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Improving coverage of antenatal iron and folic acid supplementation and malaria prophylaxis through targeted information and home deliveries in Côte d'Ivoire: a cluster randomised controlled trial

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ABSTRACT

Introduction Coverage of antenatal iron and folic acid (IFA) supplementation and malaria chemoprophylaxis remains low in many low-income and middle-income settings. We assessed the effectiveness of personal information (INFO) sessions and personal information session plus home deliveries (INFO+DELIV) to increase coverage of IFA supplementation and intermittent preventive treatment in pregnancy (IPTp), and their effectiveness on postpartum anaemia and malaria infection.

Methods We included 118 clusters randomised to a control (39), INFO (39) and INFO+DELIV (40) arm, in a trial conducted between 2020 and 2021 with pregnant women (age ≥15 years) in their first or second trimester of pregnancy in Taabo, Côte d'Ivoire. We used generalised linear regression models to assess intervention impact in postpartum anaemia and malaria parasitaemia, and displayed resulting estimates as prevalence ratios.

Results Overall, 767 pregnant women were enrolled and 716 (93.3%) were followed up after delivery. Neither intervention had an impact on postpartum anaemia, with estimated adjusted prevalence ratios (aPRs) of 0.97 (95% CI 0.79 to 1.19, p=0.770) for INFO and 0.87 (95% CI 0.70 to 1.09, p=0.235) for INFO+DELIV. While INFO had no effect on malaria parasitaemia (aPR=0.95, 95% CI 0.39 to 2.31, p=0.915), INFO+DELIV reduced malaria parasitaemia by 83% (aPR=0.17, 95% CI 0.04 to 0.75, p=0.019). No improvements in antenatal care (ANC) coverage (aPR=1.05, 95% CI 0.81 to 1.36, p=0.692), IFA (aPR=2.00, 95% CI 0.89 to 4.46, p=0.093) and IPTp (aPR=1.03, 95% CI 0.87 to 1.21, p=0.728) compliance were found for INFO. INFO+DELIV increased ANC attendance (aPR=1.35, 95% CI 1.02 to 1.78, p=0.037) and compliance with IPTp (aPR=1.60, 95% CI 1.41 to 1.80, p<0.001) and IFA recommendations (aPR=7.06, 95% CI 3.68 to 13.51, p<0.001).

Conclusions INFO+DELIV can substantially increase compliance with IFA supplementation and improve malaria prevention. However, the increases in IFA supplementation are likely insufficient to address the prevalence of often severe anaemia in this population.

Trial registration number NCT04250428.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antenatal iron and folic acid (IFA) supplementation and intermittent preventive treatment in pregnancy (IPTp) are widely recognised as key strategies to reduce maternal anaemia and malaria in pregnancy.
⇒ Previous research has provided evidence on the use of iron-based therapies to prevent the incidence of anaemia for pregnant women and highlighted community-delivered models of malaria prophylaxis in pregnancy, finding reductions in the risk of parasitaemia between 25% and 70%.

WHAT THIS STUDY ADDS

⇒ Community-based information about antenatal care combined with monthly supply of IFA and IPTp with sulfadoxine pyrimethamine greatly increases coverage of supplementation and malaria chemoprophylaxis.
⇒ Standard IFA supplementation is not sufficient to address the high prevalence of often-severe anaemia in this low-income setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Community-based distribution of malaria chemoprophylaxis should be considered as strategy to reduce malaria exposure in pregnancy.
⇒ Standard supplementation protocols currently recommended in many low-income and middle-income countries (LMICs) are likely not sufficient to address the high burden of anaemia in many LMIC settings.
⇒ Prepregnancy supplementation, routine haemoglobin assessments during the first trimester and monitored administration of higher doses of supplements (oral or via injections) may offer potential solutions to this problem.

INTRODUCTION

Despite considerable reductions in under-5 mortality between 1990 and 2019, sub-Saharan Africa remains the region with the highest under-5 mortality rate globally.[1 2] Neonatal deaths currently account for about half of all under-5 deaths,[3] and recent evidence suggests that many of these deaths could be prevented with improved access to essential antenatal care (ANC) services. [4–6] In many settings, exposure to malaria and maternal anaemia pose a major threat to maternal and child health. Evidence from sub-Saharan Africa suggests that 46% of pregnant women are anaemic,[7] and more than 11 million cases of malaria in pregnancy were reported in 2018.[8] Both risk factors can, in principle, be addressed by adequate ANC. However, coverage of essential antenatal interventions remains limited in many low-income and middle-income countries,[9] resulting in high prevalence of anaemia[10] and limited prevention of malaria in pregnancy.[11–13] Challenges faced in many health systems include supply factors such as distance, interrupted supply and stock-outs, and high cost of care, and demand-side factors such as limited education and social–cultural barriers.[14 15] In 2018, a systematic review of studies evaluated the impact of strategies including community-based treatment, distributor incentives, distribution along kinship networks, intensified information, education and communication (IEC) activities, fixed-point delivery on the coverage of services such as vitamin A supplementation, child immunisations and mass drug administration campaigns targeting neglected tropical diseases.[16] The largest positive influence on treatment coverage was found for community-directed distribution, incentives to increase distributor motivation, distribution along kinship networks and implementation of intensified IEC. The evidence available to date suggests that interventions combining education with vouchers and other financial incentives tend to be most effective for increasing intervention coverage. [17–19]

