Drug Packaging, Health Information and Medication Adherence: Evidence from Malaria Treatment in Uganda

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June 17, 2016

Abstract

Non-adherence to infectious disease treatments increases the risk of under-treated infections and drug resistance. We conducted a randomized trial in Uganda to test the impact of several drug package designs on adherence to Artemisinin-Combination Therapy for malaria. We find that the currently-used, costly packaging with pictorial instructions does not increase adherence, but stickers with short, targeted messages increase adherence by 9%, with a much larger impact among patients whose symptoms had resolved mid-treatment. We develop a theoretical framework which, combined with our results, suggests that symptom severity, beliefs about being cured, and perceptions of drug effectiveness contribute to medication non-adherence.

JEL codes: I12, D83, O55.

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1 Introduction

When patients with infectious diseases complete the recommended treatment for their illness they benefit individually while also generating positive spillovers. For individuals, finishing the full medication regimen ("adhering" to treatment guidelines) ensures that they are cured and do not face the potential health and economic costs of an under-treated infection. There are public benefits to adherence as well: it reduces the likelihood that the disease will be transmitted to others (Gersovitz and Hammer, 2004) and lowers the risk that the pathogen will develop resistance to the drugs. Despite these benefits, many patients do not finish the full course of drugs for infectious diseases such as tuberculosis and malaria (Sabate, 2003). This increases the probability that the patient will suffer from complications of the disease, raises health system costs, and drives up the cost of research into new therapies to replace those rendered ineffective by drug resistance.

Widespread non-adherence across disease types suggests that patients face substantial costs in adhering to treatment. These could include the monetary and non-monetary costs of obtaining the drugs, adverse side effects, and difficulty following a complex treatment regimen. However, there is evidence of low patient adherence rates even when drugs are heavily subsidized or free, when side effects are minimal and when the health benefits of treatment substantially outweigh the marginal costs of taking additional pills (Senkomago et al., 2011; Thiam et al., 2007; Banek et al., 2014; Makanga et al., 2006; WHO, 2014*a*; Bangsberg et al., 2001). This suggests behavioral biases may also be important factors in non-adherence. For example, patients may underweight the benefits of continuing treatment when symptoms are not salient, or might simply forget to take pills (Baicker, Mullainathan and Schwartzstein, 2015). People may also falsely believe, perhaps as a result of insufficient information, that mid-course symptom resolution is an indication of being fully cured.

There have been a number of interventions designed to increase medication adherence including training of pharmacists, patient counseling, verbal instructions to patients, special reminder pill packaging (McDonald, Garg and Haynes, 2002; Haynes et al., 2008; Bruxvoort

et al., 2014*a*), text message reminders (Raifman et al., 2014; Pop-Eleches et al., 2011), and financial incentives (Kimmel et al., 2012; Giuffrida and Torgerson, 1997; Volpp et al., 2008; DeFulio and Silverman, 2012). None of these interventions has been consistently effective across all contexts and, overall, little progress has been made in establishing underlying reasons for non-adherence.

For infectious diseases, the public benefits of adherence make finding effective interventions of great policy concern. At the same time, to the extent that patients do not account for these positive externalities, this presents an additional challenge to ensuring the socially optimal adherence level. For example, medications are typically dosed so that some patients are cured before the full regimen has been completed (Makanga et al., 2006; Vugt et al., 1999). As a result, in some cases, it may be privately optimal to discontinue treatment, even when non-adherence is not socially optimal. In developing countries, the discord between individually and socially optimal levels of adherence may be even greater because people get sick frequently and lack easy access to healthcare, so that the value of saving pills for future illnesses may be very high.

We explore the issue of medication non-adherence in the context of malaria treatment in Sub-Saharan Africa. The current recommended treatment, artemisinin-based combination therapy (ACT), is very effective in treating malaria, has a short, three-day regimen, has few side effects, and is typically fully subsidized in public health systems. There are significant health benefits from adherence to treatment, especially for young children who are more likely to experience severe illness and mortality from malaria (Makanga et al., 2006). In malaria-endemic countries, the disease is responsible for up to 50 percent of outpatient visits and 30-50 percent of hospital admissions (WHO, 2010*b*) and parasite resistance to anti-malarial drugs has been a persistent problem, resulting not only in large impacts on mortality, but also in high research costs for newer treatments (Baird, 2005; PATH, 2013). Despite the substantial private and public benefits to adherence, ACT adherence rates are low and in some contexts less than 40 percent of patients finish the treatment (Banek et al., 2014).

