The Contribution of Patients and Providers to the Overuse of Prescription Drugs*– Experimental and Survey Design

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1 Health Care and Malaria in Mali

The public health system in Mali is organized around principles laid out in the Bamako Initiative of 1987, which advocates for decentralized community-based primary health care funded by user fees. At the foundation of this system are *Centres de Santé Communiautaire* (CSComs) – community-based primary care clinics managed by the local health association. The local health association retains revenues from sales of medications and other user fees, which are in turn used to fund the operations of the CSCom. CSComs are one of the most important sources of care for Malians: according to the 2012-2013 DHS, 47 percent of mothers in Bamako who sought care for a child under 5 with fever or cough took the child to a CSCom; the corresponding figure for the country as a whole is 40 percent.

One of the most commonly-treated illnesses in CSComs is malaria. In spite of recent progress, the parasite reamains a major threat to public health in Mali: malaria is still the leading cause of mortality, accounting for roughly 20 percent of all deaths and nearly a third of deaths among children under 5 (IHME, 2016). Although the parasite is endemic in all parts of the country except the sparsely populated northern desert, rates of transmission are substantially lower in urban areas. For example, in 2015 the estimated prevalence of the parasite in children under 5 in Bamako was 6 percent, as compared to 36 percent in

*Please see the research paper of the same title for more detail.

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the country as a whole (PNLP et al., 2016). Malaria infections are classified as either "simple/uncomplicated" or "severe". Simple malaria is not life threatening if treated promptly, and is characterized by non-specific, flu-like symptoms including fever, chills, and headache. If left untreated, simple malaria can progress (sometimes rapidly) to severe malaria. In this stage of the disease, patients experience life-threatening complications including loss of consciousness/coma, respiratory failure, renal failure, and/or severe anemia (Trampuz et al., 2003). Patients with severe malaria require prompt, aggressive treatment to avoid death and should be hospitalized until their symptoms stabilize.

Mali's national malaria control strategy emphasizes prevention, diagnosis, and effective treatment. The national malaria policy requires that suspected malaria cases be confirmed via a positive microscopy or rapid diagnostic test (RDT) before dispensing treatment (Ministère de la Santé (2013)). RDTs are meant to be free in public health facilities (including CSComs) to ensure that cost is not a barrier to accurate diagnosis. Artemisinin combination therapies (ACTs) – which combine an artemisinin-based medication with an older "partner" antimalarial – are recommended for simple malaria, while severe malaria cases should be treated with injectible artesunate followed by a dose of ACTs once the patient is stable.[1] The national policy allows for an initial dose of quinine to treat severe malaria in cases where an injectible artemisinin-based therapy is not available. ACTs are an essential component of treatment for both severe and simple malaria because administering artemisinin-based "monotherapies" alone facilitaties emergence of artemisinin-resitant parasites, which is already a major concern in some parts of Asia (WHO, 2014).[2] In public facilities, ACTs are free for children under 5 and subsidized for older individuals, but there are no subsidies for the artemisinin monotherapies and quinine needed for severe malaria treatment (PMI, 2016).

2 Experimental Design

Sampling Frame At the outset of our study, field staff used administrative data for a list of all CSComs in the city of Bamako and in nearby Kati and Kalaban Coro in Koulikoro. After conducting a census of these CSComs, we dropped some CSComs that had closed, excluded

[1] Artesunate is a derivative of artemisinin. Artemisinin-based antimalarials are the most effective treatments for malaria in Sub-Saharan Africa, where the emergence of drug-resistant parasites has rendered earlier generations of antimalarials ineffective. Qunine can also effectively treat both simple and severe malaria infections in this region, but the drug is less effective than artemisinin and has more side effects (Achan et al., 2011), and Malian policy reserves it for pregnant mothers.

[2] Artemisinin has a short half-life and works quickly to kill most parasites in a patient's blood stream. By combining an artemisinin therapy with a longer half-life partner drug, ACTs substantially reduce the probability that drug resistance emerges, since a parasite would need to be resistance to both medications instead of just one.

CSComs that were more than 15 km away, and removed 21 CSComs that were working with a local NGO to offer subsidized and improved malaria care to patients – this yielded a final sample of 60 CSComs. Four care providers (doctors, nurses, and pharmacists) at each CSCom enrolled in the study were invited to attend a refresher training that covered Mali's official malaria diagnosis and treatment guidelines. The basic refresher training included two sessions: one on Mali's official diagnostic and treatment guidelines for malaria and one on how to administer an RDT.

The training materials were prepared by the research team in cooperation with Dr. Seydou Doumbia (University of Bamako) Dr. Seydou Fomba (*Programme National de Lutte contre le Paludisme*, or PNLP, Mali's department of malaria control) and Dr. Issaka Sagara (Malaria Research and Training Center Bamako), and conducted by five trainers from the PNLP and one trainer from the regional health directorate (Direction Régionale de la Santé, or DRS) of Bamako. All CSComs sent at least two providers to the training, with the average CSCom sending 3.9 providers.