The nationally recommended intervention package suggests iron and folic acid (IFA) supplementation in pregnant women at a dose of 30–60 mg of elemental iron plus 0.4 mg of folic acid, daily and a direct observed therapy (DOT) of three tablets of sulfadoxine pyrimethamine (SP) (each tablet containing 500 mg/25 mg SP) giving the total required dosage of 1500 mg/75 mg SP per month.[20]

In this study, we report the results of a cluster randomised controlled trial set up to assess the efficacy of two potential strategies to increase coverage of the currently recommended interventions to the target population in low resource settings. The trial was conducted in the area of the Taabo health and demographic surveillance system (HDSS) in the south-central part of Côte d'Ivoire. The interventions consisted of an information package (INFO), designed to increase uptake of essential antenatal services through targeted information, and an information plus home delivery intervention (INFO+DELIV), designed to provide both information and immediate access to supplements and chemoprophylaxis. The trial was registered at ClinicalTrials.gov as NCT04250428 and the protocol of this trial with the analysis plan published in 2020.[21]

METHODS

Trial design and setting

The study was designed as a cluster randomised controlled trial with three parallel arms using an allocation ratio of 1:1:1. The trial was conducted in the Taabo HDSS, which is located approximately 180 km north-west of Abidjan, the economic capital of Côte d'Ivoire. Previous studies conducted in this area have highlighted the high prevalence of anaemia in this setting,[22] with 61% of children and 48% of non-pregnant women found to be anaemic in 2011.[23] For the trial, clusters were defined as neighbourhoods ('quartier') in villages and hamlets outside of the main villages.[24] All 118 clusters in the Taabo HDSS were initially included in the study. Pregnancies were reported in 90 of these clusters during the enrolment period. Further details pertaining to the study design and methods are available in the previously published protocol paper.[21]

Participants and eligibility

The target population of the trial were pregnant women who were in their first or second trimester of pregnancy, and living in the surveillance area of the Taabo HDSS. Gestational length was computed based on maternal reports of conception dates or date of last menstruation. Key informants living in the surveillance area were recruited for identifying pregnancies in their communities and paid a reward of US$2 for each pregnancy reported. Trained field enumerators visited pregnant women and invited them to partake in the study. Conditional to women's written informed consent, a short baseline questionnaire was conducted.

Study setting

Details on the surveillance area covered by the Taabo HDSS have been presented elsewhere.[21 24] Since 2012, the government of Côte d'Ivoire mandates free access to maternal and child care in public healthcare facilities, including outpatients care for mothers and children under the age of 5 years, family planning and prenatal care. Intermittent preventive treatment in pregnancy (IPTp) is also offered free of charge through a separate programme. When our trial was implemented, the study area was composed of 13 health facilities, including 8 health centres and 5 dispensaries in the rural area, and a 12-bed hospital located in Taabo-Cité considered as semi-urban.

Randomisation and masking

A total of 118 study clusters were randomly assigned to one of three study arms with equal probability: 39 clusters were randomly assigned to the control group, 39 clusters to the INFO group and 40 clusters to INFO+DELIV

group. Minimum-maximum randomisation was used to minimise differences across study arms.[25] Using Stata 15 SE software, we created 100 random allocations, and then computed mean differences in terms of cluster size (number of births) and ANC attendance (percentage of women attending ANC) across the three groups. We then selected the draw with the smallest differences across study arms for the final group allocation.

Given the nature of the intervention, blinding of participants was not possible. However, interviewers who conducted the endline survey were not aware of women's treatment status, and data analysis was conducted by the senior author (GF) using a fully blinded data set.

Procedures

During a 3-day workshop, study nurses were trained to deliver key information as well as supplements. The practice consisted of test sessions with women not eligible for the study. During the training, emphasis was placed on the delivery of awareness messages in French and local languages, particularly the most common Malinké and Baoulé languages. The message was developed based on the national recommendations for IFA/IPTp and ANC in Côte d'Ivoire. Further details on the content of the sessions are provided in online supplemental material 1. The message was developed based on the national recommendations for IFA/IPTp and ANC in general.[20] The study involved a baseline and an endline survey, which was to be completed by all participants. In the INFO arm, nurses visited pregnant women at their homes 1–2 weeks after study enrolment. During this visit, nurses provided pregnant women with information regarding the importance of antenatal IPTp as well as IFA supplementation, potential adverse events of both interventions and the optimal timing for taking supplements. Nurses also highlighted the importance of using routine ANC services to ensure safe pregnancies. At the end of the visit, a mobile phone number was given to women in case they had any further related questions.

In the INFO+DELIV arm, all women received the same initial information session at home. This first home visit was followed by monthly home visits, during which women received a monthly supply of IFA supplements and IPTp (starting from the second trimester) from study staff, unless women indicated they had already received supplements or chemoprophylaxis as part of the ANC visits. Overall, 1257 home delivery visits were made, which implies an average of 6 visits per woman. During the intervention period, every month, nurses travelled by motorbike throughout the study area for individual home deliveries of IFA and SP. The current standard of SP is a DOT of three tablets SP (each tablet containing 500 mg/25 mg SP) giving the total required dosage of 1500 mg/75 mg SP (online supplemental figure SF 1). IFA supplementation was implemented using locally used Agifer-X capsules containing an equivalent of 100 mg of iron and 550 µg of folic acid (see online supplemental figure SF3 for packaging information).

