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Effectiveness of Intermittent Screening and Treatment of Malaria in Pregnancy on Maternal and Birth Outcomes in Selected Districts in Rwanda: A Cluster Randomized Controlled Trial

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention (CDC) or the US Agency for International Development (USAID).

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Abstract

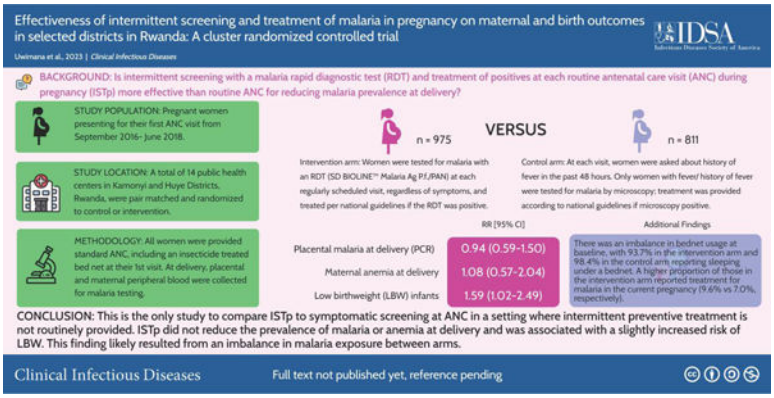
Background.—Malaria during pregnancy can cause serious consequences including maternal anemia and low birthweight (LBW). Routine antenatal care (ANC) in Rwanda includes malaria symptom screening at each ANC visit. This cluster randomized controlled trial investigated whether adding intermittent screening with a malaria rapid diagnostic test at each routine ANC visit and treatment of positives during pregnancy (ISTp) is more effective than routine ANC for reducing malaria prevalence at delivery.

Methods.—Between September 2016 and June 2018, pregnant women initiating ANC at 14 health centers in Rwanda were enrolled into ISTp or control arms. All women received an insecticide-treated bed net at enrollment. Hemoglobin concentration, placental and peripheral parasitemia, newborn outcome, birthweight, and prematurity were assessed at delivery.

Results.—Nine hundred seventy-five women were enrolled in ISTp and 811 in the control group. Routine ANC plus ISTp did not significantly reduce polymerase chain reaction–confirmed placental malaria compared to control (adjusted relative risk [aRR], 0.94 [95% confidence interval {CI}, .59–1.50]; $P = .799$). ISTp had no impact on anemia (aRR, 1.08 [95% CI, .57–2.04]; $P = .821$). The mean birthweight of singleton newborns was not significantly different between arms (3054 g vs 3096 g, $P = .395$); however, women in the ISTp arm had a higher proportion of LBW (aRR, 1.59 [95% CI, 1.02–2.49]; $P = .042$).

Conclusions.—This is the only study to compare ISTp to symptomatic screening at ANC in a setting where intermittent preventive treatment is not routinely provided. ISTp did not reduce the prevalence of malaria or anemia at delivery and was associated with an increased risk of LBW.

Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/effectiveness-of-intermittent-screening-and-treatment-of-malaria-in-pregnancy-on-maternal-and-birth-outcomes-in-selected-districts-in-rwanda-a-cluster-randomized-controlled-trial

Keywords

intermittent screening; malaria; pregnancy; Rwanda

Malaria occurs across Rwanda (2015 incidence: 301 cases/1000 population) with greatest burden in the Eastern and Southern Provinces [1]. Malaria among pregnant women is particularly concerning. Laboratory-confirmed malaria was the leading indirect obstetric cause of severe maternal anemia (13.6% of all underlying causes) [2]. Although adults in endemic regions usually acquire immunity from past exposure, *Plasmodium* parasites bind specifically to placental chondroitin sulfate A [3], making pregnant women, especially those in their first pregnancies who have not yet developed pregnancy-specific immunity, more vulnerable to the effects of malaria. Malaria infection in pregnancy (MIP) has been associated with severe maternal anemia and placental parasitemia that can interfere with the maternal–fetal exchange of oxygen and nutrients, leading to fetal loss, prematurity, and low birthweight (LBW) infants [4–6].

To prevent malaria, Rwanda distributes insecticide-treated bed nets (ITNs) country-wide, and indoor residual spraying (IRS; spraying of interior house walls with insecticide) is implemented in 12 high-burden districts. ITN ownership and use is relatively high in Rwanda. In 2017, 84% of households owned at least 1 ITN whereas in 2019, 66% did; among households with at least 1 ITN, 82% of pregnant women reported sleeping under an ITN the previous night in both 2017 and 2019 [7, 8].

According to Rwandan national guidelines, routine antenatal care (ANC) includes provision of an ITN at first ANC visit, counseling on the importance of ITN use for malaria prevention, provision of iron–folate supplementation at each visit to combat anemia, and clinical screening for malaria (asking about history of fever in the past 48 hours) at each ANC visit. Pregnant women with fever are tested for malaria by microscopy or rapid diagnostic test (RDT) and treated according to national guidelines if test positive. Intermittent preventive treatment (IPTp)—provision of a treatment dose of sulfadoxine-pyrimethamine (SP) to asymptomatic pregnant women at each ANC visit starting in the second trimester without testing for malaria—has not been implemented in Rwanda since 2008 due to emergence of SP resistance [1, 9].

