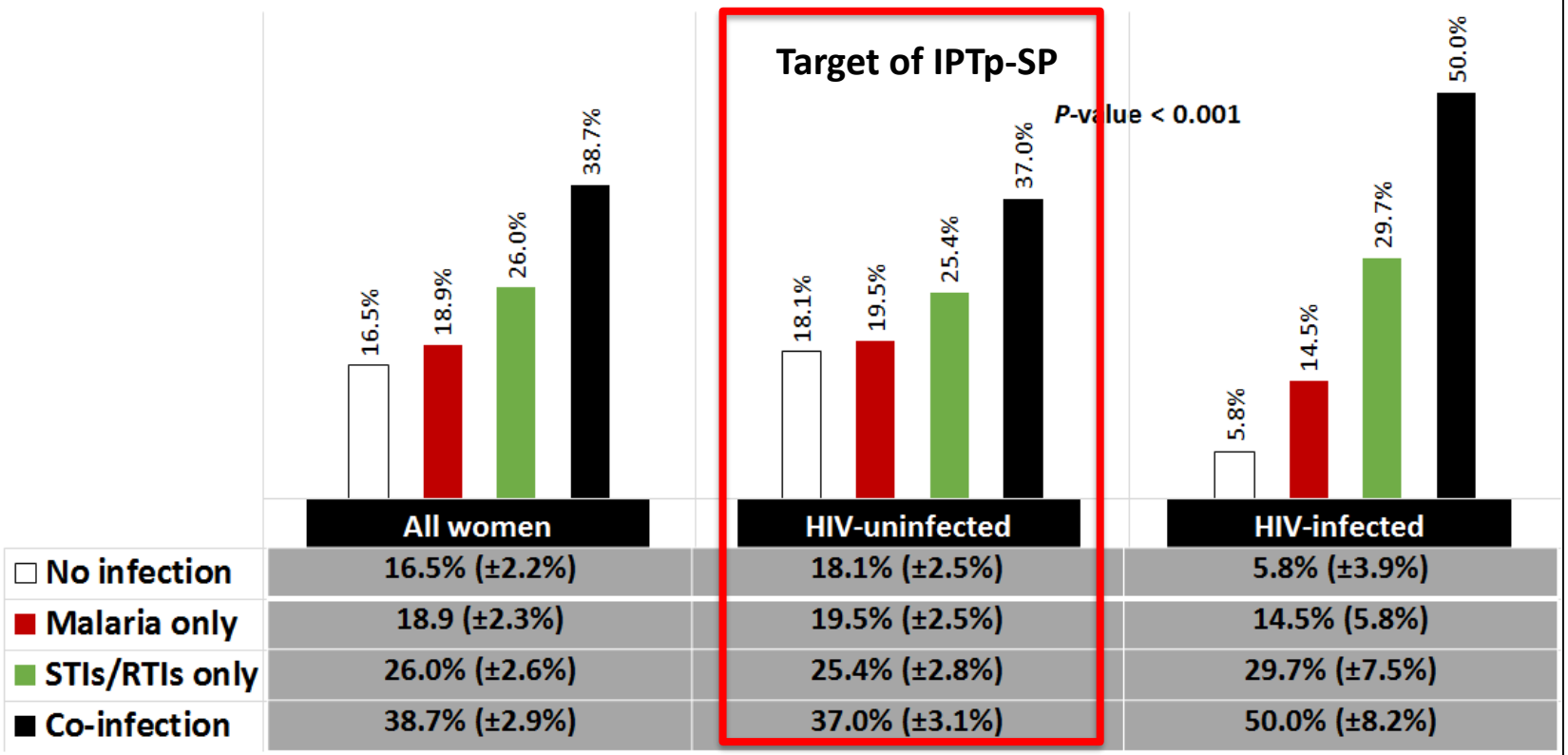
Prevalence of PCR-diagnosed malaria and any curable STI/RTI co-infection among pregnant women at antenatal care facilities in Nchelenge District, Zambia (2013-14)