Detailed monitoring data on home visits were collected for the two arms throughout the study period. An independent team of laboratory technicians conducted the haemoglobin (Hb) assessments and administered the malaria rapid diagnostic test (RDT). Hb-level and malaria infection status were collected at endline within the first 2 weeks after delivery through trained staff members at women's homes. Hb was assessed using HEMOCUE 201+devices (Hemocue; Ängelholm, Sweden). Malaria RDTs were conducted using CareStart Malaria Pf (HRP2) Ag RDTs (Access Bio; Somerset, USA) (see online supplemental figure SF4 for further information).

Study outcomes

The primary outcomes were maternal postpartum anaemia and malaria parasitaemia. Postpartum anaemia was defined as an Hb concentration of less than 110 g/L. For malaria parasitaemia, the primary outcome was a positive RDT at endline.

Self-reported compliance with antenatal IFA supplementation, IPTp, as well as ANC visit, miscarriages, stillbirths and low birthweight deliveries were considered as secondary outcomes. Self-reported adherence to antenatal IFA supplementation and ANC attendance was measured using an endline-based questionnaire determining the number of supplements, ANC visits as well as the period and frequency of use. ANC attendance was coded as adequate if women reported to have completed at least four ANC visits. Compliance with IFA recommendations was coded as the (continuous) proportion of months (starting from the third month of gestation) for which mothers reported to have taken supplements daily (range 0–1). Compliance with malaria chemoprophylaxis was coded as having taken at least three doses of SP during pregnancy.

Power calculations

With 240 women in each arm, the study was powered to detect a 20% difference in maternal anaemia with power 0.8 and alpha 0.05. We assumed a control group anaemia prevalence of 50%, 6 women per cluster and an intraclass correlation of 0.25 based on a previous analysis of ANC access patterns in the Taabo HDSS.[21]

Statistical analysis

We used generalised linear regression models to assess intervention impact in postpartum anaemia and parasitaemia, as well as for all binary secondary outcomes and displayed resulting estimates as prevalence ratios. Based on normal distribution assumptions, all continuous secondary outcomes (birth weight and Hb levels) were analysed using linear regression models. Cluster-robust SEs were used to correct for residual correlation at the cluster level.[26] All models were estimated both without covariates (unadjusted) and with a prespecified set of mother socio-demographic covariates (ie, age, marital status, school attendance, parity and wealth quintile). To better understand the relationship between IFA

