Treatment seeking, access to care and child health: Evidence from the Taabo health and demographic surveillance site (HDSS) in Côte d'Ivoire

INAUGURAL DISSERTATION

to

be awarded the degree of Dr. sc. med.

presented at

the Faculty of Medicine

of the University of Basel

by

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from

Côte d'Ivoire

Basel, 2022

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Basel, 20.06.2022

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Summary

Background: Despite substantial progress over the last two decades, under-five mortality remains high in many African settings. Current estimates suggest that Sustainable Development Goal 3.2 of reducing under-5 mortality (U5MR) to levels below 25 deaths per 1000 live births by 2030 will not be achieved in sub-Saharan Africa. In countries with high under-five mortality, further improvements in child mortality will only be possible if essential health services become available and accessible for those most in need. Access is a complex concept. Even if there is easy access to health facilities and an adequate supply of services, the extent to which specific populations access these services depends on the livelihood of the household, the community, and the wider society. Half of all under-five deaths are neonatal deaths many of which could be prevented through improved antenatal care (ANC). Access to adequate health care in remote areas, including prenatal and post-natal health services, as well as delayed attendance of health facilities have been identified as key determinants of the continued high burden of under-five mortality in these settings. Child mortality and its underlying factors vary substantially across and within countries. Thus, a local understanding of under-five mortality and its relation with treatment seeking and access to care is important in the development of local sustainable intervention strategies aiming to reduce the continued high burden of under-five mortality.

Goal and specific objectives: The overall objective of this PhD project was to identify effective ways to improve health service access and child health in low and middle-income country settings in general, and in the Taabo health and demographic surveillance system (HDSS) in Côte d'Ivoire in particular. To address this general objective, we pursued three specific aims. First, we aimed to identify the most critical household and community characteristics influencing treatment seeking for under-five children. Second, we assessed whether the construction of additional health facilities can improve treatment seeking and child health outcomes. Third, we assessed whether access to essential antenatal services as well as maternal and child health can be improved through community programmes.

Methods: The thesis pursued three complementary approaches to address key challenges in health care access and delivery. For the first aim, we used prospectively collected data from 736 non-fatal and 82 fatal cases reports of under-five children during the year 2017 from the Taabo HDSS. Caregivers of children with a recent non-fatal illness episode residing in the Taabo health district, south-central Côte d'Ivoire were interviewed using a social autopsy questionnaire. For the second aim, we used detailed demographic surveillance data obtained

from the Taabo HDSS. Since 2009, the Taabo HDSS has been continuously monitoring a population of over 40,000 inhabitants by reporting vital events such as pregnancies, births, deaths, and migration through surveillance rounds. We used panel data from the HDSS covering all children under age five born in the HDSS between 2010 and 2018. Between 2010 and 2018, four new health facilities were constructed within the Taabo HDSS area with the ambition to reduce distance and travel times to health facilities, and ultimately to improve health outcomes. We conducted a quasi-experimental study assessing the impact of newly constructed facilities. For the third aim, we conducted a three-arm cluster Randomized Control Trial (cRCT) to assess the effectiveness of two complementary strategies in increasing iron and folic acid supplementation and malaria chemoprophylaxis coverage among pregnant women. We randomly assigned 39 clusters to the control group, 39 clusters to the information group, and 40 clusters to the information plus home delivery of iron and folic acid (IFA) supplements group. Trial participants were pregnant women who were at least 15 years old and in their first or second trimester. The interventions consisted of an information package, designed to increase uptake of essential antenatal services through targeted information, and an information plus home delivery intervention, designed to provide both information and immediate access to supplements and chemoprophylaxis. Through an end line survey within the first two weeks after delivery, we assessed the relative effectiveness of each intervention.

Results: In this primarily rural part of Côte d'Ivoire, treatment seeking was largely directed towards modern medicine. In non-fatal cases, modern treatment seeking was associated with child-specific factors (age, relationship with caregiver), caregiver education, and household proximity to the nearest health facility as well as clinical signs such as fever, severe vomiting, inability to drink, convulsion, and inability to play. In fatal cases, modern healthcare was sought only for signs of lower respiratory disease. The lack of awareness regarding disease-related clinical danger signs were identified as the potential barriers to accessing health care.

The results of our quasi-experimental study showed that local provision of new health facilities declined the average distance to the nearest health facility. However, this decline did not improve neonatal survival outcome or maternal health services utilization. Positive impacts were found for post-neonatal infant mortality, which was reduced by 46%.

Our intervention trial suggest that community-based programs can improve compliance with IFA supplementation and malaria chemoprophylaxis during pregnancy. High compliance with

Sulfadoxine-pyrimethamine (SP) treatment was sufficient to largely remove the risk of malaria infection. Increased compliance with standard IFA supplementation was insufficient to address the high prevalence of postpartum anemia in the study setting.

Conclusion:

The findings presented here from a primarily rural part of Côte d'Ivoire suggest that a large proportion of caregivers seek modern care for their under 5-year-old children, but that some mild and severe illness cases continue to remain untreated. Interventions promoting prompt healthcare seeking and the recognition of danger signs may help improve treatment seeking in rural settings of Côte d'Ivoire, and can potentially help further reduce under-five mortality. Our study suggests that local construction of new health centers in a mainly rural part of south-central Côte d'Ivoire may have only relatively limited impact on healthcare utilization and overall population health. More research will be needed to better understand the somewhat limited impacts seen in this study as well as to identify the health infrastructure needed more generally for improving health outcomes in this setting. The results from our trial suggest that combining information with direct home delivery of supplements and chemoprophylaxis can increase compliance with IFA supplementation and malaria prevention and reduce the risk of malaria infection. However, more powerful interventions are likely needed to address the high burden of anemia in this population.

Acknowledgements

First and foremost, I am deeply indebted and grateful to Prof. Dr. Günther Fink (Swiss TPH), who acted as my main thesis supervisor. Thank you very much indeed, Dr. Fink, for your availability, continuous support and advice, patience during my PhD study, belief in me, and for the funding support that has allowed me to undertake these studies. I am most grateful to Prof. Dr. Nicole Probst-Hensch for her invaluable supervision, support and insightful comments and suggestions. I am also grateful to Prof. Dr. Isaac Tiembre who kindly accepted to act as an external referee for this thesis. I further thank Prof. Dr. Jürg Utzinger for his unwavering support and his interest in each of my manuscripts. You are the one who allowed the first contact between Dr. Fink and me. Thank you for trusting me. Many words of thanks go to Christine Mensch for all her support throughout the PhD. I would like to express my sincerest words of thanks to Mr. ISSA Issouf and Eveline Hürlimann (my guardians in Basel) for their hospitality throughout the PhD.

Special thanks have to be addressed to my parents and my wife for their tremendous understanding and encouragement. Of course, I would also like to thank all district authorities, village authorities and health care workers and – last but not least – all individuals and families in the Taabo region, who participated in our studies or supported our work in one or the other way. Thank you very much to the Direction of the CSRS for having allowed this alternation between training and work. Many thanks to all the colleagues of the Taabo health demographic surveillance system for their support and facilitation of the study and the continuous demographic data collection.

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List of abbreviations

ANC	Antenatal Care
CHERG	Child Health Epidemiology Reference Group
CSRS	Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
HDSS	Health and Demographic Surveillance System
IFAS	Iron and Folic Acid Supplementation
INDEPTH	International Network for the continuous Demographic Evaluation for Populations and Their Health
INFO	Information only
INFO+DELIV	Information plus delivery
INS	Institut National de la Statistique
IPTp	Intermittent Preventive Treatment of Malaria in Pregnancy
LMICs	Low- and Middle-Income Countries
MDG	Millenium Development Goal
MSLS	Ministère de la Santé et de la Lutte Contre le Sida
NCDs	Non-Communicable Diseases
NTDs	Neglected Tropical Diseases
ODK	Open Data Kit
PHC	Primary Health Care
RDT	Rapid Diagnostic Test
SDGs	Sustainable Development Goals
SP	Sulfadoxine-Pyrimethamine
SSA	sub-Saharan African
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Swiss TPH	Swiss Tropical and Public Health Institute
UNICEF	United Nations International Children's Emergency Fund
UNI-IGEME	United Nations Inter-agency Group for Child Mortality Estimation
VA	Verbal Autopsy
WFP	World Food Programme
WHO	World Health Organization

1. Introduction

The Sustainable Development Goals (SDGs) set in 2015, call for all countries to reach an under-5 mortality rate of at least as low as 25 deaths per 1000 livebirths and a neonatal mortality rate of at least as low as 12 deaths per 1000 livebirths by 2030 (UN, 2022). In Côte d'Ivoire, in 2020, under-five mortality was 78 deaths per 1,000 live births and neonatal mortality 33 deaths per 1,000 live births (UN-IGME, 2019). Under-five and neonatal mortality should be reduced by 53 and 21, respectively, until the set year. The proposed thesis aims not only to improve our understanding of the main drivers of under-five mortality in low-income settings, but also hopes to identify key interventions for reducing the continued high burden of mortality in this setting.

1.1. Definition of mortality

Mortality refers to the number of deaths caused by the health event under investigation. It is often presented as a rate or as an absolute number (Hernandez JBR, 2021). A mortality rate is a measure of the frequency of occurrence of death in a defined population during a specified interval (Health et al., 2006). An age-specific mortality rate is a mortality rate limited to a particular age group.

1.1.1. Definition of child mortality

In demography, child mortality or under-five mortality rate is the probability for a child to die before reaching the age of five, if subject to current age-specific mortality rates. Under-five mortality rate was a Millennium Development Goal (MDG) indicator that summarizes the living conditions in which children (and other members of society) live, including their health care (UN-IGME, 2019), and also part of the SDGs. Under-5 deaths occur at different ages. Data on child deaths should be disaggregated by age and geographical location to identify vulnerable populations. Studies examine age-specific mortality for under-five children: neonatal mortality (i.e., the probability of dying within the first 30 days of life), postneonatal infant mortality (i.e., the probability of dying between days 30 and 364 of life) , infant mortality (i.e., the probability of dying before the first birthday) and child mortality (i.e., the probability of dying between the first and fifth birthdays), separately (Mejia-Guevara et al., 2019; Rajaratnam et al., 2010; Wang H et al.; H. Wang et al., 2014).

1.1.2. Burden of child mortality

Despite substantial global progress has been made in reducing childhood mortality since 1990, the burden of child mortality remains large. Worldwide, under-five deaths have declined from 12.6 million in 1990 to 5.0 million in 2020 (UN-IGME, 2021). Under-five mortality is declining unevenly across countries and age groups. Assessing the achievability of the Sustainable Development Goals (SDGs) mortality targets by 2030 (2050 when possible) for 31 Sub-Saharan African (SSA) countries, marked differences were found in mortality profiles by age and levels across countries over time (Mejia-Guevara et al., 2019). An analysis of the distribution of under-five deaths in 64 low-and middle-income countries revealed that an increasing proportion of under-5 deaths occurs in the neonatal period (Zhihui Li et al., 2021). In 2020, nearly half (47 per cent) of all under-five deaths occurred during the neonatal period. SSA ranks first with the highest rates of mortality in the world at 74 (68-86) deaths per 1000 live births (Figure 1.1) and represents 54% of all under-five deaths globally (UN-IGME, 2021).

From 1990 to 2020, declines in deaths in the first month of life have been slower than the declines in deaths of older children. In the same period the overall mortality among children under age 5 decreased by 78 (60 - 100) per 1000 live births with 2.5 (1.4 - 3.1) annual rate of reduction. If further partitioned into early and later childhood, neonatal mortality declined from 104 (98 - 111) deaths per 1000 in 1990 to 58 deaths (46 - 72) per 1000 in 2020 whereas infant mortality increased from 52 (49 - 56) deaths per 1000 to 53 (42 - 65) deaths per 1000 (UN-IGME, 2021).

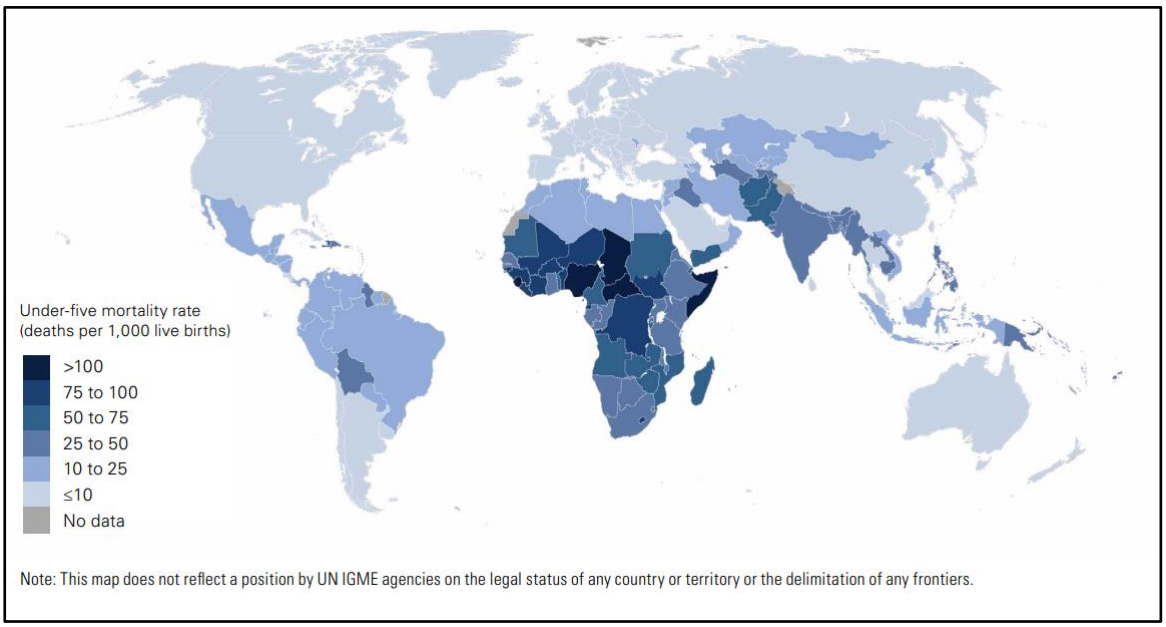

Figure 1-1: Under-five mortality rate (deaths per 1,000 live births) by country, 2020 (UN-IGME, 2019)

1.2. Etiology of infant and child mortality

Understanding the etiologies of child deaths is critical for designing health systems interventions, and may help directing efforts towards achieving the ambitious SDG goals. SDG 3.2 aims to end preventable deaths of newborns and children under 5 years of age by 2030, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births. This requires an adequate understanding of the causes of deaths and barriers to healthcare for children. Due to the absence of robust registration policies for deaths and the underlying causes, very little is known about the mortality and causes of death in remote areas in large parts of sub-Saharan Africa (Mathers et al., 2006). To address this situation, a growing number of studies relies on community-based data sources such as verbal autopsies and social autopsies surveys to fill the data gap on biological and non-biomedical causes of child mortality (Basera et al., 2021; Gupta et al., 2018; Moyer et al., 2017).

1.2.1. Biological causes of death

In pursuit of the goal of reducing child mortality, knowledge of the biological causes of child death is important. The continuously high burden of child deaths are a direct result of infectious diseases, including pneumonia, diarrhea and malaria, along with pre-term birth complications, birth asphyxia, trauma and congenital anomalies (WHO, 2020). A recent systematic review analysis of global, regional, and national causes of under-5 mortality in 2000–2019 reported 5.30 million deaths among children younger than 5 years, primarily due to preterm birth complications (17.7%), lower respiratory infections (13.9%), intrapartum-related events (11.6%), and diarrhea (9.1%). Overall, 49.2% of deaths were due to infectious diseases (Kolola et al., 2016; Perin et al., 2022; Wambui et al., 2018).

1.2.2. Non-biomedical causes of death

Verbal autopsies are conducted to determine the most likely biomedical cause of death. Social autopsies are conducted in the same way to determine household, community and health system factors that have contributed to the failure of saving a child and to identify missed opportunities. The success of programs to reduce child mortality depends critically on a better understanding of the modifiable cultural, social and health factors that influence access to and use of health care. Social autopsy questionnaires are based on the three delays model covering (i) the delay of seeking care; (ii) the delay related to transport and distance; and (iii) health services delays

(thus delay in administering appropriate care). The tools summarize essential information on home care practices, care seeking, treatments and compliance, and the reasons for taking particular actions during the fatal illness of a child in several countries (Kalter et al., 2011; Thaddeus & Maine, 1994).

1.3. Health care seeking behavior

Health care seeking behavior is defined as any action taken by individuals who suspect they – or their dependents - are ill to find an appropriate remedy (Ward et al., 1997). People seek health care services differently. Some seek formal health care immediately, while others wait until their health status has seriously deteriorated before initiating a sequence of measures to remedy the perceived illness. For under-five children, health seeking behavior is preceded by a decision making process which is mainly the responsibility of the parent or caregiver. Early decision-making and appropriate treatment are likely to slow the progression from mild disease to severe disease and death (UN-IGME, 2019). A study investigating health care seeking behavior for children with acute childhood illnesses in 24 countries in sub-Saharan Africa showed that appropriate health care was not always sought for under-five childhood illnesses (Yaya et al., 2021). Indeed, households face a number of financial and non-financial barriers to access adequate health care. Such obstacles are common in low- and middle-income countries where health care seeking behavior is a multidimensional issue (Obrist et al., 2007), and factors determining health behaviors go beyond the individual level and are rather dynamic, collective and interactive.

1.3.1. Health care access barriers

Facing disease and morbidity, mothers or child caregivers depending on disease perception rely on diverse and plural treatment seeking behaviors to choose the best option between self-medication, traditional or modern medicine (Ilunga-Ilunga et al., 2015; Towns et al., 2014). When deciding to seek conventional care, caregivers come up against a variety of health care access barriers. Health service studies apply determinants' models and evaluate a set of five dimensions, such as availability, affordability, accessibility, adequacy, and acceptability to identify health care access barriers in terms of health services utilization (Andersen, 1995; Fiedler, 1981; Penchansky & Thomas, 1981). In order to reduce disparities and increase access to health care in low-income countries, particularly in Africa, Obrist et al. (2007) developed the "Health Access Livelihood Framework" (Figure 1.2) combining health service and health-

seeking approaches and addressing access in five complementary dimensions in a livelihood insecurity basis (Obrist et al., 2007).

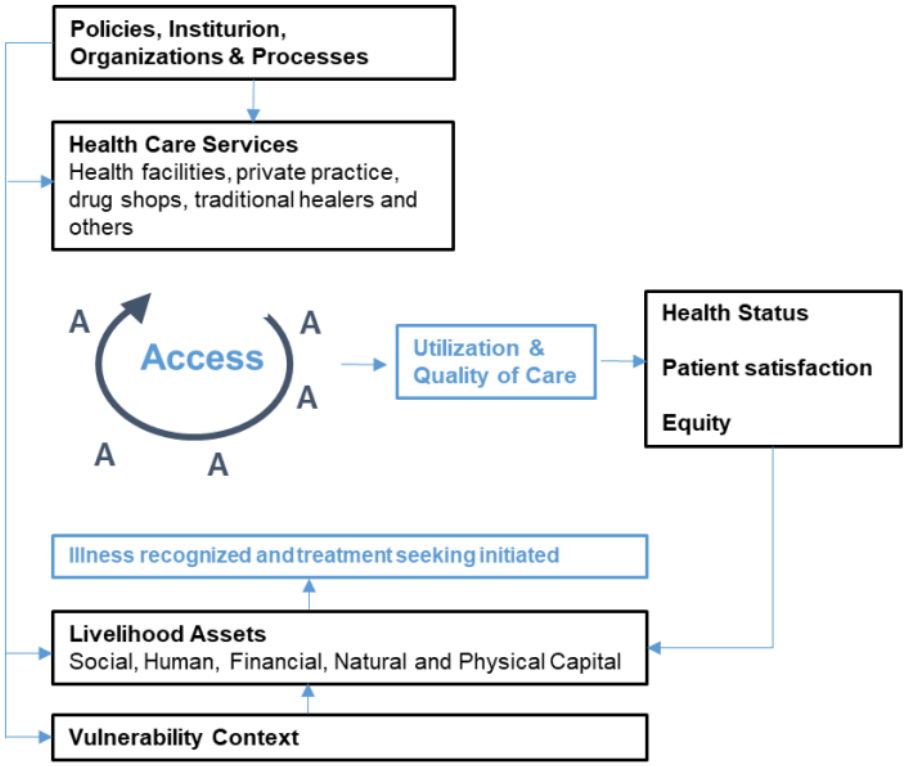

Figure 1-2: The Health Access Livelihood Framework by Obrist et al. (2007)

The five dimensions of access (availability, accessibility, affordability, adequacy, and acceptability) (Table 1.1) influence the process of health seeking. Access improves as the health care services and the broader policies, organizations, and processes that govern the services better suit the livelihood assets people can mobilize in particular vulnerability contexts.

Table 1-1: Five dimensions of access to health services

Dimensions	Questions
Availability: The existing health services and goods meet clients' needs.	What types of services exist? Which organizations offer these services? Is there enough skilled personnel? Do the offered products and services correspond with the needs of poor people? Do the supplies suffice to cover the demand?
Accessibility: The location of supply is in line with the location of clients.	What is the geographical distance between the services and the homes of the intended users? By what means of transport can they be reached? How much time does it take?
Affordability: The prices of services fit the clients' income and ability to pay.	What are the direct costs of the services and the products delivered through the services? What are the indirect costs in terms of transportation, lost time and income, bribes, and other "unofficial" charges?
Adequacy: The organization of health care meets the clients' expectations.	How are the services organized? Does the organizational set up meet the patients' expectations? Do the opening hours match with schedules of the clients, for instance the daily work schedule of small-scale farmers? Are the facilities clean and well kept?
Acceptability: The characteristics of providers match with those of the clients.	Does the information, explanation, and treatment provided take local illness concepts and social values into account? Do the patients feel welcome and cared for? Do the patients trust in the competence and personality of the health care providers?

doi:10.1371/journal.pmed.0040308.t001

1.3.2. Challenges of health care access in rural settings

Access to health care is recognized as a fundamental human right globally. People living in rural areas make up about half of the world's population (Working Party on Rural Practice, 2013). Rural settings have a number of health disadvantages compared to urban areas, including less access to health care and worst health conditions. Major challenges faced in rural areas of most countries include transportation and communication, funding inequalities in health, and shortage and unequal distribution of healthcare personnel, with worse working conditions (International Labour Office, 2015; Strasser, 2003). Due to the greater socioeconomic vulnerability of the population in rural and remote territories, the majority of people still suffer financial barriers. Health insurance programs leave out the rural poor, making it difficult to cover medical care when you have to pay out of pocket, even in an emergency (Fenny et al., 2018). In rural and remote areas, primary health care is often the only resource to health (Strasser, 2003; Working Party on Rural Practice, 2013).

Furthermore, the first 28 days of life (neonatal period) is the most vulnerable time for a child's survival (Kokebie et al., 2015). Thus, to overcome the high burden of under-five mortality, primary health care units in rural areas need to provide effective neonatal health care.

Unfortunately, the majority of primary health centers only have limited capacity to deliver quality neonatal health services (Yitbarek et al., 2019). Even though rural health centers are available in rural areas, their access and utilization often remain limited. A study in rural areas of Zambia highlights poor quality of health services, unavailability of medicines, financial constraints, weak outreach programs, bad scheduling of health programs, poor communication, long distance to rural health centers and low awareness levels of the importance of taking children for child health campaigns or routine services among caretakers as key barriers (Halwindi et al., 2013).

1.4. Overview of maternal and child health in Côte d'Ivoire

In the Taabo HDSS and other rural areas of Côte d'Ivoire, infectious diseases are still the dominant cause of death (Kone et al., 2015b). In Côte d'Ivoire, intermittent preventive treatment of malaria in pregnancy (IPTp) has been adopted since 2005. However, the effectiveness of protecting the mothers and unborn children against malaria depends on the adherence to this policy, on coverage, and on the number of antenatal care visits of the expectant mothers (RBM Partnership to End Malaria, 2015; World Health Organization, 2014b). In terms of current health service access, the proportion of the population living within 5 km of a health center increased from 44% in 2012 to 67% in 2015 in Côte d'Ivoire (Institut National de la Statistique - INS/Côte d'Ivoire and ICF International, 2012). At the same time, only a minority of women received antenatal iron supplementation consistently throughout their pregnancy and less than one third of women received IPTp (World Health Organization, 2004). However, assessments on the use and the impact of these services by the communities concerned are virtually non-existent. A recent study identified a number of risk factors for an unfavorable fetal or early neonatal outcome, involving the expectant mothers' socio-demographic characteristics, use of preventive measures and health services, and the experience of pregnancy-related or concomitant health conditions (Kone et al., 2018). It appeared that only a small proportion of pregnant women received and benefitted from standard prevention packages during antenatal visits, such as a rubella test (4.8%), HIV testing (18.6%), iron/folic acid supplementation (28.0%), and 2 doses of tetanus vaccination (44.3%). These observations suggest either a generally low quality of provided antenatal care or the presence of stock-outs for material needed for essential interventions.

