Reducing low birth weight by adding two doses of azithromycin to the intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine: a randomized controlled trial in Burkina Faso

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Background

- Low birth weight (LBW) = birth weight <2500g [1]
- Predictor of neonatal mortality (> 80% of 1 million death/ year in Africa) (Lawn et al., 2014)[2]
- High prevalence in Burkina Faso > 10% birth
- Malaria in pregnancy (MiP) & sexually transmitted infections (STIs) > 50% of adverse birth outcomes (ABO) such as LBW in endemic countries
- For Malaria WHO recommended IPTp-SP
- STIs: Syndromic diagnosis & antibiotic treatment
- Particularity: STIs in pregnancy asymptomatic++
- Consequences: Misdiagnosis & missed treatment
- **Opportunity**: Azithromycin (AZ) an azalide macrolide is effective on major STIs and was proven effective as alternative to SP for IPTp
- **Combination:** Probable double benefit of preventing malaria and STIs effects on ABO

Hypothesis

A systematic treatment of curable bacterial STIs & malaria in pregnancy with SP- AZ could reduce the risk of LBW in the rural area of Burkina Faso

Methods

- 2-parallel-arms, open-label Randomized Controlled Trial (RCT)
- Pregnant women (≤ 24 gestational weeks) in BFA , inform consent
- **Control arm:** Monthly SP from the 13th weeks of pregnancy (1,500/75 mg) (IPTp-SP)
- **Intervention:** azithromycin (1 g daily for 2 days) in the second and third trimester plus monthly IPTp-SP (1,500/75 mg) (SP-AZ)
- **Sample size**: 80% power to detect an effect to reduce of LBW from 10% to 5%, allowing for a 10% loss to follow-up, with a two-sided 95% confidence level, 960 pregnant women included.
- **Follow-up:** Monthly until 28 days after delivery
- **Main Outcome:** LBW measured with calibrated electronic scales with 10 grams resolution & a precision of 5 g
- **Secondary outcomes**: Stillbirth, preterm, miscarriage, and safety

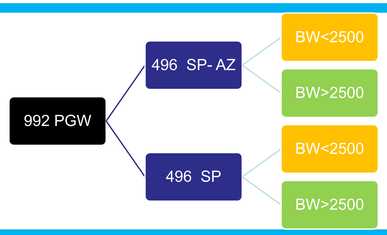


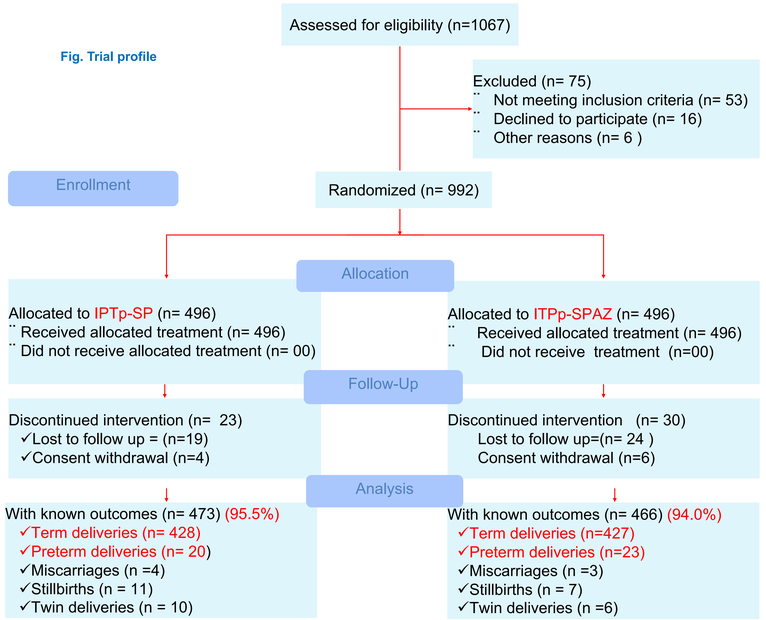
Fig . *Treatment allocation*

Results

Table 1. Baseline characteristics of study participants (n = 992)