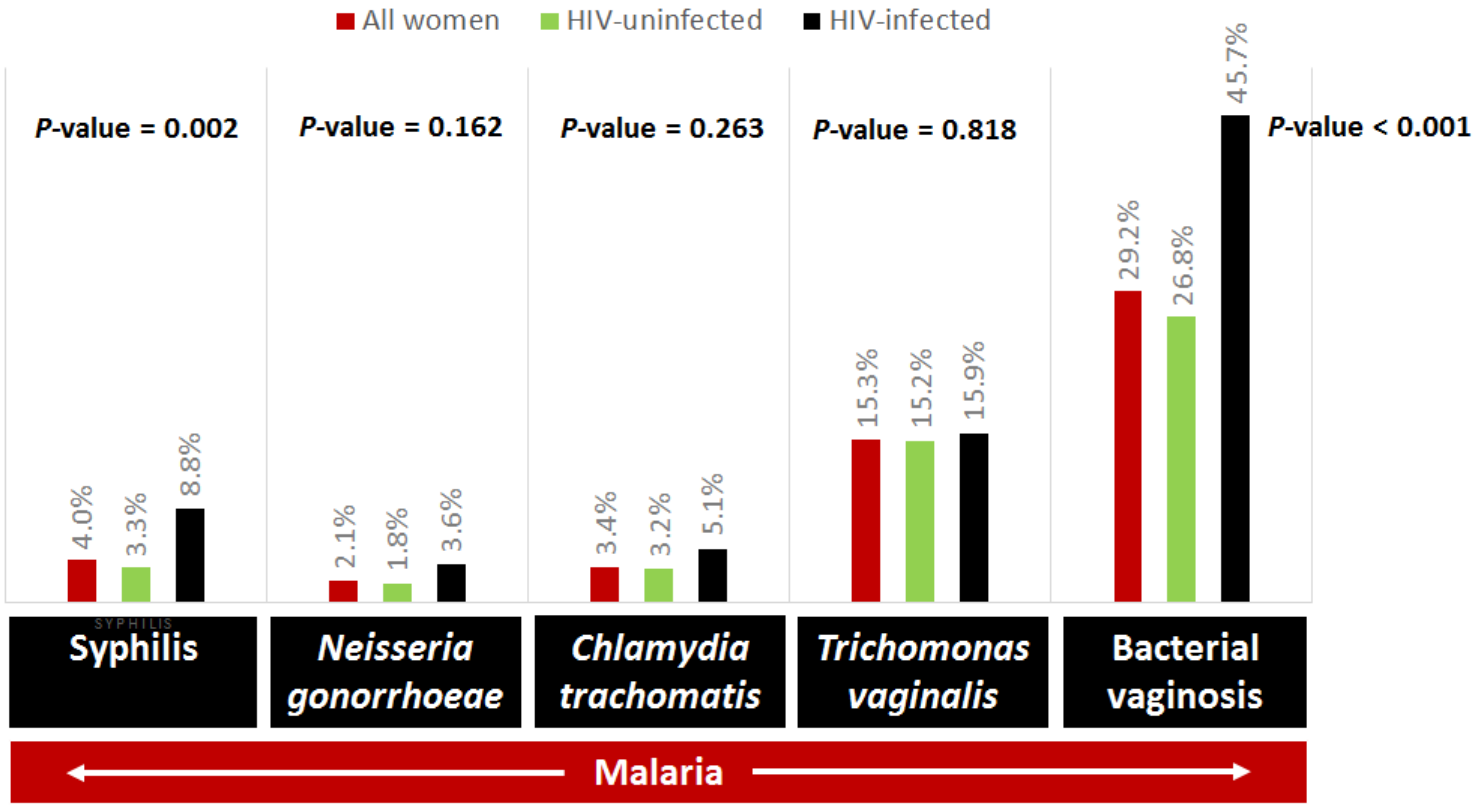


	All women	HIV-uninfected	HIV-infected
No infection	16.5% (±2.2%)	18.1% (±2.5%)	5.8% (±3.9%)
Malaria only	18.9 (±2.3%)	19.5% (±2.5%)	14.5% (5.8%)
STIs/RTIs only	26.0% (±2.6%)	25.4% (±2.8%)	29.7% (±7.5%)
Co-infection	38.7% (±2.9%)	37.0% (±3.1%)	50.0% (±8.2%)
	100%	100%	100%

Chaponda EB, Chico RM, Bruce J, et al. Malarial Infection and Curable Sexually Transmitted and Reproductive Tract Infections among Pregnant Women in a Rural District of Zambia. *American Journal of Tropical Medicine and Hygiene*, Volume 95, Issue 5, Nov 2016, pp. 1069-1076

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Prevalence of PCR-diagnosed malaria and individual curable STIs/RTIs among pregnant women at antenatal care facilities in Nchelenge District, Zambia (2013-14)



Chaponda EB, Chico RM, Bruce J, et al. Malarial Infection and Curable Sexually Transmitted and Reproductive Tract Infections among Pregnant Women in a Rural District of Zambia. *American Journal of Tropical Medicine and Hygiene*, Volume 95, Issue 5, Nov 2016, pp. 1069-1076

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Observational cohort study of IPTp-SP: malaria and curable STIs/RTIs

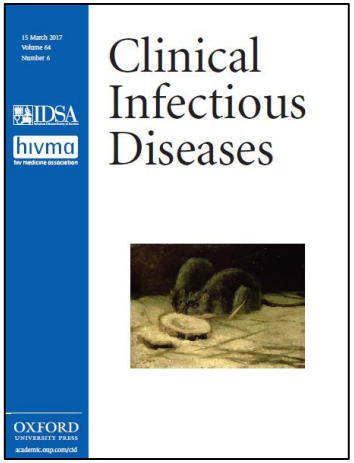
Clinical Infectious Diseases

MAJOR ARTICLE

Sulfadoxine-Pyrimethamine Exhibits Dose-Response Protection Against Adverse Birth Outcomes Related to Sexually Transmitted and Reproductive Tract Infections

R. Matthew Chico,[1] Enesia Banda Chaponda,[1,2] Cono Ariti,[3] and Daniel Chandramohan[1]

[1]Department of Disease Control, London School of Hygiene & Tropical Medicine, United Kingdom; [2]Department of Biological Sciences, University of Zambia, Lusaka; and [3]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, United Kingdom



Chico RM, Chaponda EB, Ariti C, Chandramohan D, Sulfadoxine-pyrimethamine exhibits dose-response protection against sexually transmitted and reproductive tract infections and related adverse birth outcomes. *Clinical Infectious Diseases*; 3 March 2017.

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Adverse birth outcomes by exposure to 0-1 dose vs 2 vs ≥ 3 doses

Birth outcome	No. women	Outcomes	Unadjusted OR	95% CI	Adjusted OR[1]	95% CI	*P*-value
Any adverse outcome							
0-1 dose	126	58	1.00		1.00		**0.002**
2 doses	310	108	0.63	0.41, 0.96	0.55	**0.36, 0.86**	
≥ 3 doses	280	84	0.50	0.33, 0.78	0.43	**0.27, 0.68**	
Stillbirth							
0-1 dose	126	4	1.00		1.00		0.143
2 doses	310	2	0.20	0.04, 1.10	0.21	0.04, 1.19	
≥ 3 doses	280	6	0.67	0.19, 2.41	0.68	0.18, 2.57	
Low birthweight							
0-1 dose	126	32	1.00		1.00		0.261
2 doses	310	67	0.80	0.49, 1.30	0.71	0.42, 1.19	
> 3 doses	280	57	0.74	0.45, 1.22	0.64	0.37, 1.09	
Preterm delivery							
0-1 dose	126	50	1.00		1.00		**<0.001**
2 doses	310	71	0.45	0.29, 0.71	0.42	**0.27, 0.67**	
≥ 3 doses	280	37	0.23	0.14, 0.38	0.21	**0.13, 0.35**	
Intrauterine growth retardation							
0-1 dose	126	7	1.00		1.00		0.318
2 doses	310	34	1.64	0.70, 3.87	1.55	0.64, 3.77	
≥ 3 doses	280	43	2.12	0.91, 4.93	1.88	0.78, 4.54	

[1]Adjusted for sexually transmitted and reproductive tract co-infection, gravidae and HIV infection
[2]*P*-value for likelihood ratio test

Categories of maternal infection and exposure to doses 0 – 1 versus ≥ 2 doses of IPTp-SP among women with adverse birth outcomes