1.5. Study area

Côte d'Ivoire is a country located in West Africa with a population of 28 088 455 inhabitants. With an area of 322,462 km2, it is bordered by Mali to the northwest, Burkina Faso to the northeast, Ghana to the east, Liberia to the southwest, Guinea to the northwest and the Atlantic Ocean to the south (Figure1.3). The economy is mainly based on agriculture, with coffee and cocoa production booming in the last two decades.

The field work for this PhD thesis was conducted in the Taabo HDSS, located 160 km north-west of Abidjan, the economic capital of Côte d'Ivoire. The study area is mainly rural and located between the forest and the savannah, which makes it a clear epidemiological transition zone. The Taabo HDSS is situated in the health district of Tiassalé, which has an estimated population of 200,000 people. In 2008, the sub-department of Taabo was chosen as first HDSS in Côte d'Ivoire.

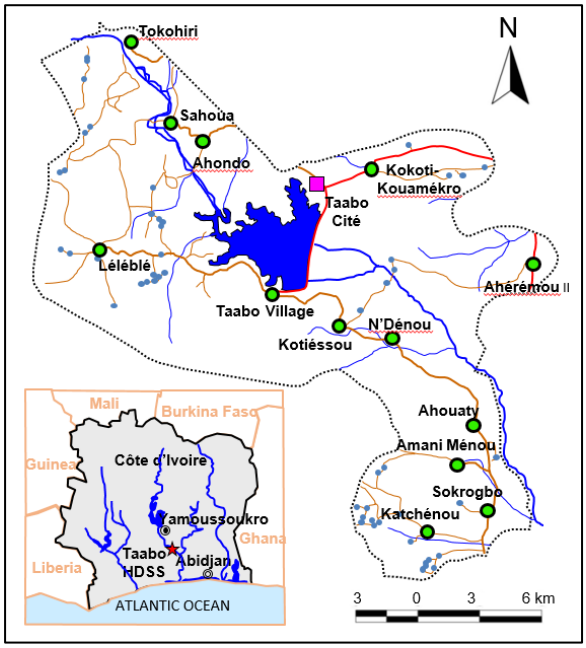

Figure 1-3: Map of the study area (Koné et al., 2015a)

Four partner institutions set up the Taabo HDSS: the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS), the Université Félix Houphouët-Boigny (FHB), the Swiss Tropical and Public Health Institute (Swiss TPH) and Fairmed. Demographic data (i.e. pregnancy, birth, death, and in- and out-migration) are collected longitudinally at the individual and household level, usually in three data collection rounds per year (Kone et al., 2015a) (Figure 1.4). Deaths

are reported by key informants and verbal autopsies are conducted using standard protocols to determine causes of death.

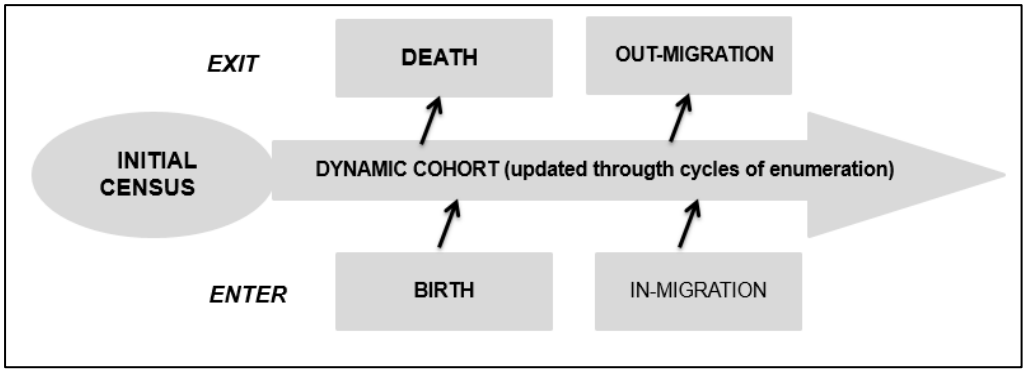

Figure 1-4: Functioning of a health and demographic surveillance system (HDSS)
Source: www.indepth.com, access 30 March 2022.

A key eco-epidemiological characteristic of the Taabo HDSS is a large embankment dam (maximum length: 7.5 km) constructed across the Bandama River in the late 1970s. The dam was constructed for hydroelectric power production (N'Goran et al., 1997) and forms a reservoir with a surface area of approximately 69 km^2.

The Taabo HDSS was established to serve as a platform for evaluating interventions and health systems strengthening, with the ultimate goal of reducing mortality and morbidity, especially due to malaria and NTDs.

1.6. Goal and specific objectives

The PhD thesis presented here is part of a 3-year project entitled "Treatment seeking, access to care and child health: Evidence from the Taabo HDSS in Côte d'Ivoire", funded by the Eckenstein-Geigy Professorship in collaboration with Swiss Tropical and Public Health Institute (Swiss TPH) and the CSRS. In this thesis, we aim to first improve our general understanding of barriers to health service access in the context of rural Côte d'Ivoire using novel data set from the HDSS in Taabo. In a second step, we analyze the impact of health center construction as a supply side intervention to improve access currently pursued by the government. Last, we assess new community based models to increase access to essential antenatal services through a randomized controlled trial.

The overarching goal of my thesis is to identify effective ways to improve health service access and child health in low and middle-income country settings in general, and in the Taabo HDSS

in Côte d'Ivoire in particular. In order to achieve this aim, the following three specific objectives were pursued:

i. To identify the most critical household and community characteristics influencing treatment seeking for under-five children. To elicit the effect of household and community factors on treatment seeking for children with sickness in the Taabo HDSS and understand the relationship between risk exposure and treatment seeking.

ii. To assess whether additional health facilities construction can improve treatment seeking and child health outcomes. To assess the impact of additional health facility construction on antenatal care attendance, facility-based deliveries and child health.

iii. To assess whether access to essential antenatal services and maternal and child health can be improved through community programs. To estimate the programs impact on the prevalence of postpartum anemia, malaria infection as well as on the coverage of iron and folic acid and malaria chemoprophylaxis.

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2. Paper 1 – Determinants of Modern Paediatric Healthcare Seeking in Rural Côte d'Ivoire

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This article has been published in

International Journal of Public Health 2022, 66: 1604451

2.1. Abstract

The objective was to determine factors that influence healthcare seeking among children with fatal and non-fatal health problems. Last disease episodes of surviving children and fatal outcomes of children under 5 years of age were investigated by means of an adapted social autopsy questionnaire administered to main caregivers. Descriptive analysis and logistic models were employed to identify key determinants of modern healthcare use. Overall, 736 non-fatal and 82 fatal cases were assessed. Modern healthcare was sought for 63.9% of non-fatal and 76.8% of fatal cases, respectively. In non-fatal cases, young age, caregiver being a parent, secondary or higher education, living <5 km from a health facility, and certain clinical signs (i.e., fever, severe vomiting, inability to drink, convulsion, and inability to play) were positively associated with modern healthcare seeking. In fatal cases, only signs of lower respiratory disease were positively associated with modern healthcare seeking. A lack of awareness regarding clinical danger signs was identified in both groups. Interventions promoting prompt healthcare seeking and the recognition of danger signs may help improve treatment seeking in rural settings of Côte d'Ivoire and can potentially help further reduce under-five mortality.

Keywords: determinants, child health, modern healthcare, Côte d'Ivoire, health and demographic surveillance system, mortality, Taabo

2.2. Introduction

Despite considerable progress made over the past two decades, under-five mortality remains high in many low- and middle-income countries (LMICs). Although countries have committed to providing equitable access to quality care for their citizens within the 2030 Agenda for Sustainable Development (2030 Agenda, in short), this objective remains a major challenge (Oliver & Mossialos, 2004), particularly in settings characterized by persistent socioeconomic disparities in health and access to healthcare services (D. R. Gwatkin, 2001; Davidson R. Gwatkin et al., 2005; Victora et al., 2003). To reach the ambitious mortality reduction goals set in the 2030 Agenda, improvements at the health system levels will likely have to go beyond basic provision of medical care (Amy. BS et al., 2017; Fund, 2018; Schoeps et al., 2011).

An estimated proportion of 50% of the modifiable determinants of health hashave been attributed to community specific factors, which often determine an individual's willingness and ability to access healthcare services (Fund, 2018; Oliver & Mossialos, 2004). To deepen the understanding of the biomedical and social factors that influence disease progression, particularly in potentially fatal cases, social autopsy using a pathway analysis approach has been introduced in some countries (Boschi-Pinto et al., 2010; Kalter et al., 2011; Koffi et al., 2020). Different from (complementary) verbal autopsies focusing on biomedical causes (Thomas et al., 2018), social autopsies directly aim at determining factors contributing to health outcomes at the household, community, and health systems level. An improved understanding of these factors at different levels might aid prevention of morbidity and mortality, which seems particularly important in the context of infectious diseases (e.g., malaria), where timely provision of quality care is essential for patient survival. In this study, we draw on rich social autopsy data obtained from the Taabo health and demographic surveillance system (HDSS), located in the south-central part of Côte d'Ivoire to identify key determinants of modern healthcare seeking for paediatric illness.

2.3. Methods

2.3.1. Ethics statement

This study received ethical approval from Côte d'Ivoire (reference no. 172/MESRS/DGRSIT/tm) and Switzerland (reference no. EKBB: 263/13). Written informed consent was obtained from parents or legal guardians. Participants could withdraw from the study anytime without further obligations.

2.3.2. Study setting

The study was conducted in the Taabo HDSS. Established in late 2008 with an initial population of 37,792 (Kone et al., 2015a; Kone et al., 2015b; Stock, 1983), by the end of 2018, the population in the Taabo HDSS had grown to approximately 48,000. The Taabo HDSS is located in a transition zone between tropical rain forest in the South and the savanna in the North, in a primarily rural area. There are 13 villages, over 100 hamlets, and one small town (i.e., Taabo-Cité). The health system is composed of a small hospital in Taabo-Cité and 10 primary healthcare centres located in the main villages. In the hamlets, no health facilities are available but community health workers (CHWs) provide basic health advice, guidance and services. According to verbal autopsy data collected over 3 years (from 2009 to 2011), 85% of child deaths were due to infectious diseases, with most deaths attributed to malaria and respiratory tract infections (Kone et al., 2015b; P. K. Streatfield et al., 2014).

2.3.3. Study design and data collection

We designed a prospective study with two complementary samples; 1) a sample of fatal episodes; and 2) a sample of non-fatal morbidity episodes. We defined fatal cases as children aged 1–59 months, who died in the Taabo HDSS within a 1-year period from January 2017 to January 2018. Child deaths were identified using a standard key informant system as part of regular demographic data collection rounds within the Taabo HDSS. Non-fatal cases were randomly selected in the main villages from households inhabited by at least one child under the age of 5 years surveyed between January 2017 and January 2018. Overall, there were 780 household visits. During the visits, all illness episodes (not resulting in death) among children under the age of 5 years in the preceding 30 days were recorded. Whenever multiple episodes of illness occurred within the past 30 days, only information on the most recent illness episode was collected. Of note, both for fatal and non-fatal cases, the study excluded newborns (< 29 days of age), as to explicitly focus on the post-natal period).

2.3.4. Social Autopsy

Social autopsy consisted of a face-to-face interview with the primary caregivers, usually the mother of the child, 2–8 weeks after the child's death. The questionnaire was inspired by the Child Health Epidemiology Reference Group (CHERG) and the International Network for the continuous Demographic Evaluation for Populations and Their Health (INDEPTH) social autopsy questionnaires (Kalter et al., 2011). After initial questions on household characteristics,

child survival, signs and symptoms observed as well as disease recognition, questions explored the healthcare seeking behaviour (i.e., decision-making, choice and source of different home-based treatments, traditional and modern medicine providers, potential access barriers including accessibility, acceptability, availability, affordability, adequacy, and cultural factors). Presenting signs and symptoms were investigated with a special focus on those that 1) give information on the general state of the child; 2) indicate potentially severe disease; and 3) likely warrant consultation of a modern healthcare facility. The questionnaire used for non-fatal cases was somewhat shorter, but was designed to cover the main aspects of the social autopsy form. The Open Data Kit (ODK) was used to build questionnaires in the national language French. Tablets were used for data collection by trained senior staff. ODK data as well as pictures of signed consent forms were uploaded and stored on a secure server.

2.3.5. Quantitative variables

The primary outcome of interest was a binary variable for modern healthcare seeking for a given illness episode. All caregivers who answered "yes" to the question "Have you consulted a provider of modern medicine?" were considered to have used modern medicine. Modern healthcare providers included hospitals and public or private health centers. Explanatory variables included 1) sociodemographic characteristics of the concerned child (i.e., age, sex, twin status, and relationship with the caregiver); 2) household and caregivers' characteristics (socioeconomic status, distance to nearest health facility, educational attainment, age, etc.); and 3) signs and symptoms observed by the caregivers. Socioeconomic status was determined using a household-based asset approach using principal component analysis (PCA) with stratification into wealth quintiles (Filmer & Pritchett, 2001). We relied on household and health centers' geographical coordinates to estimate the distance from child's place of residence to the nearest health facility by means of Statageodist package (Picard, 2010).

2.3.6. Statistical analysis

All statistical analyses were performed in Stata version 15.0 (StataCorp; College Station, TX, United States) (StataCorp, 2017). Data records from caregivers with complete information on disease-related morbidity were considered for analysis. Multivariable standard logistic regression models were estimated to identify associations between modern healthcare seeking and a range of child, household, and community characteristics. Logistic regression results were

presented as marginal effects (dy/dx), including 95% confidence interval (CI). Differences and relationships with a p-value below 0.05 were considered statistically significant.

2.4. Results

2.4.1. Study sample

Overall, 754 children with recent non-fatal episodes and 104 deaths of children aged 1–59 months were identified through household visits in the Taabo HDSS over a 1-year period. Among the non-fatal cases, 736 had complete data records, and hence, were considered as final study sample (Appendix Supplementary Materials SF1).

Among the fatal cases, 22 were excluded due to incomplete information, resulting in a final analytical sample of 82 fatal cases (Appendix Supplementary Materials SF2).

2.4.2. Caregivers, child socio-demographic characteristics, and modern treatment seeking during child's illness

Table 2.1 summarizes socio-demographic characteristics of caregivers and children, stratified by whether or not children were seeking modern care, both for fatal and non-fatal cases. Of the 736 children in the non-fatal sample, there were more boys (n = 412) than girls (n = 324). Among the 82 fatal cases, there were 43 boys and 39 girls. On average, children in the fatal cases group were younger (mean age: 14.9 vs. 29.8 months in the non-fatal group). While in the non-fatal cases, 12.4% of children were younger than 1 year, this age group accounted for 47.6% among fatal cases. More than 85% of caregivers were 20 years and above. Among both non-fatal and fatal cases, more than 80% of children lived in households headed by at least one biological parent or grandparent. In general, the children were taken care of by either parents (fatal cases: 51.2% vs. non-fatal cases: 54.8%) or grandparents (fatal cases: 43.9% vs. non-fatal cases: 34.8%). Grandparents of non-survivors were less likely to have sought care at health services compared to parents or other caregivers (fatal cases grandparents: 61.1% vs. fatal cases biological parents: 85.7% or fatal cases other parents: 100%). In the group of surviving children, care was less frequently sought for children not being a direct offspring. When the main caregiver was the biological mother of the child, she was also asked about the number of live births and previous experiences of child loss. On average, mothers of fatal cases had given birth more often (fatal cases: 4.2 vs. non-fatal cases: 3.7 live births) and had experienced a previous loss of a child more frequently than mothers of non-fatal cases (44.3% vs. 30.1%). Mothers who had already lost a child were overall less likely to use modern healthcare than those who

had not experienced a loss (fatal cases: 81.5% vs. non-fatal cases: 55.9%). More than half of the main caregivers never attended school (54.5% in non-fatal cases sample vs. 80.5% in the fatal case sample). More than 80% of the children lived in households within 5 km of modern healthcare services (85.4% in non-fatal cases vs. 89.0% in fatal cases).

Table 2-1: Socio-demographic characteristics, stratified by modern healthcare seeking for fatal and non-fatal cases. Social Autopsy Project, Côte d'Ivoire, 2017.

	Non-fatal cases			Fatal cases		
	N (%)	Modern healthcare seeking	No modern healthcare seeking	N (%)	Modern healthcare seeking	No modern healthcare seeking
Full sample	736 (100)	470 (63.9)	266 (36.1)	82 (100)	62 (75.6)	20 (24.4)
Child sex						
Male	412 (56.0)	272 (66.0)	140 (34.0)	43 (52.4)	28 (65.1)	15 (34.9)
Female	324 (44.0)	198 (61.1)	126 (38.9)	39 (47.6)	34 (87.2)	5 (12.8)
Child age (months)						
1–11	91 (12.4)	65 (71.4)	26 (28.6)	39 (47.6)	27 (69.2)	12 (30.8)
12–23	176 (23.9)	136 (77.3)	40 (22.7)	25 (30.5)	22 (88.0)	3 (12.0)
24–35	178 (24.2)	106 (59.6)	72 (40.4)	10 (12.2)	5 (50.0)	5 (50.5)
35–47	153 (20.8)	81 (52.9)	72 (47.1)	7 (8.5)	7 (100)	-
48–59	138 (18.7)	82 (59.4)	56 (40.6)	1 (1.2)	1 (100)	-
Child twin status						
Twin birth	17 (2.3)	11 (64.7)	6 (35.3)	3 (3.7)	1 (33.3)	2 (66.7)
Single birth	719 (97.7)	459 (63.8)	260 (36.2)	79 (96.3)	61 (77.2)	18 (22.8)
Maternal age (years)						
15–19	96 (13.0)	63 (65.6)	33 (34.4)	9 (11.0)	3 (33.3)	6 (66.7)
20–34	414 (56.3)	267 (64.5)	147 (35.5)	56 (68.3)	46 (82.1)	10 (17.8)
≥35	226 (30.7)	140 (62.0)	86 (38.0)	17 (20.7)	13 (76.5)	4 (23.5)
Average number of live birth*						
Number of live birth	3.7	3.6	3.9	4.2	4.3	3.9
Previous child death						
Yes	179 (35.7)	100 (55.9)	79 (44.1)	27 (51.9)	22 (81.5)	5 (18.5)
No	322 (64.3)	211 (65.5)	111 (34.5)	25 (48.1)	21 (84.0)	4 (16.0)
NA **	235 (.)	159 (.)	76 (.)	30 (.)	22 (.)	8 (.)
Child relationship with the caregiver						
Biological parents	403 (54.8)	263 (65.3)	140 (34.7)	42 (51.2)	36 (85.7)	6 (14.3)
Grandparents	256 (34.8)	165 (64.4)	91 (35.6)	36 (43.9)	22 (61.1)	14 (38.9)
Other	77 (10.4)	42 (54.6)	35 (45.4)	4 (4.9)	4 (100)	-
Main caregiver education						
None	401 (54.5)	250 (62.3)	151 (37.7)	66 (80.5)	49 (74.2)	17 (25.8)
Primary	221 (30.0)	142 (64.2)	79 (35.8)	5 (6.1)	3 (60.0)	2 (40.0)
Secondary or higher	86 (11.7)	64 (74.4)	22 (25.6)	10 (12.2)	9 (90.0)	1 (10.0)
Coranic	28 (3.8)	14 (50.0)	14 (50.0)	1 (1.2)	1 (100)	-
Household's socioeconomic status						
Most poor	148 (20.1)	89 (60.1)	59 (39.9)	17 (20.7)	14 (82.3)	3 (17.7)
Less poor	148 (20.1)	90 (60.8)	58 (39.2)	16 (19.5)	10 (62.5)	6 (37.5)
Middle	147 (20.0)	97 (66.0)	50 (34.0)	17 (20.7)	10 (58.8)	7 (41.2)
Rich	152 (20.6)	106 (69.7)	46 (30.3)	18 (22.0)	16 (88.9)	2 (11.1)
Most rich	141 (19.2)	88 (62.4)	53 (37.6)	14 (17.1)	12 (85.7)	2 (14.3)
Household distance to nearest health facility (km)						
<1	160 (21.7)	107 (66.9)	53 (33.1)	18 (21.9)	15 (83.3)	3 (16.7)
1–4.9	469 (63.7)	308 (65.7)	161 (34.3)	55 (67.1)	38 (69.1)	17 (30.9)
≥5	107 (14.5)	55 (51.4)	52 (48.6)	9 (11.0)	9 (100)	-

*If mother is the main caregiver.

**No previous child or mother not main caregiver.

2.4.3. Description of disease symptoms

Table 2.2 summarizes children's general health state as well as signs and symptoms of diseases, as observed by caregivers, stratified by healthcare seeking for fatal and non-fatal cases, respectively. Modern care was sought for 63.9% and 75.6% of the children with non-fatal and fatal health problems, respectively. Among surviving children, fever was the most commonly recognized symptom concerning nearly all investigated cases (95.4%). Among fatal cases, the reported fever prevalence was 72.0%. Signs of respiratory disease were reported in nearly 60% of non-fatal cases, of which approximately 10% showed signs of lower respiratory tract involvement. Lower respiratory tract involvement concerned fatal cases more frequently than non-fatal cases (15.8% vs. 5.6%). Gastrointestinal symptoms as well as symptoms of dehydration were common in both groups. Extreme thirst was more frequently observed by caregivers in the non-fatal group, whereas both severe vomiting and the inability to drink were stated nearly twice as often in the fatal group. Convulsions were five times more common in the fatal group (fatal cases: 23.2% vs. non-fatal cases: 4.8%). Reduced or loss of consciousness were frequently reported both among surviving children (61.1%) and in the fatal disease group (92.7%). Urinary changes were more commonly observed in the non-fatal group, and pallor or cyanoses were observed twice as often in the fatal (63.4%) than in the non-fatal group (30.4%). No child died due to an accident.

Table 2-2: Description of disease symptoms by modern healthcare seeking for fatal and non-fatal cases. Social Autopsy Project, Côte d'Ivoire, 2017.