Characteristics (statistics)	SP-arm (N = 496)		SPAZ-arm (N=496)	
Age in years ,(mean, sd)	25.2	5.7	25.6	5.7
Height in cm, (mean, sd)	162.3	5.9	163.0	5.8
Fundal height in cm, (mean, sd)	20.4	2.4	20.5	2.2
Gestational age in weeks, (mean, sd)	22.4	2.0	22.4	2.0
Hemoglobin at inclusion in g/dL, (mean, sd)	10.5	1.4	10.5	1.3
Proportion of anemia (Hb<11 g/dL) (n, %)	215	59.4	219	60.2
Number of pregnancies (n, %)				
Primigravidae (1)	149	30.0	143	28.8
Secundigravidae (2)	121	24.4	103	20.8
Multigravida (≥ 3)	226	45.6	250	50.4
Bed net use the night prior enrolment (n, %)	406	81.9	383	77.2
Proportion with parasitemia at inclusion (n, %)	84	17.4	70	14.6
Women with income-generating activities (n, %)	98	19.8	82	16.6
Maternal history of miscarriage /stillbirth (n, %)	80	16.1	77	15.5
IPTp-SP uptake before enrolment (n, %)	40	8.1	28	5.6

Fig. Trial profile



Intervention coverage

- Median SP doses = 4 [IQR:3-5]
- 95% received ≥ 3 doses of SP in each group
- Interveniton goup: 93.3% received 4 g AZI

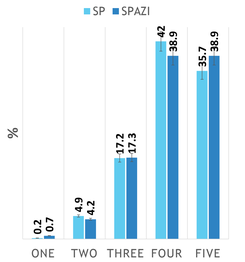


Fig. Number of SP doses received by PGW

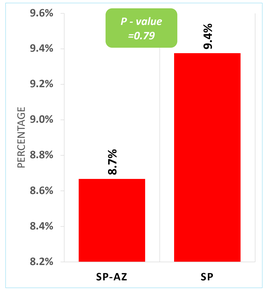


Fig. Proportion of low birth weight according to treatment arm,

Table 2. Preterm birth, miscarriage, & stillbirth by treatment arm

Birth outcomes	Intervention arm SPAZ % (n/N)	Control arm SP % (n/N)	RR [95% CI]
Preterm birth	5% (23/460)	4.3% (20 /463)	1.16 [0.64 - 2.08]
Miscarriage	0.7% (3/460))	0.9% (4/463)	0.75 [0.17 - 3.35]
Stillbirth	1.5% (7/460)	2.4% (11/463)	0.64 [0.25 - 1.64]

Table 3. Safety profile of the study

	Intervention arm SPAZ (N=496)	Control arm SP (N=496)	
Adverse events	N (%)	N (%)	P-
Total events reported	152 (30.6)	176 (35.5)	0.12
Serious AEs	**67 (13.5)**	**83 (16.7)**	**0.18**
Non-serious AEs	85 (17.1)	93 (18.8)	0.56
Serious events			
Eclampsia	2 (0.4)	1 (0.2)	0.47
Severe malaria	10 (2.0)	14 (2.8)	0.41
Neonatal death	5 (1.0)	4 (0.8)	0.73
Premature rupture of membrane	3 (0.6)	6 (1.6)	0.13

Conclusions

- Results from this study support the hypothesis that monthly SP can reduce low birth weight in Burkina Faso
- Azithromycin adjunction to monthly SP did not greatly improve the effect of the IPTp regimen in reducing LBW, and given the risk of azithromycin antimicrobial resistance, the yielded benefits were not enough to recommend AZI use in routine for the prevention of LBW
- Other association of sulfadoxine-pyrimethamine plus an alternative effective drug may be considered

References

1. Cutland CL, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017 Dec 4;35:6492-6500.

2. Lawn JE, et al : Every Newborn: progress, priorities, and potential beyond survival. Lancet. 2014 Jul 12;384:189-205.

3.Valia, D. et al,. Use of WATCH antibiotics prior to presentation to the hospital in rural Burkina Faso. Antimicrob Resist Infect Control 11, 59 (2022).

PGW: pregnant women, **SP:** sulfadoxine-pyrimethmine, **AZ**: azitromycin, **RR**: risk-ratio, **LBW**: low birth weight, **BW**: birth weight, **sd**: standard deviation, **%:** percentage