An alternative to IPTp is intermittent screening and treatment of malaria in pregnancy (ISTp), testing pregnant women with a malaria RDT at each ANC visit (regardless of symptoms) and treating if RDT positive. Previous studies have shown that ISTp was not inferior to IPTp-SP in preventing third-trimester maternal anemia, LBW, and placental malaria, but the incidence of outpatient visits and malaria episodes during pregnancy was higher with ISTp than IPTp-SP [10–14]. A recent analysis confirmed that ISTp with the current generation of RDTs should not be provided in place of IPTp [15]; however, there is currently no evidence on the effect of ISTp when compared with symptomatic management of MIP in the absence of IPTp (current practice in Rwanda).

In 2016, to explore potential strategies to address MIP in Rwanda, the Malaria and Other Parasitic Diseases Division (MOPDD) of the Rwanda Biomedical Center launched a cluster

randomized field trial to assess the impact of ISTp compared with routine care (screening for fever and testing only febrile women) on women's risk for placental and peripheral malaria at the time of delivery in 2 districts in Southern Province. This study was unique in that it examined ISTp in contrast to routine ANC in a setting that does not include IPTp-SP.

METHODS

This study was conducted from September 2016 to June 2018, in the relatively high-malaria-burden districts Kamonyi and Huye, in Southern Province, Rwanda. The incidence of confirmed malaria cases during 2018 was 499 and 414 cases per 1000 population in Kamonyi and Huye districts, respectively, ranking them 7th and 11th highest among the 30 districts in Rwanda (MOPDD, unpublished data). IRS with a carbamate insecticide was conducted in April 2017 in Huye, but not Kamonyi District, with coverage of 96.6%; residual efficacy is expected for at least 4–5 months after spraying. All public health centers in the districts (8 in Huye, 6 in Kamonyi) were included. Within each district, facilities were pair-matched based; 1 facility in each pair was randomly allocated to ISTp and the other to the control arm.

Sample size was calculated using Stata version 13 software (StataCorp, College Station, Texas) for 2-sample comparison of proportions to detect a 50% reduction in the prevalence of placental malaria between control (estimated 10% prevalence) and intervention groups (5% prevalence), accounting for clustering by facility. Assuming a statistical significance of 0.05, power ≥0.80, and intracluster correlation coefficient of 0.005, an estimated 714 women were needed per arm. Allowing for 20% loss to follow-up, 893 women per arm, a total of 1786 participants, were targeted for enrollment.

Pregnant women presenting for their first ANC visit were consecutively enrolled. Eligibility criteria included age ≥18 years, residence in the study area, willingness to have a supervised delivery, and providing signed informed consent. In control health centers, an ITN was provided and baseline hemoglobin (Hb) concentration was determined at first ANC, while clinical screening for malaria (ie, asking about history of fever in the past 48 hours) was performed at each visit. Only women reporting fever were tested (by microscopy); treatment was provided according to national guidelines if microscopy positive. At ISTp health centers, the same care was provided, except all women were tested for malaria with an RDT (SD BIOLINE Malaria Ag P.f./PAN [05FK67] RDT, Standard Diagnostics, Yongin-si, Gyeonggi-do, Korea) [16] at each regularly scheduled visit, regardless of symptoms, and treated per national guidelines if the RDT was positive (Supplementary Methods). At the time of delivery, maternal peripheral and placental blood samples were collected on filter paper for malaria testing in all facilities. Birth outcome, birthweight, and prematurity were recorded (Supplementary Methods). Peripheral blood was tested for Hb concentration (HemoCue Hb201+; HemoCue AB, Ängelholm, Sweden). Peripheral and placental dried blood spots were tested for malaria and human actin using TaqMan polymerase chain reaction (PCR) [17].

Maternal anemia was classified as any (Hb <11 g/dL) or moderate to severe (Hb <10 g/dL) [18]. Prematurity was defined as delivery <37 weeks' gestation, and LBW as <2500 g.

Analyses were done using SAS version 9.4 software (SAS Institute, Cary, North Carolina) (proc genmod) and R4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) (R package "gee") [19] accounting for facility-level clustering; *P* values <.05 were considered statistically significant. Relative risks (RRs) were derived from a log-binomial regression model, mean differences were calculated with linear regression. Study arm (based on cluster allocation), gestational age at enrollment, self-reported treatment for malaria prior to enrollment, fever during pregnancy (≥1 episode; self-reported), IRS in the 6 months prior to or during the study, age, education, marital status, human immunodeficiency virus, total ANC visits, ITN use, and district were assessed as potential covariates and retained if significant. Gravidity was included in all models given the known association with maternal malaria infection and infant outcomes [10, 12]. Models for maternal malaria were adjusted for study arm, gravidity, total ANC visits, fever during pregnancy, and IRS. Maternal anemia outcome models were adjusted for study arm, gravidity, baseline Hb level, and IRS. Infant models were adjusted for study arm, gravidity, baseline Hb level, treatment for MIP prior to enrollment, and IRS; the model for LBW was additionally adjusted for number of ANC visits. Attempted inclusion of number of ANC visits to the preterm model rendered the model unstable. The number needed to test to identify 1 positive case among afebrile women was calculated by dividing the number of cases by number of women tested.