	Non-fatal cases			Fatal cases		
	Full sample	Modern healthcare seeking	No modern healthcare seeking	Full sample	Modern healthcare seeking	No modern healthcare seeking
	N = 736 (100%)	N = 470 (63.9%)	N = 266 (36.1%)	N = 82 (100%)	N = 62 (75.6%)	N = 20 (24.4%)
Fever						
Fever	702 (95.4)	459 (65.4)	243 (34.6)	59 (72.0)	49 (83.1)	10 (16.9)
Respiratory signs	438 (59.5)	264 (60.3)	174 (39.7)	18 (22.0)	13 (72.2)	5 (27.8)
Low respiratory	41 (5.6)	30 (73.2)	11 (26.8)	13 (15.8)	12 (92.3)	1 (7.7)
Diarrhoea	294 (40.0)	200 (68.0)	94 (32.0)	26 (31.7)	23 (88.5)	3 (11.5)
Severe diarrhoea[a]	210 (28.5)	149 (71.0)	61 (29.0)	23 (28.1)	20 (87.0)	3 (13.0)
Other diarrhoea	87 (11.8)	52 (59.8)	35 (40.2)	4 (4.9)	4 (100)	-
Vomiting	282 (38.3)	203 (72.0)	79 (28.0)	28 (34.1)	26 (92.9)	2 (7.1)
Severe vomiting[b]	74 (10.1)	62 (83.8)	12 (16.2)	15 (18.3)	14 (93.3)	1 (6.7)
Other vomiting	208 (28.3)	141 (67.8)	67 (32.2)	13 (15.8)	12 (92.3)	1 (7.7)
Risk of dehydration	418 (56.8)	295 (70.6)	123 (29.4)	44 (53.7)	37 (84.1)	7 (15.9)
Extremely thirsty	282 (38.3)	193 (68.44)	89 (31.6)	16 (19.5)	14 (87.5)	2 (12.5)
Unable to drink	66 (9.0)	57 (86.4)	9 (13.6)	18 (22.0)	13 (72.2)	5 (27.8)
Neurological signs	455 (61.8)	321 (70.6)	134 (29.4)	78 (95.1)	61 (78.2)	17 (21.8)
Convulsion	35 (4.8)	34 (97.1)	1 (2.9)	19 (23.2)	15 (79.0)	4 (21.0)
Stiff neck	7 (0.9)	7 (100)	-	2 (2.4)	2 (100)	-
Reduced or loss of consciousness	450 (61.1)	317 (70.4)	133 (29.6)	76 (92.7)	63 (82.9)	13 (17.1)
Urinary change	408 (55.4)	289 (70.8)	119 (29.2)	7 (8.5)	6 (85.7)	1 (14.3)
Bad smell	249 (33.8)	161 (64.7)	88 (35.3)	4 (4.9)	4 (100)	-
Dark urine	321 (43.6)	231 (72.0)	90 (28.0)	4 (4.9)	3 (75.0)	1 (25.0)
Pollakiduria or/and dysuria	9 (1.2)	8 (88.9)	1 (11.1)	-	-	-
Less urine	7 (0.9)	6 (85.7)	1 (14.3)	1 (1.2)	1 (100)	-
Blood in urine	3 (0.4)	3 (100)	-	-	-	-
Eyes	262 (35.6)	195 (74.4)	67 (25.6)	22 (26.8)	18 (81.8)	4 (18.2)
Very swollen	5 (0.7)	1 (20.0)	4 (80.0)	-	-	-
Red or discharging	7 (0.9)	6 (85.7)	1 (14.3)	-	-	-
Yellow	183 (24.9)	131 (71.6)	52 (28.4)	8 (9.8)	8 (100)	-
Other	67 (9.1)	57 (85.1)	10 (14.9)	14 (17.1)	10 (71.4)	4 (28.6)
Rash						
Rash	53 (7.2)	38 (71.7)	15 (28.3)	6 (7.3)	5 (83.3)	1 (16.7)
Strong pain	80 (10.8)	48 (60.0)	32 (40.0)	4 (4.9)	4 (100)	-
Stomach	32 (4.3)	19 (59.4)	13 (40.6)	3 (3.7)	3 (100)	-
Head	23 (3.1)	13 (56.5)	10 (43.5)	-	-	-
Thorax	9 (1.2)	7 (77.8)	2 (22.2)	1 (1.2)	1 (100)	-
Other	16 (2.2)	9 (56.3)	7 (43.7)	-	-	-
Change of colour of skin	232 (31.5)	167 (72.0)	65 (28.0)	53 (64.6)	44 (83.0)	9 (17.0)
Pallor or cyanoses	224 (30.4)	161 (71.9)	63 (28.1)	52 (63.4)	43 (82.7)	9 (17.3)
Jaundice	15 (2.0)	13 (86.7)	2 (13.3)	2 (2.4)	2 (100)	-
General state at disease recognition						
Vigilance	359 (48.8)	247 (68.8)	112 (31.2)	75 (91.5)	62 (82.7)	13 (17.3)
Alert	336 (45.6)	197 (58.6)	139 (41.4)	6 (7.3)	3 (50.0)	3 (50.0)
Reduced	356 (48.4)	244 (68.5)	112 (31.5)	75 (91.5)	62 (82.7)	13 (17.3)
Unconscious	3 (0.4)	3 (100)	-	-	-	-
Doesn't know	41 (5.6)	26 (63.4)	15 (36.6)	-	-	-
Sudden death	-	-	-	1 (1.2)	-	1 (100)
Activity (play)	605 (82.2)	413 (68.3)	192 (31.7)	74 (90.2)	61 (82.4)	13 (17.6)
Active	118 (16.0)	45 (38.1)	73 (61.1)	7 (8.5)	4 (57.1)	3 (42.9)
Reduced activity	456 (62.0)	291 (63.8)	165 (36.2)	40 (48.8)	36 (90.0)	4 (10.0)
None	149 (20.2)	122 (81.9)	27 (18.1)	34 (41.5)	25 (73.5)	9 (26.5)
Doesn't know	13 (1.8)	12 (92.3)	1 (7.7)	-	-	-
Sudden death	-	-	-	1 (1.22)	-	1 (100)
Food intake	532 (72.3)	359 (67.5)	173 (32.5)	73 (89.0)	62 (84.9)	11 (15.1)
Normal food intake	203 (27.6)	110 (54.2)	93 (45.8)	8 (9.8)	3 (37.5)	5 (62.5)
Less good	428 (58.2)	283 (66.1)	145 (33.9)	54 (65.8)	50 (92.6)	4 (7.4)
None	104 (14.1)	76 (73.1)	28 (26.9)	19 (23.2)	12 (63.2)	7 (36.8)
Doesn't know	1 (0.1)	1 (100)	-	-	-	-
Sudden death	-	-	-	1 (1.2)	-	1 (100)

(Continued on following page)

Table 2-2: Description of disease symptoms by modern healthcare seeking for fatal and non-fatal cases. Social Autopsy Project, Côte d'Ivoire, 2017

	Non-fatal cases			Fatal cases		
	Full sample	Modern healthcare seeking	No modern healthcare seeking	Full sample	Modern healthcare seeking	No modern healthcare seeking
	N = 736 (100%)	N = 470 (63.9%)	N = 266 (36.1%)	N = 82 (100%)	N = 62 (75.6%)	N = 20 (24.4%)
General state when worst[c]						
Vigilance	447 (60.7)	314 (70.3)	133 (29.7)	-	-	-
Alert	272 (37.0)	142 (52.2)	130 (47.8)	-	-	-
Reduced	431 (58.5)	299 (69.4)	132 (30.6)	-	-	-
Unconscious	16 (2.2)	15 (93.7)	1 (6.3)	-	-	-
Doesn't know	17 (2.3)	14 (82.4)	3 (17.6)	-	-	-
Activity (play)	665 (90.3)	447 (67.2)	218 (32.8)	-	-	-
Active	71 (9.6)	23 (32.4)	48 (67.6)	-	-	-
Reduced activity	412 (56.0)	262 (63.6)	150 (36.4)	-	-	-
None	253 (34.4)	185 (73.1)	68 (26.9)	-	-	-
Food intake	619 (84.1)	413 (66.7)	206 (33.3)	-	-	-
Normal food intake	115 (15.6)	56 (48.7)	59 (51.3)	-	-	-
Less good	431 (58.6)	283 (65.7)	148 (34.3)	-	-	-
None	188 (25.5)	130 (69.2)	58 (30.8)	-	-	-
Doesn't know	2 (0.3)	1 (50.0)	1 (50.0)	-	-	-

[a]*Severe diarrhoea: more than 4–5 liquid stools/day or at least 3x/day for 48 h.*
[b]*Severe vomiting: frequent vomiting for more than 24 h or vomiting everything a child tries to drink over a period of several hours.*
[c]*General state when worst: child general state when the health problem was most severe.*

2.4.4. Factors associated with modern healthcare seeking

Table 2.3 presents results from the fully adjusted model, summarizing the associations between modern healthcare seeking and the characteristics of the child, household, and main caregiver. In non-fatal cases, children aged 1–11 months were 11%-points (95% CI: −2%-points to 24%-points; p-value <0.1) and children aged 12–23 months were 16%-points (95% CI: 6%-points to 27%-points; p-value <0.01) more likely to benefit from modern care than children aged 48–59 months. Caregivers who never attended school and those who attained primary and coranic school levels were 11%-points (95% CI: −22%-points to 1%-point; p-value <0.05), and caregivers only attending coranic schools were 27%-points (95% CI: −47%-point to −7%-point; p-value <0.01) less likely to utilize modern medicine treatment than more highly educated caregivers. Households living less than 1 km from the nearest health facility had a 14%-points (95% CI: 1%-point to 26%-point; p-value <0.05) higher likelihood, and households living 1–4 km away a 12%-points (95% CI: 2%-points to 23%- points, p-value <0.05) higher propensity to attend a modern healthcare provider than those living at least 5 km away. Among fatal cases, caregivers or mothers aged 15–19 years were 41%-points less likely to seek modern healthcare than women aged 35 and older (95% CI: −77%-point to −6%-point; p-value <0.05).

Table 2-3: Association between socio-demographic factors and modern healthcare seeking. Social Autopsy Project, Côte d'Ivoire, 2017.

	Non-fatal cases	Fatal cases
	dy/dx (95% CI)	dy/dx (95% CI)
Child sex: Reference: male		
Female	−0.05 (−0.12, 0.02)	0.06 (−0.12, 0.25)
Child age (months): Reference: 48–59 months		
1–11	0.11* (−0.02, 0.24)	0.07 (−0.56, 0.70)
12–23	0.16*** (0.06, 0.27)	0.13 (−0.47, 0.73)
24–35	−0.02 (−0.13, 0.09)	−0.22 (−0.91, 0.48)
35–47	−0.09 (−0.21, 0.03)	0.04 (−0.66, 0.75)
Child twin status: Reference: twin		
Single	−0.01 (−0.24, 0.22)	0.33* (−0.00, 0.67)
Child relationship with the main caregiver: Reference: biological parent		
Grandparent	0.15** (0.02, 0.27)	−0.13 (−0.42, 0.15)
Other	0.01 (−0.18, 0.20)	0.01 (−0.56, 0.59)
Maternal age (in years): Reference: ≥35 years		
15–19	0.01 (−0.10, 0.13)	−0.41** (−0.77, −0.06)
20–34	0.01 (−0.07, 0.09)	0.12 (−0.13, 0.36)
Main care giver education: Reference: secondary or higher		
None	−0.11** (−0.22, −0.01)	−0.02 (−0.28, 0.24)
Primary	−0.11* (−0.22, 0.00)	−0.20 (−0.61, 0.22)
Coranic	−0.27*** (−0.47, −0.07)	−0.05 (−0.67, 0.57)
Household's socioeconomic status: Reference: most poor		
Poor	0.00 (−0.10, 0.11)	0.10 (−0.22, 0.42)
Middle	0.03 (−0.08, 0.14)	0.08 (−0.23, 0.38)
Rich	0.08 (−0.03, 0.19)	0.26 (−0.08, 0.60)
Most rich	−0.03 (−0.14, 0.09)	0.02 (−0.30, 0.35)
Household distance to nearest health facility: Reference ≥5 km		
<1 km	0.14** (0.01, 0.26)	−0.21 (−0.54, 0.12)
1–4.9 km	0.12** (0.02, 0.23)	−0.19 (−0.45, 0.07)
Observations	736	82

***p < 0.01.
**p < 0.05.
*p < 0.1.
Coefficients displayed are dy/dx = marginal effect is a change in the probability that Y = 1 with a specific change in X with 95% confidence intervals (CIs) in parentheses; adjusted models control for household, child, and caregiver's characteristics.

2.4.5. Observed symptoms associated with modern healthcare seeking

Table 2.4 shows the predicted effects of disease signs and symptoms on modern healthcare seeking from alternative logistic models. In the adjusted analysis of fatal cases (model 5), only signs of lower respiratory track involvement were positively associated with modern healthcare seeking (dy/dx = 0.42; 95% CI: 0.14–0.70; p-value <0.05). In contrast, dark urine was negatively associated with modern healthcare seeking (dy/dx = −0.60; 95% CI: −0.97 to −0.23; p-value <0.05). No associations between modern healthcare seeking and any other symptoms were observed. In non-fatal cases, when considering only disease-related symptoms, fever (dy/dx = 0.25; 95% CI: 0.09–0.41; p-value <0.01), inability to drink (dy/dx = 0.19; 95% CI: 0.02–0.36; p-value <0.05), convulsions (dy/dx = 0.54; 95% CI: 0.12–0.96; p-value <0.05), dark urine (dy/dx = 0.08; 95% CI: 0.01–0.16; p-value <0.05), and eye infection (dy/dx = 0.15; 95% CI: 0.01–0.29; p-value <0.05) were positively associated with modern healthcare seeking. Bad-smelling urine was negatively associated with treatment seeking (dy/dx = −0.08; 95% CI: −0.16 to −0.01; p-value <0.05).

Similar marginal effects and trends in symptoms were observed when the general state of the child's health at the beginning of the disease and during the disease's severity was taken into account. Children who were less able to play than usual at the beginning of the disease episode were associated with an 18%-point (95% CI: 7%-point to 29%-point; p-value <001) increase in modern treatment seeking, and those who were not able to play at all with a 50%-point (95% CI: 34%-point to 66%-point; p-value <0.01) increase. Unconsciousness was associated with a 7%-point increase in treatment seeking (95% CI: −1%-point to 14%-point; p-value <0.1). Similar results were obtained when disease severity symptoms at the point when the disease was most severe were analyzed (model 3). In contrast, modern treatment seeking was not taken up when the child ate less than usual or could not eat at all.

With regard to symptoms in fatal cases, fever (dy/dx = 0.26; 95% CI: 0.06–0.46; p-value <0.05) and lower respiration tract infections (dy/dx = 0.38; 95% CI: 0.12–0.65; p-value <0.01) were positively associated with modern healthcare seeking (model 4). The change of urine colour was negatively associated with modern treatment seeking.

Table 2-4: Association between disease symptoms factors and modern healthcare seeking. Social Autopsy Project, Côte d'Ivoire, 2017.

Variable	Non-fatal cases			Fatal cases	
	Model 1	Model 2	Model 3	Model 4	Model 5
	dy/dx (95% CI)	dy/dx (95% CI)	dy/dx (95% CI)	dy/dx (95% CI)	dy/dx (95% CI)
Disease signs and symptoms					
Fever	0.25*** (0.09, 0.41)	0.13 (–0.03, 0.29)	0.20** (0.03, 0.37)	0.26** (0.06, 0.46)	0.18 (–0.08, 0.43)
Lower respiratory	–0.03 (–0.20, 0.15)	0.06 (–0.11, 0.23)	–0.02 (–0.19, 0.14)	0.38*** (0.12, 0.65)	0.42*** (0.14, 0.70)
Severe diarrhoea	0.03 (–0.05, 0.11)	0.03 (–0.06, 0.11)	0.00 (–0.08, 0.09)	0.18 (–0.09, 0.44)	0.14 (–0.15, 0.43)
Severe vomiting	0.19*** (0.06, 0.33)	0.13** (0.00, 0.27)	0.16** (0.03, 0.30)	0.06 (–0.26, 0.37)	0.21 (–0.09, 0.50)
Extremely thirsty	0.06 (–0.02, 0.14)	0.05 (–0.03, 0.12)	0.06 (–0.02, 0.13)	0.26 (–0.15, 0.68)	0.21 (–0.16, 0.58)
Inability to drink	0.19** (0.02, 0.36)	0.19** (0.03, 0.35)	0.19** (0.03, 0.35)	0.04 (–0.18, 0.26)	0.00 (–0.26, 0.26)
Convulsion	0.54** (0.12, 0.96)	0.53*** (0.13, 0.92)	0.52** (0.11, 0.93)	–0.10 (–0.35, 0.15)	–0.08 (–0.33, 0.17)
Bad-smelling urine	–0.08** (–0.16, –0.01)	–0.10*** (–0.18, –0.03)	–0.08** (–0.16, –0.00)	0.20 (–0.38, 0.78)	0.32 (–0.10, 0.73)
Dark urine	0.08** (0.01, 0.16)	0.09** (0.01, 0.17)	0.06 (–0.02, 0.14)	–0.65*** (–1.10, –0.19)	–0.60*** (–0.97, –0.23)
Less urine	0.33 (–0.12, 0.77)	0.34 (–0.08, 0.76)	0.31 (–0.13, 0.75)	0.15 (–0.33, 0.64)	–0.07 (–0.55, 0.42)
Yellow eyes	0.06 (–0.03, 0.15)	0.08* (–0.01, 0.16)	0.05 (–0.04, 0.14)	0.14 (–0.31, 0.60)	0.08 (–0.29, 0.45)
Other eye affections (swollen, discharging, other)	0.15** (0.01, 0.29)	0.15** (0.01, 0.29)	0.11 (–0.04, 0.25)	–0.19* (–0.39, 0.01)	–0.03 (–0.27, 0.21)
Skin rash	0.11 (–0.03, 0.26)	0.08 (–0.06, 0.22)	0.10 (–0.04, 0.24)	–0.09 (–0.42, 0.25)	–0.14 (–0.47, 0.20)
Strong pain	–0.07 (–0.18, 0.04)	–0.09 (–0.19, 0.02)	–0.11** (–0.22, –0.01)	0.26 (–0.44, 0.95)	0.12 (–0.37, 0.62)
Change of colour of skin	–0.01 (–0.10, 0.08)	–0.01 (–0.10, 0.08)	–0.00 (–0.09, 0.09)	0.11 (–0.12, 0.35)	0.06 (–0.20, 0.32)
General state at disease beginning					
Played less than usual		0.18*** (0.07, 0.29)			0.14 (–0.54, 0.81)
Did not play at all		0.50*** (0.34, 0.66)			–0.24 (–0.95, 0.48)
Ate less than usual		–0.14*** (–0.24, –0.04)			0.03 (–0.42, 0.47)
Did not eat at all		–0.27*** (–0.44, –0.10)			0.13 (–0.40, 0.66)
Awareness decreased/unconsciousness		0.07* (–0.01, 0.14)			0.09 (–0.88, 1.06)
General state at worst disease state					
Played less than usual			0.24*** (0.10, 0.39)		
Did not play at all			0.36*** (0.19, 0.53)		
Ate less than usual			–0.12* (–0.25, 0.02)		
Did not eat at all			–0.23*** (–0.39, –0.06)		
Awareness decreased/unconsciousness			0.08** (0.00, 0.16)		
Observations	736	736	736	82	82

*p < 0.1.
**p < 0.05.
***p < 0.01.
Coefficients displayed are dy/dx = marginal effect is a change in the probability that Y = 1 with a specific change in X with 95% confidence intervals (CIs) in parentheses. Model 1 and model 4 control for disease's symptoms only; model 2 and model 5 control for disease's symptoms and child's general state at the beginning of the disease; model 3 controls for disease's symptoms and child's general state at worst disease state.

2.4.6. Reasons for not seeking modern care

Figure 2.1 shows the primary reasons caregivers stated for not seeking care. In non-fatal cases, among the 231 respondents, 50.2% felt that the child was not sick enough, 48.5% highlighted financial constraints, 15.6% did not consider consulting useful, while 6.9% indicated to know what the child was suffering from without consultation. Only 2.2% of caregivers said that they had used drugs already available at home instead of going to a health facility. Transportation difficulties, the absence of the child's father, and unpleasant previous experience with modern health service were reported by 1.7%, 1.3%, and 0.9% of respondents, respectively. In fatal cases, the main reason for not seeking care was that the child was not considered sick enough (50%). Other reasons were the perception that the disease was not treatable by modern medicine (25%) or the fact that the child died so soon after occurrence of symptoms (25%).

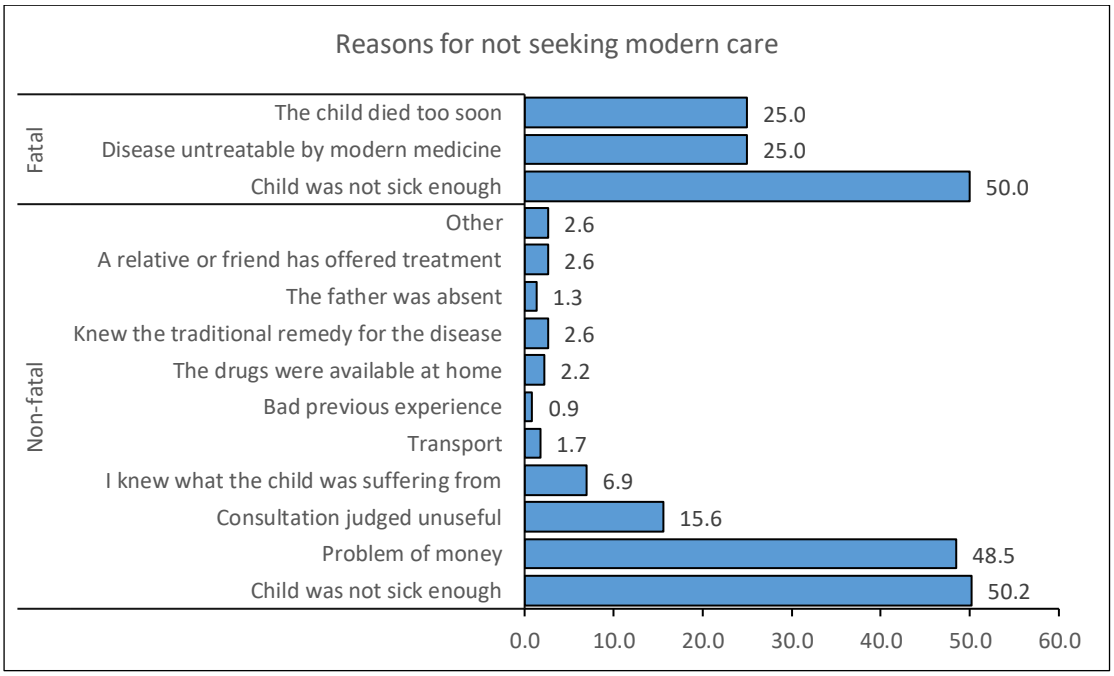

Figure 2-1: Reasons for not seeking modern healthcare, stratified by cases. Social Autopsy Project, Côte d'Ivoire, 2017.

2.5. Discussion

This study identified several determinants of modern healthcare seeking in a primarily rural setting in the south-central part of Côte d'Ivoire. Almost two-third (64%) of caregivers of children aged 1–59 months experiencing a non-fatal health condition sought care. This percentage is considerably higher than the 45.2% reported in a national study in 2016 (INS/ICF, 2012). Our estimates exclusively focus on the use of modern healthcare services. However, in the African context, care-seeking behaviors are complex and often characterized by a combination of modern and traditional medicine (Ishaga C, 2010; Sy I, 2010), and sequential treatment seeking at different systems (Médah R, 2006; Pilkington H, 2004). Increased treatment-seeking propensity among younger children, among children living with their grandparents, and among caregivers with higher educational attainment appear well aligned with previous research (Dagnew et al., 2018; Pierce et al., 2016; Vikram et al., 2012). Preceding studies have highlighted geographical distance and socioeconomic status (Begashaw et al., 2016; Borah H, 2016; Weldesamuel et al., 2019) as key determinants for health services use. In our study, close proximity to the nearest healthcare facility was associated with increased health seeking for non-fatal cases. Though financial resources were mentioned as a factor for not accessing modern healthcare, we did not find any significant association across socioeconomic groups. This finding is explained by healthcare officially being offered free of charge in Côte d'Ivoire to pregnant women and children under the age of 5 years since 2012 (MSLS, 2012). In Burkina Faso, user fee removal was associated with increased use of modern health services across all socioeconomic groups, but this was without adjustment for health needs and distance to health centers (Ridde et al., 2013). Other studies have shown the positive effect of wealth on health seeking behavior and, hence, attributed delays to shortages of financial resources (Gelaw et al., 2014; Scott et al., 2014). More than three-quarters of fatal cases sought modern care prior to the death of the child. Caregivers aged <20 years were 41% less likely to bring their child to a modern healthcare provider than those aged ≥35 years, which is in line with previous research (Dagnew et al., 2018; Gelaw et al., 2014; Weldesamuel et al., 2019). A likely explanation of this observation is that older mothers are more experienced. Compared to those caring for twins, caregivers caring for a single child were more likely to use modern healthcare, suggesting that increased care duties may interfere with timely treatment seeking.