We conducted a field experiment with 2,641 households in Uganda to study patient adherence to ACTs purchased from private drug shops. Approximately 35 percent of patients did not complete the full treatment, with similar rates of non-adherence for young children. We experimented with several ACT packages designed to increase adherence to the medication. One current approach to boosting ACT adherence rates, used by Ministries of Health and social marketing organizations in several African countries, is specialized packaging that includes pictorial instructions for illiterate patients, and a colorful, glossy design. We find that, despite raising the production cost of the drug by 10 to 50 percent, this package had no significant effect on adherence. On the other hand, inexpensive stickers affixed to the standard ACT package, with short messages emphasizing either the importance of adherence for being cured of malaria, or the benefits of adherence for the community, increased treatment completion by 5.7 percentage points, a 9 percent increase in the overall probability of adherence. The stickers also led to a 33 percent decrease in the number of pills remaining. We find that these messages improved adherence largely among patients whose symptoms had resolved mid-treatment and patients who believed that their malaria episode was cured early in the treatment course. While our study was not powered to detect potential impacts on malaria transmission, we use published estimates of the impact of adherence on malaria cure rates to show that these simple stickers cost approximately $1-$4 per averted malaria infection.

Our paper contributes to the economics literature in several ways. First, we contribute new evidence on treatment-seeking behavior in developing countries, in particular the central role played by the private sector, where the quality of treatment and instructions provided varies greatly and where diagnostic testing and continuity of care are very limited (Banerjee, Deaton and Duflo, 2004; Cohen, Dupas and Schaner, 2015; Das, Hammer and Leonard, 2008; Leonard, 2013; Leonard and Masatu, 2007). Our results should have relevance beyond malaria; in particular, there are similarities to treatment-seeking for bacterial infections (such as pneumonia) where non-adherence to short course antibiotics is also a serious public health

concern (Kardas, 2002; Llor et al., 2013).

Second, we build on the literature exploring when and what types of information influence people's health behaviors. While some studies find that people respond to health-related information (Dupas, 2011; Fitzsimons et al., 2013; Jalan and Somanathan, 2008; Madajewicz et al., 2007; Thornton, 2008), others find little impact of information on health behaviors (Kremer and Miguel, 2007; Jamison, Karlan and Raffler, 2013; Luo et al., 2012). The degree to which information affects health behaviors likely depends not only on the information content, and whether it changes people's subjective beliefs (Delavande and Kohler, 2012; Oster, Shoulson and Dorsey, 2013; Godlonton and Thornton, 2013; Paula, Shapira and Todd, 2013; Thornton, 2012; Boozer and Philipson, 2000), but also on how the information is presented. For example, there is evidence that, for some preventive health behaviors, emphasizing the benefits of the behavior is more effective than highlighting the costs of not doing the behavior (Gallagher and Updegraff, 2012; Rothman et al., 2006). Other research suggests that there may be a tradeoff in message effectiveness between additional information content and the length of the message (Pop-Eleches et al., 2011; Raifman et al., 2014).

Third, we contribute evidence on the degree to which messaging can encourage people to engage in socially beneficial behaviors. Previous work has suggested that messages that provide information about social norms (either information about what people should do in a given situation, or information about what most other people actually do in that situation), can be effective ways to motivate people to use less electricity (Schultz et al., 2007; Nolan et al., 2008) and less water (Ferraro and Price, 2013), reduce littering (Reno, Cialdini and Kallgren, 1993), contribute to charities (Frey and Meier, 2004), and vote (Gerber and Rogers, 2009).

Finally, we contribute to a growing literature on interventions designed to increase medication adherence (Haynes et al., 2008; McDonald, Garg and Haynes, 2002; Nieuwlaat et al., 2014; Pop-Eleches et al., 2011; Raifman et al., 2014; Bruxvoort et al., 2014*b*). Many of these interventions are tacitly built on the assumption that people *want* to adhere but face

obstacles in doing so–for example, they forget to take pills, do not understand how to take pills, or face time inconsistency problems. Our main contribution to this literature is to test interventions that target some of the reasons patients may choose non-adherence, for example because they believe they are cured or because they want to save pills for future illness episodes. In particular, we outline a theoretical framework of the adherence decision to show how patients' symptoms mid-way through treatment may affect adherence by influencing patients' subjective beliefs about their illness and treatment.

The remainder of the paper proceeds as follows: Section 2 provides background on malaria treatment-seeking behavior in this study context and on private sector ACT subsidy programs. Section 3 provides a theoretical framework of the adherence decision, highlighting some of the reasons for non-adherence. Section 4 describes the experimental design and interventions tested in detail. In Section 5 we present the results of our intervention, and in Section 6 we use the theoretical framework to explore patterns of non-adherence in our data and how they are related to the interventions we tested. In Section 7 we estimate the cost-effectiveness of the sticker interventions. Section 8 concludes.

2 Background on Malaria Treatment in Africa and the Affordable Medicines Facility-malaria

Malaria is caused by a single-cell parasite which is transmitted to humans through a mosquito bite. Although malaria deaths have declined by 47 percent over the past 15 years, it remains the cause of roughly 600,000 deaths and 200 million illnesses per year. The increased availability of ACTs to treat malaria infection has contributed significantly to the recent mortality decline, along with other malaria control interventions such as the distribution of insecticide-treated bed nets and indoor residual insecticide spraying (WHO, 2014*b*).