Ethics Statement

The ethics committees at the Johns Hopkins Bloomberg School of Public Health and the Rwanda Biomedical Center approved the study. The Centers for Disease Control and Prevention (CDC) Human Research Protections Office reviewed and approved CDC participation as nonengaged. Written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (NCT03508349).

RESULTS

Overall, 1786 pregnant women were enrolled, 975 in the intervention arm (ISTp) and 811 in the control arm. Of these, 1688 (94.5%) completed the study: 94.4% in the intervention arm and 94.7% in the control arm (Figure 1). Baseline characteristics did not differ significantly between the 2 study arms, except for self-reported treatment for malaria during the current pregnancy (9.6% in the ISTp group vs 7.0% in the control group, $P < .001$) and bed net utilization the night before the first ANC visit (93.7% and 98.4% for ISTp and control, respectively, $P < .001$; Table 1). While mean age did not differ between groups, there was a significant difference in age categories, with more women aged 20–34 in the control arm (76.8% vs 71.7%, $P = .044$).

Among women with delivery data, 72.0% and 66.8% of those in the ISTp and control groups, respectively, attended ≥3 ANC visits, with a mean of 2.98 visits for women in the ISTp arm versus 2.87 visits in the control arm ($P = .011$).

Among women in the ISTp arm, RDT positivity decreased from 10.6% to 3.2% from the first to fourth ANC visit (Table 2). Approximately half of all women with a positive RDT reported fever in the preceding 48 hours. RDT positivity among those without reported fever was 5.6% at first ANC, 2.8% at second ANC, and 1.1% at fourth ANC. The prevalence of

self-reported fever in the preceding 48 hours also decreased with each successive ANC visit from 7.0% at first visit to 2.5% by the fourth visit. The number of afebrile persons needed to be tested to diagnose 1 person with malaria increased from 17.8 persons initially to 91.3 persons by fourth ANC.

Among all women with delivery data, 12.8% of women enrolled in the intervention group received an artemisinin combination therapy (ACT) during the study compared to only 2.2% in the control group. Only 14 women in the intervention arm received >1 course of ACT, and the maximum any woman received was 2 courses. None of the women in the control group received >1 course of ACT. The risk of LBW was not associated with receipt of ACT treatment.

ISTp was not associated with detection of either placental (15.0% and 15.3% in the ISTp and control arms, respectively; aRR, 0.94 [95% confidence interval {CI}, .59–1.50]; P = .799) or peripheral (10.5% vs 10.3%; aRR, 0.96 [95% CI, .69–1.34]; P = .825) malaria at delivery by PCR or peripheral malaria by RDT compared to control (4.5% vs 4.4%; aRR, 0.91 [95% CI, .34–2.43]; P = .853) (Table 3). Compared to PCR, the sensitivity and specificity of RDT at delivery were 21.6% and 98.2%, respectively (Supplementary Results). ISTp was also not associated with any significant difference in any anemia (aRR, 1.08 [95% CI, .57–2.04]; P = .821) or moderate to severe anemia (RR, 0.87 [95% CI, .37–2.08]; P = .760) at delivery.

Fever during pregnancy was associated with an increased risk of placental malaria at delivery (aRR, 1.90 [95% CI, 1.32–2.74]; P = .001), whereas IRS was associated with a decreased risk (aRR, 0.33 [95% CI, .23–.48]; P < .001) (Table 4). Having had 1 previous pregnancy reduced the risk of moderate to severe anemia (aRR, 0.37 [95% CI, .21–.68]), as did higher baseline Hb (aRR, 0.71 [95% CI, .62–.81]). IRS was marginally associated with a reduced risk of moderate to severe anemia (aRR, 0.43 [95% CI, .18–1.02]) (Table 4).

There were 930 newborns (including 20 twins) delivered in the intervention arm and 776 newborns (including 16 twins) delivered in the control arm. Excluding twins and stillborn infants, there were 897 live singleton newborns in the intervention arm and 747 in the control arm. The mean (standard deviation) birthweight of live singletons did not vary significantly between study arms (3054 g [448] vs 3096 g [443] for the ISTp and control arms, respectively; P = .395; Table 3). Compared to routine care, ISTp was associated with a higher proportion of LBW (7.3% vs 4.4%, P = .035) and preterm births (8.1% vs 5.1%, P = .207). In adjusted analyses, women in the ISTp group remained at a statistically significantly higher risk of LBW (aRR, 1.59 [95% CI, 1.02–2.49]; P = .042); while the point estimate for preterm birth was similar, this remained nonsignificant (aRR, 1.48 [95% CI, .79–2.76]; P = .219). Treatment for malaria before enrollment was associated with a statistically significantly increased risk of LBW (aRR, 1.54 [95% CI, 1.03–2.30]; P = .035; Table 5).