Interestingly, mothers of the fatal cases were more likely to have already experienced the loss of a child. Both in surviving and non-surviving children, mothers with a previous loss

were less likely to attend healthcare. Targeted interventions with a non-blaming, empathetic approach focusing on families who have already lost a child, may help increase treatment seeking among high-risk populations and prevent further deaths among young children. Previous studies indicate the knowledge of danger signs and perceived severity of the illness to be associated with seeking modern healthcare (Kolola T, 2016; Wambui WM, 2018). In our study, signs and symptoms most strongly associated with healthcare seeking were fever, severe vomiting, inability to drink, convulsion, or dark urine and factors inherent to a child's general state (e.g., child playing less than usual, complete inactivity, decreased vigilance, or unconsciousness). Strikingly, while in surviving children all but one who presented with convulsions were brought in for modern care, the same was true in as many as 20% among one in five children with fatal disease outcomes, suggesting a lack of recognition of danger signs as a key barrier to timely treatment seeking with severe disease. While higher rates of signs and symptoms typical for potentially severe disease are expected for fatal cases (e.g., signs of lower respiratory infection), a generally worse state at the time of disease onset may not just be due to more severe disease but also due to late recognition thereof. For non-fatal cases, not seeking external healthcare on the basis that the child was not sick enough, as revealed in the present study, suggests a non-recognition or an underestimation of the signs and symptoms shown by the child and a lack of knowledge on diseases (Geldsetzer et al., 2014; Weldesamuel et al., 2019). Poor recognition may also hold for fever, the most frequently reported symptom in our study setting, which was only recognized in 72% of fatal cases, while in non-fatal cases fever was reported in 95%. The high rates of fever and the results with respect to the general state variables indicate that many surviving children may have had severe disease, and that pauci-symptomatic illnesses go unnoticed or are not classified as "a child being sick" by caregivers in the Taabo HDSS.

In our study, 36.1% and 24.4% of caregivers did not seek modern healthcare in non-fatal and fatal cases, respectively. Rather strikingly, in fatal cases, two thirds of the caregivers who did not seek modern healthcare were grandparents and teenage caregivers. Some of the caregivers (with fatal outcomes) appear to have shied away from seeking modern healthcare because they felt a consultation would not be useful, suggesting somewhat limited trust in the local health system. In some cases, a very poor general state (i.e., inactivity, loss of consciousness, and inability to drink) also appears to have resulted in caregivers considering the case lost (too late to seek care). Even though grandparents should have more experience, exposure to modern medicine may be more limited, while past experiences with death may

induce beliefs that severe disease courses may be irreversible. Local norms and beliefs regarding the etiology of disease (Dougherty et al., 2020; M. K. Kouadio et al., 2013) appear important. For example, a mother who lost a child in our study reported that the grandparents prevented a child being brought to a modern healthcare facility, becausethey believed that the disease could be treated through prayer alone.. In that sense, our results are consistent with several other studies, which have highlighted the importance of the caregivers' skills and educational attainment in child health management (Dougherty et al., 2020; Geldsetzer et al., 2014; Kolola T, 2016).

In this study, we used data prospectively collected within a population of more than 45,000 continuously monitored individuals in a well-defined geographical area. This has the advantage of identifying fatalities thoroughly and drawing on a representative sample. While other studies looking at determinants of healthcare seeking have focused on specific pathologies, signs and symptoms, or on fatal cases only, our study provides a more general analysis in both non-fatal and fatal cases of children aged 1–59 months. The fact that the data used relate to the last episode of illness may limit our conclusions as care seeking may vary from one episode to another. In order to gain as representative a picture as possible though, we ensured homogenous data collection over a 1-year period, thus also including seasonal variations. Furthermore, not every caregiver will adhere to the same definition of disease. While the two groups examined cannot be compared directly as the nature of diseases are likely to have been different with numerous illnesses with spontaneous resolution in the surviving group, the focus on signs and symptoms warranting consultation allows for a certain comparison of likelihood of action taken and importance attributed to them. As the responses collected from caregivers relate to the most recent event, a certain recall bias cannot be excluded, though episodes did not lay far back. Social desirability may have played a role though confidentiality was ensured and a very respectful, non-judgmental attitude was observed to try and minimize this issue.

2.6. Conclusion

The findings presented here from a primarily rural part of Côte d'Ivoire suggest that an increasingly large proportion of caregivers seek modern care for their under 5-year-old children. Nonetheless, a quarter of fatal, and more than a third of non-fatal diseases, were not seen by modern healthcare providers. Increasing the perceived need and urgency of treatment for severe

cases as well as improving the overall quality of care are of critical importance if further improvements reducing child mortality are to be achieved in LMICs.

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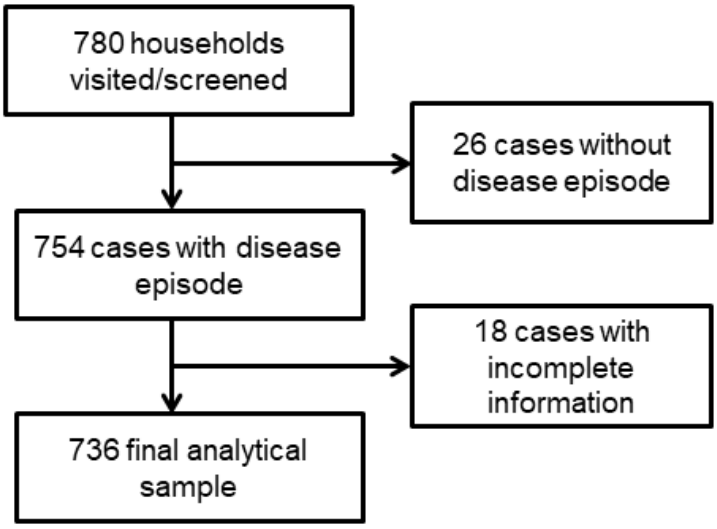
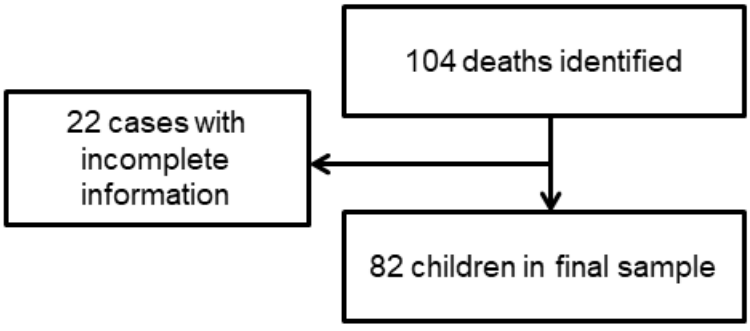
2.8. Appendix 1: Determinants of modern paediatric healthcare seeking in rural Côte d'Ivoire

2.8.1. Supplemental Materials Figure SF1-1: Flow chart indicating non-fatal cases registered in 2017 in the Taabo health and demographic surveillance system in the south-central part of Côte d'Ivoire



2.8.2. Supplemental Materials Figure SF1-2: Flow chart indicating fatal cases registered in 2017 in the Taabo health and demographic surveillance system in the south-central part of Côte d'Ivoire



3. Paper 2 – Impact of newly constructed primary healthcare centers on antenatal care attendance, facility delivery and all-cause mortality: quasi-experimental evidence from Taabo health and demographic surveillance system, Côte d'Ivoire

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This article has been published in

BMJ Open 2022, 12: 054355

3.1. Abstract

Access to quality care remains limited, particularly in low and middle-income countries. Although better health outcomes for families living in close proximity to healthcare facilities have been documented in cross-sectional studies, evidence on the extent to which additional health facilities can contribute to improved population health remains scanty. We aimed to estimate the causal impact of newly constructed primary healthcare facilities within a health and demographic surveillance site (HDSS) in Côte d'Ivoire. We conducted a quasi-experimental study. Logistic and Cox proportional hazards regression models were used to estimate the impact of new healthcare facilities on healthcare-seeking behavior and all-cause mortality. Data were collected prospectively through the Taabo HDSS located in south-central Côte d'Ivoire between 2010 and 2018. We analysed 2957 deaths across 440 973 person-year observations as well as 14 132 live births. The primary outcomes were antenatal care (ANC) attendance, facility delivery and mortality. Logistic and Cox proportional hazards models were employed to estimate the impact of the new health facilities on ANC attendance, facility delivery as well as child and adult mortality. Average distance to the nearest healthcare facility declined from 5.5 km before to 2.8 km after opening of four new healthcare facilities in targeted villages. No improvement was observed for ANC attendance, institutional deliveries and adult mortality. New facilities reduced the risk of post-neonatal infant mortality by 46% (HR 0.54, 95% CI 0.31 to 0.94, $p<0.05$), suggesting a mortality gradient of 2 deaths per 1000 for each additional km (Coef=0.002, 95% CI 0.000 to 0.004, $p<0.05$).

Our results suggest that new facilities do not necessarily improve healthcare utilization and health outcomes. Further research is needed to identify the best ways to ensure access to quality care in resource-constrained settings.

3.2. Strengths and limitations of the study

- We used 9 years of longitudinal surveillance data from a well-characterised population-based cohort to estimate the impact of newly constructed health facilities on the utilisation of essential maternal health services as well as child and adult mortality.
- The health facilities evaluated are representative of a considerable number of primary healthcare centers built in recent years in Côte d'Ivoire and elsewhere in low and middle-income countries.

- Our results are based on a small number (n=4) of newly constructed health facilities with only one staff member and limited diagnostic tools. Hence, observed impacts may be different in other settings.
- The relatively small number of child deaths in our sample limits our statistical power for child mortality outcomes.
- Euclidean distance calculation from the household to the nearest health facility underestimates true distances and travel times on the ground.

3.3. Introduction

While substantial progress has been made in reducing under-5 mortality worldwide from 1990 to 2015, the decline in child mortality has only been moderate in many parts of sub-Saharan African (SSA), making it increasingly challenging to reach the ambitious targets set within the Sustainable Development Goals agenda (You et al., 2015). As of 2015, an estimated 2.9 million under-5 deaths were reported in SSA (Liu et al., 2016). A large proportion of these deaths could be avoided by quality obstetric and medical care (Lawn et al., 2009). However, gaps in the access to quality care remain substantial in many regions (Bhutta et al., 2014; Escamilla et al., 2018; Mortality & Causes of Death, 2016), despite major efforts to expand access to essential services (Liu et al., 2019; UNICEF et al., 2019; WHO, 2013). One of the most obvious ways to increase access to healthcare is to reduce the distance to health facilities through the construction of additional health centers. While several cross-sectional studies suggest better health outcomes and high utilization of health services for families living in close proximity to health facilities (Buor, 2003; Gao & Kelley, 2019; Leslie et al., 2016), evidence on the impact of increased health facility availability on child mortality, antenatal care (ANC) attendance and skilled delivery is inconclusive and somewhat contradictory (Doctor et al., 2018; Okwaraji & Edmond, 2012; Quattrochi et al., 2020; Rutherford et al., 2010).

Côte d'Ivoire has made major efforts to increase the number of first contact health establishments in the past decade. Between 2012 and 2018, 726 new health facilities have been constructed throughout the country (Malmberg B & Lindh T, 2004; Prskawetz A et al., 2004), increasing the total number of primary healthcare (PHC) centers by 41% from 1753 facilities in 2012 to 2479 facilities in 2018. Over the same period, child mortality declined from 108 to 81 deaths per 1000 live births (UNICEF et al., 2013, 2019), use of ANC and facility delivery increased respectively from 91% to 93% and from 57.4% to 69.8% (Institut National de la Statistique & ICF International, 2012; Institut national de la statistique & UNICEF, 2017). However, little is known regarding the contributions of the national health infrastructure efforts towards these improved health services utilisation and health outcomes.

In this study, we used detailed demographic surveillance data obtained from the Taabo health and demographic surveillance system (HDSS), located in the south-central part of Côte d'Ivoire. Our objective was to assess the extent to which newly established healthcare facilities improved local population health as well as the utilisation of health services.

3.4. Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional reporting guidelines (von Elm et al., 2007) throughout the manuscript.

3.4.1. Study design

A quasi-experimental study was conducted to assess the impact of new healthcare facilities on treatment seeking and mortality outcomes. At the beginning of the study 7 out of 13 villages had their own health center. In 2010, a local committee decided to build four additional health centers. To assess the causal impact of these new facilities, we compared village-level changes in child mortality before and after opening of new facilities to the changes observed in communities with constant health facility access over the same period. All empirical models included village and year fixed effects (intercepts) to rule out confounding by time-invariant unobserved characteristics.

3.4.2. Setting and participants

This study was conducted in the Taabo HDSS. The Taabo HDSS is located in the south-central part of Côte d'Ivoire and covers a surface area of approximately 980 km^2. The area is mainly rural and comprises 13 villages as well as an urban settlement (Taabo-Cité) (Figure 3.1). The primary economic activity of the region is agriculture, dominated by cocoa and rubber but also featuring subsistence crops such as cassavas, plantains, vegetables and yams.

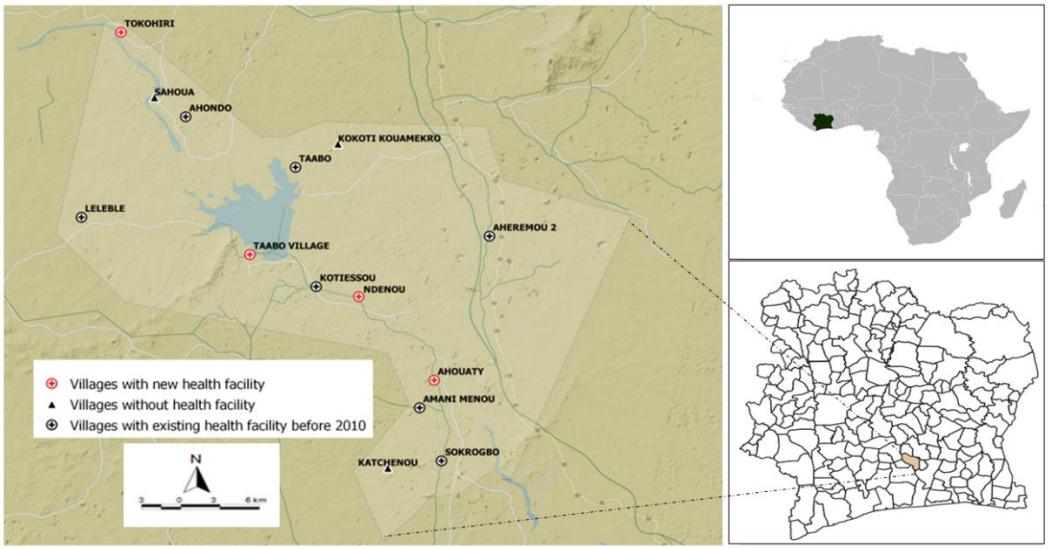

Figure 3-1: Map of the Taabo health and demographic surveillance system in south-central Côte d'Ivoire

Under-5 mortality was 94 per 1000 children born alive in 2010 (Kone et al., 2015a). The primary causes of death in the area are malaria (18.0%), acute respiratory infections (15.4%), HIV/AIDS (11.2%) and pulmonary tuberculosis (6.5%). Non-communicable diseases (NCDs) represented 18.9% of deaths, mainly due to acute abdomen (5.3%), while unspecified cardiac diseases, digestive neoplasm and severe malnutrition accounted for less than 3% each. Maternal and neonatal conditions accounted for 8.3% of all deaths (Kone et al., 2015b).

All women of reproductive age whose pregnancy started and ended between January 2010 and December 2018 and all deaths registered during this 9-year period were included in the analysis. Each household of the Taabo HDSS was visited three times per year for detailed registration of births, deaths, in-migrations, out-migrations and pregnancies. New pregnancies were followed-up longitudinally and all women with a new pregnancy were interviewed using a specific pregnancy questionnaire. This questionnaire includes the date of last menstrual period and pregnancy outcome; hence, facilitating enumerators to be aware of neonatal deaths. Key informants in communities continuously observed and reported any death occurring in the surveillance zone. More detailed information on routine monitoring activities have been described elsewhere (Kone et al., 2015a). All individuals registered and living in the Taabo HDSS between 2010 and 2018 were included in the study.

3.4.3. The FAIRMED health infrastructure intervention programme

As mentioned above, only 7 of the 13 villages had their own health facilities in 2010. These PHC centers were supported by a 12-bed hospital in Taabo-Cité. In 2010, FAIRMED, a non-governmental organisation, launched activities to reduce mortality and morbidity due to malaria and neglected tropical diseases. During the initial engagement of stakeholders, distance to facilities was highlighted by community members as the primary health system constraint, and construction of new health centers in the area was requested. Based on population size and access to facilities in 2010, four out of the six villages without health centers in 2010 were selected for new primary care health facilities. These facilities were designed to run by a nurse or midwife and included a dispensary, a small maternity ward and a pharmacy. Primary care facilities were supposed to offer the local population a minimum package of essential health services including routine immunisation of children, curative care for common ailments, prenatal and postnatal consultations, and family planning, deliveries assistance, prevention of mother-to-child transmission of HIV, as well as the promotion of essential family practices with the support of community relays. The first new health center was opened in Tokohiri in May

2013. In January 2015, a new health center started its operations in Taabo-Village. Finally, in January and February 2017, new health centers were opened in Ahouaty and N'Denou. Figure 3.1 illustrates the location of these new health facilities, while Figure 3.2 illustrates the timeline of the project.

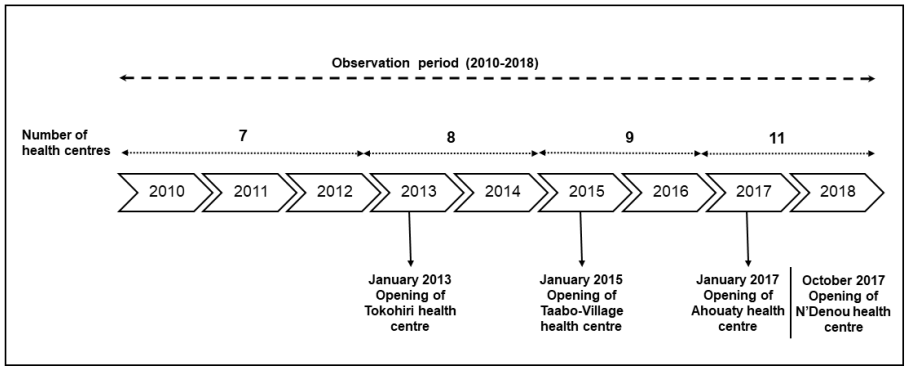

Figure 3-2: Health facility coverage in the Taabo HDSS from 2010 to 2018. HDSS, health and demographic surveillance system

3.4.4. Study variables

The primary outcome variables were ANC attendance, facility delivery and all-cause mortality. ANC attendance was a binary variable taking value 0 if the woman had not made any prenatal consultation and value 1 if she made at least one prenatal consultation. Facility delivery was a binary value with 0 for all deliveries outside a health facility and value 1 for all deliveries at a health facility (health center or hospital). We defined four age-specific mortality variables for children: (1) neonatal mortality (ie, the probability of dying within the first 30 days of life); (2) postneonatal infant mortality (ie, the probability of dying between days 30 and 364 of life); (3) infant mortality (ie, the probability of dying before the first birthday) and (4) child mortality (ie, the probability of dying between the first and fifth birthdays) (Rajaratnam et al., 2010). For adults, we analysed mortality by age groups: 18–39, 40–59, 60–79 and ≥80 years. To minimise the risk of confounding through other factors that may have changed over time, we controlled for age and sex of child, twin status, child year of birth and mother and household characteristics (maternal age, religion, education, marital status, number of previous pregnancies and household socioeconomic status) in all child mortality models. Health facility delivery and ANC attendance were adjusted only for mother and household characteristics (maternal age, religion, education, marital status, number of previous pregnancies and household socioeconomic status). We used principal component analysis of household assets to divide

households into wealth quintile (ie, poorest, poor, medium, rich and richest) (Phillips et al., 2000).

The primary exposure variable of interest was the availability of a health facility in the village of residence during the exposure period. For the four period-specific mortality variables (ie, neonatal, postneonatal, infant and child mortality), local facility availability was coded as 1 if the facility was operational in the month of birth. For ANC attendance and facility delivery, local facility availability was coded as 1 if the facility was operational when the pregnancy started.

3.4.5. Statistical analysis

Data collected during this study were cross-checked and managed using a household registration system implemented in Windev V.12.0 (PC Soft; Montpellier, France). We also computed distance to the nearest facility for all households using the Stategeodist package (Picard, 2019). We then displayed minimum, average and maximum for distance before and after the health center was operational in each village.

Descriptive statistics of the study sample included means, minimum and maximum of quantitative variables and frequencies (%) of categorical variables. We used Cox proportional hazards model to estimate impacts on mortality. We also used instrumental variable regression models to estimate the impact of distance on child survival, using the local facility availability as predictors of household distance. In a sensitivity analysis, we employed linear probability models to ensure the robustness of the postneonatal mortality outcomes with respect to the empirical model.

We used multivariate logistic regression with clustering at village and year level to investigate the relationship between ANC attendance, health facility delivery and local health center availability. All models included child and mother characteristics as well as village and year fixed effects (intercepts) to rule out confounding by time-invariant unobserved characteristics. Standard errors were corrected to allow for residual correlation both at the household and community level using Huber's cluster-robust variance estimator (David E.Bloom & Richard B. Freeman, 1986). All statistical analyses were performed in Stata V.15.0 (StataCorp).

3.4.6. Patient and public involvement statement

Patients were not involved in the design and implementation of this study.

3.5. Results

3.5.1. Study sample and demographic characteristics

Between January 2010 and December 2018, a total of 14 132 pregnancies were registered in the Taabo HDSS. Supplemental appendix Table 7.1 presents the key characteristics of this sample. Most of the women were in a common-law or married union; 72.0% attended at least one ANC consultation and 52.3% gave birth in a health facility. Sixty-nine percent of the women were aged between 20 and 34 years. Only 30% of the women had completed elementary school, while 56.0% had never attended school.

Table 3.1 presents crude numbers of deaths and mortality rates per subgroup and 1000 person-years. A total of 440 973 person-year observations were included in the mortality analysis. There were 2957 deaths reported in the study period. Overall mortality was 6.7 (95% CI 6.5 to 7.0) deaths per 1000 person-years, with a higher rate in males compared with females (7.3 vs 6.1 deaths per 1000 person-years). Highest mortality rates (8.1 deaths per 1000, 95% CI 7.5 to 8.7) were observed in the poorest households and lowest mortality rates (4.9 deaths per 1000, 95% CI 4.5 to 5.4) were observed among households in the highest asset quintile. A similar socioeconomic gradient was observed for education, with 12.2 deaths per 1000 for individuals who had never attended school, compared with 3.0 per 1000 for individuals with completed secondary education.

As shown in Figure 3.3, slightly less than half of the child deaths were infant deaths (age at death <1 year), and 25% of death occurred between 12 and 23 months of age.

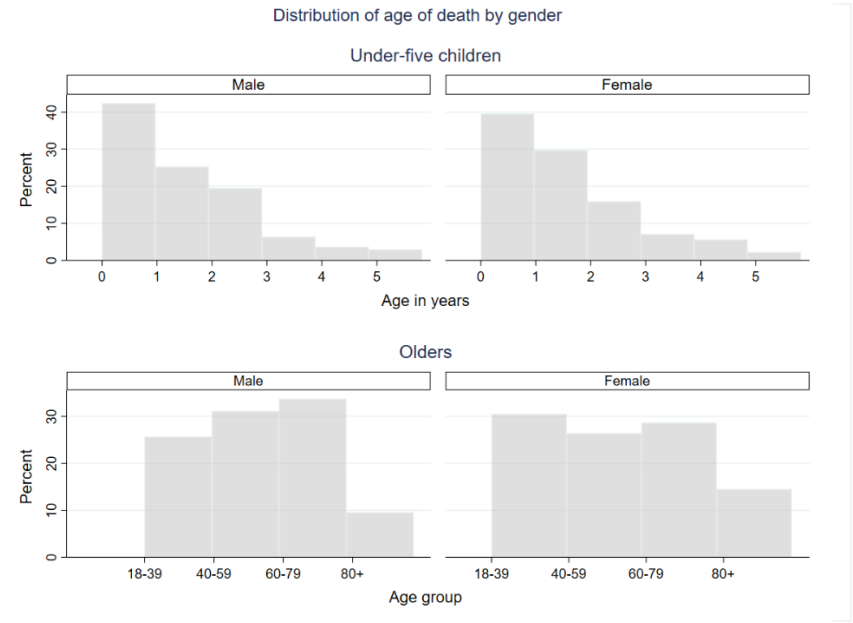

Figure 3-3: Distribution of age at death, stratified by gender and age

As regards the association of mortality and distance to the nearest health facility, smaller distance was associated with lower mortality (< 1km: 6.1 (95% CI 5.7 to 6.6), 1–4 km: 6.7 (95% CI 6.4 to 7.0) and ≥5 km: 7.6 (95% CI 7.0 to 8.2) deaths per 1000 person-years).