By completing the full course of ACTs, a person with malaria ensures that they are fully cured of the disease. Clinical studies of Artemether Lumefantrine (AL) – a type of ACT –

have found that the 28-day cure rates of malaria are 10-30 percentage points higher when patients take the recommended six doses of the drug instead of only four doses (Makanga et al., 2006; Vugt et al., 1999).[1] While approximately 60-70 percent of patients are cured of malaria with only four doses of the drug, the difficulty in identifying such patients ex-ante leads to the recommendation that all patients with suspected malaria complete the full course of drugs (WHO, 2010*a*).[2] Patients who take less than the complete treatment course are more likely to have detectable parasites remaining in their body, which is associated with an increased likelihood of a recurrence of the infection (Stepniewska et al., 2010; Muhindo et al., 2014; Beshir et al., 2013). This is not only potentially harmful for the patient, but may also place an additional burden on the health system in malaria-endemic countries.

Non-adherence to ACTs also increases the risk that the malaria parasite will develop resistance to the drug. A sub-therapeutic dose of ACTs can kill all sensitive parasites while allowing the more resistant parasites to survive (thus "selecting" for resistant parasites) (White et al., 2009). Resistance to artemisinin –the primary component of ACTs– has already been identified in parts of Southeast Asia and widespread resistance to the drug would pose a major threat to malaria-control efforts (Ashley et al., 2014; White, 2012; Slater et al., 2016).

As others have noted, decisions about malaria treatment in Sub-Saharan Africa occur in a noisy learning environment (Bjorkman-Nyqvist, Svensson and Yanagizawa-Drott, 2013; Cohen, Dupas and Schaner, 2015; Adhvaryu, 2014). Many suspected malaria episodes are treated based on symptoms, rather than a confirmed diagnosis through a blood test. The

[1]The "28-day cure rate" is defined as the clearance of asexual parasites within 7 days of beginning treatment without recrudescence (reappearance) in 28 days. In highly endemic areas, it is possible for a person to get re-infected with malaria within this time frame. Thus, in some cases, genetic analysis is used to distinguish between a recurrence of the same infection and a new infection so that the latter are not counted as treatment failures.

[2]For example, according to the World Health Organization (WHO), "in endemic regions, some semi-immune malaria patients could be cured using an incomplete dose or treatment regimens that would be unsatisfactory in patients with no immunity. In the past, this had led to different recommendations for patients considered as semi-immune and those considered as non-immune. This practice is no longer recommended. A full treatment course with a highly effective ACT is required whether or not the patient is considered to be semi-immune." (WHO, 2010*a*)

symptoms of malaria, however, are non-specific and overlap with many other diseases, most notably pneumonia, but also a range of viral illnesses (D'Acremont et al., 2014; Källander, Nsungwa-Sabiiti and Peterson, 2004). The WHO recommends, however, that all patients who start taking ACTs complete the treatment whether or not a confirmed diagnosis of malaria was received (WHO, 2010*a*).[3]

Across all countries, approximately 40 percent of patients with suspected malaria first seek treatment in the private sector which includes both private clinics and retail establishments like pharmacies and informal drug shops (WHO, 2014*b*). While these outlets are usually more accessible than public sector clinics (closer proximity, open longer hours, etc), they vary widely in the quality of advice and product they make available. In Sub-Saharan Africa, a substantial share of antimalarials sold in the private sector are the older, less effective non-artemisinin medications such as chloroquine and sulfadoxine/pyrimethamine which are both cheaper than ACTs, and are likely more familiar to patients in this region. The variety of medicines available–with their varying efficacy and dosing schedules–may lead to confusion among malaria patients about which medicines they should take and how to take them. The prevalence of counterfeit antimalarials means that patients may be even less certain that the drug that they purchased is effective in treating malaria (Bjorkman-Nyqvist, Svensson and Yanagizawa-Drott, 2013; Nayyar et al., 2012).

At the time of study launch, ACTs were free in the public sector in Uganda but were frequently out of stock (Zurovac et al., 2008). When they were available in the private sector, ACTs were approximately 5-10 times more expensive than less effective antimalarial drugs (O'Connell et al., 2011). As a result, only about 23 percent of suspected malaria episodes in Uganda among children under the age of five were being treated with ACTs (Uganda Bureau of Statistics , UBOS) while in Africa overall, approximately 15 percent of children

[3]According to the WHO "another potentially dangerous practice is to give only the first dose of the treatment course for patients with suspected but unconfirmed malaria, with the intention of giving full treatment if the diagnosis is eventually confirmed. This practice is also unsafe and not recommended. If malaria is suspected and the decision to treat is made, then a full effective treatment is required whether or not the diagnosis is confirmed by a test" (WHO, 2010*a*).