Adverse birth outcomes *Categories of maternal infection*	0-1 dose IPTp-SP		≥ 2 doses IPTp-SP		Crude OR	95% CI	Adjusted OR[1]	95% CI
	No. women	No. outcomes	No. women	No. outcomes				
Any adverse outcome								
Malaria only	20	13	129	41	0.25	0.09, 0.88	**0.24**	**0.09, 0.66**
Malaria and NG and/or CT	3	1	27	11	1.38	0.11, 17.09	1.17	0.09, 15.89
Malaria and TV and/or BV	38	15	182	67	0.89	0.44, 1.83	0.96	0.45, 2.02
Syphilis and any other infection(s)	1	1	17	7	0.80	0.00, 31.20	0.80	0.00, 31.20
NG and/or CT only	6	4	14	2	0.08	0.01, 0.80	**0.08**	**0.01, 0.64**
TV and/or BV only	32	12	124	42	0.85	0.38, 1.91	0.72	0.32, 1.65
No identified infection	26	12	97	22	0.34	0.14, 0.85	**0.27**	**0.11, 0.68**
Low birthweight								
Malaria only	20	6	129	25	0.56	0.20, 1.60	0.59	0.19, 1.82
Malaria and NG and/or CT	3	1	27	7	0.7	0.05, 8.97	0.49	0.03, 7.35
Malaria and TV and/or BV	38	10	182	46	0.95	0.43, 2.10	1.08	0.46, 2.54
Syphilis and any other infection(s)	1	0	17	5	NA	NA	NA	NA
NG and/or CT only	6	2	14	1	0.15	0.01, 2.18	0.12	0.01, 1.90
TV and/or BV only	32	5	124	27	1.5	0.53, 4.27	1.22	0.41, 3.59
No identified infection	26	8	97	13	0.35	0.13, 0.96	**0.24**	**0.08, 0.68**

[1]Adjusted for sexually transmitted and reproductive tract co-infection, gravidae and HIV infection

Categories of maternal infection and exposure to doses 0 – 1 versus ≥ 2 doses of IPTp-SP among women with adverse birth outcomes

Adverse birth outcomes *Categories of maternal infection*	0-1 dose IPTp-SP		≥ 2 doses IPTp-SP		Crude OR	95% CI	Adjusted OR[1]	95% CI
	No. outcomes	No. women	No. outcomes	No. outcomes				
Preterm delivery								
Malaria only	20	10	129	21	0.19	0.07, 0.53	0.19	0.07, 0.53
Malaria and NG and/or CT	3	0	27	6	NA	NA	NA	NA
Malaria and TV and/or BV	38	14	182	37	0.44	0.21, 0.93	0.45	0.21, 0.97
Syphilis and any other infection(s)	1	1	17	5	0.50	0.00, 19.50	0.50	0.00, 19.50
NG and/or CT only	6	4	14	2	0.08	0.01, 0.80	0.07	0.01, 0.73
TV and/or BV only	32	11	124	25	0.48	0.21, 1.13	0.43	0.18, 1.03
No identified infection	26	10	97	12	0.23	0.08, 0.61	0.20	0.07, 0.54

[1]Adjusted for sexually transmitted and reproductive tract co-infection, gravidae and HIV infection

Categories of maternal infection and exposure to 2 doses versus ≥ 3 doses of IPTp-SP among women with adverse birth outcomes

Adverse birth outcomes *Categories of maternal infection*	2 doses IPTp-SP		≥ 3 doses IPTp-SP		Crude OR	95% CI	Adjusted OR[1]	95% CI
	No. outcomes	No. women	No. outcomes	No. outcomes				
Preterm delivery								
Malaria only	66	13	63	8	0.59	0.23, 1.55	0.59	0.22, 1.54
Malaria and NG and/or CT	18	4	9	2	1.00	0.15, 6.85	0.83	0.12, 5.82
Malaria and TV and/or BV	86	25	96	12	0.34	0.16, 0.74	0.33	0.15, 0.73
Syphilis and any other infection(s)	7	3	10	2	0.33	0.04, 2.87	0.23	0.03, 2.06
NG and/or CT only	12	1	2	1	11	0.35, 345.06	14.4	0.45, 463.93
TV and/or BV only	71	19	53	6	0.35	0.13, 0.95	0.34	0.13, 0.94
No identified infection	50	6	47	6	1.07	0.32, 3.59	1.19	0.35, 4.03

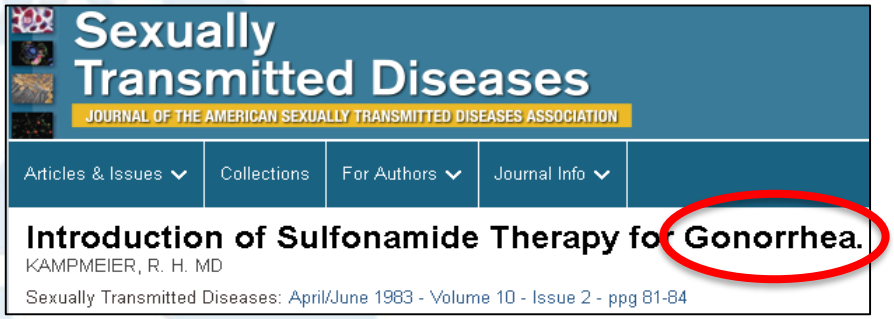
[1]Adjusted for sexually transmitted and reproductive tract co-infection, gravidae and HIV infection

Why might this be?

- Sulphadoxine is derived from sulphonamide, the world's first mass produced antibiotic that was first synthesised in the 1930s.