Table 3-1: Person-years structure, total number of death, and mortality rate by sociodemographic characteristics, 2010-2018

	Person-years	Number of death	Rate per 1000 years	95% CI
Child age (years)				
<1	13 381	285	21.3	19.0 to 23.9
1-4	61 339	761	12.4	11.6 to 13.3
Adult age (years)				
18 to 39	135 884	420	3.1	2.8 to 3.4
40 to 59	50 740	474	9.3	8.5 to 10.2
60 to 79	16 111	514	31.9	29.3 to 34.9
≥80	2162	225	104	91.3 to 118.6
Gender				
Male	223 846	1632	7.3	6.9 to 7.6
Female	217 126	1325	6.1	5.8 to 6.4
Socioeconomic status				
Most poor	77 903	630	8.1	7.5 to 8.7
Poor	89 225	575	6.4	5.9 to 7.0
Middle	95 421	649	6.8	6.3 to 7.3
Rich	90 195	668	7.4	6.9 to 8.0
Most rich	88 228	435	4.9	4.5 to 5.4
School level				
Never attended	186 501	2274	12.2	11.7 to 12.7
Primary	172 474	421	2.4	2.2 to 2.7
Secondary or higher	59 646	179	3.0	2.6 to 3.5
Coranic	22 351	83	3.7	3.0 to 4.6
Religion				
Christian	241 045	1477	6.1	5.8 to 6.4
Muslim	123 864	862	7.0	6.5 to 7.4
Other religion	76 063	618	8.1	7.5 to 8.8
New health facility opening				
Yes	317 800	2045	6.4	6.2 to 6.7
No	123 172	912	7.4	6.9 to 7.9
Distance to health facility				
<1km	109 918	675	6.1	5.7 to 6.6
1 to 4km	253 341	1691	6.7	6.4 to 7.0
≥5km	77 714	591	7.6	7.0 to 8.2
Total	440 973	2957	6.7	6.5 to 7.0

3.5.2. Health facilities opening and change in physical access with distance

Table 3.2 shows distance to the nearest health facility before and after the opening of the new health centers in Ahouaty, N'Denou, Taabo-Village and Tokohiri. Across the four villages, the average distance from households to the nearest health facility was reduced from 5.5 km before to 2.8 km after the opening of the new health centers. The largest reduction in average distance to health facility was observed in Tokohiri (6.4 km), followed by Taabo-Village (4.1 km). In Ahouaty and N'Denou the average distance was reduced from 3.4 km to 1.5 km and from 2.2 km to 1.3 km, respectively. An overview of the households' location in relation to the nearest

health facility prior to the construction of the new health centers is presented in Appendix Figure 7.3.

Table 3-2: Summary statistics of distance to nearest health facility before and after health facility opening

Village	min	Mean	max
Ahouaty			
Before health facility opening	2.10	3.43	4.24
After health facility opening	0.46	1.53	2.29
Difference	-1.64	-1.90	-1.95
N'Denou			
Before health facility opening	1.38	2.20	7.63
After health facility opening	0.05	1.25	1.74
Difference	-1.32	-0.96	-5.88
Taabo-village			
Before health facility opening	1.28	6.83	9.45
After health facility opening	0.30	2.77	7.34
Difference	-0.99	-4.06	-2.12
Tokohiri			
Before health facility opening	3.55	9.42	12.88
After health facility opening	0.56	3.02	8.53
Difference	-3.00	-6.40	-4.35
Total			
Before health facility opening	1.28	5.47	12.88
After health facility opening	0.05	2.76	8.53
Difference	-1.23	-2.71	-4.35

3.5.3. Effects of health facility opening on ANC and facility delivery

Table 3.3 presents the estimated causal impact of health facility opening and ANC and facility delivery. On average, new facilities increased the odds of ANC attendance by 24% (OR 1.24, 95% CI 0.96 to 1.60, p <0.05). We found no evidence of increased use of institutional deliveries after new facility opening (OR 0.87, 95% CI 0.70 to 1.07 in adjusted models).

Table 3-3: Estimated impact of facility opening on antenatal care attendance and institutional delivery

	Antenatal care attendance		Institutional delivery	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Health facility opened: no				
Yes	1.24* (0.960 to 1.60)	1.21 (0.91 to 1.61)	0.87 (0.71 to 1.06)	0.87 (0.70 to 1.07)
Observations	14 132	14 132	14 132	14 132

All estimates are based on logistic regressions with clustering at the village-year level. OR are displayed with 95% CIs in parentheses. Unadjusted models control for year and village fixed effects only. Adjusted models control for mother's characteristics as well as village and year fixed effects. *** p<0.01, ** p<0.05, * p<0.1.

Figure 3.4 shows the total number of deaths from 2010 to 2018 in the four villages of the Taabo HDSS where new health facilities were constructed. The vertical red line in each graph indicates when the health facility opened.

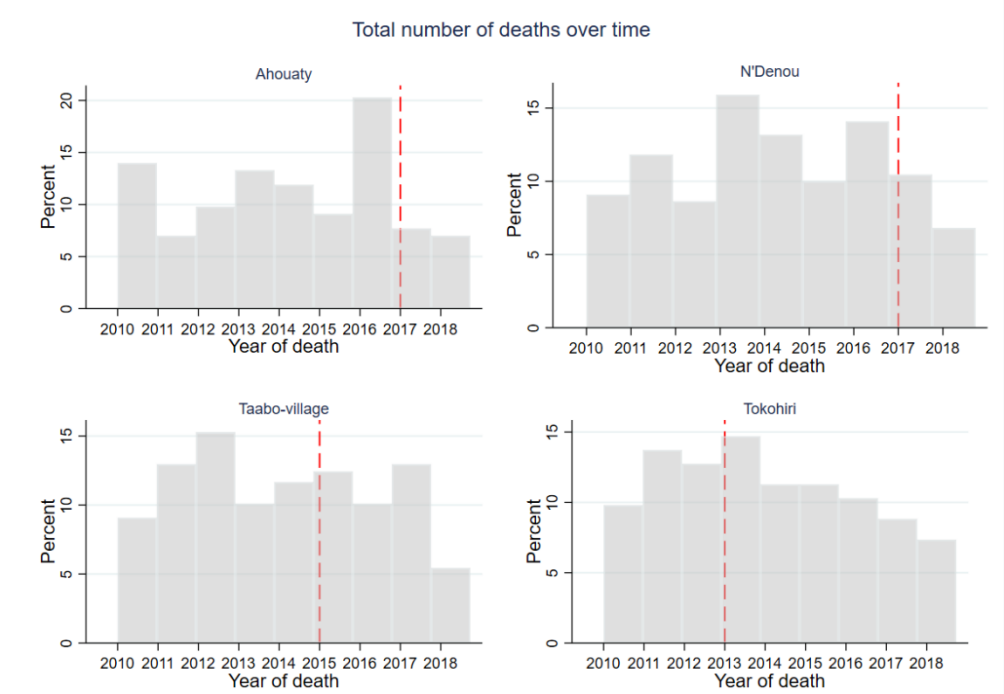

Figure 3-4: Number of all ages deaths over time in the four villages with new health facilities

Table 3.4 presents the main impacts on child survival. New facilities reduced the likelihood of post-neonatal infant death by 46% (HR 0.56, 95% Cl 0.31 to 0.99, p <0.05). No impact was found on neonatal and child mortality.

Table 3-4: Estimated impact of facility opening on child mortality

	Under to five mortality			
	Neonatal	Post-neonatal	Infant	Child
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Health facility opened: no				
Yes	1.29 (0.41 to 4.02)	0.56** (0.31 to 0.99)	0.65* (0.39 to 1.08)	1.11 (0.68 to 1.82)
Child's sex: male				
Female	1.31 (0.81 to 2.12)	1.04 (0.82 to 1.33)	1.08 (0.87 to 1.34)	1.06 (0.85 to 1.34)
Twin: no				
Yes	14.00*** (6.21 to 31.57)	2.12** (1.04 to 4.31)	3.72*** (2.24 to 6.19)	1.45 (0.54 to 3.90)
Number of previous pregnancies				
Pregnancies	1.15* (1.00 to 1.32)	1.07** (1.00 to 1.15)	1.09*** (1.02 to 1.16)	0.98 (0.92 to 1.05)
Maternal age				
Age	0.94** (0.89 to 0.99)	0.98** (0.95 to 1.00)	0.97*** (0.95 to 0.99)	0.99 (0.97 to 1.01)
Socioeconomic status: most poor				
Poor	0.75 (0.36 to 1.57)	0.59** (0.39 to 0.90)	0.60*** (0.42 to 0.87)	1.09 (0.76 to 1.57)
Middle	0.62 (0.29 to 1.31)	0.96 (0.65 to 1.40)	0.85 (0.61 to 1.20)	0.72 (0.48 to 1.07)
Rich	0.75 (0.36 to 1.57)	1.01 (0.68 to 1.49)	0.92 (0.65 to 1.30)	0.87 (0.60 to 1.27)
Most rich	0.47 (0.1 to 1.26)	1.09 (0.68 to 1.75)	0.92 (0.60 to 1.40)	0.92 (0.59 to 1.45)
Observations	5478	24 845	30 323	79 288

All estimates are based on Cox regressions. Coefficients displayed are HRs with 95% CIs in parentheses. All models control for child and mother characteristics as well as year, village and mother fixed effects. *** p<0.01, ** p<0.05, * p<0.1.
Neonatal: The probability of dying within the first 30 days of life.
Post-neonatal: The probability of dying between the first 30 days and 364 days of life.
Infant: The probability of dying before the first birthday.
Child: The probability of dying between the first and fifth birthdays.

Table 3.5 shows estimated impacts on adult mortality. We observed no statistically significant associations (p>0.05) between health facility opening and adults mortality.

Table 3-5: Estimated impact of facility opening on adult mortality

	Age groups			
	18 - 39.9	40 - 59.9	60 - 79.9	80+
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Health facility opened: no				
Yes	1.22 (0.75 to 1.99)	0.77 (0.50 to 1.19)	0.97 (0.64 to 1.47)	0.90 (0.47 to 1.72)
Gender: male				
Female	1.10 (0.88 to 1.38)	0.65*** (0.53 to 0.82)	0.60*** (0.47 to 0.75)	1.05 (0.69 to 1.59)
Socioeconomic status: most poor				
Poor	0.73* (0.53 to 1.00)	0.77* (0.57 to 1.03)	0.95 (0.70 to 1.30)	0.90 (0.49 to 1.64)
Middle poor	0.81 (0.59 to 1.11)	0.73** (0.54 to 0.99)	1.02 (0.76 to 1.37)	0.99 (0.57 to 1.73)
Rich	0.80 (0.57 to 1.11)	0.81 (0.61 to 1.09)	0.95 (0.70 to 1.30)	0.97 (0.55 to 1.71)
Most rich	0.92 (0.62 to 1.38)	0.51*** (0.33 to 0.78)	0.90 (0.61 to 1.33)	1.03 (0.54 to 1.97)
Marital status: single				
Common, law union	0.55*** (0.42 to 0.71)	0.93 (0.68 to 1.28)	0.88 (0.53 to 1.46)	1.25 (0.22 to 7.00)
Married	0.41*** (0.31 to 0.54)	0.55*** (0.42 to 0.72)	0.74* (0.53 to 1.03)	0.62 (0.31 to 1.24)
Divorced/widowed	0.31** (0.11 to 0.86)	0.87 (0.60 to 1.26)	0.80 (0.57 to 1.13)	0.64 (0.34 to 1.22)
Observations	343 088	129 636	40 826	4698

All estimates are based on Cox regressions. Coefficients displayed are HRs with 95% CIs in parentheses. All models control sociodemographic characteristics as well as year and village fixed effects. *** p<0.01, ** p<0.05, * p<0.1.

3.5.4. Sensitivity analysis

Table 3.6 summarises results from a sensitivity analysis, using linear probability models restricted to post-neonatal mortality to ensure the robustness of the post-neonatal mortality outcomes with respect to the empirical model. On average, we found that each additional km in distance increased post-neonatal mortality by 2 deaths per 1000 (Coef=0.002, 95% CI 0.000 to 0.004, p <0.05; Table 3.6).

Table 3-6: Estimated linear effect of health facility opening and distance on post-neonatal and infant mortality

	Post-neonatal mortality		Infant mortality	
	Model (1)	Model (2)	Model (3)	Model (4)
VARIABLES	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)
Health facility opened: no				
Yes	-0.007*** (-0.010 to -0.003)	-0.011*** (-0.018 to -0.004)	-0.005** (-0.009 to -0.001)	-0.006* (-0.012 to 0.001)
Observations	25 047	27 827	30 531	33 749
R-squared	0.005	0.375	0.005	0.341
Distance				
Distance	0.002*** (0.001, 0.003)	0.002** (0.000, 0.004)	0.002*** (0.000, 0.003)	0.002** (0.000, 0.003)
Observations	25 047	25 047	30 531	30 531
R-squared	0.002	0.002	0.004	0.004

All estimates are based on linear regressions. Coefficients are displayed with 95% CIs in parentheses.
Model 1 and model 3 control for child and mother characteristics as well as village and round fixed effects only,
Model 2 and model 4 control for child, mother characteristics, village, round as well as mother fixed effects. *** p<0.01, ** p<0.05, * p<0.1.

3.6. Discussion

In this study, we used longitudinal surveillance data from a well-characterised population-based cohort in the Taabo HDSS in south-central Côte d'Ivoire to estimate the impact of newly constructed health facilities on the utilisation of essential maternal health services as well as child and adult mortality. Even though the construction of new facilities was initiated in response to local demand and a local needs assessment, overall impacts seem relatively limited. Specifically, and contrary to previous cross-sectional studies (Karra et al., 2017; McKinnon et al., 2014), we found no changes in mortality for the neonatal period (where most child death occur) or for adults. For adults, 80.5% of deaths have been attributed to NCDs, which are not generally supported by PHC centers (Kone et al., 2015b). The lack of a mortality impact on adults could thus be partly explained by health systems in low and middle-income countries being still relatively ill-prepared for chronic disease management (Allotey et al., 2014; Tham et al., 2018).

The lack of impact on neonatal mortality seems less surprising given the lack of impact on institutional deliveries. Limited change in institutional deliveries is likely due to relatively limited infrastructure available at the new health centers; this in turn limits the health personnel's ability to deal with complicated deliveries that cause most of the neonatal deaths (Abdullah et al., 2016; Mortality & Causes of Death, 2016). A recent study from Malawi (Leslie et al., 2016) shows that having a high-quality facility in close proximity to households is associated with large reductions in neonatal mortality, but that similar patterns cannot be observed for lower quality health facilities. Quality care remains a key challenge in many settings (Kinney et al., 2010; Oleribe et al., 2019), and is likely of particular importance for neonatal mortality (McKinnon et al., 2014). This may be different for the post-neonatal period, where timely treatment may be of paramount importance, and basic treatment for the most common conditions (malaria and respiratory infections) can be provided even by health centers with very limited supplies. The lack of impact of new health facilities on ANC utilisation, where distance has been highlighted as key barrier to access, is somewhat more surprising than the mixed impacts on mortality. Several studies have highlighted the associations between travel time and treatment seeking behavior, and argued that mortality penalties for children and adults can be lowered through easier access (Karra et al., 2017; Kelly et al., 2016; Quattrochi et al., 2020; Sarrassat et al., 2019). On the other hand, our results are well aligned with a study from Malawi, which also found that newly constructed facilities in the 1990s resulted neither in changes in utilisation of ANC and skilled delivery, nor in changes in mortality outcomes

(Quattrochi et al., 2020). The lack of impact of new health facilities on care utilisation is not explained by high baseline levels that would not allow for any improvements. Less than three-quarter (72.0%) of women had attended at least one prenatal consultation, while slightly more than half (52.3%) had given birth in a health facility in our sample. Estimates from the national Demographic and Health Survey conducted in 2012 look fairly similar (Institut National de la Statistique & ICF International, 2012). Research from Côte d'Ivoire suggests that lack of access to supplements and drugs may be a key barrier to ANC access (Murielle GEA, 2019). It is also conceivable that additional out-of-pocket payments contribute to the generally low demand for ANC services (Moyer & Mustafa, 2013; Sambo et al., 2013). In order to increase beneficiary satisfaction and utilisation of the health centers, incentives (availability and utilisation of health services, posting and respect of fees for healthcare procedures, availability of drugs and strategic inputs, existence and functionality of management committees, and the conduct of sensitisation sessions on the priority health problems of the village) have more recently been put in place.

The main strength of our study is the continuous prospective collection of surveillance data through the HDSS, which allowed to closely monitor and measure changes in healthcare seeking behaviors and health outcomes over time. The study also benefits from the central decision on the timing and location of new facilities, providing a plausible natural experiment for assessing facility impacts.

Nevertheless, our study is subject to certain limitations. First, the results are based on only a small number (n=4) of new health facilities constructed. Even though we believe that these facilities are fairly representative in the national efforts in Côte d'Ivoire to strengthen PHC, observed impacts may be different in other settings. It is also conceivable that average health facility distances prior to the construction of facilities may be larger in other areas. In our setting, average distance to health facilities prior to the opening of new centers was 5 km. These distances are likely substantially larger in other, less densely populated settings, even though some recent papers suggested that most households now live fairly close to facilities in SSA (Karra et al., 2017; Wigley et al., 2020). Second, from a quality of care perspective, both equipment and staffing provided to facilities are of critical importance. On average, the four new health centers had only one staff member and limited diagnostic tools. Hence, the estimates presented here lack representation for an establishment of larger and better equipped places. Third, we only had a relatively small number of child (post-infancy under 5) deaths in our sample, limiting our statistical power. Larger studies may be able to detect smaller

improvements. Fourth, we opted for Euclidean distances calculation from the household to the nearest health facility. This likely underestimates the true distance and travel time on the ground, and may thus bias our distance estimates (Okwaraji et al., 2012; Okwaraji & Edmond, 2012).

3.7. Conclusion

Our study suggests that local construction of new health centers in a mainly rural part of south-central Côte d'Ivoire may have only relatively limited impact on healthcare utilisation and overall population health. More research will be needed to better understand the somewhat limited impacts seen in this study as well as to identify the health infrastructure needed more generally for improving health outcomes in this setting.

3.8. Acknowledgements

We thank the population in the four study villages for their collaboration, the Taabo HDSS team and field enumerators for data entry and staff management, and the key informants for their untiring help in the field, particularly for data collection and processing. We are most grateful to Fairmed, the Health District of Tiassalé, the Taabo-Cité Public Hospital, the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, the Université Félix Houphouët-Boigny and the Swiss Tropical and Public Health Institute for the partnership and vision, which facilitated the establishment of the Taabo HDSS some 15 years ago.

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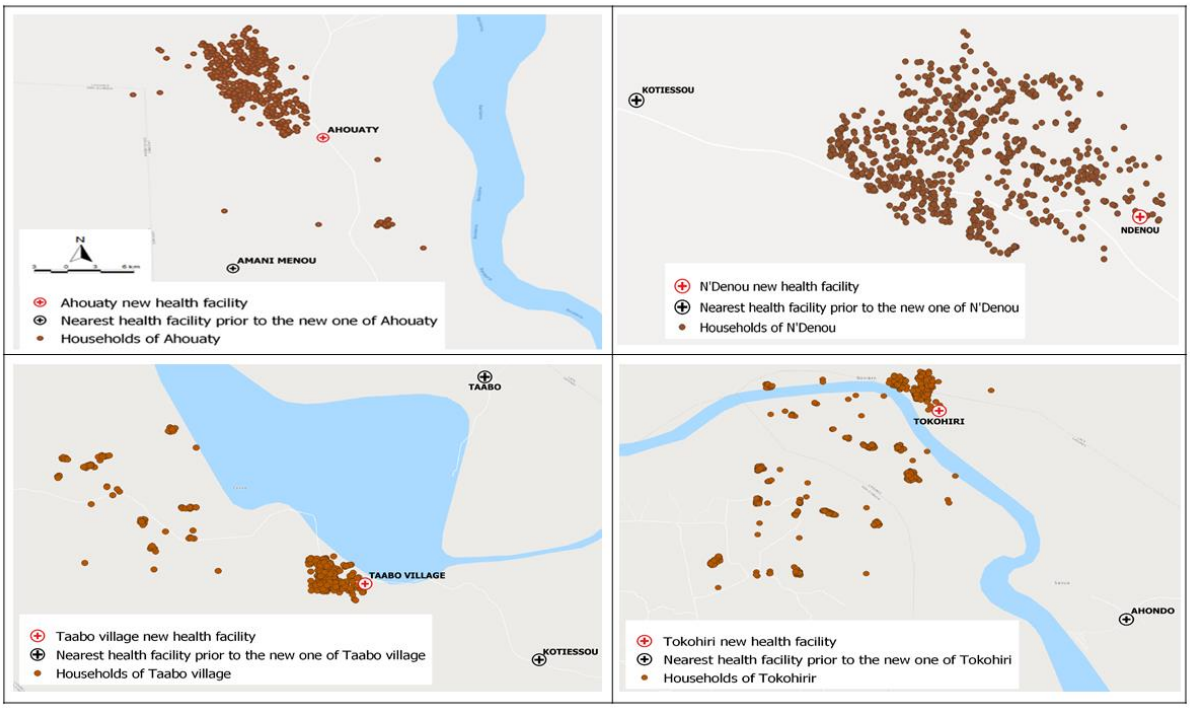
3.10. Appendix 2: Impact of new infrastructure facility on antenatal care attendance, facility delivery and child health: evidence from Taabo health and demographic surveillance system, Côte d'Ivoire

3.10.1. Supplemental Materials Table ST2-1: Characteristics of pregnant woman

	Sample of pregnant women	
	N	(%)
ANC attendance		
At least one ANC	10162	71.9
No ANC	3970	28.1
Place of delivery		
Health facility	7396	52.3
Home	6681	47.3
Other	55	0.4
Mother marital status		
Single	1226	8.7
Common-law union	5406	38.2
Married	7403	52.4
divorced/widowed	97	0.7
Mother religion		
Christian	8276	58.6
Muslim	4483	31.7
Other	1373	9.7
Socioeconomic status		
Most poor	2844	20.1
Poor	2825	20.0
Middle	2818	19.9
Rich	2826	20.0
Most rich	2819	20.0
Mother school level		
Never attended	7853	55.6
Primary	4238	30.0
Secondary/higher	1246	8.8
Coranic	795	5.6
Maternal age		
15-19	2197	15.5
20-34	9708	68.7
≥35	2227	15.8
Total	14132	100.0

3.10.2. Supplemental Materials Figure SF2-1: Households location map (with old and new health facilities



4. Paper 3 – Study protocol of a cluster randomized controlled trial of strategies to increase antenatal iron and folic acid supplementation and malaria prophylaxis in rural-central Côte d'Ivoire

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This article has been published in

BMC Public Health 2020, 20: 1609

4.1. Abstract

Coverage of antenatal iron and folic acid supplementation (IFAS) and intermittent preventive treatment of malaria in pregnancy (IPTp) remains low in many countries. Evidence on the most effective ways to increase both IFAS and IPTp is mixed overall, with only few studies directly identifying cost-effective ways to increase coverage of both interventions. The proposed study aims to assess the cost, impact, and relative cost-effectiveness of two complementary strategies of increasing IFAS and malaria chemoprophylaxis coverage among pregnant women relative to the current default system in a rural low-income setting of sub-Saharan Africa. This study will be carried out in the Taabo health and demographic surveillance system (HDSS) in south-central Côte d'Ivoire. This is a cluster-randomized trial targeting 720 consenting pregnant women aged ≥15 years. The 118 clusters constituting the Taabo HDSS monitoring area will be randomly allocated to one of the following three groups with equal probability: a control group, an information only group, and an information plus home delivery group. To assess the relative effectiveness of each strategy, we will conduct an endline survey within the first 2 weeks after delivery. The primary outcomes of the trial will be maternal post-partum anemia and malaria infection. Anemia will be assessed using HEMOCUE devices; malaria infections will be assessed using standard rapid diagnostic tests named CareStart™ Malaria Pf (HRP2) Ag RDT (Multi Kit with capped lancet and inverted cup specimen transfer device). Other outcomes will include self-reported adherence to supplementation and malaria chemoprophylaxis, as well as miscarriages, stillbirths, and low birth weight deliveries. This study will assess the cost-effectiveness of two alternative strategies to increase antenatal IFAS and malaria chemoprophylaxis coverage among pregnant women in rural Côte d'Ivoire and similar settings. Trial registration: ClinicalTrials.govNCT04250428; Registered 31 January 2020.