with fevers were being treated with ACTs (WHO, 2014*b*). In an effort to increase access to ACTs, the Affordable Medicines Facility-malaria (AMFm) program was established in 2009 and introduced nationally in seven African countries, including Uganda. The AMFm subsidized the cost of ACTs by 95 percent to first line buyers in the private and public sectors (Laxminarayan and Gelband, 2009; Gelband et al., 2004) and studies of the pilot phase of the program suggest that it was effective in increasing the availability and use of ACTs, particularly at private for-profit outlets (Cohen et al., 2013; Fink et al., 2013). However, the increased availability of ACTs, especially through informal channels, created an urgent need to ensure that the drugs were being used appropriately. For example, the rapid scale-up in the availability of rapid diagnostic tests (RDTs) is an effort to ensure that ACTs are only used to treat confirmed malaria cases (Bastiaens, Bousema and Leslie, 2014; WHO, 2010*a*, 2014*b*). The field experiment described below tests another potential "supporting intervention" for private sector ACT distribution through specialized messaging and packaging, which could maintain the benefits in terms of private sector ACT access, while ensuring that the drugs are taken appropriately.

3 Theoretical Framework

In this section we present a simple theoretical framework of the adherence decision. A more detailed model, considering different assumptions about patient beliefs and about perceptions of drug effectiveness, is presented in Appendix A. We use this framework to help interpret some of the main results presented in Section 5, highlighting predictions about heterogeneity in adherence by symptom severity, beliefs about drug effectiveness, and beliefs about whether the illness is malaria. We also use this framework to discuss how certain types of interventions could boost adherence.

We consider a two-period adherence decision in which, in period one, a patient is hit with an illness shock that he believes is malaria and begins taking medication.[4] In period two the

[4]We limit our empirical analyses to those who begin treatment.

patient decides whether to finish taking the pills or to stop treatment. The patient faces a tradeoff between the benefits of being cured of the disease and the costs of adhering to the medication. The benefit of adherence is the utility of being healthy, including productivity and wage benefits as well as the intrinsic value of good health. Patients may also value the positive externalities to the community of their being cured (lower malaria transmission, less likelihood of parasite resistance to the drug), to the extent that they are aware of them. The cost of adherence includes things such as side effects, the effort required to remember to take pills, and the opportunity cost of consuming pills that could otherwise be used to treat future malaria episodes. When a patient adheres (i.e. goes on to finish the medication in period two), he guarantees that he will have the benefit of good health, but he incurs the cost of adhering. Since there is some probability that he is already cured after the first few doses he has taken in period one, it is possible that he is paying the cost of adherence unnecessarily. On the other hand, if he does not adhere, he faces some probability of continuing to suffer from malaria.

We assume that the subjective probability of still having malaria is increasing with mid-course symptom severity–that is, the better the patient feels partway through treatment, the more likely he is to believe he is cured. We take symptom severity after period one as exogenous to adherence since, in our data, nearly all patients take the first few doses of treatment properly (i.e. period one adherence is nearly perfect). If the patient believes that the medication he is taking is effective (so that adhering definitely will cure him) then the patient will choose to adhere if the belief that he still has malaria in period two exceeds a threshold value that is increasing in the cost of adherence and decreasing in the utility of being healthy. Patients are thus more likely to adhere when mid-course symptom severity is high, when the costs of adhering are low (few side effects, low value of saved pills, etc.), and when the benefit to being healthy is high (see Figure 1A).

Now consider the case where the patient is unsure whether the drugs he is taking are effective in treating malaria. We assume that the belief that the drugs are effective is a

decreasing function of mid-course symptom severity. That is, the sicker the patient feels after the first few doses, the less likely he is to believe the drugs are working. This reduces the expected benefit of adherence: if the drugs may not work, then adherence will not guarantee good health. In this case, the likelihood of adhering still increases with the utility of being healthy and decreases with the cost of adhering. However, since the probability of still having malaria is increasing in symptom severity and the probability of medication effectiveness is decreasing in symptom severity, there is a non-linear relationship between the probability of adhering and the severity of symptoms (see Figure 1B). Patients who feel much better mid-course are most likely to believe the drugs are effective but also most likely to believe they are already cured and thus the expected value of adhering for them is low. Patients who still feel very sick mid-course are more likely to believe that they still have malaria, but also to believe the drugs are ineffective, so the expected utility of adhering for these patients is again low. The expected utility of adhering is therefore maximized at intermediate levels of symptom severity in the second period.

Finally, we consider the case where a patient is uncertain about whether the illness is malaria but is confident that the drug is effective in treating malaria. We assume that the sicker the patient feels mid-way through treatment, the more likely he is to believe that his illness is not malaria. This results in adherence patterns that are very similar to when the patient is uncertain about the effectiveness of the drug and is outlined in Figure 1B. When symptom severity is low in period two, the patient is likely to conclude that he is cured regardless of whether he believes he had malaria or any other illness. At high symptom severities in period two, however, the patient is likely to conclude either that the drug is not effective (if, in period one he strongly believed that the illness was malaria), or that he did not have malaria to begin with (if, instead, in period one he was very confident that the drug treated malaria). In both cases, the expected benefit of completing the treatment is low when the patient feels very unwell mid-way through treatment. Adherence is therefore highest at intermediate levels of symptom severity in period two.