DISCUSSION

In districts in Rwanda with moderate malaria transmission, ISTp, compared to testing only symptomatic women for malaria, did not provide protection against malaria infection or anemia at delivery. Newborn outcomes were not improved by ISTp compared with routine ANC; on the contrary, women who received ISTp were more likely to have LBW infants than those who received routine care. That ISTp had no impact on placental malaria or birthweight was surprising, as one would expect that routine testing would have a greater impact than testing only symptomatic women. Prior studies suggested that ISTp performs similarly to IPTp-SP regarding the prevention of maternal malaria and adverse newborn outcomes [11, 13, 14], although not against febrile episodes during pregnancy [4, 10, 12]; as IPTp is better than placebo, one would expect that ISTp would provide benefit over passive screening for malaria.

The paradoxical failure to detect a reduction in malaria at delivery and the lower birthweight in the ISTp arm is likely related to greater exposure to malaria, indicated by the higher proportion of women reporting malaria prior to enrollment as well as the higher number of fever cases reported in the ISTp arm. Although facilities were randomized, the relatively small number of facilities may not have adequately eliminated confounding with respect to discrete hotspots of malaria transmission.

Alternatively, that half of all RDT-positive women had fever might indicate that in this population, asymptomatic malaria is rare, limiting the utility of universal screening. Although the areas chosen had higher burden of malaria than other areas in Rwanda, they have a much lower burden of malaria than other areas where ISTp has been studied, where malaria at delivery ranged from 16.9% to 38.2%, versus 15.3% [15]. Due to the lower prevalence of malaria in Rwanda, women have less pre-existing immunity; thus, a high proportion of cases were symptomatic. It is likely that ISTp would be more beneficial if the proportion of asymptomatic, RDT-positive women were higher. Furthermore, the overall proportion of women with fever was only 7% at the first visit and subsequently declined.

It is possible that more sensitive diagnostic tests would improve the efficacy of an ISTp strategy. In this study, placental and peripheral PCR detected approximately 2 and 3 times as many malaria infections at delivery as peripheral RDTs. Had a more sensitive test detected these subpatent malaria infections during ANC screenings, treatment of these presumably lower-level infections might have improved outcomes. Submicroscopic infections, which may be asymptomatic and remain undetected by routine RDTs, have been shown to be associated with poor birth outcomes [15]. Similar findings have been observed in prior studies from Malawi and Kenya. RDTs detected about 45% of the PCR-positive infections in paucigravidae and about 30% in multi-gravidae, allowing the majority of infections to persist in the placenta, potentially making ISTp less effective owing to a failure to detect low-level parasitemias. Highly sensitive RDTs could improve the sensitivity, and potentially the impact, of ISTp and deserve further study.

While ISTp cannot be recommended based on results from this study, consideration could be given to testing asymptomatic women at the first ANC visit only. RDT positivity is

consistently higher at first visit [10, 12, 13, 20]; in this study, RDT positivity among asymptomatic women declined sharply from 5% at the first ANC visit to 1% by the fourth ANC visit, meaning that the number of afebrile women tested for each 10 malaria infections detected by RDT increased from 177 initially to 913 by the fourth ANC visit. In addition to potentially improving outcomes of women and their infants, screening at first ANC visit could provide highly granular data for surveillance and monitoring, as several studies have demonstrated that parasitemia prevalence in pregnant women corresponds well to that among children aged <5 years [21–24].

Though not the goal of the study, as 1 district conducted IRS while the other did not, there was an opportunity to assess the impact of IRS on malaria and anemia among pregnant women. Similar to findings from Uganda [25], IRS was associated with significant reduction in the risk of malaria at delivery and a marginal reduction in moderate to severe anemia after controlling for other factors.

Limitations

The imbalance in ITN use prior to enrollment, prior reported malaria, and fever during the study suggest that malaria exposure was lower in the control arm, likely resulting in a biased outcome. While the facilities were randomized, the relatively small number of clusters may have contributed to the imperfect balance between arms. Although the analysis controlled for these factors, it is possible that confounding was not fully removed, and thus it is possible that these results are not generalizable. Additionally, the relatively low proportion of febrile women and the small number of asymptomatic, RDT-positive women likely also substantially reduced the difference in effect between ISTp and usual care, suggesting that the benefit of routinely testing all women decreases as transmission decreases. Finally, the use of last menstrual period and fundal height measurements rather than ultrasound to determine gestational age may have resulted in misclassification in outcome for preterm delivery for some infants, though this would not be expected to be biased across arms.