- Sulphonamides have been used for decades to treat curable STIs/RTIs

Sulphonamide and STIs/RTIs


Sexually Transmitted Diseases

JOURNAL OF THE AMERICAN SEXUALLY TRANSMITTED DISEASES ASSOCIATION

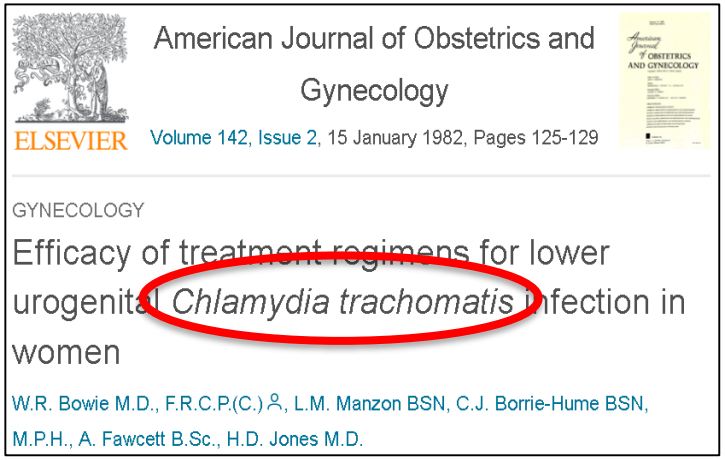
Articles & Issues | Collections | For Authors | Journal Info

Introduction of Sulfonamide Therapy for Gonorrhea.

KAMPMEIER, R. H. MD

Sexually Transmitted Diseases: April/June 1983 - Volume 10 - Issue 2 - ppg 81-84

Sulphonamide curative of *N. gonorrhoea*


American Journal of Obstetrics and Gynecology

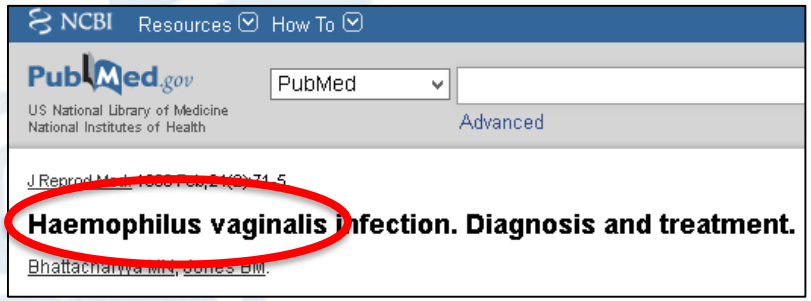
ELSEVIER Volume 142, Issue 2, 15 January 1982, Pages 125-129

GYNECOLOGY

Efficacy of treatment regimens for lower urogenital *Chlamydia trachomatis* infection in women

W.R. Bowie M.D., F.R.C.P.(C.), L.M. Manzon BSN, C.J. Borrie-Hume BSN, M.P.H., A. Fawcett B.Sc., H.D. Jones M.D.

Sulphisoxazole curative of *C. trachomatis*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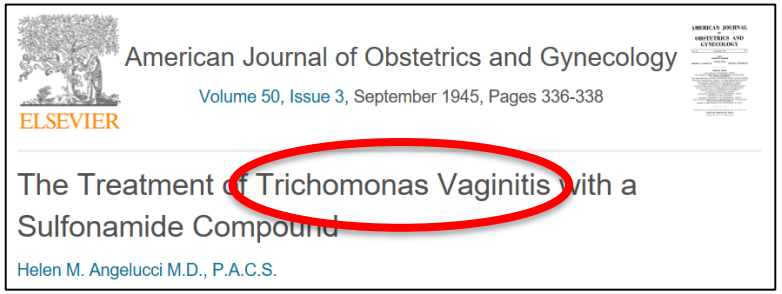
PubMed Advanced

J Reprod Med. 1988 Feb;2(2):74-5.

Haemophilus vaginalis infection. Diagnosis and treatment.

Bhattacharyya MH, Jones BM.

Sulphonamide curative of *Gardnerella vaginalis* (common BV-associated bacteria)


American Journal of Obstetrics and Gynecology

ELSEVIER Volume 50, Issue 3, September 1945, Pages 336-338

The Treatment of Trichomonas Vaginitis with a Sulfonamide Compound

Helen M. Angelucci M.D., P.A.C.S.

Sulphonamide curative of *T. vaginalis*

Is SP curing these STIs/RTIs?

Probably not, but…

- SP may reduce the bacterial and parasitic load of amongst women with curable STIs/RTIs
- SP may reduce the inflammatory response of amongst women with curable STIs/RTIs. Maternal inflammation can trigger a 'fight or flight' response and preterm birth

What does this mean?

The Zambia study may help to explain:

1. Why there is no transmission intensity below which IPTp-SP is no longer protective against low birthweight

2. Why IPTp-SP has been superior to IPTp-DP against low birth weight and preterm birth

Implications

- Despite these encouraging findings, candidate replacements for IPTp-SP are needed for many reasons. The intervention remains sub-optimal for against malaria endpoints when compared to more potent antimalarial therapies.

- Candidate replacements for IPTp-SP should offer superior protection against malaria AND curable STIs/RTIs.

Azithromycin as a partner drug

EXPERT REVIEWS

On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections

Expert Rev. Anti Infect. Ther. 11(12), 1303–1332 (2013)

R Matthew Chico*[1], Berkin B Hack[2], Melanie J Newport[2], Enesia Ngulube[1] and Daniel Chandramohan[1]

[1]*London School of Hygiene and Tropical Medicine Keppel Street, London, WC1E 7HT, UK*
[2]*Brighton and Sussex Medical School, Brighton, East Sussex, BN1 9PX, UK*
**Author for correspondence:*
Tel.: +44 20 7636 8636 ext. 2841
Fax: +44 207 927 2918
matthew.chico@lshtm.ac.uk

The WHO recommends the administration of sulfadoxine-pyrimethamine (SP) to all pregnant women living in areas of moderate (stable) to high malaria transmission during scheduled antenatal visits, beginning in the second trimester and continuing to delivery. Malaria parasites have lost sensitivity to SP in many endemic areas, prompting the investigation of alternatives that include azithromycin-based combination (ABC) therapies. Use of ABC therapies may also confer protection against curable sexually transmitted infections and reproductive tract infections (STIs/RTIs). The magnitude of protection at the population level would depend on the efficacy of the azithromycin-based regimen used and the underlying prevalence of curable STIs/RTIs among pregnant women who receive preventive treatment. This systematic review summarizes the efficacy data of azithromycin against curable STIs/RTIs.

Keywords: azithromycin • bacterial vaginosis • Chlamydia • gonorrhea • malaria • pregnancy • reproductive tract infections • sexually transmitted infections • sub-Saharan Africa • syphilis • trichomoniasis

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Review of Anti-infective Therapy.* 2013; Volume 11, Issue 12, pp. 303-1332.