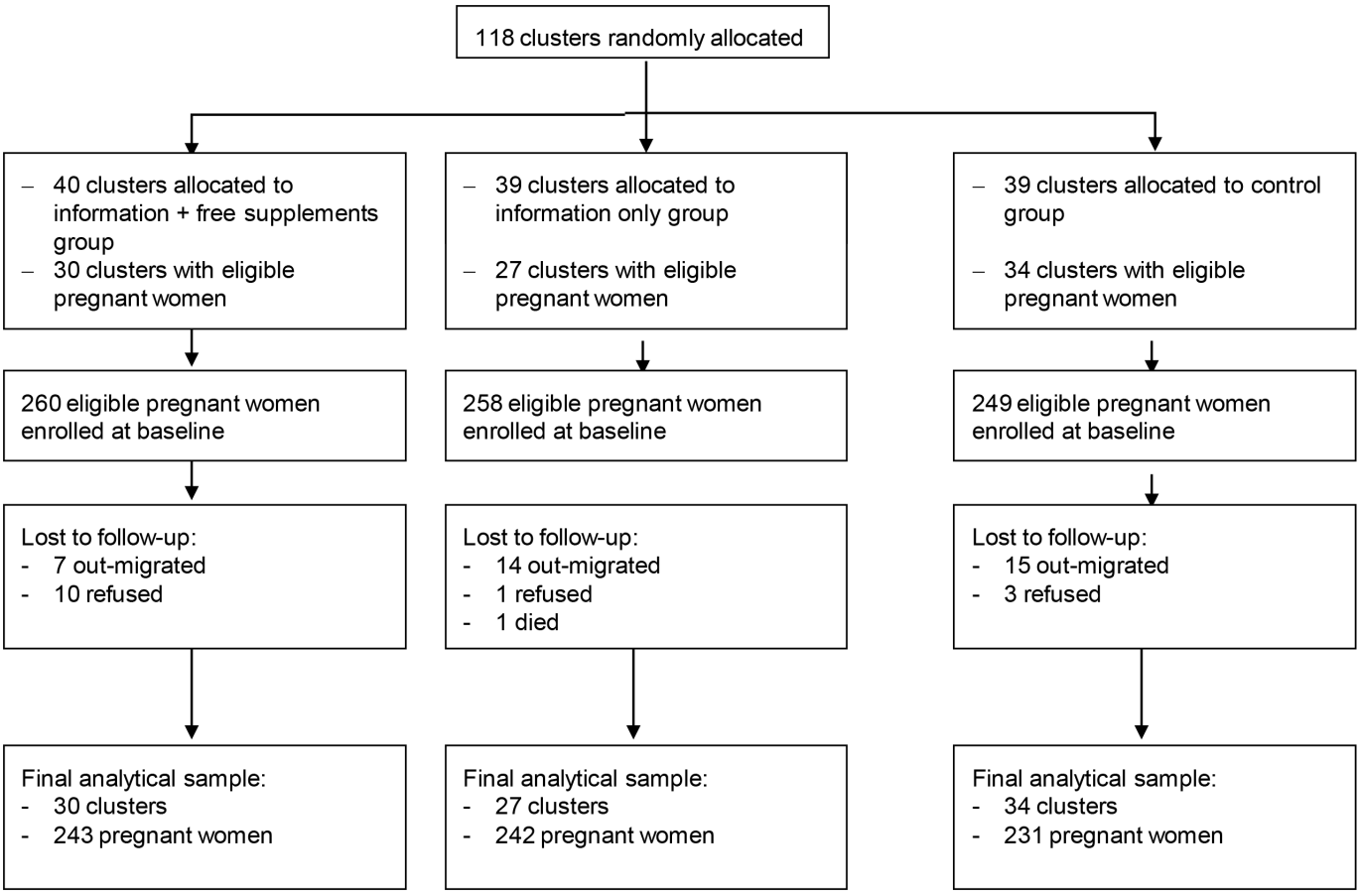

Figure 1 CONSORT flow diagram.

supplementation and the observed changes in anaemia, we also plotted average changes in Hb levels as a function of self-reported intake of IFA supplements during pregnancy (post-hoc analysis). To address multiple testing concerns with two treatment groups and two outcomes, we indicate both estimates with p values<0.05 (unadjusted significance cut-off) as well as estimates with p values<0.0125 (Family-Wise Error Rate (FWER)-corrected significance cut-off).

Trial registration and changes to protocol

The trial was registered at ClinicalTrials.gov as NCT04250428. There were no changes to the protocol after the trial started.

Patient and public involvement

Patient partners were not involved in the design or conduct of this study. Author reflexivity statement: see online supplemental file 2.

RESULTS

Study population

Study participants were recruited from 7 May 2020 to 25 June 2021 and followed up from 10 November 2020 to 26 November 2021. Figure 1 shows a CONSORT flow diagram, summarising study design and participants retention. Overall, 118 clusters were randomly assigned to either control (39 clusters and 249 pregnant women), INFO (39 clusters and 258 pregnant women) or INFO+DELIV intervention (40 clusters and 260 pregnant women). At baseline, 767 pregnant women were enrolled across 91 clusters and 716 women (93.3%) were reinterviewed at endline. In 27 of the original 118 clusters, no births were reported during the study period. No statistically significant differences were found in follow-up rates across the three study arms (p=0.90) (online supplemental table ST1).

As shown in table 1, the study participants lived an average of 2.2 km away from the nearest health facility and 69.5% (n=533) were between 20 and 34 years of age. Mean gestational age at enrolment was 4.1 months and the distribution was quasi-similar in the three groups (INFO=4.2, INFO+DELIV=4.1 and control=4.1). Slightly more than half (52.8%, n=405) of the women never attended school, 31.0% (n=238) attended primary school and 16.2% (n=124) attained secondary or higher education. Almost half (48.9%, n=375) of the women were in common-law, while 42.4% (n=325) were married. Baseline Hb was collected for a subsample of 171 women (control=63, INFO=51 and INFO+DELIV=57). The overall prevalence of anaemia at baseline was 70.2%.

Table 1 Sample baseline characteristics by study arm

	Control		Information only		Information+home delivery		Total	
	N	%	N	%	N	%	N	%
Anaemia prevalence at baseline*								
Prevalence	40	63.5	37	72.5	43	75.4	120	70.2
Mother age (years)								
15–19	42	16.9	48	18.6	37	14.2	127	16.6
20–34	167	67.1	174	67.4	192	73.8	533	69.5
35–49	40	16.1	36	14.0	31	11.9	107	14.0
School attendance								
Never attended	134	53.8	137	53.1	134	51.5	405	52.8
Primary	84	33.7	74	28.7	80	30.8	238	31.0
Secondary or higher	31	12.4	47	18.2	46	17.7	124	16.2
Parity								
1	41	16.5	50	19.4	43	16.5	134	17.5
2+	208	83.5	208	80.6	217	83.5	633	82.5
Wealth quintile								
Most poor	59	23.7	63	24.4	37	14.2	159	20.7
Poor	63	25.3	42	16.3	56	21.5	161	21.0
Middle	43	17.3	49	19.0	51	19.6	143	18.6
Rich	45	18.1	45	17.4	61	23.5	151	19.7
Most rich	39	15.7	59	22.9	55	21.2	153	19.9
Marital status								
Single	17	6.8	30	11.6	20	7.7	67	8.7
Common-law union	135	54.2	110	42.6	130	50.0	375	48.9
Married	97	39.0	118	45.7	110	42.3	325	42.4

Notes: Statistics reported are N and % for all variables except for age and distance to nearest health facilities, where N and the mean value are reported.
*Hb concentration at baseline was only collected for a subsample of 171 women (control=63, information only=51 and information+home delivery=57).