This framework suggests how several packaging-based interventions could increase adherence to medications. First, one could target the perception that once symptoms resolve, the patient is cured of the disease. This type of intervention would increase adherence rates primarily among patients who feel relatively healthy mid-way through treatment and who stop taking pills because they believe that they are cured of the disease (in Figure 1B, it would raise the left side of the curve). Second, one could target the perception that the drugs are not effective in treating malaria. This intervention would increase adherence rates for all patients, but primarily among those who experience severe symptoms after taking a few doses of the drug, some of whom may stop treatment because they conclude that the drugs are not working (in Figure 1B, it should raise the right hand side of the curve). Other interventions could address the cost of adhering to the treatment, such as the desire to save pills for future episodes. One could also try to increase the perceived benefit of adherence, by increasing the salience of the disease externality. Also, if patients do not understand how to take the medication, the packaging of the drug could be used to improve patient comprehension of dosing. Uncertainty about whether the illness is malaria could be targeted by offering diagnostic testing, an intervention that is not based on packaging but which was also tested as part of this study and which we consider in a companion paper (Saran et al., 2016).

4 Study Design and Data Collection

4.1 Experimental Design and Data Collection

The study took place in Luwero district, Uganda, located in Uganda's central region, between November 2010 and September 2011.[5] Despite its proximity to the capital city of Kampala

[5]On May 13, 2011 the Ministry of Health of Uganda confirmed a fatal case of Ebola Haemorrhagic Fever in Luwero District. As a result, the study was halted for approximately a month between May 18, 2011 and June 16, 2011. While surveying and project research stopped during this time, we ensured a steady supply of ACTs at shops during this period. We find no evidence that this break in study implementation affected adherence rates.

(about 68 km), Luwero district is rural and poor, with the majority of households engaged in subsistence farming. Luwero has a high level of malaria endemicity, with an average of over 100 infective bites per person per year (Uganda Bureau of Statistics , UBOS). The study area constitutes the catchment areas surrounding nine drug shops that were located in and around three small trading centers in the east of the district. Two of the trading centers (Busiika and Zirobwe) each had four participating drug shops, while the third trading center (Wabitungu) had the remaining one.[6]

The experimental study design is illustrated in Figure 2. A household census was conducted in catchment areas of roughly 2.5 km (approximately one hour walking distance in each direction) around each shop. In November and December 2010, a team of enumerators traveled to each household in the study area to enroll participants and conduct a baseline survey. Households were then given a Purchase ID card (see Appendix Figure A1), which enabled any household member to purchase ACTs at a 95 percent subsidy at any of the nine participating drug shops. No restrictions were placed on the number of times the card could be used during the study period and no expiration date was given.[7] 2,641 households and 12,572 individuals were enrolled in the study at baseline.[8]

The objective of the project was to assess the impact of various forms of ACT packaging and short messages on adherence (we define this outcome in detail below). To evaluate this, we randomized the type of packaging/messaging an individual received each time they came

[6]Drug shops were selected from a list of licensed shops provided by the Luwero District Area Drug Inspector. Shops were selected based on shop owner qualifications, length of time the shop had been in business, daily customer traffic and operating days/hours. We selected shops that were well qualified and established and that had sufficient customer traffic to reach the desired sample size in a five month period but were not so large that the traffic would be unmanageable for our survey team.

[7]No restrictions were placed on the number of times the card could be used in order to avoid intra-household rationing. However, the project had a limited budget and could not accomodate excessive purchases caused, for example, by hoarding. Hoarding did not turn out to be a serious problem and our approach to this was informal. In the limited cases in which a household seemed to be purchasing an excessive number of ACT doses (34 households, or 3 percent of households that purchased an ACT, bought more than 6 doses of ACTs over the course of the study), we would have a surveyor visit the household and inquire about the health of the members, reminding the household head that the cards were only to be used for patients in the household who were currently sick. This approach worked very well throughout the study.

[8]This is the same number of households that were found in the census activity. No households refused to participate in the study.

to the participating shops to purchase ACTs using their Purchase ID card. The treatment arms were randomly assigned at the shop-day level. That is, an ex-ante schedule was laid out using a random number generator that indicated that Shop 1 got package A on March 1, package B on March 2, and Shop 2 got package C on March 1, etc. Surveyors assigned to each shop brought the control or treatment packs for that particular day with them, and both the study team and shop owners were blinded to the treatment assignment until the day of sale. Prior to the intervention, participating drug shop owners received a training session led by a Ugandan Ministry of Health official on storage and appropriate use of Lumartem (Artemether Lumefantrine, manufactured by Cipla), the type of ACT used in this study.[9] Attendants were instructed to follow their normal prescribing protocol for Lumartem and other anti-malarials. If the patient had a study ID card and wanted to purchase Lumartem they were sent to our survey team member, who sat at a table in the shop to check IDs, dispense the Lumartem in the appropriate packaging and administer a short survey, described below.