Azithromycin dosing

Azithromycin has been used safely in all trimesters of pregnancy against curable STIs.

STIs/RTIs	Dose
Syphilis	1 and 2 grams (curative)
Gonorrhoea	1 and 2 grams (curative)
Chlamydia	1 gram (curative)
Trichomoniasis	1 gram (partially preventive)
Bacterial vaginosis	Unknown

Azithromycin as a partner drug in pregnancy

Country [ref]	Site	Gravidae	IPTp (standard)		IPTp monthly		IPTp monthly + AZ x 2	
			LBW	Preterm	LBW	Preterm	LBW	Preterm
Malawi [109]	Mangochi	0 previous pregnancies	12.9% 52/402	30.0% 33/110	9.1% 36/394	18.7% 20/107	7.9% 32/406	14.6% 13/89
		1 previous pregnancy		17.4% 15/86		24.4% 19/78		18.8% 15/80
		2 previous pregnancies		12.6% 30/239		11.3% 29/256		8.9% 24/271
		All gravidae		17.9% 78/435		15.4% 68/441		11.88% 52/440
Malawi [110]	Southern	All gravidae	2.99 kg (n=769)	17.4% 189/1,087	-	-	3.03 kg (n=739)	16.8% 184/1,096

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Azithromycin as a partner drug in pregnancy

Country [ref]	Site	Gravidae	IPTp (standard)		IPTp monthly + AZ x 2		AZ+CQ	
			LBW	Preterm	LBW	Preterm	LBW	Preterm
Papua New Guinea [114]	Madang Province	All gravidae	17.4%[2] 175/1,008		12.8% 130/1,013	RR = 0.62 95% CI: 0.43,0.89, *P* = 0.010		
Pfizer [118]	Multicentre	All gravidae	5.7% 68/1188	3.7% 45/1211			5.0% 57/1138	4.0% 47/1164

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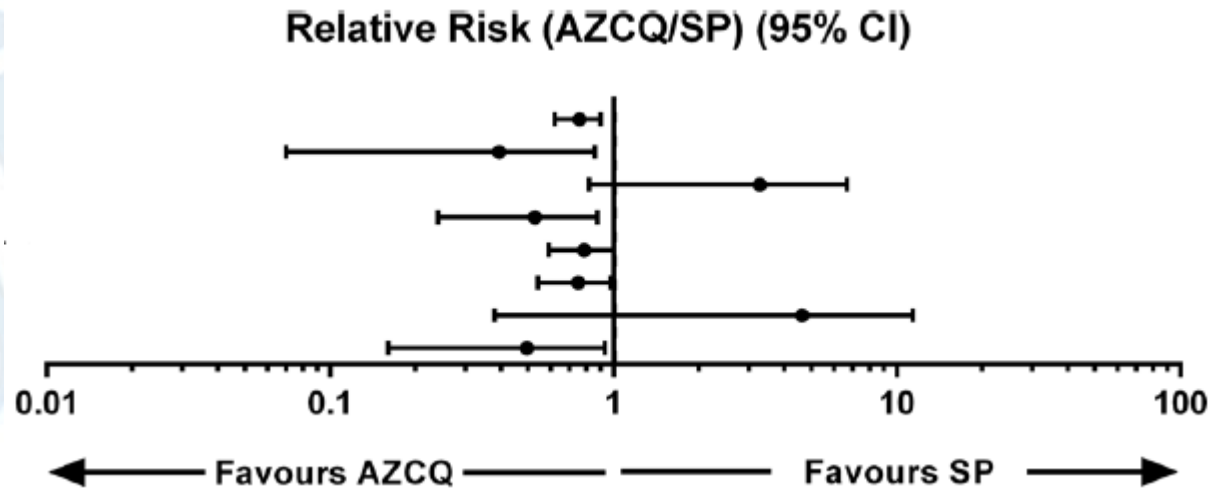
Azithromycin as a partner drug in pregnancy

Key Secondary Outcomes	ACZQ n/N (%)	SP n/N (%)
STI between first dose and week 36 to 38 of gestation*	178/1445 (12.3%)	238/1445 (16.5%)
Neisseria gonorrhoeae infection	3/746 (0.4%)	13/794 (1.6%)
Chlamydia trachomatis infection	11/746 (1.5%)	5/794 (0.6%)
Treponema pallidum infection	7/751 (0.9%)	16/797 (2.0%)
Trichomonas vaginalis infection	88/1068 (8.2%)	122/1143 (10.7%)
Bacterial vaginosis	64/746 (8.6%)	94/794 (11.8%)
Ophthalmia neonatorum	4/1140 (0.4%)	2/1190 (0.2%)
Pneumonia and other lower respiratory tract infections†	7/1445 (0.5%)	18/1445 (1.3%)



Kimani et al. PLOS One 2016

Azithromycin as a partner drug in pregnancy

IPTp-DP plus azithromycin may be superior to IPTp-SP because:

- DP is more potent against malaria infections compared to SP
- azithromycin is likely more curative of bacterial infections compared to sulphadoxine

Conclusions

- IPTp-SP continues to be an essential ANC intervention and is protective against adverse birth outcomes attributable to malaria and curable STIs/RTIs

- Candidate replacements for IPTp-SP will likely need to offer superior protection against malaria AND curable STIs/RTIs.

- Azithromycin may be a suitable partner drug alongside DP with caveats related to drug resistance and cardio-safety.