Impact of intervention on primary and secondary outcomes

Table 2 shows primary and secondary outcomes for each group and the sample overall. On average, across the three groups, 39.5% (n=283) women were anaemic; 19.8% (n=142) were mildly anaemic (Hb, range 100 to <110 g/L), 18.6% (n=133) were moderately anaemic (Hb, range 70 to <100 g/L) and 1.1% (n=8) were severely anaemic (Hb<70 g/L). A positive malaria RDT was registered in 3.4% (n=24) of the women. About one out of nine (11.5%, n=64) children were born with birth weight <2500 g. Ninety-two per cent (n=658) of pregnancies in the sample resulted in live births, 3.6% (n=26) of pregnancies resulted in miscarriage, 3.6% (n=26) resulted in stillbirths and 6 pregnancies (0.8%) were aborted. At least four ANC visits were recorded by 40.2% (n=291) of the women. More than half (54.0%, n=414) of the women reported compliance with daily IFA supplementation. Almost three-quarter (73.9%, n=513) received at least three doses of SP for IPTp.

As shown in table 3, neither intervention had an impact on anaemia (INFO: adjusted prevalence ratio (aPR)=0.97, 95% CI 0.79 to 1.19, p=0.770; INFO+DELIV: aPR=0.87, 95% CI 0.70 to 1.09, p=0.235). INFO+DELIV increased Hb marginally by 1.65 g/L (95% CI −1.08 to 4.42) (online supplemental table ST2). Online supplemental table ST3 shows more detailed results for mild, moderate and severe anaemia. No impact on malaria parasitaemia was found for INFO (aPR=0.95, 95% CI 0.39 to 2.31, p=0.915). INFO+DELIV reduced malaria parasite prevalence of 83% (aPR=0.17, 95% CI 0.04 to 0.75, p=0.019).

Impact on coverage and ANC attendance

Table 4 summarises the interventions' impact on ANC attendance, IFA supplementation and IPTp compliance. The INFO package had no impact on ANC compliance (aPR=1.05, 95% CI 0.81 to 1.36, p=0.692), IFA supplementation (aPR=2.00, 95% CI 0.89 to 4.46, p=0.093) and IPTp compliance (aPR=1.03, 95% CI 0.87 to 1.21, p=0.728). INFO+DELIV increased recommended ANC attendance by 35% (aPR=1.35, 95% CI 1.02 to 1.78, p=0.037) and compliance with malaria chemoprophylaxis by 60%

Table 2 Primary and secondary study outcomes

	Control		Information only		Information plus home delivery		Total	
	N	%	N	%	N	%	N	%
Anaemia*	97	42.0	99	40.9	87	35.9	283	39.5
Mild anaemia	52	22.5	46	19.0	44	18.1	142	19.8
Moderate anaemia	40	17.3	52	21.5	41	16.9	133	18.6
Severe anaemia	5	2.2	1	0.4	2	0.8	8	1.1
Postpartum malaria infection	11	4.8	11	4.5	2	0.8†	24	3.4
Low birth weight	27	14.8	18†	9.6	19	10.1	64	11.5
Live birth	209	90.5	222	91.7	227	93.4	658	92.0
Miscarriage	12	5.2	8	3.3	6	2.5	26	3.6
Stillbirth	9	3.9	11	4.5	6	2.5†	26	3.6
Abortion	1	0.4	1	0.5	4	1.6	6	0.8
At least 3 doses of SP	137	60.9	146	64.0	230	95.4†	513	73.9
IFA full compliance	111	44.4	120	46.3	185	70.8†	414	54.0
At least 4 ANC	81	34.5	91	37.3	119	48.6†	291	40.2

*Number of women sampled for anaemia is 716 women (control=231, information only=242 and information+home delivery=243).
†p<0.05
ANC, antenatal care; IFA, iron and folic acid.

(aPR=1.60, 95% CI 1.41 to 1.80, p<0.001). Women in the INFO+DELIV group were 7.1 times as likely to comply with antenatal IFA supplementation (aPR=7.06, 95% CI 3.68 to 13.51, p<0.001).

Table 5 shows results for pregnancy outcomes. No differences were found for miscarriage (INFO: aPR=1.18, 95% CI 0.57 to 2.42, p=0.659; INFO+DELIV: aPR=0.56, 95% CI 0.20 to 1.58, p=0.272). No impact was found on average birth weight (INFO: mean difference=11.4 g, 95% CI −97.2 to 120.1, p=0.835; INFO+DELIV: mean difference=18.9 g, 95% CI −113.7 to 151.4, p=0.778), and the prevalence of low birth weight (INFO: aPR=0.64, 95% CI 0.38 to 1.10, p=0.106; INFO+DELIV: aPR=0.69, 95% CI 0.38 to 1.29, p=0.248). Unlike the INFO intervention which had no impact on stillbirth (aPR=0.61, 95% CI 0.32 to 1.17, p=0.136), INFO+DELIV reduced the prevalence of stillbirth by 60% (aPR=0.40, 95% CI 0.21 to 0.76, p=0.005).

Figure 2 provides further details on IFA compliance per month. The proportion of women reporting daily intake increased from 0% in month 2 to 73% in month 6 and from 0.4% in month 2 to a level of 73.4% in the 6th month of pregnancy in both the control and INFO groups. In the INFO+DELIV group, IFA compliance increased from 1.2% in month 2 to 93.1% in month 6.