CONCLUSIONS

ISTp did not reduce placental malaria or maternal anemia at delivery compared to routine care. Paradoxically, ISTp was associated with a statistically significantly higher risk of LBW (though not mean birthweight) compared to passive case detection for malaria only. This was most likely related to higher malaria exposure in the intervention group, as suggested by the significantly higher proportion of women who reported having had malaria in pregnancy prior to the study enrollment as well as the higher proportion of fever during the study. This study failed to show any benefit of implementing ISTp for malaria control in pregnancy. It may still be worthwhile to screen asymptomatic women at first ANC visits to provide surveillance data for monitoring parasitemia prevalence. This may also provide some benefit to pregnant women by detecting low-density infections early in pregnancy. RDTs with greater sensitivity could potentially identify more asymptomatic malaria cases among pregnant women and improve the efficacy of ISTp; further investigation into the utility of highly sensitive RDTs for ISTp is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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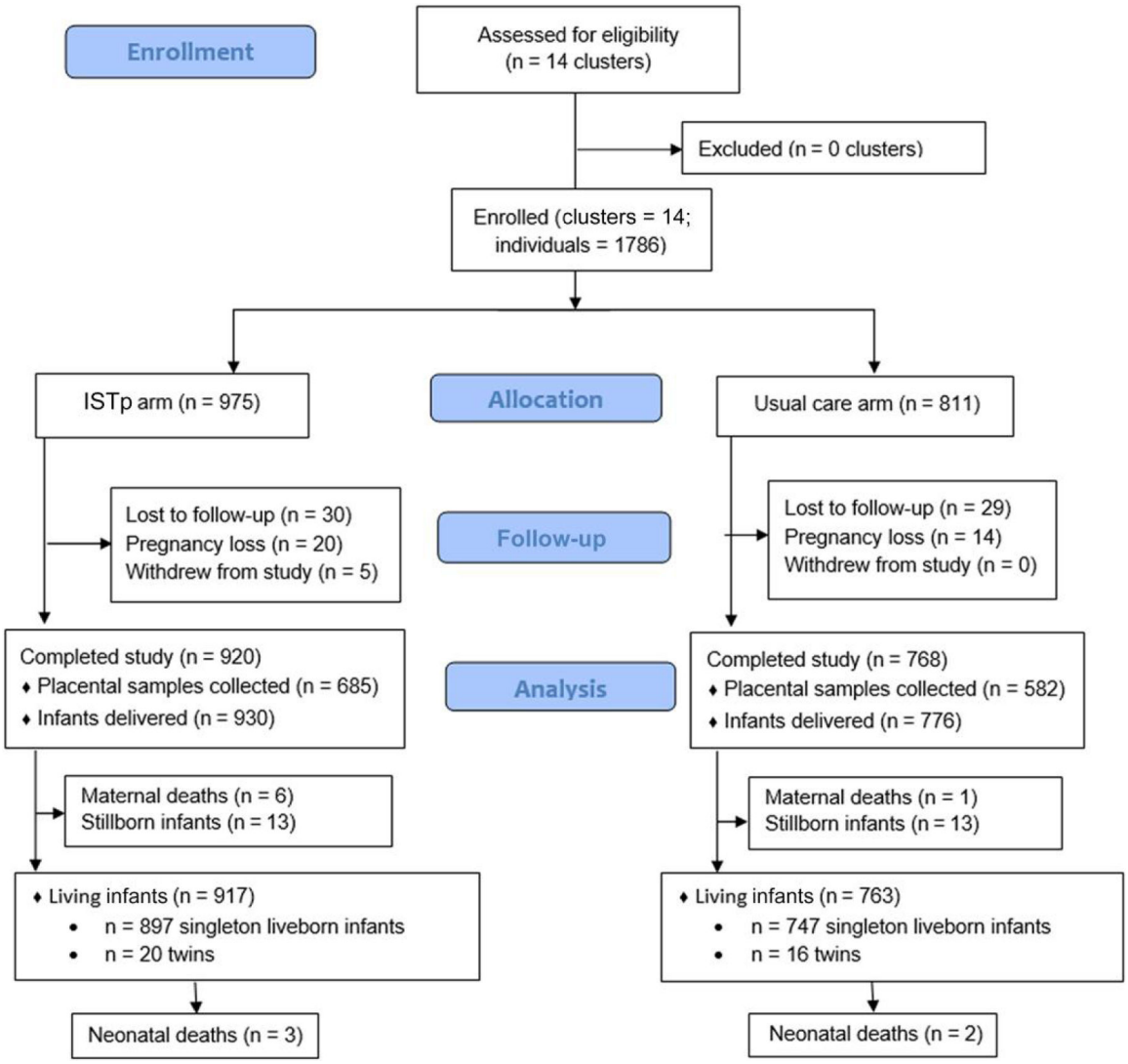

Figure 1. Study flow diagram. Abbreviation: ISTp, intermittent screening and treatment of malaria in pregnancy.

Table 1.