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Characteristics at enrolment: 0-1 dose versus ≥ 2 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	0-1 dose (n = 126)		≥ 2 doses(n = 590)		
Age of participants					0.498
Mean (SD)	25.8	(6.5)	25.4	(6.4)	
Median (IQR)	24.0	(20.0, 31.0)	24.0	(20.0, 30.0)	
Marital status					0.175
Single	19	(15.1)	123	(20.8)	
Married, divorced/separated or widowed	107	(84.9)	467	(79.2)	
Age at sexual debut					0.733
< 15 years of age	13	(10.3)	49	(8.3)	
≥ 15 years of age	96	(76.2)	455	(77.1)	
Unknown	17	(13.5)	86	(14.6)	
Number of lifetime sexual partners					0.362
1 partner	52	(41.3)	272	(46.6)	
2 partners	45	(35.7)	161	(27.6)	
3 partners	18	(14.3)	94	(16.1)	
4 or more partners	11	(8.7)	57	(9.8)	
Gravidae					0.301
Primigravidae	27	(21.4)	165	(28.0)	
Secundigravidae	19	(15.1)	77	(13.1)	
Multigravidae	80	(63.5)	348	(59.0)	

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at enrolment: 0-1 dose versus ≥ 2 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	0-1 dose (n = 126)		≥ 2 doses(n = 590)		
Wealth Quintiles					0.048
Lowest	21	(16.7)	115	(19.5)	
Second	32	(25.4)	111	(18.8)	
Middle	31	(24.6)	113	(19.2)	
Fourth	14	(11.1)	122	(20.7)	
Highest	28	(22.2)	129	(21.9)	
Bed net ownership					0.493
No	68	(54.0)	297	(50.3)	
Yes	58	(46.0)	293	(49.7)	
Used insecticide treated net on previous night					0.840
No	77	(61.1)	366	(62.4)	
Yes	49	(38.9)	221	(37.6)	
Missing	0		3		
Indoor residual spraying in the previous 12 months					0.186
No	103	(83.1)	439	(77.6)	
Yes	21	(16.9)	127	(22.4)	
Missing	2		24		

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at enrolment: 0-1 dose versus ≥ 2 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	0-1 dose (n = 126)		≥ 2 doses(n = 590)		
Experienced miscarriage before					0.869
No	86	(86.9)	371	(87.3)	
Yes	13	(13.1)	54	(12.7)	
None reported by primigravidae	27		165		
Delivered a premature baby before					1.000
No	94	(94.9)	401	(94.4)	
Yes	5	(5.1)	24	(5.6)	
Not applicable to primigravidae	27		165		
Delivered a stillborn before					0.307
No	94	(94.9)	387	(91.1)	
Yes	5	(5.1)	38	(8.9)	
Not applicable to primigravidae	27		165		
HIV status					0.186
Negative	105	(83.3)	519	(88.0)	
Positive	21	(16.7)	71	(12.0)	
Malaria and curable STIs/RTIs					
Malaria (PCR diagnosis)	62	(49.2)	346	(59.3)	0.047
Syphilis (high titre)	1	(0.8)	17	(2.9)	0.223
Neisseria gonorrhoeae	1	(0.8)	21	(3.6)	0.152
Chlamydia trachomatis	8	(6.3)	26	(4.4)	0.357
Trichomonas vaginalis	30	(23.8)	140	(23.7)	1.000
Bacterial vaginosis	59	(46.8)	277	(46.9)	1.000

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at delivery: 0-1 dose versus ≥ 2 doses

Characteristics at delivery	Doses of SP received – number (%)				*P*-value
	0 - 1 dose (n = 126)		≥ 2 doses (n = 590)		
Place of delivery					0.233
Hospital	119	(94.4)	551	(93.4)	
Clinic	1	(0.8)	19	(3.2)	
Home	6	(4.8)	20	(3.4)	
Delivery performed by					0.240
Doctor	3	(2.4)	38	(6.4)	
Midwife	115	(91.3)	524	(88.8)	
Family member	5	(4.0)	17	(2.9)	
Other	3	(2.4)	11	(1.9)	
Type of labour					0.296
Spontaneous	126	(100.0)	558	(97.4)	
Induced	0	(0.0)	9	(1.6)	
Augmented	0	(0.0)	6	(1.0)	
Type of delivery					0.092
Vaginal	123	(97.6)	551	(93.4)	
C-section	3	(2.4)	39	(6.6)	




Characteristics at delivery: 0-1 dose versus ≥ 2 doses

Characteristics at delivery	Doses of SP received – number (%)				*P*-value
	0 - 1 dose (n = 126)		≥ 2 doses (n = 590)		
Hypertension					0.296
No	110	(96.5)	506	(98.1)	
Yes	4	(3.5)	10	(1.9)	
Maternal haemoglobin					0.786
Normal	103	(85.1)	470	(83.5)	
Anaemic	18	(14.9)	93	(16.5)	
Sex of baby					0.008
Female	78	(61.9)	287	(48.6)	
Male	48	(38.1)	303	(51.4)	
Received curative treatment for malaria infection					0.102
No	115	(92.0)	508	(86.4)	
Yes	10	(8.0)	80	(13.6)	
Received curative treatment for any STI/RTI					1.000
Untreated	116	(92.1)	540	(91.5)	
Treated	10	(7.9)	50	(8.5)	





Characteristics at enrolment: 2 doses versus ≥ 3 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	2 doses (n = 310)		≥ 3 doses (n = 280)		
Age of participants					0.521
Mean (SD)*	25.6	(6.4)	25.2	(6.4)	
Median (IQR)*	25.0	(20.0, 30.0)	24.0	(20.0, 30.0)	
Marital status					0.479
Single	61	(19.7)	62	(22.1)	
Married, divorced/separated or widowed	249	(80.3)	218	(77.9)	
Age at sexual debut					0.328
< 15 years of age	21	(6.8)	28	(10.0)	
≥ 15 years of age	241	(77.7)	214	(76.4)	
Unknown	48	(15.5)	38	(13.6)	
Number of lifetime sexual partners					0.460
1 partner	150	(49.0)	122	(43.9)	
2 partners	83	(27.1)	78	(28.1)	
3 partners	48	(15.7)	46	(16.5)	
4 or more partners	25	(8.2)	32	(11.5)	
Gravidae					0.936
Primigravidae	86	(27.7)	79	(28.2)	
Secundigravidae	42	(13.5)	35	(12.5)	
Multigravidae	182	(58.7)	166	(59.3)	
Wealth Quintiles					0.379
Lowest	68	(21.9)	47	(16.8)	
Second	58	(18.7)	53	(18.9)	
Middle	59	(19.0)	54	(19.3)	
Fourth	56	(18.1)	66	(23.6)	
Highest	69	(22.3)	60	(21.4)	