Assessments of changes in individual Hb concentration from baseline to endline among a subsample of women showed that average Hb levels increased by 9 g/L in the control and INFO groups, and by 15 g/L in the INFO+DELIV arm (online supplemental figure SF1). Figure 3 shows changes in Hb levels as

Table 3 Intervention impact on anaemia and malaria

	Panel A: Unadjusted impact estimates			
	Anaemia		Malaria	
Unadjusted	**PR (95% CI)**	**P value**	**PR (95% CI)**	**P value**
INFO	1.07 (0.82 to 1.39)	0.623	1.05 (0.44 to 2.49)	0.918
INFO+DELIV	0.86 (0.67 to 1.12)	0.268	0.18 (0.04 to 0.76)	0.02
Adjusted	**aPR (95% CI)**	**P value**	**aPR (95% CI)**	**P value**
INFO	0.97 (0.79 to 1.19)	0.770	0.95 (0.39 to 2.31)	0.915
INFO+DELIV	0.87 (0.70 to 1.09)	0.235	0.17 (0.04 to 0.75)	0.019
Intracluster correlation coefficient	−0.009		0.038	
Observations	716		716	

aPR, adjusted prevalence ratio.

Table 4 Intervention impact on ANC visit, IFA full compliance and SP compliance

	PANEL A: Unadjusted impact estimates							
	Any ANC		≥ 4 ANC visits		IFA full compliance		≥3 doses of SP	
Unadjusted	**PR (95% CI)**	**P value**	**PR (95% CI)**	**P value**	**PR (95% CI)**	**P value**	**PR (95% CI)**	**P value**
INFO	0.98 (0.95 to 1.02)	0.348	1.08 (0.85 to 1.38)	0.525	1.93 (0.86 to 4.30)	0.11	1.03 (0.87 to 1.21)	0.720
INFO+DELIV	1.00 (0.97 to 1.03)	0.829	1.41 (1.06 to 1.87)	0.019	7.67 (3.96 to 14.86)	<0.001	1.61 (1.43 to 1.81)	<0.001
Adjusted	**aPR (95% CI)**	**P value**	**aPR (95% CI)**	**P value**	**aPR (95% CI)**	**P value**	**aPR (95% CI)**	**P value**
INFO	0.98 (0.95 to 1.01)	0.248	1.05 (0.81 to 1.36)	0.692	2.00 (0.89 to 4.46)	0.093	1.03 (0.87 to 1.21)	0.728
INFO+DELIV	1.00 (0.96 to 1.03)	0.780	1.35 (1.02 to 1.78)	0.037	7.06 (3.68 to 13.51)	<0.001	1.60 (1.41 to 1.80)	<0.001
Intracluster correlation coefficient	0.019		0.170		0.158		0.319	
Observations	716		716		716		716	

* p<0.5, ** p<0.01, *** p<0.001
ANC, antenatal care; aPR, adjusted prevalence ratio; IFA, iron and folic acid; SP, sulfadoxine pyrimethamine.

Table 5 Intervention impact on miscarriage, stillbirth, birth weight and low birth weight

	Panel A: unadjusted impact estimates							
	Miscarriage		Stillbirth		Birth weight		Low birth weight	
Unadjusted	**PR (95% CI)**	**P value**	**PR (95% CI)**	**P value**	**Coeff (95% CI)**	**P value**	**PR (95% CI)**	**P value**
INFO	1.41 (0.69 to 2.86)	0.347	0.65 (0.33 to 1.29)	0.217	22.7 (–100.4 to 145.7)	0.715	0.70 (0.39 to 1.26)	0.232
INFO+DELIV	0.65 (0.24 to 1.73)	0.385	0.45 (0.23 to 0.89)	0.021	31.6 (–101.9 to 165.1)	0.639	0.68 (0.34 to 1.35)	0.267
Adjusted	**aPR (95% CI)**	**P value**	**aPR (95% CI)**	**P value**	**Coeff (95% CI)**	**P value**	**aPR (95% CI)**	**P value**
INFO	1.18 (0.57 to 2.42)	0.659	0.61 (0.32 to 1.17)	0.136	11.4 (–97.2 to 120.1)	0.835	0.64 (0.38 to 1.10)	0.106
INFO+DELIV	0.56 (0.20 to 1.58)	0.272	0.40 (0.21 to 0.76)	0.005	18.8 (–113.7 to 151.4)	0.778	0.69 (0.38 to 1.29)	0.248
Control group average (constant)	0.01 (0.01 to 0.02)	<0.001	0.01 (0.01 to 0.02)	<0.001	3026.3 (2940.4 to 3112.2)	<0.001	0.04 (0.03 to 0.05)	<0.001
Observations	716		716		557		557	

All estimates are based on linear regressions with clustering at the study cluster (n=91) level. Coefficients are displayed with 95% CIs in parentheses. Panel A is the unadjusted models control for home delivery and information interventions fixed effects only. Panel B is the adjusted models control for mother's and household's characteristics with clustering at the neighbourhood ('quartier') level.
*p<0.05, **p<0.01, ***p<0.001.
aPR, adjusted prevalence ratio.