Baseline Characteristics by Study Arm Among Participants Who Completed the Study

Characteristic	ISTp (Intervention) (n = 920)	Usual Care (Control) (n = 768)	*P* Value
District			
Huye	480 (52.2)	401 (52.2)	
Kamonyi	440 (47.8)	367 (47.8)	.987
Age, y, mean (SD)	29.4 (6.4)	28.8 (6.1)	.052
Age category, y			
<20	44 (4.8)	25 (3.3)	
20–34	660 (71.7)	590 (76.8)	
≥35	216 (23.5)	153 (19.9)	.044
Marital status			
Single	78 (8.5)	47 (6.1)	
Married/cohabitating	835 (90.7)	713 (92.8)	
Divorced/separated	7 (0.77)	8 (1.04)	.156
Highest education level			
None	42 (4.6)	32 (4.2)	
Primary/vocational	788 (85.6)	660 (85.9)	
Secondary or higher	90 (9.8)	76 (9.9)	.923
HIV status[a]			
Positive	16 (1.8)	17 (2.2)	
Negative	900 (97.9)	742 (96.6)	.221
Gravidity			
Primigravid	252 (27.4)	210 (27.3)	
Secundigravid	221 (24.0)	190 (24.7)	
Multigravid (third or more)	447 (48.6)	368 (47.9)	.938
Mean (range)	2.8 (1–10)	2.7 (1–10)	.349
Gestational age at first ANC visit, wk, mean (SD)	17.4 (5.6)	19.3 (6.7)	<.0001
Hemoglobin, g/dL, mean (SD)	12.3 (1.8)	12.5 (1.5)	.002
Received a bed net during first ANC	916 (99.6)	767 (99.9)	.252
Slept under bed net the night before first ANC	862 (93.7)	756 (98.4)	<.0001
IRS within 6 mo prior to enrollment	415 (45.1)	331 (43.1)	.408
Treated for malaria during current pregnancy prior to enrollment			
Yes	88 (9.6)	54 (7.0)	<.001
Uncertain	21 (2.3)	46 (6.0)	
No. of ANC study visits			.082
1	42 (4.6)	49 (6.4)	
2	216 (23.5)	206 (26.8)	
3	379 (41.2)	306 (39.8)	
≥4	283 (30.8)	207 (27.0)	
Mean (SD)	2.98 (0.85)	2.87 (0.88)	.011

Characteristic	ISTp (Intervention) (n = 920)	Usual Care (Control) (n = 768)	*P* Value
Mean No. of days between last ANC visit and delivery (SD)	30.3 (26.0)	28.7 (24.35)	.202

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ANC, antenatal care; HIV, human immunodeficiency virus; IRS, indoor residual spraying; ISTp, intermittent screening and treatment of malaria in pregnancy; SD, standard deviation.

[a]HIV status was indeterminate or not tested for 4 women in the ISTp arm and 9 women in the usual care arm.

Table 2.

Reported Fever and Malaria Test Results by Antenatal Care Visit

	Routine Care (Control)			ISTp (Intervention)							
ANC Visit	Total Participants, No.	Reported Fever in Preceding 48 h	RDT or Microscopy Positive (Febrile Women Only)	Total Participants, No.	ReportedFever in Preceding 48 h	RDT or Microscopy Positive (Regardless of Symptoms)	RDT Positive With Fever	RDT Positive Without Fever	RDT Positivity if Febrile	RDT Positivity if Afebrile	NNT Among Afebrile, No.
1	768	50/768 (6.5)	28 (3.7)[a]	920	64/920 (7.0)	97 (10.6)[a]	49 (50.5)	48 (49.5)	76.6%	5.6%	17.8
2	719	8/719 (1.1)	2 (0.28)	874	3/878 (3.8)	47 (5.3)	23 (48.9)	24 (51.1)	69.7%	2.8%	36.3
3	511	4/511 (0.78)	1 (0.20)	658	18/662 (2.7)	26 (3.8)	13 (50.0)	13 (50.0)	72.2%	2.0%	49.2
4	207	2/207 (0.97)	0 (0)	281	7/282 (2.5)	9 (3.2)	6 (66.7)	3 (33.3)	85.7%	1.1%	91.3

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ANC, antenatal care; ISTp, intermittent screening and treatment of malaria in pregnancy; NNT, number needed to test to find a single positive malaria case; RDT, rapid diagnostic test.

[a]At first ANC, in the ISTp arm, 51 of 97 received artemether-lumefantrine (AL; the others received quinine), while in the control arm 13 of 28 received AL. At subsequent visits, all women who tested positive were treated with AL. Overall, there were 128 fever cases among 118 women in the ISTp arm and 64 fever cases among 61 women in the routine care arm.

Table 3.