Keywords: Antenatal iron and folic acid supplementation, Malaria chemoprophylaxis, Maternal and child health, Cluster randomized controlled trial, Health and demographic surveillance system, Cost-effectiveness

4.2. Introduction

Despite major progress in antenatal care access over the past years, coverage of essential antenatal interventions remains limited in many low- and middle-income countries (Christian et al., 2003). At the same time, prevalence of maternal anemia (Black et al., 2013; WHO/WFP/UNICEF, 2007) and exposure to malaria in pregnancy remain high (World Health Organization, 2016). In Côte d'Ivoire, 59% of pregnant women are estimated to be anemic (hemoglobin< 110g/L), only a minority of women receives antenatal iron supplementation consistently throughout their pregnancy and less than one third of women receive the recommended three doses of intermittent preventive treatment of malaria in pregnancy (IPTp) (INS/ICF, 2012; WHO, 2012a, 2016b). Iron supplementation and malaria chemoprophylaxis have been shown to be highly effective for reducing the risk of stillbirth, prematurity, and low birth weight, and have been highlighted as essential for reducing the burden of malnutrition in the 2013 Lancet series (Bhutta et al., 2013a).

Low coverage rates of essential antenatal care interventions have been attributed to lacking demand from beneficiaries (e.g. low antenatal care attendance), weak early health system contact with women, limited funding, stock outages and ineffective management of supplies (Bhutta et al., 2013a; Pokharel RK, 2009; Sharma et al., 2004; Trowbridge & Martorell, 2002). In general, limited coverage of essential health services as well as limited adherence to national protocol have been attributed to multiple challenges in the health system. These challenges include the lack of knowledge on importance of medication, interrupted supply and stock outs, high cost of care, lack of availability of services, and demand-side barriers such as distance, education, opportunity cost, and cultural and social barriers (Ensor & Cooper, 2004; Ensor et al., 2002; MoH, 2013-2017; "National Healthcare Quality Report," 2013). To address these challenges successfully, many community-based studies assessed a range of interventions including community-based distribution of drugs, vaccines, or other public health services. In 2018, a systematic review of strategies identified 28 studies evaluating the treatment coverage in community-based public health programs (Deardorff et al., 2018). These studies covered a range of different strategies, including community-based treatment, distributor incentives, distribution along kinship networks, intensified information, education, and communication activities, fixed-point delivery, conversion from school- to community-based delivery, and management by a non-governmental organization. Services delivered included community-based public child health programs such as vitamin A supplementation, child immunizations, and mass drug administration campaigns targeting neglected tropical diseases. The largest

positive influence on treatment coverage was found for 4 strategies: community-directed distribution, incentives to increase distributor motivation, distribution along kinship networks and implementation of intensified information education and communication activities. A 2016 Cochrane review evaluated the effectiveness of community-based health education and household monetary incentives in child immunization coverage in low and middle-income countries. Overall, health education at village meetings or at home, as well as household monetary incentives had little or no effect on full immunization coverage (Oyo-Ita et al., 2016). Vouchers have also been widely used to promote maternal and newborn health in LMICs: a systematic review based on seven previously published systematic reviews (Bellows et al., 2011) found that reproductive health voucher programmes increased utilization of reproductive health services, improved quality of care, and improved population health outcomes. In another Cochrane review focusing on antenatal care, 34 randomized controlled trials testing community-based interventions to improve uptake of antenatal care (media campaigns, education, or financial incentives for pregnant women), and health systems interventions (home visits for pregnant women or equipment for clinics) were identified. The review highlighted several potentially effective interventions and suggested a combination of interventions for stronger impact (Mbuagbaw et al., 2015). Overall, evidence on the most effective ways to increase both IPTp and antenatal IFAS remains mixed, with very few studies directly identifying cost-effective ways to increase coverage of both interventions. The objective of the proposed research is to assess both the cost, effectiveness, and relative cost-effectiveness of two of the most commonly used strategies in a rural low-income setting compared to the default system. Our main hypothesis is that uptake of preventive antenatal services can be improved by both demand and supply side intervention strategies, but that supply side interventions are more cost-effective and equitable than demand side interventions despite their higher relative cost. The results of this study will help to identify the most effective ways to increase antenatal IFAS and IPTp coverage among pregnant women in rural Côte d'Ivoire and similar settings.

4.3. Methods

4.3.1. Study design

The main idea of this study is to directly test and compare the relative effectiveness and cost-effectiveness of demand and supply side interventions encouraging preventive care use through a single trial. Secondary objectives include determining program impact (a) on the prevalence of post-partum anemia and malaria infection, and (b) on children's birthweight.

The study will be designed as a cluster-randomized experiment with three parallel arms: a control arm, an information only or "demand generation" arm, and an information plus direct distribution arm. We expected to recruit approximately 240 pregnant women for each arm, for a total sample size of 720 women. This study will be carried out in the HDSS of Taabo in south-central Côte d'Ivoire. The Taabo HDSS has continuously monitored a population of approximately 45,000 since 2009. The pilot study will target 720 pregnant women across the 118 neighborhoods with in the HDSS monitoring area. Each cluster corresponds to either a neighborhood ("quartier") in larger villages, or a smaller separate settlement ("hamlet"). The 118 clusters will be split into three groups: a control group (39 clusters), an information group (39 clusters), and a distribution of free supplements group (40 clusters) (Figure 4.1).

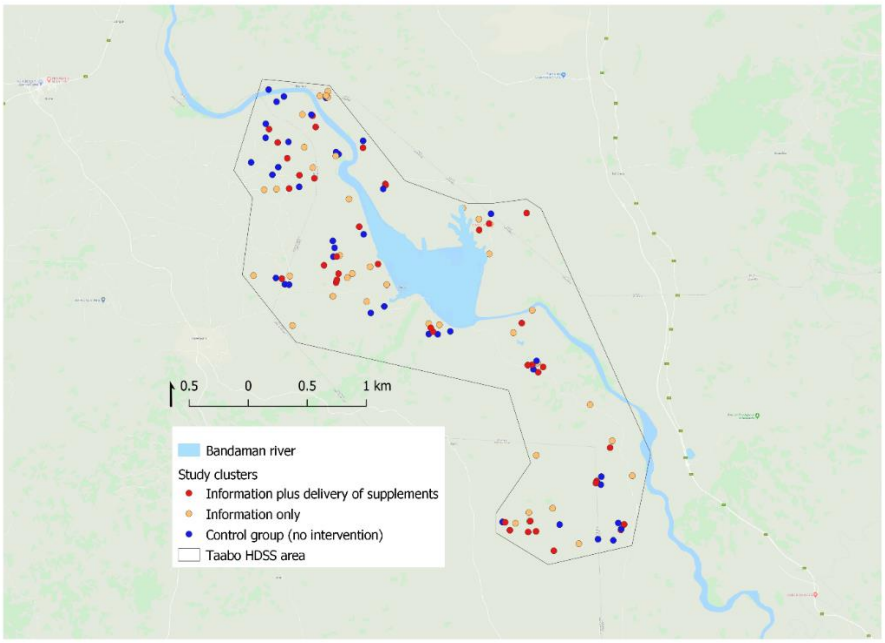

Figure 4-1: Map of the study area and clusters.

Notes: The map was generated using QGIS geospatial database software 3.4.4. Administrative boundary data and cluster centroids were collected through the HDSS. The base background layer showing roads, rivers and lakes was extracted from earth using QGIS

A study overview showing the main components and timeline is given in Figure 4.2.

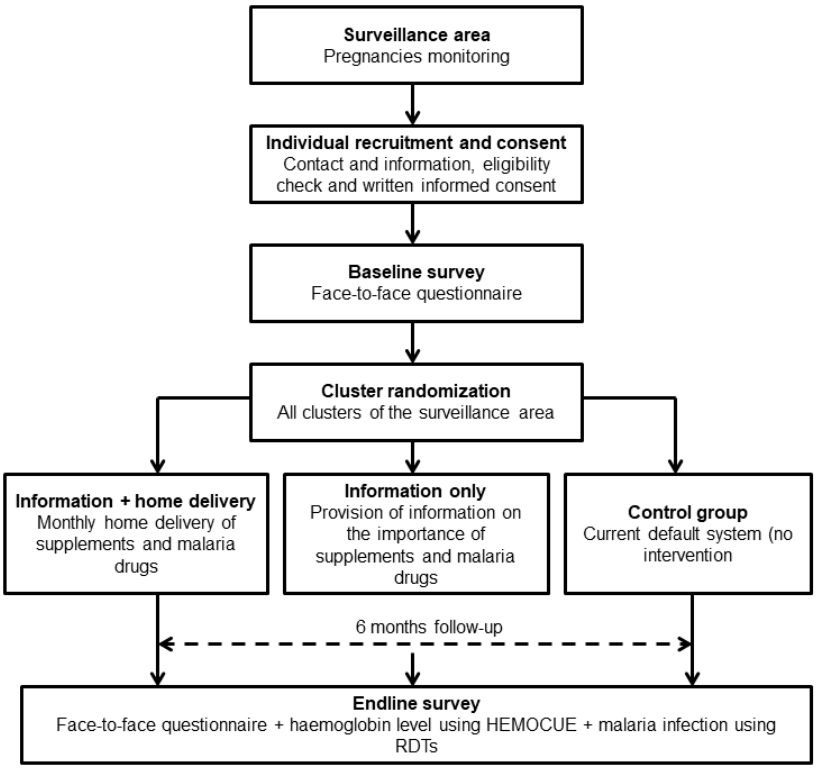

Figure 4-2: Study overview

4.3.2. Setting

The proposed research will be implemented in the Taabo HDSS area in the sub-prefecture of Taabo. The HDSS covers an area of 980 km^2 and comprises one small town (Taabo-Cité), 13 villages and over 100 smaller hamlets attached to the same villages (Kone et al., 2015a). In terms of health infrastructure, the HDSS features one general hospital and 10 health centers. Population surveillance is implemented three times per year and focuses on pregnancies, births, deaths and migration of residents (Fürst et al., 2012; Kone et al., 2015a). For all deaths reported, verbal autopsies (VAs) are conducted using WHO VA instrument to establish likely causes of death (Byass et al., 2012; Fottrell & Byass, 2010; Kone et al., 2015b; World Health Organization, 2007). Data collected between 2009 and 2011 highlights the high prevalence of communicable diseases such as malaria, acute respiratory infections, HIV/AIDS and pulmonary tuberculosis (Kone et al., 2015b). In 2018, 1436 pregnancies were reported in the Taabo HDSS. 73% of the local population are Ivorians (predominantly Akans); most non-Ivorians are from Burkina Faso (Kone et al., 2015a).

4.3.3. Selection of study participants

Recruitment

Pregnant women in the first or second trimester of their pregnancy, living in the HDSS with an age ≥15 and ≤ 49 years will be eligible to participate in this study. Gestational length will be assessed based on self-reported date of conception or date of last menstrual period. Key informants will be recruited by the study team in all areas to report pregnancies as early as possible to the study staff. Key informants will be given a reward of 1,000 CFA (USD 2) for each pregnancy reported. Once the study coordinator has been informed about a new pregnancy, a local field enumerator will be sent out to invite pregnant women to participate in the study. Conditional on her consent, the women will be automatically assigned to a group based on her residence and a short baseline questionnaire will be conducted.

4.3.4. Participant information and consent

We will use two separate informed consent forms for this study. A general study participation consent form that will primarily cover the baseline and endline surveys, and consent forms for the two interventions. Mothers in the information (intervention) arm will be informed about the objective of this intervention. Mothers in the supplements arm will be informed about the objective of the arm as well as the intervention package they are going to receive. These intervention consent forms will be short and administered by study staff at the beginning of their first visit. For mothers under the age of 18 years, permission to participate in the study will be sought from a legal representative in the household. For illiterate mothers, we will use a thumbprint instead of a signature on the consent form. Participants may decide not to continue participating in the study at any time and for any reason if they wish to do so without any particular involvement. The investigator may decide to remove a participant from the study for reasons of ethical concerns or insufficient participant recruitment.

4.3.5. Intervention

As part of this study, we will test two interventions: an information only intervention and an information plus delivery intervention. The information only intervention focuses on empowering pregnant mothers to adopt appropriate health practices and health behavior. Health staff (midwives and nurses) will visit all women in this arm at the beginning of their pregnancy (after baseline) and inform women regarding the importance of antenatal IFAS as well as IPTp. Specifically, the nurse will talk with participating women about the benefits, adverse events,

and when, why, and how to take IFAS and sulfadoxine-pyrimethamine (SP). The nurse will also provide pregnant women with a phone number they can call in case they have questions related to antenatal care, supplements or IPTp, and will encourage women to attend antenatal care in accordance with national guidelines.

In the information plus delivery arm, women will receive a similar first visit by a study nurse, followed by monthly home visits. During the initial visit, study staff will inform women about recommended antenatal care attendance and supplementation and inquire about supplements received. All women not having received supplements from their antenatal care visits will then be directly provided with a monthly supply of iron and folic acid. Similarly, all women in their second or third trimester not having received SP will be directly provided SP together with additional information and instructions on how to take the medication each month. At the end of each monthly visit, study staff will remind women about their next antenatal care appointment and remind them to take supplements daily.

4.3.6. Data collection

Table 4.1 presents a summary of all measurements conducted in the study. Data will be collected by a trained researcher team. In addition to the baseline collection, we will collect detailed monitoring data on home visits as well as cost data for the two arms. To assess the relative effectiveness of each strategy, we will conduct an endline survey within the first 2 weeks after delivery. The form to be used to conduct the endline survey among women will combine both information on prenatal supplementation and IPTp (supplements, doses, period, frequency, and date, anemia and malaria status), socio-demographic characteristics e.g. (maternal age, education attainment and household assets), and pregnancy outcome (e.g. live birth, still birth, preterm birth and birth weight). Given that we expect women's self-report on antenatal IFAS not be very accurate, we will collect haemoglobin level and malaria infection prevalence as primary study outcome measures at endline. Hemoglobin levels will be assessed using HEMOCUE devices; malaria infection will be tested using standard rapid diagnostic tests (RDTs). All endline surveys will be conducted by study nurses who are familiar with both test procedures.

Table 4-1: Overview of study outcomes and measurements

	Baseline	Endline (6 months)
Household's characteristics		
Primary source of drinking water	X	
Source of lighting	X	
Materials and equipment	X	
Woman's characteristics		
Date of birth	X	
Marital status	X	
Level of education	X	
Pregnancy duration	X	
Number of live births	X	
Total number of pregnancies	X	
ANC attendance	X	X
Gestational age at first ANC visit	X	
Pregnancy related information after delivery		
Pregnancy outcome		X
Child's sex		X
Birth weight		X
Place of delivery		X
Assistance during delivery		X
Delivery process		X
Delivery cost		X
Performed tests during ANC		X
AIFAS uptake (number, dose)		X
Malaria prevention (number, dose)		X
Side effects from iron uptake		X
Haemoglobin level		X
Malaria infection		X

ANC: antenatal care; IFAS: iron and folic acid supplements

4.3.7. Data handling

The interview data will be collected by trained field enumerators using portable electronic devices (tablets) with incorporated data entry forms. Open Data Kit (ODK) will be used for entering data. The master database will be managed in a secure server. HEMOCUE devices and standard RDT results linked to unique numbers will be recorded in lab sheets and entered into a database.

Project data will be handled with utmost discretion and will only be accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. To ensure confidentiality, in the questionnaire and lab forms, participants are only identified by a unique participant number, which will be anonymized and cannot be traced back to the person without a separate ID key.

We will prevent the problem of missing data by well planning the study and collecting the data carefully. In case of missing data, we will use multiple imputation to replace the

missing values with a set of plausible values that contain the natural variability and uncertainty of the right values.

To maintain data security and prevent unauthorized access, the data server will be restricted with a security password, and access will be given only to selected personel. A backup of the data file will be done periodically and kept in a different place. Following the study, the data will be archived in location and period in accordance with the local regulations.

This project is part of the Taabo HDSS, which is affiliated to the Centre Suisse de Recherches Scientifiques (CSRS) en Côte d'Ivoire and the Swiss Tropical and Public Health Institute (Swiss TPH) in Switzerland. The data resulting from this project will therefore be stored on both the CSRS and the Swiss TPH servers. The codebook document will contain information on study design, sampling methodology, fieldwork, variable-level detail, and all information necessary for a secondary analyst to use the data accurately and effectively.

All data collected as part of this project will be made publicly available after publication of the main study results.

4.3.8. Sample determination

The unit of randomization will be neighborhoods, locally referred to as "quartiers" or "hamlets". The study is powered to detect a 20%pt. decline in maternal anemia with power 0.8 and alpha 0.05, assuming a control group anemia prevalence of 50%, 6 women per cluster, and an intra-class correlation (ICC) of 0.25. The ICC estimate was based on a previous analysis of antenatal care access patterns in the Taabo HDSS. Assuming a follow-up rate of 90%, this requires an initial enrolment of 240 women per arm, or a sample of 720 women in total. Given the birth rates observed in the past 3 years, we anticipate to enrol the 720 women over a 6-month period. Based on the latest Demographic and Health Survey conducted in the region, we expect 21% of women in the control group to be malaria positive. In order to achieve power 0.8, we would need a two third reduction in RDT positivity after birth with the intervention.

4.3.9. Randomization procedures

Neighbourhoods were randomized to the three groups using min-max randomization (M. Bruhn, and David McKenzie. , 2009). Specifically, 100 random allocations were created using the Stata 15 SE software package. For each random draw, the three groups were compared with respect to the average number of births and average antenatal care attendance in the 2016-2018

period. The random draw with the smallest differences between the three groups (largest minimum p-value) was used for final treatment assignment.
The group assignment of women will only be known to the study coordinator, who will directly manage all interventions.

4.3.10. Blinding procedures

Given that we wish to study the best delivery of interventions, we cannot blind subjects to treatment. Treatment status will, however, not be revealed to the survey team conducting the endline assessment. Un-blinding of subjects will not be necessary.

4.3.11. Statistical analyses

The health outcomes to be studied are post-partum anemia, malaria infection, and birth weight. Post-partum anemia will be defined as a hemoglobin concentration less than 11 g/dL and malaria infection will be defined by a positive result of the RDT. Logistic regression models will be used to compare post-partum anemia and malaria infection in the two intervention groups to the control group. For birth weight as well as hemoglobin levels as continuous variable, we will use basic linear regression models. Generalized estimating equations with robust variance-covariance estimation will be used to account for clustering (Huang et al., 2016; M. Wang & Long, 2011). The basic regressions models will compare outcomes in treated and control women, with standard error corrections for grouped data. In adjusted estimates, we will control for basic maternal covariates such as age, education, and residence. The power calculations were done as two-group comparisons, allowing to estimate differences between either of the two intervention groups and the control group. Additional subgroup analysis focusing only on a dose-response analysis will also be conducted to estimate average treatment effects on the treated.

4.3.12. Access to care during and after the trial and compensation

All subjects will have access to public antenatal and post-natal care during and after the trial. Women in both treatment and control groups with diagnosed malaria infections and haemoglobin levels below 11 g/dl will be referred to the nearest health center for further testing and treatment. No compensation will be provided to study subjects.

4.3.13. Cost and cost-effectiveness

Throughout the trial, detailed cost data for implementing both intervention arms will be collected. The data will be used to compare the observed increases in supplementation coverage to the cost of each arm. Incremental cost effectiveness ratios will be defined as additional cost per pregnant woman divided by the observed increase in the probability of receiving appropriate ANC (IPTp + IFAS).

4.4. Discussion

This paper describes the design of a cluster-randomized study that will evaluate the effectiveness and cost-effectiveness of two alternative strategies in increasing IFAS and malaria chemoprophylaxis coverage among pregnant women relative to the current default system. To our knowledge, this is the first study in Côte d'Ivoire using data stemming from an HDSS, which is a well-characterized population-based cohort that is subject to longitudinal surveillance. Results from this study will help to identify the most effective and cost-effective strategy to increase antenatal IFAS and IPTp coverage in rural Côte d'Ivoire and similar settings. The results of the study will be shared through a peer-reviewed article as well as through the communication offices at the CSRS and the Swiss TPH.

The choice of interventions is made not only based on the results of past studies (Bellows et al., 2011; Deardorff et al., 2018; Oyo-Ita et al., 2016) but also on the priority of national challenges in maternal and child health. The latest number from the HDSS suggests that prenatal supplementation with iron and folic acid covers less than 50% of pregnant women. IPTp has been adopted since 2005. However, the effectiveness of protecting the mothers and unborn children from adverse events from malaria depend on the rigorous adherence of this policy, coverage, and the number of ANC visits of the expectant mothers (WHO, 2014b; WHO/RBM, 2015).

The implementation of this project into the Taabo HDSS will make recruitment of the participants easy. The project will also be conducted in close collaboration between the CSRS, Swiss TPH, local physicians and nurses, and community leaders based on mutual agreement with local authorities from the whole HDSS's area to guarantee smooth implementation. The Taabo HDSS platform reduces the risk for loss to follow-up since the fieldwork teams hold close contact with the local population.

Although the study is designed as a cluster-randomized controlled trial, contamination between hamlets or neighbourhoods cannot be excluded. In cases where clusters correspond to

hamlets, the next settlement is typically at least 1 km away. For urban neighbourhoods, distances are much smaller, with households on the opposite side of the street receiving opposite treatments in some cases. For the direct delivery arm, spillovers seem somewhat unlikely, because the study team will simply not deliver the same intervention to non-treated women. For the information only treatment, spillovers are certainly possible, and would bias the estimated impacts towards zero. We will explore such contamination effects through spatial analysis in our sensitivity checks.

The project team may also face some push-back or complaints regarding adverse events related to iron consumption. We will make subjects aware of this risk in the informed consent form and use the initial information session to further prepare pregnant women for this. We will also try to minimize these adverse events by asking mothers who have complaints to take supplements after major meals. Another problem is that some women may not attend ANC if they receive supplements at home. ANC attendance is critical for preparing women for delivery, for understanding warning signs during pregnancy and childbirth, and for the prevention of pregnancy-related morbidity factors. To ensure attendance to ANC, all women will be reminded to attend the scheduled visits during the first visit in both arms, and during each of the visits by our study team in the home delivery arm.

Last, there are some concerns that folic acid supplementation may increase the rate of treatment failures with SP (Verhoef et al., 2017). Given that national protocols demand both iron and folic acid supplements, we cannot investigate this question experimentally in our study – post-hoc analysis of relative SP efficacy among women taking and not taking iron and folic acid supplements may however be possible.

4.5. Acknowledgements

We would like to thank the directors and staff of CSRS in Côte d'Ivoire and Swiss TPH in Switzerland as well as the staff at the Taabo HDSS and the Departmental Director of health and staff of Tiassalé health district for their support of this project.

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5. Paper 4 - Improving coverage of antenatal iron and folic acid supplementation and malaria prophylaxis through targeted information and home deliveries in Côte d'Ivoire: a cluster-randomized controlled trial

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This article has been submitted to

Lancet Global Health

5.1. Abstract

Coverage of antenatal iron and folic acid (IFA) supplementation and intermittent preventive treatment of malaria in pregnancy (IPTp) remains low in many LMIC settings, contributing to the continued high burden of anemia and malaria in pregnancy. We conducted a cluster-randomized controlled trial in the south-central part of Côte d'Ivoire to assess the effectiveness of two strategies for increasing IFA supplementation and IPTp coverage: a personal information session with at least 15 years old pregnant women in the first or second trimester (INFO), and a personal information session followed by monthly home deliveries of IFA supplements and IPTp (INFO+DELIV). Overall, 118 cluster were randomly allocated with equal probability to control (39 clusters), INFO (39 clusters), and INFO+DELIV (40 clusters). The primary outcomes were maternal postpartum anemia (haemaglobin <110 g/l) and malaria infection (positive CareStart™ Malaria Pf (HRP2) Ag RDT). Self-reported antenatal IFA supplementation and IPTp coverage, as well as antenatal care visit, miscarriages, stillbirths, and low birth weight deliveries were considered as secondary outcomes. Assessors and analysts were blinded to treatment, and analysis was conducted using an anonymized blinded data set. The trial was registered at clinicaltrials.gov under the identifier: NCT04250428.