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at enrolment: 2 doses versus ≥ 3 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	2 doses (n = 310)		≥ 3 doses (n = 280)		
Bed net ownership					0.564
No	160	(51.6)	137	(48.9)	
Yes	150	(48.4)	143	(51.1)	
Used insecticide treated net on previous night					0.932
No	193	(62.7)	173	(62.0)	
Yes	115	(37.3)	106	(38.0)	
Missing	2		1		
Indoor residual spraying in the previous 12 months					0.002
No	247	(82.9)	192	(71.6)	
Yes	51	(17.1)	76	(28.4)	
Missing	12		12		
Experienced miscarriage before					0.470
No	193	(86.2)	178	(88.6)	
Yes	31	(13.8)	23	(11.4)	
None reported by primigravidae	86		79		
Delivered a premature baby before					0.297
No	214	(95.5)	187	(93.0)	
Yes	10	(4.5)	14	(7.0)	
Not applicable to primigravidae	86		79		





P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at enrolment: 2 doses versus ≥ 3 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	2 doses (n = 310)		≥ 3 doses (n = 280)		
Delivered a stillborn before					0.737
No	205	(91.5)	182	(90.5)	
Yes	19	(8.5)	19	(9.5)	
Not applicable to primigravidae	86		79		
HIV status					0.528
Negative	270	(87.1)	249	(88.9)	
Positive	40	(12.9)	31	(11.1)	
Malaria and curable STIs/RTIs					
Malaria (PCR diagnosis)	171	(56.1)	175	(62.9)	0.092
Syphilis (high titre)	7	(2.3)	10	(3.6)	0.462
Neisseria gonorrhoeae	15	(4.8)	6	(2.1)	0.117
Chlamydia trachomatis	16	(5.2)	10	(3.6)	0.423
Trichomonas vaginalis	73	(23.5)	67	(23.9)	0.923
Bacterial vaginosis	145	(46.8)	132	(47.1)	0.934

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at delivery: 2 doses versus ≥ 3 doses

Characteristics at delivery	Doses of SP received – number (%) 0 - 1 dose (n = 126)		≥ 2 doses (n = 590)		*P*-value
Place of delivery					0.233
Hospital	119	(94.4)	551	(93.4)	
Clinic	1	(0.8)	19	(3.2)	
Home	6	(4.8)	20	(3.4)	
Delivery performed by					0.240
Doctor	3	(2.4)	38	(6.4)	
Midwife	115	(91.3)	524	(88.8)	
Family member	5	(4.0)	17	(2.9)	
Other	3	(2.4)	11	(1.9)	
Type of labour					0.296
Spontaneous	126	(100.0)	558	(97.4)	
Induced	0	(0.0)	9	(1.6)	
Augmented	0	(0.0)	6	(1.0)	
Type of delivery					0.092
Vaginal	123	(97.6)	551	(93.4)	
C-section	3	(2.4)	39	(6.6)	

P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Characteristics at delivery: 2 doses versus ≥ 3 doses

Characteristics at enrolment	Doses of SP received – number (%)				*P*-value
	2 doses (n = 310)		≥ 3 doses (n = 280)		
Hypertension					0.198
No	276	(98.9)	230	(97.0)	
Yes	3	(1.1)	7	(3.0)	
Maternal haemoglobin					0.429
Normal	249	(84.7)	221	(82.2)	
Anaemic	45	(15.3)	48	(17.8)	
Sex of baby					1.000
Female	151	(48.7)	136	(48.6)	
Male	159	(51.3)	144	(51.4)	
Received curative treatment for malaria infection					0.810
No	269	(86.8)	239	(86.0)	
Yes	41	(13.2)	39	(14.0)	
Received curative treatment for any STI/RTI					0.038
Untreated	291	(93.9)	249	(88.9)	
Treated	19	(6.1)	31	(11.1)	