Adherence was assessed through follow-up visits to the home of the patient roughly three days after the time of ACT purchase. Not all patients received a follow-up visit: 75 percent of households were randomly assigned ex-ante to receive a follow-up visit if any member of the household purchased ACTs.[10] 96 percent of patients who purchased ACTs, and were members of households assigned to receive a follow-up survey, were successfully reached for a follow-up visit. Individuals were not told of the intent to follow up in order to avoid influencing behavior, but an additional round of informed consent was sought at the time of follow-up. To further limit Hawthorne effects, enumerators asked to see the medication blisterpack and packaging in order to check the lot number, expiration date and other quality

[9]We refer to "shop owners" throughout the paper loosely to refer to either the shop owner him/herself or to the shop attendants (who man the shop but might not be owners). All shop personnel were trained on ACT dosing and prescribing.

[10]In early July 2010, the probability of follow up was increased to 85 percent because we found that we had the survey team capacity to do additional follow up surveys. As this was the last month of the study, it did not increase the overall probability of follow-up among our sample of ACT-purchasing households by much. Overall, of the 2516 patients purchasing ACTs over the course of the study 76.8 percent of them were members of households that were assigned to receive a follow-up visit.

control measures, rather than to explicitly count the number of pills.

Lumartem is a six-dose treatment (with the number of pills per dose varying by age) intended to be taken over three days. The subsidized ACT price depended on the age of the patient and ranged from 200-800 USH (approximately \$0.09-\$0.35 at the time of the study; see Appendix Table A1 for dosing details). The follow-up survey was scheduled for 72 hours after the time of the ACT purchase unless this time fell at night, in which case the interview occured first thing on the following morning. The timing was designed so as to allow patients sufficient time to have completed their medication while minimizing the risk that they would have already disposed of their blisterpacks.[11] Appendix Figure A2 describes the choice of follow-up window in more detail.

4.2 Treatment Arms

Shops were randomized by day into either a control package or one of four treatment packages, shown in Figure 3. There were two main objectives to the study design. The first was to test the status quo approach to promoting adherence through specialized packaging (the "CAPSS Package"). The second was to test whether some simple, inexpensive additions to the standard package, something that a pharmaceutical manufacturer could easily implement on a large scale, could increase adherence rates. Since Uganda does not have a national language, and because we wanted to test interventions that did not need to be tailored at the national (or sub-national) level, all the packages were in English. Though many Ugandans do not speak or read much English, the CAPSS Package – which we did not develop– was already in English. The messages we developed used very simple language with English words that were field tested to be familiar to many Ugandans.

A randomized, cross-cutting intervention was conducted in which a rapid diagnostic test (RDT) for malaria was offered to a sub-sample of patients at the time they purchased ACTs.

[11] The first two doses of ACT are to be taken eight hours apart and the remaining doses should be taken every 12 hours, generally in the morning and evening so that the entire course should take 56 hours from initial dose to completion

We evaluate the impact of diagnostic testing on adherence in a separate companion paper (Saran et al., 2016). For the analysis of the packaging and messaging treatments presented here, we always control for the (orthogonal) RDT offer and present robustness checks showing the impact of the various treatment arms for the sample of patients randomly assigned to not receive the offer of testing (see Appendix Table A4).

Control Package

The control package in this study was the standard package in which Lumartem was sold in Uganda and elsewhere in Africa. The box, shown in Figure 3, had the name, brand and manufacturer of the medication. Inside the box was a blister pack which grouped the pills by dose and day and a paper insert –similar to what is seen inside most medication boxes in the United States and elsewhere – with small print about dosing, side effects, etc.

CAPSS Package and Handout

We refer to the first package as the "CAPSS" package since it was the ACT package used in Uganda during the Consortium for ACT Private Sector Subsidy pilot program (run by the Uganda Ministry of Health, Medicines for Malaria Venture, Population Services International and others). The CAPSS program was a pilot designed to test the feasibility of a private sector ACT subsidy prior to the AMFm.[12] The ACT CAPSS package, which is similar to the packaging used for other ACT subsidy programs in Tanzania and in Rwanda, was intended to serve several purposes. First, it differentiated the subsidized private sector ACTs from those in the public sector (which were intended to be free). Second, it served as a form of branding and quality assurance, providing "consumers with the instant recognition that they were purchasing a high quality and effective anti-malarial at an affordable price" (Talisuna et al., 2012). Finally, it was designed to encourage correct use of the product, incorporating features like colorful pictorial instructions on how to take the medicine, principally to assist

[12]The CAPSS study took place between August 2007 and May 2010 in five districts. CAPSS was completed six months before this study took place and was not in (or near) Luwero district.

illiterate patients and caregivers. Several messages on the CAPSS package relate directly to adherence, such as: 1) "Complete the full course, even if the child improves. This is important for your child's full recovery.", 2) "Only effective if treatment is completed." and 3) "Do not share this drug." These messages are just a few of many pieces of information on the package, including information related to side-effects, storage, proper dosing, etc.