Maternal and Newborn Outcomes at Delivery by Study Arm

Outcome	ISTp (Intervention) No. (%)	Routine Care (Control) No. (%)	Unadjusted Model		Adjusted Model[a]		Intercluster Correlation
			RR (95% CI)	*P* Value	aRR (95% CI)	*P* Value	
Maternal malaria at delivery							
Placental malaria at delivery by PCR	103/685 (15.0)	89/582 (15.3)	0.98 (.48–2.02)	.964	0.94 (.59–1.50)	.799	0.079
Maternal peripheral malaria at delivery by RDT	38/850 (4.5)	29/665 (4.4)	1.03 (.39–2.7)	.960	0.91 (.34–2.43)	.853	0.030
Maternal peripheral malaria at delivery by PCR	77/737 (10.5)	63/610 (10.3)	1.01 (.61–1.67)	.964	0.96 (.69–1.34)	.825	0.023
Maternal anemia at delivery							
Any anemia (Hb <11 g/dL)	92/863 (10.7)	59/677 (8.7)	1.22 (.62–2.42)	.563	1.08 (.57–2.04)	.821	0.042
Moderate to severe anemia (Hb <10 g/dL)	28/863 (3.2)	21/677 (3.1)	1.05 (.42–2.62)	.924	0.87 (.37–2.08)	.760	0.015
Newborn outcomes[b]							
Mean birthweight, g (SD)[c]	3054 (448)	3096 (443)	−45 (−148 to 58)	.395	−53 (−168 to 62)	.367	0.004
Low birthweight	65/894 (7.3)	33/745 (4.4)	1.64 (1.03–2.6)	.035	1.59 (1.02–2.49)	.042	0.009
Prematurity	73/897 (8.1)	38/747 (5.1)	1.60 (.77–3.32)	.207	1.48 (.79–2.76)	.219	0.071

All models (unadjusted and adjusted) account for clustering at the health facility level.

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; Hb, hemoglobin; ISTp, intermittent screening and treatment of malaria in pregnancy; PCR, polymerase chain reaction; RDT, rapid diagnostic test; RR, relative risk; SD, standard deviation.

[a]Maternal malaria outcomes were adjusted for study arm, gravidity, total number of antenatal care (ANC) visits, fever during pregnancy (at least 1 episode), and indoor residual spraying (IRS) in the last 6 months. Maternal anemia outcome models were adjusted for study arm, gravidity, baseline Hb level, and IRS in the 6 months prior to or during the study. Infant outcome models were adjusted for study arm, gravidity, baseline Hb level, treatment for malaria during pregnancy prior to enrollment, and IRS in the 6 months prior to or during the study; the model for low birthweight was additionally adjusted for number of ANC visits. The addition of this variable to the preterm model caused it to become unstable.

[b]Among singleton liveborn newborns.

[c]Birthweight was missing for 3 newborns in the intervention arm and 2 newborns in the control arm.

Table 4.

Risk Factors Associated With Any Placental Malaria at Delivery Detected by Polymerase Chain Reaction and Moderate to Severe Maternal Anemia at Delivery

	Placental Malaria at Delivery Detected by PCR[a]				Moderate to Severe Maternal Anemia at Delivery[b]			
Characteristic	**Unadjusted RR (95% CI)**	***P* Value**	**Adjusted RR[c] (95% CI)**	***P* Value**	**Unadjusted RR (95% CI)**	***P* Value**	**Adjusted RR[c] (95% CI)**	***P* Value**
Intervention vs control	0.98 (.48–2.02)	.9635	0.94 (.59–1.5)	.799	1.05 (.42–2.62)	.924	0.87 (.37–2.08)	.76
Age category, y								
20–34 vs <20	0.77 (.47–1.26)	.2987	…		1.02 (.27–3.79)	.98	…	
≥35 vs <20	0.91 (.47–1.76)	.7692	…		0.81 (.24–2.78)	.738	…	
Gravidity								
Secundigravid vs primigravid	1.07 (.86–1.32)	.5497	0.95 (.78–1.16)	.593	0.36 (.19–.7)	.003	0.36 (.18–.72)	.004
Multigravid vs primigravid	1.05 (.75–1.48)	.7812	0.96 (.71–1.29)	.786	1.09 (.75–1.58)	.657	1.12 (.69–1.8)	.648
No. of ANC visits	0.82 (.7–.96)	.0149	0.86 (.75–1)	.044	0.78 (.57–1.08)	.138	…	
Fever self-reported during pregnancy (≥1 episode)	1.95 (1.15–3.33)	.0137	1.90 (1.32–2.74)	.001	2.43 (1.23–4.79)	.01	…	
Baseline Hb level	0.91 (.85–.99)	.023	…		0.7 (.61–.81)	<.0001	0.71 (.62–.81)	<.0001
Gestational age at first ANC	1.04 (1.01–1.06)	.0026	…		1.01 (.96–1.07)	.589	…	
IRS 6 m prior to or during study	0.31 (.21–.47)	<.0001	0.33 (.23–.48)	<.0001	0.39 (.15–1.05)	.061	0.43 (.18–1.02)	.055
ITN use reported during first ANC	1.35 (.61–3)	.4567	…		0.69 (.3–1.56)	.371	…	
Treated for malaria before enrollment								
Yes vs no	1.32 (.78–2.22)	.3051	…		1.8 (.88–3.69)	.105	…	
Uncertain vs no	0.97 (.4–2.36)	.9409	…		0.56 (.08–3.91)	.558	…	
District, Huye vs Kamonyi	0.33 (.22–.5)	<.0001	…		1.02 (.41–2.59)	.96	…	
Marital status								
Married/cohabitating vs single	1.00 (.70–1.43)	.9931	…		0.91 (.42–1.97)	.802	…	
Divorced/separated vs single	0.66 (.10–4.16)	.6556	…		1.93 (.16–23.72)	.606	…	
Education level								
Primary or vocational vs none	0.91 (.34–2.45)	.8479	…		0.44 (.11–1.74)	.241	…	
Secondary or higher vs none	1.04 (.49–2.22)	.9136	…		0.54 (.21–1.41)	.206	…	