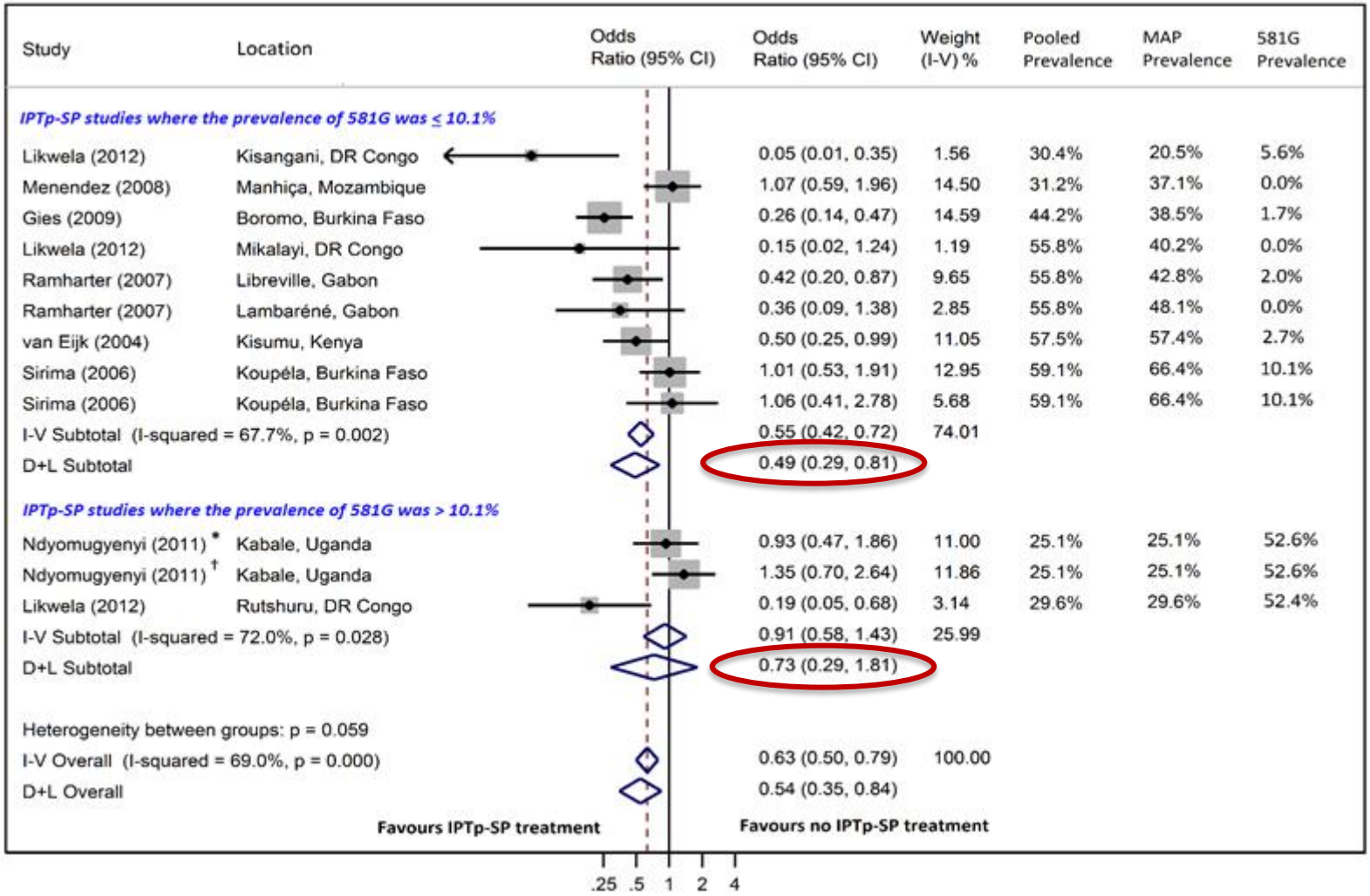




P-values are from Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Drug resistance and SP

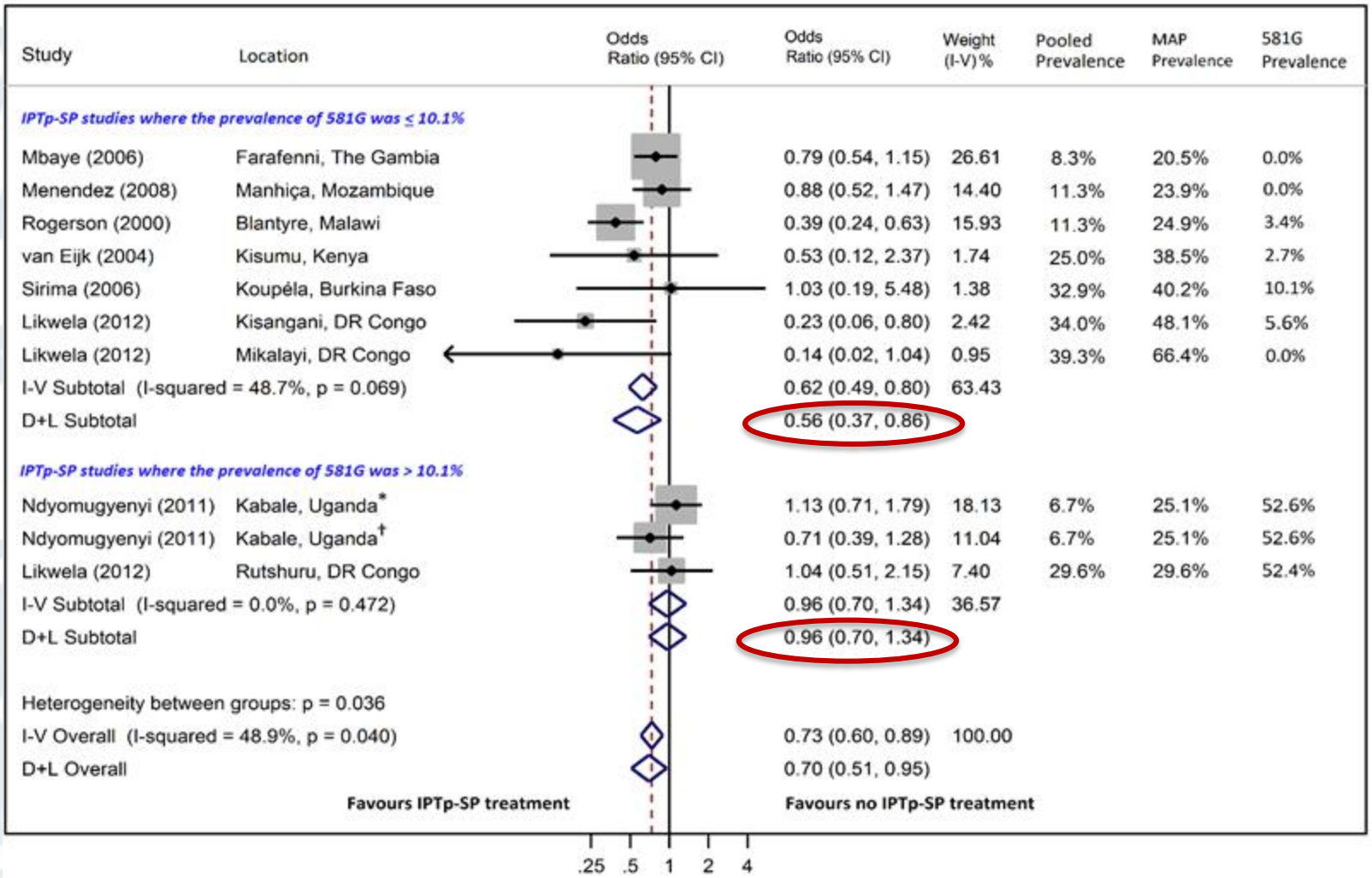
Odds ratio of LBW among **paucigravidae** following two or more doses of IPTp-SP vs. placebo or no IPTp-SP stratified by low and high prevalence estimates of the 581G resistance mutation



Chico RM, Cano J, Ariti C, Collier TJ, Chandramohan D, Roper C, Greenwood B. (2015). **Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and meta-analysis**. *Trop Med Int Health*, 20(12), 1621-1633. doi: 10.1111/tmi.1259

Drug resistance and SP

Odds ratio of LBW among **multigravidae** following two or more doses of IPTp-SP vs. placebo or no IPTp-SP stratified by low and high prevalence estimates of the 581G resistance mutation



Chico RM, Cano J, Ariti C, Collier TJ, Chandramohan D, Roper C, Greenwood B. (2015). **Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and meta-analysis**. *Trop Med Int Health*, 20(12), 1621-1633. doi: 10.1111/tmi.1259