Doctor Information (Across-CSCom Randomization) Half the CSComs were randomly selected to receive the "Doctor Information" intervention. CSComs in this group received an enhanced refresher training that included the "basic information" referenced above and an additional session on the diagnostic accuracy of RDTs. This training was informed by our qualitative scoping work, which indicated that doctors had low levels of trust in RDTs and thought the tests were only capable of diagnosing malaria when parasite concentrations in the blood were very high. The session began by reviewing the sensitivity rate of the RDTs used in CSComs according to the most recent WHO quality assurance testing (World Health Organization (2015)). The trainer then introduced a validation study of the same RDT conducted in Mali by a team of Malian researchers (see Djimde et al. (2016)). The trainees were shown a video in which one of the study's principal investigators (a Malian M.D.-Ph.D.) described the results of the study. Key messages were: (1) Over 99 percent of true malaria blood samples tested RDT positive (the sensitivity of the test), (2) 73 percent of malaria negative blood samples tested negative (the specificity of the test) and (3) RDT sensitivity remained very high (89-92 percent) at low parasite loads (1-100 parasites/μL). The session closed by reviewing several other studies from sub-Saharan Africa and discussing why it is medically appropriate to refrain from prescribing ACTs to "suspect" malaria cases with a negative RDT.

The training invitation letters did not specify which training the CSCom was selected for – as a result, average attendance rates were identical across the doctor information and control groups. CSComs were trained in six groups in November 2016.

Patient Information and ACT Subsidies (Within-CSCom Randomization) The other three experimental interventions were randomized within-CSCom across different days during a two-week observation period. The first intervention was designed to improve patient and caregiver information about malaria treatment and diagnostic guidelines. The information was conveyed through a short narrative video, which depicted a mother taking her child to a CSCom for a suspected malaria case. The video described the symptoms of malaria, emphasized that all suspected malaria cases should be confirmed with either an RDT or microscopy test, noted that RDTs should be available for free at the CSCom, and described recommended treatment for simple and severe malaria. The video also showed a demonstration of an RDT test and described how to differentiate a positive versus negative test result. The main objective of the video was to inform patients about Mali's offical malaria treatment guidelines and give patients the information needed to request and verify the results of a malaria test if they so desired.

The last two interventions involved distributing vouchers for free treatment for simple malaria (ACT tablets) at CSComs on selected days. The objective of these interventions was to reduce the cost of treatment for simple malaria, while leaving the cost of other types of treatment fixed.[3] We distributed the vouchers in two different ways to assess the role of patient demand in driving malaria treatment decisions. In the "Patient Voucher" intervention, vouchers were distributed directly to patients when they first arrived at the CSCom. Patients and/or caregivers were informed that the voucher would pay for simple malaria treatment (ACT tablets) provided the doctor determined that this was the appropriate course of action (vouchers were not valid unless they received the doctor's signature). Patients then went to consult the doctor and signed vouchers were processed at the CSCom pharmacy after the consultation was complete. In the "Doctor Voucher" intervention, the vouchers were instead left directly with the doctors, who could assign the vouchers to patients as the doctors saw fit. The field staff did not inform patients about voucher availability before the consultation.

Note that all treatments could affect treatment outcomes through two channels: the first is a direct effect, whereby the treatment status of a given patient could change based on experimental condition. The second is a selection effect, whereby the pool of patients visiting the CSCom could change in response to experimental conditions. Although the total effect is important for policy analysis, isolating the direct effect is more useful for identifying theoretical mechanisms – we therefore randomized treatments within-CSComs whenever possible in order to minimize the selection effect. The within-CSCom randomization (and associated data collection) were conducted after the doctor trainings in November and December 2016.

Figure 1 illustrates the design of the within-CSCom randomization. We divided the 60

[3]Patients treated for severe malaria were not eligible to redeem the vouchers.

CSComs into three 20-CSCom cohorts based on geography. Each of the three cohorts rotated through two weeks of data collection and experimental intervention. Within each cohort, we randomly assigned each CSCom to one of 20 intervention schedules depicted in Figure 1.[4]

Field staff visited each CSCom six times over the two week observation period. Although all CSComs were informed of the upcoming study activities and interventions in advance, CSCom staff did not receive prior notice of the actual intervention schedule – rather, study staff informed them of the day's intervention on the morning of an observation day. On observation days, two "survey team" enumerators were tasked with recording the details of each clinic visit for an acute illness. On all days except control days, we also stationed an "intervention officer" at the CSCom, who was charged with implementing the interventions (e.g. showing patients/caregivers the informational video, distributing vouchers to doctors or patients, and verifying all voucher redemptions). The survey team and intervention officers were stationed at different parts of the CSCom and intervention eligibility was not tied to survey consent.

3 Data Collection

In order to differentiate between different theoretical mechanisms, we require detailed data on testing and treatment outcomes, doctor and patient beliefs, and patients' underlying malaria status. We therefore make use of data from several sources.