While the potential benefits to this type of specialized packaging are substantial, the CAPSS package, and others like it, add roughly 15-20 cents to the cost of the ACT and can be a source of bottlenecks in the drug supply chain. Because the costs are high, we also tested a packaging type that conveyed the same information content at a significantly lower cost. We created a handout that was a simple black and white photocopy of the CAPSS package and wrapped it around the control package when distributing the medication at the drug shop. The purpose of this treatment arm was to explore, if the CAPSS package was successful at increasing adherence rates, whether the improvement was due to the information and pictorial instructions, or whether it was also linked to the product quality and differentiation conveyed by the special, glossy packaging. We refer to this treatment as the CAPSS-Information Only pack.

Simple Sticker Messages: "Malaria is Not Gone Until..." and "Don't Save Pills..."

We also tested simple, targeted messages to promote adherence delivered via stickers attached to the control packaging, an approach that is often used to encourage patients to finish their medications when prescribed antibiotics. The first sticker was designed to address non-adherence based on the belief that the illness is cured when symptoms have improved or resolved. It said "Malaria is NOT gone until ALL tablets are finished"[13]. The second sticker message aimed to discourage the saving of pills for the next malaria episode and to

[13]Although this message may not be true for some patients, there is a general consensus that people are more likely to respond to simple messages rather than more complex, nuanced messaging (Cutler, 2002; Randolph and Viswanath, 2004).

also internalize the externality associated with non-adherence. It said "Finish ALL tablets. Saving tablets for later can be harmful for malaria control in your community." Both stickers were yellow and placed in the front and center of the box of medicines.[14]

4.3 Survey Tools and Measurement

Surveys were conducted at four points through the study period: at baseline, at the drug shop during the time of ACT purchase, several days after ACT purchase ("follow up") and at study endline. The baseline survey was conducted in the home with the female head of household and collected information about demographics and about malaria treatment and prevention activities. The second point of survey was at the time of ACT purchase, and was administered at the shop with the patient or with the caretaker if the patient was a young child. In 71 percent of ACT purchases for patients over age 12 (i.e. patients who were old enough to answer for themselves), the patient was at the shop and could answer these questions for themselves. The questions primarily concerned the severity of the symptoms that the patient was currently experiencing, and their beliefs about the likelihood that the illness was malaria.

The follow-up surveys took place three days after ACT purchase at the home of patients who were members of households that were ex-ante randomly assigned to be followed up with. The main purpose of this survey was to determine whether the patient had completed their medications by counting the number of pills remaining in the medication blisterpack. The follow-up survey also included questions about the day and approximate time the patient took each dose of the drug, how sick they felt each day while taking the medication, and their current level of health. The respondent for the follow-up survey was the patient if the patient was 18 years old or above, and the caregiver if the patient was under the age of 12. If the patient was between the ages of 12 and 18, the patient was interviewed in the presence

[14] An additional treatment arm was also included in the study with a sticker that provided the actual (non-subsidized) price of the medicines. However, due to budgetary reasons, this treatment had to be phased out early in the study before we obtained a reasonable sample size. We control for this treatment arm in all analyses but do not present the results.

of the caregiver.

At the end of the data collection period, field officers visited each of the participating households and informed them that the study was ending. At this time, field officers collected the Purchase ID Card and asked the female head of household a few more questions about their knowledge and beliefs about malaria treatment and elicited their understanding of the dosing instructions on the packages used in this study. The enumerators discussed the benefits of adhering to treatment regimens and the dangers of non-adherence. Households were also informed that a national ACT subsidy program (the AMFm, described above) was now in place and was being scaled up in their area.

Our primary outcome is a binary measure of adherence which we define as having no remaining pills in the blisterpack at the time of the follow-up survey. In the 13 percent of cases where the blisterpack was not seen, we relied on the patient or caregiver's report on the number of pills remaining. This definition of adherence is standard in the literature, with the majority of studies using a combination of pill counts and self-reports in order to measure adherence (Bruxvoort et al., 2014*a*; Banek et al., 2014).We also look at the number of doses and tablets remaining as additional outcomes of the intervention. Any improvement in the intensive margin is likely to still be beneficial both in treating the disease and in minimizing the likelihood of the development of resistance by reducing the number of parasites remaining in the patient (Stepniewska et al., 2010).

4.4 Trial Registry and Ethics Approval

The trial was registered at https://www.socialscienceregistry.org with registry number AEARCTR-0000490. Ethical approval for this study was given by the Harvard School of Public Health (protocol # CR-19527-02) and the Uganda National Council for Science and Technology (protocol # HS-832).