A total of 767 pregnant women were enrolled and 716 (93%) were followed-up after delivery. Neither intervention had an impact on postpartum anemia, with estimated adjusted odds ratios (aORs) of 0.97 (95% confidence interval [CI]: 0.70-1.33) for INFO and 0.80 (95% CI: 0.57-1.11) for INFO+DELIV. While INFO had no effect on malaria (aOR=0.90; 95% CI: 0.35-2.33; p-value >0.05), INFO+DELIV reduced the odds of malaria by 83% (aOR=0.17; 95% CI: 0.03-0.72; p-value <0.05). No differences in IFA compliance were found for INFO (mean difference 0.02 (95% CI: -0.01-0.05). INFO+DELIV increased compliance with IFA supplementation by 16 percentage points (95% CI: 0.11-0.22; p-value <0.01) and IPTp compliance by 35 percentage points (95% CI: 0.27-0.43).

Information plus home delivery of supplements can substantially increase compliance with IFA supplementation and improve malaria prevention. However, the resulting increases in IFA supplementation are likely insufficient to address the high prevalence of often severe anemia in this population.

Keywords: Randomised controlled trial, Taabo HDSS, iron and folic acid supplementation, intermittent preventive treatment of malaria in pregnancy, antenatal care

5.2. Research in context

Evidence before this study

IFA supplementation and malaria chemoprophylaxis are widely recognized as key strategies to reduce maternal anemia and malaria in pregnancy. We reviewed the literature evaluating strategies to improve the coverage of community-based public health programs and more specifically the coverage of IFA supplementation and IPTp using PubMed on January 7, 2022. Most of the currently available evidence is summarized in a 2016 Cochrane review as well as a subsequent systematic review published in 2018 and suggests that interventions combining education with vouchers and other financial incentives tend to be most effective for increasing intervention coverage.

Added value of this study

To our knowledge, this is the first randomised controlled trial to assess the effectiveness of targeted information sessions as well as home deliveries of supplements and chemoprophylaxis as strategies to improve maternal and child health in this setting. We find that the combined interventions greatly increase coverage of supplementation and malaria chemoprophylaxis. Although these improvements are sufficient to largely remove the risk of malaria infection, standard supplementation does not appear to be sufficient to address the high prevalence of often-severe anemia in this low-income setting.

Implications of all the available evidence

The results presented here confirm what previous studies were suggesting, namely that community-based distribution of malaria chemoprophylaxis works as strategy to reduce malaria exposure in pregnancy. For IFA supplementation, the results presented here suggest that standard supplementation protocols currently recommended in many LMICs are likely not sufficient to address the high burden of anemia in many LMIC settings. Pre-pregnancy supplementation, routine hemoglobin assessments during the first trimester and monitored administration of higher doses of supplements (oral or via injections) may offer potential solutions to this problem.

5.3. 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 (UNICEF, 2021; WHO, 2019a). Neonatal deaths currently account for about half of all under-5 deaths (van den Broek, 2019), and recent evidence suggests that many of these deaths could be prevented with improved access to essential antenatal care (ANC) services (Bhutta et al., 2013b; E. T. Konje et al., 2018; Papaioannou et al., 2019). In many settings, exposure to malaria and maternal anemia pose a major threat to maternal and child health. Recent evidence from sub-Saharan Africa suggests that 46 percent of pregnant women are anemic (WHO : Global Health Observatory Data Repository, 2019), and more than 11 million cases of malaria in pregnancy were reported in 2018 (WHO, 2019b). Both risk factors can in principle be address by adequate antenatal care. However, coverage of essential antenatal interventions remains limited in many low- and middle-income countries (LMICs) (Christian et al., 2003), resulting in high prevalence of anemia (Sun et al., 2021) and limited prevention of malaria in pregnancy (INS/ICF, 2012; WHO, 2016a). 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 (Ensor & Cooper, 2004; Ensor et al., 2002). A large number of community-based interventions have been tested to increase coverage (Deardorff et al., 2018). 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 (Bellows et al., 2011; Mbuagbaw et al., 2015; Oyo-Ita et al., 2016).

In this study, we report the results of a cluster-randomized controlled trial set up to assess the efficacy of two potential strategies to increase coverage of IFA supplementation and malaria chemoprophylaxis in pregnancy in low resource settings. The trial was conducted in 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 published in 2020 (Kone et al., 2020).

5.4. Methods

5.4.1. Trial design and setting

The study was designed as a cluster-randomized 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 150 km north-west of Abidjan, the economic capital of Côte d'Ivoire. Previous studies conducted in this area have highlighted the high prevalence of anemia in this setting (A. A. Righetti et al., 2013), with 61% of children and 48% of non-pregnant women found to be anemic in 2011 (Aurélie A. Righetti et al., 2012). For the trial, clusters were defined as neighbourhoods ("quartier") in villages and hamlets outside of the main villages (Kone et al., 2015a). A total of 118 clusters were included in the study. Further details pertaining to the study design and methods are available in the previously published protocol paper (Kone et al., 2020). The study protocol was reviewed and approved by the local Ethics Committee in Côte d'Ivoire (IRB000111917) and the national Review Board in Switzerland (Ethikkommission Nordwest- und Zentralschweiz).

5.4.2. 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 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 of the Taabo HDSS 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.

5.4.3. Randomization 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.

Min-max randomization was used to minimize differences across study arms (Bruhn et al., 2009). Using Stata version 15 SE software, we created 100 random allocations, and then computed mean differences in terms of cluster size (number of births) and antenatal care (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 were not aware of women's treatment status, and data analysis was conducted by the senior author (GF) using a fully blinded data set.

5.4.4. Procedures

The study involved a baseline and an endline survey, which was supposed to be completed by all participants. In the INFO arm, nurses visited pregnant women at their homes 1-2 weeks after study enrolment. During these visits, nurses provided pregnant women with information regarding the importance of antenatal intermittent preventive treatment of malaria in pregnancy (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. Detailed monitoring data on home visits were collected for the two arms throughout the study period.

Baseline surveys were conducted between May 7, 2020 and June 25, 2021. Endline surveys were scheduled within two weeks of delivery, and conducted between November 10, 2020 and November 26, 2021. An independent team of laboratory technicians conducted the hemoglobin (Hb) assessments and administered the malaria rapid diagnostic test (RDT). 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).

5.4.5. Study outcomes

The primary outcomes were maternal postpartum anemia and malaria. Postpartum anemia was defined as an Hb concentration of less than 110 g/l. For malaria, 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 birth weight deliveries were considered as secondary outcomes. 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 sulfadoxine-pyrimethamine (SP) during pregnancy.

5.4.6. Statistical analysis

We used logistic regression models to assess intervention impact in postpartum anemia and malaria, as well as for all binary secondary outcomes. All continuous secondary outcomes (birth weight and Hb levels) were analysed using linear regression models. Cluster-robust standard errors were used to correct for residual correlation at the cluster level (Huber, 1967). All models were estimated both without covariates (unadjusted) and with a pre-specified set of mother socio-demographic covariates (i.e., age, marital status, school attendance, parity, and wealth quintile). To better understand the relationship between IFA supplementation and the observed changes in anemia, we also plotted average changes in Hb levels as a function of self-reported intake of IFA supplements during pregnancy (post-hoc analysis).

5.4.7. Trial registration and changes to protocol

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

5.5. Results

5.5.1. Study population

Figure 5.1 shows a Consort flow diagram, summarizing 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). From the 767 targeted pregnant women, 716 (93.3%) were re-interviewed at endline. No statistically significant differences were found in follow-up rates across the three study arms (p=0.90) (Supplementary Materials Table ST2).

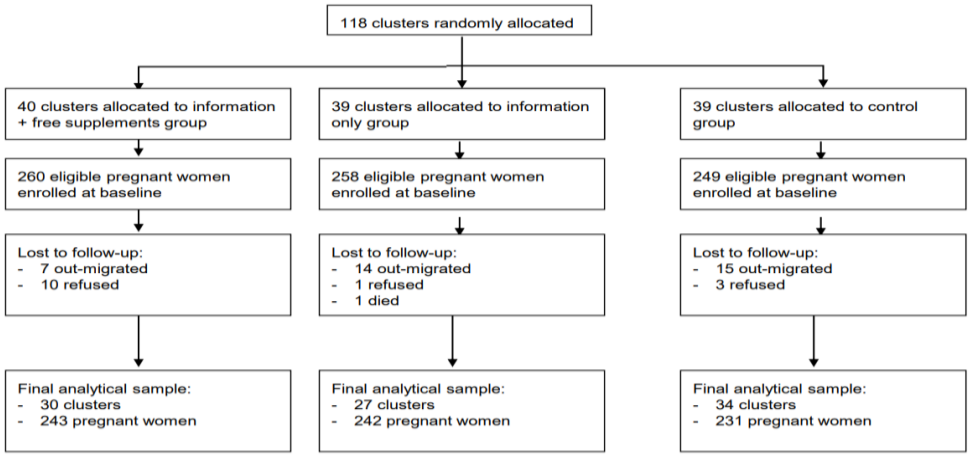

Figure 5-1: Consort flow diagram

As shown in Table 5.1, the majority of study participants (69.5%) were between 20 and 34 years of age. Slightly more than half (53%) of the women never attended school, 31% attended primary school, and 16% attended secondary or higher education. Almost half (49%) of the women were in common-law, while 42% were married.

Table 5-1: Sample baseline characteristics by study arm

	Control		Information only		Information+home delivery		Total	
	N	%	N	%	N	%	N	%
Mother age								
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/high	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

5.5.2. Impact of intervention on primary and secondary outcomes

Table 5.2 shows primary and secondary outcomes for each group and the sample overall. On average, across the three groups, 39.5% women were anaemic; 19.8% were mildly anemic (Hb, range 100 to <110 g/l), 18.6% were moderately anemic (Hb, range 70 to <100 g/l), and 1.1% were severely anemic (Hb <70 g/l). A positive malaria RDT was registered in 3.4% of the women. About one out of nine (11.5%) children were born with birth weight <2,500 g. Ninety-two percent of pregnancies in the sample resulted in live births, 3.6% of pregnancies resulted in miscarriage, 3.6% resulted in stillbirths, and six pregnancies (0.8%) were aborted. At least four ANC visits were recorded by 40.2% of the women. More than half (54.0%) of the women reported compliance with daily IFA supplementation. Almost three-quarter (73.9%) received at least three doses of SP for IPTp.

Table 5-2: Primary and secondary outcomes

	Control		**Information only**		**Home delivery**		**Total**	
	N	%	N	%	N	%	N	%
Anemia	97	42.0	99	40.9	87	35.9	283	39.5
Mild anemia	52	22.5	46	19.0	44	18.1	142	19.8
Moderate anemia	40	17.3	52	21.5	41	16.9	133	18.6
Severe anemia	5	2.2	1	0.4	2	0.8	8	1.1
Malaria	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
Took fansidar	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
ANC4+	81	34.5	91	37.3	119	48.6	291	40.2

As shown in Table 5.3, neither intervention had an impact on anemia (INFO: aOR=0.97, 95% CI: 0.70-1.33; INFO+DELIV: aOR=0.80, 95% CI: 0.57-1.11). Supplementary Materials Table ST3 shows more detailed results for mild, moderate, and severe anemia. No impact on malaria was found for INFO (aOR=0.90; 95% CI: 0.35-2.33; p-value >0.05). INFO+DELIV reduced the odds of malaria by 83% (aOR=0.17; 95% CI: 0.03-0.72; p-value <0.05).

Table 5-3: Intervention impact on anemia and malaria

	PANEL A: Unadjusted Impact Estimates	
	Anemia	Malaria
VARIABLES	OR (95%CI)	OR (95%CI)
INFO	0.96 (0.70 - 1.31)	0.95 (0.38 - 2.41)
INFO+DELIV	0.77 (0.55 - 1.07)	0.17** (0.04 - 0.73)
Observations	716	716
	PANEL B: Adjusted Impact Estimates	
INFO	0.97 (0.70 - 1.33)	0.90 (0.35 - 2.33)
INFO+DELIV	0.80 (0.57 - 1.11)	0.17** (0.03 - 0.72)
Observations	716	716

All estimates are based on logistic regressions with clustering at the study cluster (N=91) level. Odd ratios are displayed with 95% Confidence intervals (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<0.01, ** p<0.05, * p<0.1

5.5.3. Impact on coverage and ANC attendance

Table 5.4 summarizes the interventions' impact on ANC attendance, IFA supplementation, and IPTp compliance. The INFO package had no impact on ANC compliance (β=0.03; 95% CI: -0.07-0.12, p-value >0.05), IFA supplementation (β=0.02, 95% CI: -0.01-0.05; p-value >0.05) and IPTp compliance (β=0.01, 95% CI: -0.09-0.12; p-value >0.05). INFO+DELIV increased the probability of women having completed at least four ANC visits by 12 percentage points (β=0.12, 95% CI: 0.00-0.24, p-value <0.05), the probability of full compliance with antenatal IFA supplementation by 16 percentage points (β=0.16; 95% CI: 0.11-0.22, p-value <0.01) and compliance with IPTp recommendations by 35 percentage points (β=0.35, 95% CI: 0.27-0.43, p-value <0.01).

Table 5-4: Intervention impact on ANC visits, IFA full compliance, and SP compliance

	PANEL A: Unadjusted Impact Estimates			
	Any ANC	≥ 4 ANC visits	IFA full compliance	≥ 3 doses of SP
VARIABLES	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
INFO	-0.01 (-0.04 - 0.02)	0.03 (-0.07 - 0.13)	0.02 (-0.01 - 0.05)	0.02 (-0.09 - 0.13)
INFO+DELIV	-0.003 (-0.03 - 0.03)	0.14** (0.02 - 0.26)	0.17*** (0.11 - 0.23)	0.36*** (0.28 - 0.43)
Control group average (constant)	0.98*** (0.95 - 1.00)	0.34*** (0.28 - 0.41)	0.03*** (0.01 - 0.04)	0.58*** (0.51 - 0.65)
Observations	716	716	716	716
R-squared	0.00	0.02	0.07	0.13
	PANEL B: Adjusted Impact Estimates			
INFO	-0.01 (-0.04 - 0.02)	0.03 (-0.07 - 0.12)	0.02 (-0.01 - 0.05)	0.01 (-0.09 - 0.12)
INFO+DELIV	-0.01 (-0.04 - 0.02)	0.12** (0.00 - 0.24)	0.16*** (0.11 - 0.22)	0.35*** (0.27 - 0.43)
Observations	716	716	716	716
R-squared	0.02	0.05	0.08	0.15

Table 5.5 shows results for pregnancy outcomes. No differences were found for miscarriage (INFO: β=0.01, 95% CI: -0.02-0.03; INFO+DELIV: β=-0.02, 95% CI: -0.05-0.02). INFO+DELIV reduced the probability of stillbirth (estimated difference in probability of 0.03, 95% CI: -0.06-0.00, p-value <0.05). No impact was found on average birthweight. The INFO arm marginally reduced the probability of low birth weight (β=-0.05, 95% CI: -0.10-0.01, p-value <0.1).

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

	PANEL A: Unadjusted Impact Estimates			
	Miscarriage	Stillbirth	Birth weight	Low birth weight
VARIABLES	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
INFO	0.01 (-0.02 - 0.04)	-0.02 (-0.05 - 0.01)	26.85 (-102.00 - 155.71)	-0.05 (-0.11 - 0.01)
INFO+DELIV	-0.01 (-0.05 - 0.02)	-0.03** (-0.05 - -0.00)	26.74 (-108.08 - 161.56)	-0.04 (-0.11 - 0.03)
Control group average (constant)	0.04*** (0.02 - 0.06)	0.05*** (0.03 - 0.08)	3,030.89*** (2,946.47 - 3,115.31)	0.14*** (0.10 - 0.19)
Observations	716	716	557	557
R-squared	0.002	0.004	0.001	0.005
	PANEL B: Adjusted Impact Estimates			
INFO	0.01 (-0.02 - 0.03)	-0.02 (-0.05 - 0.01)	19.18 (-89.48 - 127.85)	-0.05* (-0.10 - 0.01)
INFO+DELIV	-0.02 (-0.05 - 0.02)	-0.03** (-0.06 - -0.00)	17.94 (-118.45 - 154.33)	-0.04 (-0.10 - 0.02)
Observations	716	716	557	557
R-squared	0.044	0.014	0.05	0.05

All estimates are based on linear regressions with clustering at the study cluster (N=91) level. Coefficients are displayed with 95% Confidence intervals (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<0.01, ** p<0.05, * p<0.1

Figure 5.2 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 sixth 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.

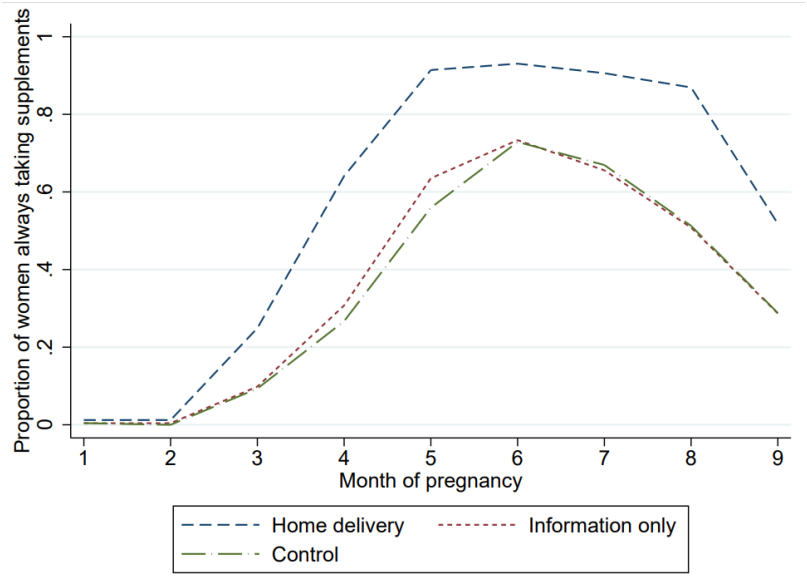

Figure 5-2: Compliance with daily IFA supplementation by month of pregnancy

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 (Supplemental Materials Figure SF4). Figure 3 shows changes in Hb levels as well as anemia 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 5.3, panel A). Half of the women (50.5%) taking supplements for 90 days or less were anemic at endline; among women reporting 180 days or more of supplements, average anemia rates were 27.7% (Figure 5.3, panel B).

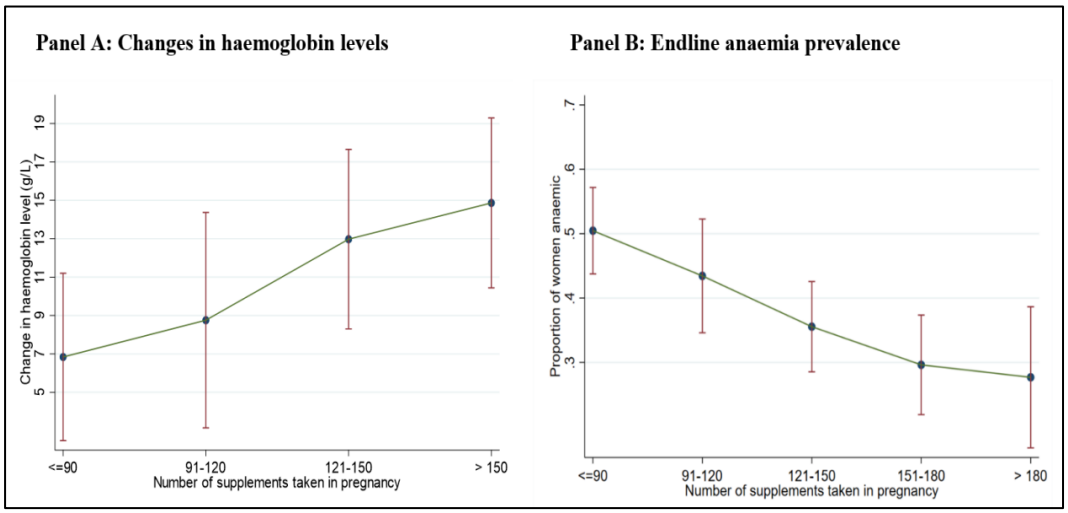

Figure 5-3: Compliance with IFA guidelines, changes in hemoglobin (Hb) levels and prevalence of anemia

5.6. Discussion

In this cluster-randomized 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 the south-central part of Côte d'Ivoire. Neither intervention had a major impact on anemia. Malaria post-pregnancy was relatively rare, but greatly reduced by the INFO+DELIV arm.

Given the relatively large increase in compliance seen in the INFO+DELIV arm (which seems consistent with a recent review of community-based distribution of IFA supplements (Kavle & Landry, 2018) the lacking intervention impact on anemia is somewhat surprising. Earlier supplementation studies suggest that substantial improvements in maternal anemia are feasible in principle with sustained intake of supplementation (Oh et al., 2020; Pena-Rosas et al., 2015; Yakoob & Bhutta, 2011).

Two factors seem to explain the relatively weak impact on anemia in this study. First, supplementation was also relatively common in the control group of this trial, with an average of 112 doses 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 anemia. 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 improved during pregnancy, but these improvements were rather small, with increases of 15 g/l seen among

women in the highest compliance category (150 daily doses or more). One potential strategy to address this challenge would be to increase IFA dosing as part of routine ANC conditional on initially low levels of Hb as recommended by the WHO (WHO, 2014a). Recent evidence from Tanzania also suggests that ferric carboxymaltose injections may offer a faster and more durable normalisation of Hb and ferritin concentrations among anemic women (Vanobberghen et al., 2021). Such higher dosing would however require both systematic initial hemoglobin 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, a coverage of 61% of three doses of SP in the control group appears to be better than in many other countries in sub-Saharan Africa (Yaya et al., 2018). Several studies presented community-based delivery of SP as a potential mean to strengthen coverage and uptake of IPTp (Anchang-Kimbi et al., 2020; Burke et al., 2021; Gutman et al., 2020). 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, we find 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 behaviors may have contributed to these improved outcomes. Larger future trials are warranted to confirm these potentially large health benefits as well as to identify the main mechanisms underlying these changes.

The study had several limitations. First, as just mentioned, our trials was not powered to detect changes in pregnancy outcomes, which hopefully can be estimated in 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 (Nongkynrih et al., 2010). Last, 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-randomization trial design but cannot fully rule out some information transmission (even though the study team came across no evidence suggesting such spillovers across study arms).

5.7. Conclusion

The results from this cluster-randomized 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 anemia in this population.