Abbreviations: ANC, antenatal care; CI, confidence interval; Hb, hemoglobin; IRS, indoor residual spraying; ITN, insecticide-treated bed net; PCR, polymerase chain reaction; RR, relative risk.

[a]Placental samples available from 685 women in the intervention group and 582 women in the routine care group.

[b] Moderate to severe anemia defined as Hb <10 mg/dL; Hb measurement at delivery was available from 861 women in the intervention arm and 677 in the control arm.

[c] Placental malaria model was adjusted for study arm, gravidity, fever during pregnancy (at least 1 episode), IRS in the last 6 months, and total number of ANC visits. Anemia model was adjusted for study arm, gravidity, baseline Hb level, and IRS in the last 6 months; the addition of fever during pregnancy or total number of ANC visits rendered the model unstable. All models (unadjusted and adjusted) account for clustering at the health facility level.

Table 5.

Risk Factors Associated With Low Birthweight and Preterm Birth

	Low Birthweight				Preterm Delivery			
Characteristic	**Unadjusted RR (95% CI)**	***P* Value**	**Adjusted RR[a] (95% CI)**	***P* Value**	**Unadjusted RR (95% CI)**	***P* Value**	**Adjusted RR[a] (95% CI)**	***P* Value**
Intervention vs control	1.64 (1.03–2.6)	.035	1.59 (1.02–2.49)	.042	1.6 (.77–3.32)	.207	1.48 (.79–2.76)	.219
Age category, y								
20–34 vs <20	0.55 (.33–.91)	.021	…		0.56 (.28–1.12)	.103	…	
≥35 vs <20	0.46 (.29–.74)	.002	…		0.74 (.33–1.62)	.448	…	
Gravidity								
Secundigravid vs primigravid	0.84 (.55–1.3)	.431	0.83 (.55–1.24)	.359	1.15 (.74–1.78)	.528	1.17 (.77–1.78)	.454
Multigravid vs primigravid	0.69 (.41–1.14)	.147	0.66 (.40–1.07)	.091	1.17 (.75–1.81)	.491	1.13 (.74–1.74)	.564
No. of ANC visits	0.72 (.58–.89)	.002	0.71 (.57–.88)	.002	0.44 (.35–.55)	<.0001	…	
Fever self-reported during pregnancy (≥1 episode)	1.42 (.9–2.24)	.130	…		0.76 (.34–1.7)	.497	…	
Baseline Hb level	0.86 (.77–.96)	.008	0.89 (.79–.99)	.038	0.89 (.81–.97)	.011	0.89 (.80–.99)	.035
Gestational age at first ANC visit	1 (.97–1.02)	.727	…		1.00 (.96–1.04)	.985	…	
IRS in the 6 m prior to or during study	0.92 (.63–1.34)	.664	1.04 (.69–1.56)	.851	1.73 (1.03–2.9)	.037	1.76 (1.03–3.02)	.039
Bed net use reported during first ANC	0.48 (.25–.92)	.028	…		1.14 (.47–2.72)	.774	…	
Treated for malaria before enrollment								
Yes vs no	1.63 (1.08–2.45)	.019	1.54 (1.03–2.30)	.035	1.54 (.98–2.43)	.062	1.33 (.89–1.98)	.167
Uncertain vs no	0.52 (.26–1.05)	.067	0.56 (.27–1.17)	.121	0.70 (.32–1.53)	.369	0.75 (.35–1.59)	.456
District, Huye versus Kamonyi	1.04 (.64–1.69)	.869	…		2.19 (1.08–4.44)	.030	…	
Marital status								
Married/cohabitating vs single	0.55 (.35–.87)	.010	…		1 (.53–1.86)	.987	…	
Divorced/separated vs single	1.32 (.23–7.61)	.755	…		1.98 (.43–9.14)	.380	…	
Education level								
Primary or vocational vs none	0.48 (.23–1)	.050	…		1.24 (.59–2.59)	.569	…	
Secondary or higher vs none	0.14 (.03–.63)	.010	…		0.76 (.41–1.41)	.388	…	

Abbreviations: ANC, antenatal care; CI, confidence interval; Hb, hemoglobin; IRS, indoor residual spraying; RR, relative risk.

[a]Models were adjusted for study arm, gravidity, baseline Hb level, treatment for malaria during the pregnancy prior to enrollment, and IRS in the 6 months prior to or during the study; the model for low birthweight was additionally adjusted for number of ANC visits. The addition of this variable to the preterm model caused it to become unstable.