Patient Surveys The survey team stationed at the CSCom was charged with recording the details of each acutely ill patient visiting the CSCom for care. We classified a patient as "acutely ill" if they were visiting the CSCom because they were feeling sick and exhibited any of the following symptoms: fever, chills, excessive sweating, nausea, vomiting, diarrhea, poor appetite, headache, cough, weakness, fatigue, or reduced consciousness. When the patient arrived at the clinic, the survey team collected basic demographic details, symptoms, and information on any prior treatment and/or diagnosis. After the patient's consultation with the doctor was complete, the survey team recorded details of all blood tests performed and medications prescribed, as well as fees paid to the CSCom.

We randomly selected a subset of patients for a more detailed home-based follow up survey, which was conducted the day after their CSCom visit. The home survey collected information on changes in the illness and any treatment and tests obtains after the CSCom visit. In addition, enumerators asked to perform an RDT on the patient to confirm their

[4]Since the share of CSComs receiving a given treatment varied across days of the week, we include day of the week fixed effects in all regressions.

Figure 1: Randomization schedule.

	WEEK 1							WEEK 2						
CSCOM Number	Mon	Tues	Weds	Thurs	Fri	Sat	Sun	Mon	Tues	Weds	Thurs	Fri	Sat	Sun
1	C	--	PV	--	DV	--	--	PI	--	PI-PV	--	PI-DV	--	--
2	DV	--	C	--	PV	--	--	PI-DV	--	PI	--	PI-PV	--	--
3	PV	--	DV	--	C	--	--	PI-PV	--	PI-DV	--	PI	--	--
4	C	--	DV	--	PV	--	--	PI	--	PI-DV	--	PI-PV	--	--
5	DV	--	PV	--	C	--	--	PI-DV	--	PI-PV	--	PI	--	--
6	PI	--	PI-PV	--	PI-DV	--	--	C	--	PV	--	DV	--	--
7	PI-DV	--	PI	--	PI-PV	--	--	DV	--	C	--	PV	--	--
8	PI-PV	--	PI-DV	--	PI	--	--	PV	--	DV	--	C	--	--
9	PI	--	PI-DV	--	PI-PV	--	--	C	--	DV	--	PV	--	--
10	PI-DV	--	PI-PV	--	PI	--	--	DV	--	PV	--	C	--	--
11	--	C	--	PV	--	DV	--	--	PI	--	PI-PV	--	PI-DV	--
12	--	DV	--	C	--	PV	--	--	PI-DV	--	PI	--	PI-PV	--
13	--	PV	--	DV	--	C	--	--	PI-PV	--	PI-DV	--	PI	--
14	--	C	--	DV	--	PV	--	--	PI	--	PI-DV	--	PI-PV	--
15	--	DV	--	PV	--	C	--	--	PI-DV	--	PI-PV	--	PI	--
16	--	PI	--	PI-PV	--	PI-DV	--	--	C	--	PV	--	DV	--
17	--	PI-DV	--	PI	--	PI-PV	--	--	DV	--	C	--	PV	--
18	--	PI-PV	--	PI-DV	--	PI	--	--	PV	--	DV	--	C	--
19	--	PI	--	PI-DV	--	PI-PV	--	--	C	--	DV	--	PV	--
20	--	PI-DV	--	PI-PV	--	PI	--	--	DV	--	PV	--	C	--

LEGEND	
--	No data collection or interventions at CSCOM
C	Data collection at CSCOM, no interventions
DV	Doctor vouchers and data collection at CSCOM
PV	Patient vouchers and data collection at CSCOM
PI	Patient information and data collection at CSCOM
PI-DV	Patient information, doctor vouchers, and data collection at CSCOM
PI-PV	Patient information, patient vouchers, and data collection at CSCOM

malaria status.[5] In addition to the test result, which measures the patient's true malaria status, we also recorded the patients' (unincentivized) beliefs about their malaria status.

Doctor Surveys We use data collected from health care providers at two points in time. First, we administered a post-training survey to doctors and other care providers who attended the refresher trainings that took place at the beginning of the study. The post-training survey tested providers' knowledge of topics covered in the basic training (e.g. recommended malaria treatments, symptoms of severe malaria) and topics only covered in the extended "doctor information" treatment (e.g. sensitivity and specificity of RDTs). We also selected up to three care providers for a post-intervention endline survey.[6] In addition to topics covered in the post-training survey, the endline asked caregivers about perceived patient knowledge and demand for drugs and personal preferences regarding malaria diagnosis and treatment.

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[5] RDTs detect antigens for malaria, which remain in the bloodstream after antimalarials have been taken and parasites have cleared. We used CareStart HRP2(Pf) tests, which detect an antigen that typically takes several weeks to become undetectable in blood samples (Humar et al., 1997; Kyabayinze et al., 2008). This test only detects the *P. falciparum* malaria parasite, which accounts for 92 percent of all malaria infections in Mali (PMI, 2016).

[6] We always interviewed the head doctor at the CSCom. Subject to the number and type of staff at a CSCom we also randomly selected one other doctor and one other care provider (including nurses, health technicians, and midwives) for interview.

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