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5.9. Appendix 3: Improving coverage of antenatal iron and folic acid supplementation and malaria prophylaxis through targeted information and home deliveries in Côte d'Ivoire: a cluster-randomized controlled trial

5.9.1. Supplemental Materials Table ST3-1: Difference in follow-up rate across arms

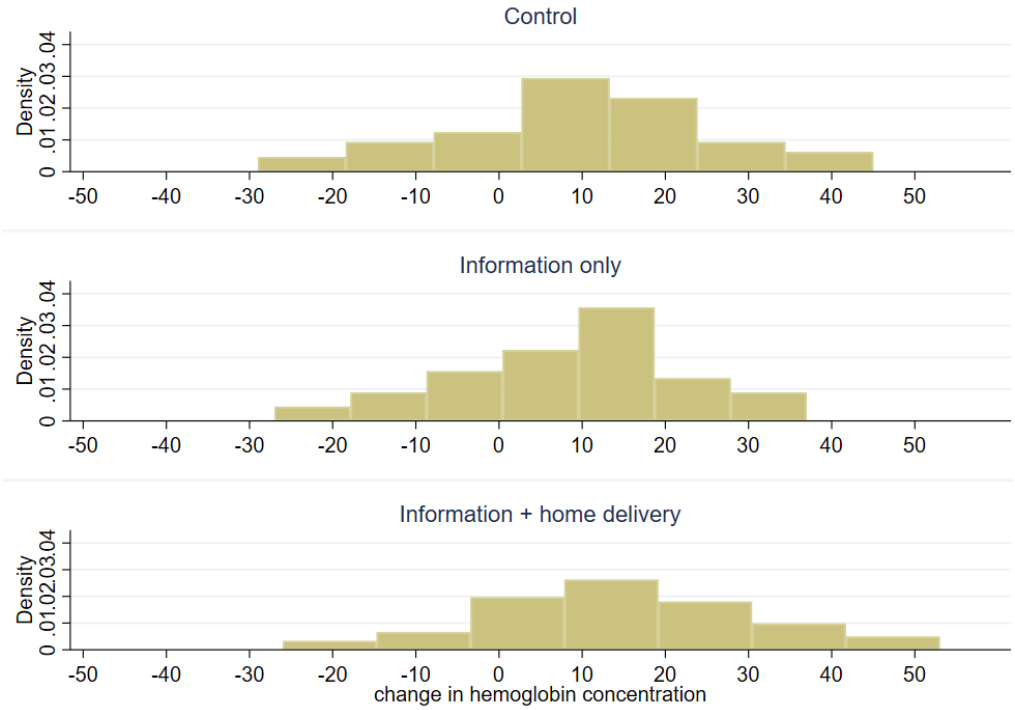
	Baseline survey	Endline survey	Follow-up rate
	N	n	%
Control	249	231	92.8
INFO	258	242	93.8
INFO+DELIV	260	243	93.5
Total	767	716	93.4
F-test	F(2, 90) = 0.11, Prob > F = 0.8990		

5.9.2. Supplemental Materials Table ST3-2: Intervention impact on mild, moderate and severe anemia

PANEL A: Unadjusted Impact Estimates			
	Mild anemia	Moderate anemia	Severe anemia
VARIABLES	OR (95%CI)	OR (95%CI)	OR (95%CI)
INFO	0.81 (0.51 - 1.29)	1.31 (0.80 - 2.15)	0.19 (0.02 - 1.75)
INFO+DELIV	0.76 (0.48 - 1.20)	0.97 (0.59 - 1.59)	0.38 (0.09 - 1.64)
Observations	716	716	716
PANEL B: Adjusted Impact Estimates			
INFO	0.84 (0.53 - 1.33)	1.27 (0.76 - 2.12)	0.17 (0.02 - 1.65)
INFO+DELIV	0.79 (0.50 - 1.25)	0.98 (0.60 - 1.61)	0.36 (0.09 - 1.41)
Observations	716	716	399

Notes: Figure shows estimated treatment impact on mild, moderate and severe anemia. Mild anemia was defined as haemoglobin concentration of 100-<110 g/L moderate anemia was defined as haemoglobin concentration of 70-<100 g/l, and severe anemia was defined as haemoglobin concentration less than 70 g/L. 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. Estimated coefficients are odds ratios with 95% CIs in parentheses.

5.9.3. Supplemental Materials Figure SF3-1: Change in haemoglobin concentration between baseline and endline by study arm



Notes: Figure shows empirical distribution of changes in haemoglobin concentrations between baseline and endline in mg/l (x-axis).

6. Discussion

This Ph.D thesis was facilitated by an existing and productive long-term research partnership between the Swiss TPH, the CSRS and the Université Félix Houphoüet Boigny (ex. Université de Cocody). The overarching goal of the research presented was to improve our understanding of the main drivers of under-five mortality in rural low-income settings, as well as to identify key intervention for reducing the high burden of mortality in this setting. The current PhD research combined three complementary approaches to address key challenges in health care access and delivery. First, we determined factors that influence healthcare seeking among children with fatal and non-fatal health problems. In this context, we were interested in the most critical household and community characteristics influencing modern healthcare seeking for under-five children. Second, we assessed the impact of additional health facility construction on treatment seeking and on child health outcomes. For this purpose, we estimate the causal impact of newly constructed primary healthcare facility on ANC attendance, facility delivery and mortality. Last, we investigated the effectiveness of community-based interventions in improving IFA coverage and malaria chemoprophylaxis in pregnancy.

The results stemming from our social autopsy and comparative cross-sectional surveys confirmed that a relatively large proportion of caregivers seek modern care for their under 5-year-old children in rural areas of Côte d'Ivoire. Nonetheless, a quarter of fatal, and more than a third of non-fatal diseases, were not seen by modern healthcare providers. This suggests that health care seeking in the African context is not always oriented toward modern medicine but caregivers continue to rely on plural and sequential treatment seeking (Ibrahima et al., 2010; Ishaga et al., 2010; Pilkington et al., 2004). We found that being a young age child, caregiver being a parent, secondary or higher education, living <5 km from a health facility, and certain clinical signs (i.e., fever, severe vomiting, inability to drink, convulsion, and inability to play) were positively associated with modern healthcare in non-fatal cases. In fatal cases, only signs of lower respiratory disease influenced modern healthcare seeking.

Our prospective study in the Taabo HDSS, allowed to closely monitor and measure changes in healthcare seeking behaviors and health outcomes over time. The findings revealed considerable impact of local provision of new health infrastructures on reducing the average distance to the nearest healthcare facility. Further analysis on antenatal care (ANC) attendance, facility delivery and all causes mortality showed significant impact on the risk of post-neonatal infant mortality only. This suggests that local construction of new health centers in a mainly

rural part of south-central Côte d'Ivoire may have only relatively limited impact on healthcare utilization and overall population health.

Our ANC intervention study suggests that combining education with home deliveries can greatly increases coverage of supplementation and malaria chemoprophylaxis, which is consistent with previous literature in this area (Deardorff et al., 2018; Oyo-Ita et al., 2016). These improvements were sufficient to largely remove the risk of malaria infection, but not sufficient to address the high burden of anemia in this low-income setting.

This PhD thesis advances the Swiss TPH nexus built on three pillars, namely innovation, validation and application (Table 6.1). It provides new evidence and significant insights for an understanding of the main drivers of under-five mortality in low-income settings, and helps also in identifying key intervention for reducing the continued high burden of mortality in this setting.

Table 6-1: Contribution of chapters of this thesis to the Swiss TPH nexus of innovation, validation and application

Chapter	Title	Innovation	Validation	Application
2	Determinants of Modern Pediatric Healthcare Seeking in Rural Côte d'Ivoire	The most predictive factors of treatment seeking at the household and community level were identified for both non-fatal and fatal cases diseases.	In the Taabo HDSS, child's age and his relationship with caregiver, caregiver sociodemographic characteristics as well as disease related symptoms are important factors of modern healthcare seeking.	
3	Impact of newly constructed primary healthcare centers on antenatal care attendance, facility delivery and all-cause mortality: quasi-experimental evidence from Taabo health and demographic surveillance system, Côte d'Ivoire.	Assessment of the effect of four newly established primary health facilities on local population health and maternal health services utilization in rural setting.	The construction of lower level health facilities reduces access distance, which does not necessarily translate into improved population health maternal health services utilization in low resource settings.	Local provision of new healthcare facility reduced average distance to the nearest facilities and reduced the risk of post-neonatal infant mortality.
4	Study protocol of a cluster randomized controlled trial of strategies to increase antenatal iron and folic acid supplementation and malaria prophylaxis in rural south-central Côte d'Ivoire.	Cluster randomized controlled trial evaluate the effectiveness of two alternative strategies.		
5	Improving coverage of antenatal iron and folic acid supplementation and malaria prophylaxis through targeted information and home deliveries in Côte d'Ivoire: a cluster-randomized controlled trial.	Comparison of information and home deliveries in rural Côte d'Ivoire for improving coverage of antenatal iron and folic acid supplementation and malaria prophylaxis.	Combined interventions greatly increases coverage of supplementation and malaria chemoprophylaxis.	Novel insights for future intervention studies on iron and folic acid and malaria prophylaxis in pregnancy.

6.1. Determinants of modern paediatric healthcare seeking

In Côte d'Ivoire, under-five mortality remains very high with approximately 108 out of 1000 children not reaching their fifth anniversary. According to mortality data obtained through verbal autopsies, most deaths were attributed to malaria and respiratory tract infections (Koné et al., 2014; P. Streatfield et al., 2014). Overall, 85% of child deaths in the Taabo HDSS were considered being of infectious origin (Koné et al., 2014) of which many would be avoidable with timely, correctly-conducted treatment. Furthermore, to address high child mortality rates, quality information on public health factors that influenced the course of disease are essential. 50% of these modifiable determinants of health have been attributed to community specific factors, which often determine an individual's willingness and ability to access healthcare services (Amy et al., 2017; Oliver & Mossialos, 2004). Pathway analysis, also called social autopsies, are increasingly used to determine cultural, social and health-systems antecedents that have contributed to the failure of saving a child and to identify missed opportunities (Källander et al., 2011; Kalter et al., 2011).

Our findings from modern pediatric healthcare seeking examination within rural communities showed that although a large proportion of caregivers seek modern care for their under 5-year-old children, there are still some quarter of fatal, and more than a third of non-fatal diseases that were not seen by modern healthcare providers. This is not surprising as in the African context, care-seeking behaviors are complex and often characterized by pluralistic health behavior which further lead to delay biomedical diagnosis and treatment (Bedford & Sharkey, 2014; Hooft et al., 2020; Mpimbaza et al., 2019; Mpimbaza et al., 2017; Umuhoza et al., 2018). Health seeking behavior is influenced by the individual knowledge, disease perception, sociodemographic factors, and the availability and accessibility of health services (Reddy et al., 2020). Sometimes, due to a wrong perception of the illness it also happens that caregiver believes that the illness will improve by itself, thus wait until appearance of another symptom. In many cases this is also true – in high income countries, fevers are pretty much always treated at home because most infections are minor. In LMICs settings, the challenge is of course to identify those cases that are potentially serious. Similar to earlier studies, caregivers' propensity to seek out healthcare was higher among younger children, among children living with their grandparents, and among caregivers with higher educational level (Dagnew et al., 2018; Pierce et al., 2016; Vikram et al., 2012). Money shortage has been also reported as a barrier for accessing modern healthcare even though any significant socioeconomic gradient across groups because of official of free health care for pregnant women and children in Côte d'Ivoire since

2012 (PNLS, 2012). In the same way, some studies highlighted the effect of wealth on health seeking behavior, and attributed delays to limited financial resources (Kassile et al., 2014; Scott et al., 2014). The age of the caregiver plays an important role in care-seeking decisions. During the illness that led to the child's death, care seeking was more common among younger mothers (Dagnew et al., 2018; Gelaw et al., 2014; Weldesamuel et al., 2019) compared to older mothers who seemed more experienced. Our study identified a lack of recognition of danger signs as a key barrier to timely treatment seeking with severe disease. This is well aligned with previous studies indicating an association between the knowledge of danger signs and perceived severity of the illness and seeking modern healthcare (Kolola et al., 2016; Wambui et al., 2018). Sometimes, local norms and beliefs regarding the etiology (Dougherty et al., 2020; M. B. K. D. Kouadio et al., 2013) of disease appear important for recommended healthcare seeking behavior. Our results highlighted the importance of the caregivers' skills and educational attainment in child health management (Dougherty et al., 2020; Geldsetzer et al., 2014; Kolola et al., 2016). Geographical distance is a key issue for health services use in rural areas (Begashaw et al., 2016; Borah et al., 2016; Weldesamuel et al., 2019). In general, rural populations travel long distances to access the most basic health services. In addition, the lack of reliable transport is a barrier to care. In our study, close proximity to the nearest healthcare facility was associated with increased health seeking. The share of sick children getting formal care was higher for small distance. On the other hand, we noticed an important share of sick children getting informal care for households who were more distant from facilities (Figure 6.1).

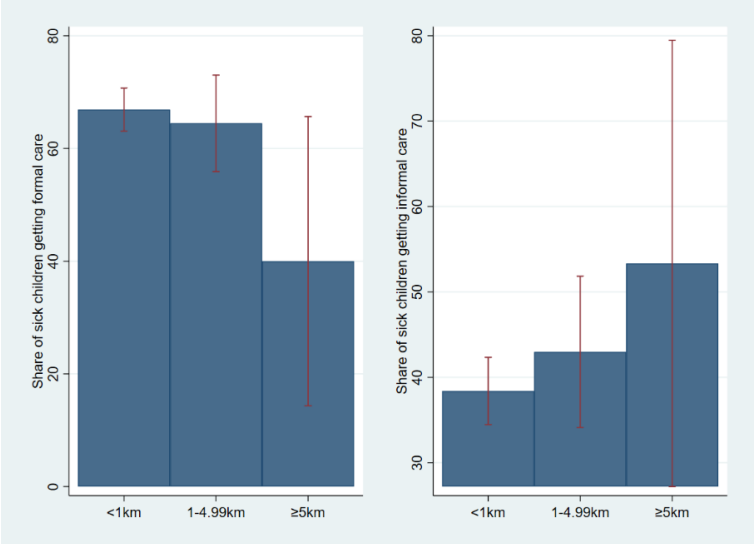


Figure 6-1: Formal and informal care seeking following distance to the nearest health facility

Health care seeking is also dependent on the availability of health infrastructure. In other words, when the village had a health center, the average treatment seeking was very high (Figure 6.2). In 2010, community members highlighted distance as the primary health system constraint. In response to this request, FAIRMED, a non-governmental organization decided to provide four out of the six villages without health centers in 2010 with new primary care health facilities. These primary care facilities were supposed to offer the local communities a minimum package of essential health services including routine immunization of children, curative care for common ailments, prenatal and postnatal consultations, and family planning, deliveries assistance, prevention of other-to-child transmission of HIV, as well as the promotion of essential family practices with the support of community relays. Nine years later, it important to assess the extent to which these newly established healthcare facilities have improved local population health as well as the utilization of health services.

Figure 6-2: Treatment seeking according to the availability of the health facility in the village

6.1.1. Impact of healthcare facilities on population health and the utilisation of health services

Assessing the causal impact of newly constructed primary healthcare facilities within a health and demographic surveillance (HDSS) site, we observed no improvement for ANC attendance, institutional deliveries and adult mortality. There are several reasons that might explain the lack of impact on adult mortality. First, we know that 85% of adult deaths in the HDSS are due to non-communicable diseases (Kone et al., 2015b) that are not supported by primary health care facilities. Secondly, in low- and middle-income countries, the health system lacks the skills to

manage chronic diseases (Allotey et al., 2014; Tham et al., 2018). With regard to ANC attendance, the limitation of some prerequisites such as infrastructures, adequately trained health professionals, infection control facilities, diagnostic equipment, supplies and essential drugs, and appropriate utilization of guidelines might constitute an obstacle to ANC attendance (Joshi et al., 2014). A study from Côte d'Ivoire suggests that lack of access to supplements and drugs may be a key barrier to ANC access (Murielle, 2019). It has been also shown that the degree of quality and availability of facility at primary health centers in rural areas was positively associated with people's decision to seek health care from primary health centers (Mustafa & Shekhar, 2021). Seen in this light, our results are certainly contradictory to several studies (Karra et al., 2017; Kelly et al., 2016), but are well aligned with a study from Malawi, which also found that newly constructed facilities in the 1990s resulted neither in changes in utilization of ANC attendance and skilled delivery, nor in changes in mortality outcomes (Quattrochi et al., 2020). Limited change in institutional deliveries may have several explanations. At one hand, this might be due to the relatively limited availability of infrastructure at the new health centers. On the other hand, it may be the result of people's perception of health facility delivery. Childbirth is perceived as a normal process, and according to people's understanding, health facility should only be called upon for complicated labor (Eveline T. Konje et al., 2020). In addition, direct payments for health care could hamper facility delivery.

We observed a significant association between new facilities and reduced risk of post-neonatal mortality. In Côte d'Ivoire and particularly in the HDSS, malaria and respiratory infections are common pathologies during the neonatal period (Kone et al., 2015b). Basic treatment for similar diseases can be provided even by health centers with very limited supplies. Research in Kenya highlighted both the potential of the primary health care system in reaching vulnerable populations and reducing malaria burden (O'Meara et al., 2009). We found no changes in mortality for the neonatal period where most child death occur. This is contradictory to previous cross-sectional studies but somewhat understandable insofar as the construction of new health facilities has not had an impact on facility deliveries. Although provided to offer a minimum package of services, primary health facilities are most often lacking adequate equipment and staff to manage complicated deliveries, which cause most of neonatal deaths (Abdullah et al., 2016; Mortality & Causes of Death, 2016). Living in close proximity to a high-quality health facility was associated with large reductions in neonatal mortality (Leslie et al., 2016) but similar patterns could not be observed for lower quality health facilities such as those in our

study. According to a multi-country analysis of under-five deaths in 64 low- and middle-income countries, neonatal deaths accounted for 53.1% of the total under-5 deaths (Z. Li et al., 2021). Neonatal mortality can be addressed by adequate antenatal care in many low- and middle-income countries (LMICs) where coverage of essential antenatal interventions remains limited. In other words, it would suggest a need for multi-layer health strategies with potentially heavier investment in newborn health. This require to fight against malaria and maternal anemia that pose a major threat to maternal and child health in LMICs. Thus, appropriate response should be given to challenges faced in many health systems including 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 (Ensor & Cooper, 2004; Ensor et al., 2002).

6.1.2. Improving coverage of iron and folic acid supplementation and malaria prophylaxis

Our ANC trial found no beneficial effect on anemia for either the information (INFO) intervention or the information plus home delivery (INFO+DELIV) of IFA supplements and SP despite the large increase in compliance seen in the INFO+DELIV arm. The missing effect on anemia is contrary to earlier supplementation studies that suggested substantial improvements in maternal anemia with sustained intake of supplementation (Oh et al., 2020; Pena-Rosas et al., 2012; Yakoob & Bhutta, 2011). The weak impact on anemia might be explained by the high prevalence of anemia in pre-pregnancy period. Indeed, at baseline and more specifically the end of the first trimester, we counted 70.2% of anemic women with a mean Hb concentration of 95 g/l. It will therefore take much more than a routine supplementation alone to address the low average Hb levels in this setting. In view of this, increase IFA dosing could be considered for women with low baseline hemoglobin as recommended by the WHO (World Health Organization, 2014a). Recent evidence from Tanzania also suggests that ferric carboxymaltose injections may offer a faster and more durable normalization of Hb and ferritin concentrations among anemic women (Vanobberghen et al., 2021).

We found a coverage of 61% for three doses of SP in the control group which is better than in many other countries in sub-Saharan Africa (Yaya et al., 2018). Home delivery showed an expected higher coverage of SP. This finding is consistent with several studies that presented community-based delivery of SP as a potential mean to strengthen coverage and uptake of IPTp (Anchang-Kimbi et al., 2020; Burke et al., 2021; Gutman et al., 2020). The improvement in adequate malaria chemoprophylaxis was sufficient to largely remove the risk of malaria

infection (Consortium, 2019). Due to the greater socioeconomic vulnerability of the population in rural and remote territories, the majority of people still suffer financial barriers.

6.2. Conclusion

The overarching goal of this PhD thesis was to deepen the understanding of the effective ways to improve health service access and child health in low and middle-income country settings in general, and in the Taabo HDSS in Côte d'Ivoire in particular. Based on the results from the work conducted for this thesis, a set of conclusions can be drawn:

- Treatment seeking is still not universal, even if health problems are severe. The perceived need and urgency of treatment for severe disease cases as well as the strengthening of overall quality of care may help improve treatment seeking in rural settings of Côte d'Ivoire and can potentially help further reduce under-five mortality in LMICs.

- The construction and operation of new health facilities reduces access distance to the nearest healthcare facility and thus can have beneficial effects on child health. Our results also make clear that just building new facilities does not necessarily improve health services utilization or health outcomes – carefully targeting the main services needed and ensuring quality care are likely key for getting the desired improvements in population health.

- Community-based intervention combining information plus direct home delivery of supplements can substantially improve malaria prophylaxis and IFA coverage. Such systematic home deliveries could be feasible by involving community health workers in community-based distribution channels targeting most vulnerable women living rural remote areas.

- Standard supplementation protocols currently recommended in many LMICs are likely not sufficient to address the high burden of anemia in many LMIC settings.

- Pre-pregnancy supplementation, routine hemoglobin assessments during the first trimester and monitored administration of higher doses of supplements (oral or via

injections) may offer potential solutions to address the high burden of anemia in this population.

6.3. Research needs and recommendations

6.3.1. Identified research needs

Several issues emerge from the results presented here. First, we need to better understand the health infrastructure needed for improving health outcomes in this setting. Second, we need to assess the potential of the health centers in terms of infrastructure available and quality care for maternal and child health. Third, we should conduct larger trials to confirm the potentially large health benefits of increased IFA supplementation, increased malaria chemoprophylaxis, or more frequent ANC visits as well as identify the main mechanisms underlying changes in pregnancy outcomes. Lastly, we need to assess the effectiveness of pre-pregnancy supplementation on postpartum anemia based on routine hemoglobin assessments during the first trimester.

6.3.2. Recommendations

In this section, I introduce some suggestions on how to improve treatment seeking and child health in the Taabo HDSS. First, we need to improve the availability and encourage the utilization of health services. Quality care requires posting and respecting fee schedules for healthcare procedures, ensuring availability of drugs and strategic inputs, ensuring the existence and functionality of management committees, and the organization of sensitization sessions on priority health problems of the village. Second, we need to implement interventions promoting prompt healthcare seeking and the recognition of danger signs for improving treatment seeking in rural settings. Third, we need to improve the quality of overall care and medical staff to enable health care facilities to carry out their assigned mission. These health facilities are supposed to offer the population a minimum package of essential health services including routine immunization of children, curative care for common ailments, prenatal and postnatal consultations, and family planning, deliveries assistance, prevention of mother-to-child transmission of HIV, as well as the promotion of essential family practices with the support of community relays. Finally, we need to increase IFA dosing as part of routine ANC or ferric carboxymaltose injections conditional on initially low levels of Hb as recommended by the WHO.

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7. Curriculum vitae

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Education /Training

2019 - 2022	**PhD in Epidemiology and Public Health** Swiss Tropical and Public Health Institute, Allschwil, Switzerland Epidemiology and Public Health department Household Economics and Health System Research Unit Thesis title: Treatment seeking, access to care and child health: Evidence from the Taabo health and demographic surveillance site (HDSS) in Côte d'Ivoire
2016 - 2018	**Msc Master Public Health in Econometric and Quantitative Methods for Health Research** Aix Marseille Université, Marseille, France Faculty of Medicine Thesis title: Evaluation of the impact of specific antenatal interventions on low birth weight in the Taabo Health and Demographic Surveillance System in Côte d'Ivoire
2005 - 2006	**DESS in Statistical Analysis** Ecole nationale Supérrieure de Statistique et d'Economie Appliquée (ENSEA), Abidjan, Côte d'Ivoire Thesis tile: Socio-demographic determinants of HIV among young people in urban areas of Côte d'Ivoire
2004 - 2005	**Msc Master of Sciences in Economics** Université de Bouaké, Bouaké, Côte d'Ivoire
2001 - 2004	**BSc Bachelor of Sciences in Economics** Université de Bouaké, Bouaké, Côte d'Ivoire

Professional experience

Since 10.2009	**Head of the Taabo Health and Demographic Surveillance Site** – Centre Suisse de Recherches Scientifiques en Côte d'Ivoire. *Define monitoring indicators, develop data collection tools. Supervise the collection, compilation, processing, management and analysis of data and draft summary reports. Train field staff to monitor demographic and health indicators, Provide technical support to researchers in the implementation of research projects. Assisting in the statistical analysis of data and the writing of scientific papers. A team of*
2020 - 2021	**Research Fellow** – Swiss Tropical and Public health Institute, Centre Suisse de Recherches Scientifiques en Côte d'Ivoire. *Designed and implemented a 24-months prospective longitudinal monitoring to Investigate the effectiveness of targeted information sessions as well as home deliveries of supplements and chemoprophylaxis as strategies to reduce anemia and malaria during pregnancy sin south-central Côte d'Ivoire. Manage a team of 20 people, logistics and public relations. Led laboratory and statistical analysis. Published first author manuscripts in international peer-reviewed journals. Presented results at meetings.*

2006 - 2008	**Research Assistant** – National School of Statistics and Applied Economics (ENSEA) of Abidjan, Côte d'Ivoire. *Supervision of research activities, development of study protocols, drafting of questionnaires and guides, and data entry masks. Training of interviewers in data collection. Data cleaning and analysis, report writing reports. Staff management and supervision. Participation in knowledge exchange and information dissemination workshops.*

Publications

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