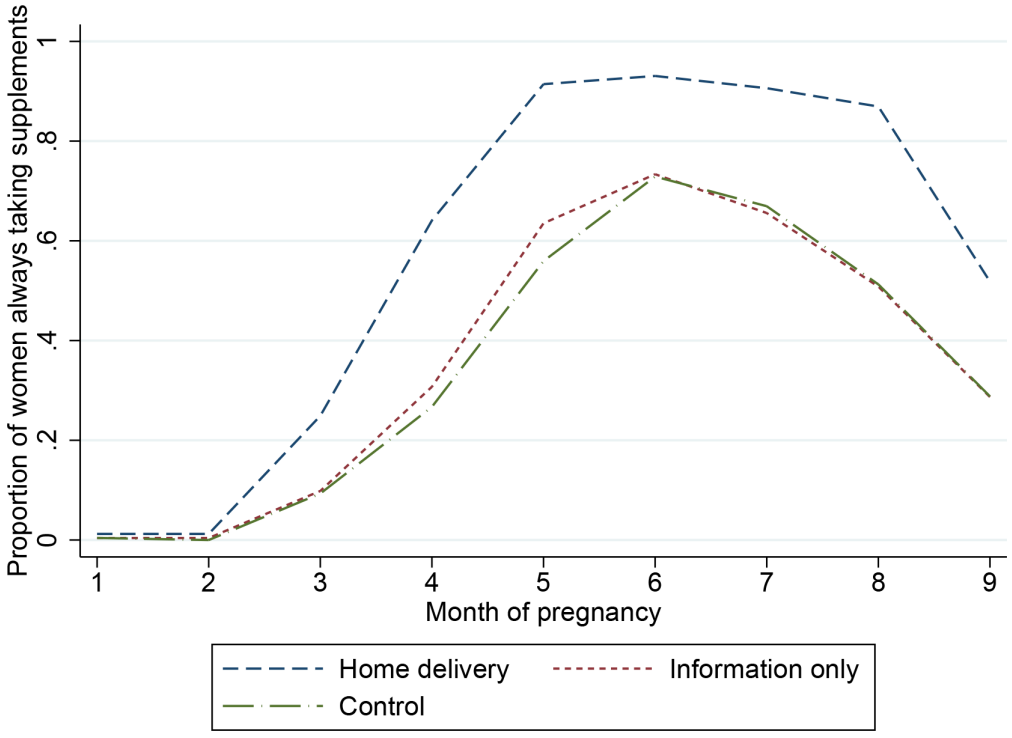

Figure 2 Compliance with daily IFA supplementation by month of pregnancy. IFA, iron and folic acid.

well as anaemia status by self-reported compliance with IFA guidelines. The average change in Hb levels among women reporting having taken supplements for less than 90 days was 7 g/L. Among women who reported to have taken supplements during 150 days or more, this change was 15 g/L (figure 3A). Half of the women (50.5%, n=362) taking supplements for 90 days or less were anaemic at endline; among women reporting 180 days or more of supplements, average anaemia rates were 27.7% (n=198) (figure 3B).

DISCUSSION

In this cluster randomised controlled trial, we assessed the effectiveness of targeted information sessions as well as home deliveries of supplements and chemoprophylaxis as strategies to increase coverage of essential ANC interventions in a typical rural low-income setting in Côte d'Ivoire. Neither intervention had a major impact on anaemia. The INFO+DELIV greatly reduced the postpartum malaria parasite prevalence. Given that only 4.8%

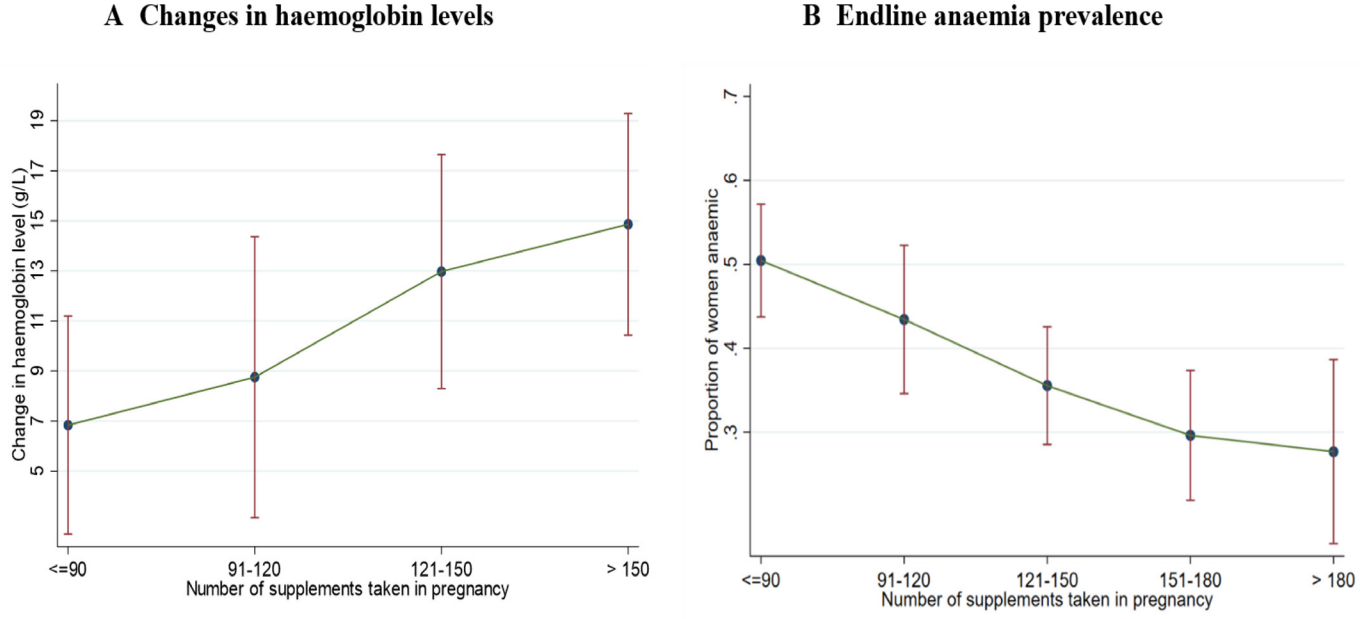

Figure 3 Compliance with IFA guidelines, changes in haemoglobin (Hb) levels and prevalence of anaemia. IFA, iron and folic acid.

of women in the control group tested positive for malaria using an RDT in the control group, the absolute reductions in malaria prevalence were however not very large (4 percentage points).

Given that women in the INFO+DELIV group were seven times more likely to comply with IFA supplementation (which seems consistent with a recent review of community-based distribution of IFA supplements,[27] the lacking intervention impact on anaemia is somewhat surprising. Earlier supplementation studies suggest that substantial improvements in maternal anaemia are feasible, in principle, with sustained intake of supplementation.[28–31]

Two factors might explain the relatively weak impact on anaemia in this study. First, supplementation was also relatively common in the control group of this trial, with an average of 112 doses (online supplemental table ST4) taken over the course of the pregnancy in the control group. Even though home deliveries increased compliance by 49 doses on average, this increase likely was not sufficient to lead to large reductions in anaemia. Second, and more importantly, our results suggest that routine supplementation alone is likely not sufficient to address the low average Hb levels in this setting. We found a mean Hb concentration of 95 g/L at the end of the first trimester (baseline), with 70.2% of women classified as anaemic. On average, Hb levels actually improved during pregnancy by 15 g/L across all groups, which is rather remarkable given the typically observed declines in Hb in between the first and third trimester due to haemodilution.[32] While we are not able to directly identify the aetiology and causes of anaemia in our study, previous evidence from the Taabo HDSS highlighted cellular iron deficiency as the main risk factor of anaemia among young women.[23] One potential strategy to address the high anaemia prevalence despite high IFA compliance would be to increase IFA dosing as part of routine ANC conditional on initially low levels of Hb as recommended by WHO.[33] Recent evidence from Tanzania also suggests that ferric carboxymaltose injections may offer a faster and more durable normalisation of Hb and ferritin concentrations among anaemic women.[34] Such higher dosing would, however, require both systematic initial Hb assessments and continued monitoring of pregnancies, which is challenging in many rural settings with often limited test equipment as well as limited staff.

As for malaria parasitaemia, a coverage of 61% for three doses of SP in the control group appears to be better than in many other countries in sub-Saharan Africa.[35] Several studies presented community-based delivery of SP as a potential mean to strengthen coverage and uptake of IPTp[36–38] and reduce malaria parasitaemia.[39] This is confirmed in our study, which shows that coverage rates above 95% are feasible with home deliveries. While the sample size of this study was too small to precisely estimate improvements in birth outcomes, the available data suggest substantial increases in the proportion of pregnancies resulting in live births in the INFO+DELIV arm (93.4% in the INFO+DELIV arm relative to 90.5% in the control group), with more than 50% declines in the proportion of pregnancies resulting in miscarriage and 40% reduction in the proportion of pregnancies resulting in stillbirths. It is not clear if these improvements are due to increased IFA supplementation, increased malaria chemoprophylaxis, or more frequent ANC visits—all three behaviours may have contributed to these improved outcomes, although the empirical links to stillbirths seem strongest for malaria infections.[40] It is also important to highlight that the deliveries of supplements within the study was done through trained nurses. Even though their primary objective was to just drop off the supplies, informal exchanges between pregnant women and study nurses were common, and likely also provided additional informational benefits to women in this arm. Larger future trials are needed to confirm these potentially large health benefits as well as to identify the main mechanisms underlying these changes.

Limitations of this study

The study had several limitation. First, as mentioned, our trial was not powered to detect changes in pregnancy outcomes, which hopefully can be addressed in larger future investigations. Second, we relied on women's self-reports for the secondary compliance measures, which may lead to an upward bias in the reported IFA supplementation coverage if there is a stronger social desirability bias in the intervention group.[41] Third, our malaria outcome only captures malaria infection status postpregnancy, which measures exposure to malaria infections throughout pregnancy only imperfectly. Furthermore, we used standard RDTs to assess infections, which are not yet able to detect malaria strains with HRP2 gene deletion.[42] This could potentially explain the relatively low parasite prevalence seen in this study. Our study also did not directly capture postpartum haemorrhage, which may worsen maternal anaemia post partum,[43] and could in part explain the high levels of anaemia despite supplementation in our trial. Lastly, it is possible that some of the information obtained during the home visits was shared with women from other villages, which may have resulted in relatively high uptake of IFA supplements in the control group. We tried to address these concerns through the cluster randomisation trial design, but cannot fully rule out some information transmission (even though the study team came across no evidence suggesting such spillovers across arms).

CONCLUSION

The results from this cluster randomised controlled trial conducted in an existing HDSS suggest that information plus direct home delivery of supplements can substantially improve malaria prophylaxis and IFA coverage. Our results also suggest that routine IFA supplementation is likely insufficient to address the high burden of anaemia in this population.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by—local Ethics Committee in Côte d'Ivoire (IRB0000111917)—national Review Board in Switzerland (Ethikkommission Nordwest- und Zentralschweiz; reference no. Req-2019-00617) Participants gave informed consent to participate in the study before taking part.

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