5 Results

We begin our discussion of results with a description of the uptake of ACTs sold through the program and some basic characteristics of the sample as well as balance across treatment arms. In Section 5.1 we present basic results on adherence and medication taking behavior in the sample. We then present visual evidence and regression-adjusted estimates of impact of the interventions. We drop the 34 ACT purchases where no medication was taken at all (i.e. the entire treatment course was remaining). Assuming the patient had malaria, the parasites were not exposed to the drug, and, therefore, were not under selective pressure to develop resistance to the drug (White et al., 2009). We also drop the 78 patients who were found for the follow-up visit more than 96 hours after they purchased the ACTs. In Appendix Table A3 we check the robustness of our main results to this sample definition.

We run OLS regressions of the following form in our analysis:

$$\begin{aligned} y_{isd} &= \beta_0 + \beta_1 CAPSS_{sd} + \beta_2 CAPSS - INFO - ONLY_{sd} + \\ &\quad \beta_3 \text{"}MALARIA - NOT - GONE\text{"} - MESSAGE_{sd} + \\ &\quad \beta_4 \text{"}DONT - SAVE - PILLS\text{"} - MESSAGE_{sd} + \\ &\quad \sigma_{shop} + \delta_{day} + \gamma_{Purchase} + \lambda_{previous} + \epsilon_{isd} \end{aligned} \tag{1}$$

where y_{isd} is the outcome for person i who bought an ACT at shop s on day d. Outcomes include a binary adherence measure equal to one if all medication is completed at the time of follow up and zero otherwise, a "tablets left" variable measuring the number of tablets remaining in the blister pack and a "doses left" variable which is the number of tablets remaining divided by the appropriate number of tablets to be taken per dose according to the age of the patient. We also include shop (σ_{shop}), day (δ_{day}), ACT purchase number ($\gamma_{Purchase}$) and previous pack types received ($\lambda_{previous}$) fixed effects. Standard errors are clustered by shop (since the random assignment was by shop*day) and, because we only

have nine shops, we also present our impact estimates with p-values based on the wild bootstrap procedure described in Cameron, Gelbach and Miller (2008).

Since the CAPSS and CAPSS-Info Only packages contain additional information from the sticker messages ("Malaria is not gone until..." and "Don't Save Pills...") and also vary substantially in the way the information is presented, we also group together these two types of interventions and estimate a pooled regression as follows:

$$\begin{aligned} y_{isd} &= \beta_0 + \beta_1 CAPSS/CAPSS-Info-Only_{sd} + \\ &\quad \beta_2 STICKER-MESSAGES_{sd} + \\ &\quad \sigma_{shop} + \delta_{day} + \gamma_{Purchase} + \lambda_{previous} + \epsilon_{isd} \end{aligned} \tag{2}$$

where the CAPSS/CAPSS-Info-Only treatment combines patients who received either the CAPSS package or the CAPSS-Info-Only package, while the Sticker Messages treatment combines patients who received either of the two sticker messages.

5.1 Uptake of ACTs, Sample Characteristics and Balance

Over the period of the study in which ACTs were available for purchase, 42 percent of households (16 percent of individuals) purchased at least one treatment course of ACT using their ID card. The mean number of ACTs purchased per household (individual) was 0.95 (0.20). We do not see much evidence for hoarding: 97 percent of study participants who ever purchased an ACT purchased only one or two over the course of the study.

Sample characteristics and balance across treatment arms are shown in Table 1. We were successful in interviewing the female head of household roughly 92 percent of the time. On average, among those who reported any education, female household heads had 7.4 years of education and their spouses had about 8.6; 42 percent of them said they could read a letter written in English (Table 1, Panel A). Households in this region are relatively poor: while

nearly 80 percent owned a mobile phone, only 17 percent had access to electricity (Table 1, Panel B).

Roughly 75 percent of households had a member with suspected malaria in the month prior to the baseline survey and about 64 percent of household members slept under a mosquito net the night before the survey. 66 percent of female household heads had heard of ACTs at baseline (Table 1, Panel C). Among patients who sought outside treatment for a previous episode of malaria (almost everyone did), 30 percent first sought care at a drug shop, while 43 percent first sought care at a private hospital or clinic (the remaining 26 percent visited a public health center or hospital). Only 15 percent received a confirmed diagnosis of malaria using microscopy or an RDT and roughly 53 percent of those who took medicines to treat the illness took ACTs (Table 1, Panel D).

Just over 60 percent of ACT purchases during the study were for children in the three lower age/dose categories (under 12 years old), while the remaining 38 percent were for the highest dosage category (individuals ages 12 and older). A small subsample of patients was randomly tested for malaria at the time of ACT purchase. Positivity rates were 66 percent among this subsample overall (higher for children) and, though there are some differences in positivity rates across treatment arms, these are likely due to the very small sample size (N=362) split across five arms (Table 1, Panel E).

While there are some significant differences in these characteristics between treatment arms and the control group, for most of the arms, only one or two variables are statistically significant, the differences are all modest in magnitude and they don't seem to vary systematically with treatment arm. The "Malaria is not gone until..." treatment group has a few notable differences from the control group, but these differences do not suggest any particular pattern. Households in this arm reported less malaria in their household, which would suggest that they were somewhat older and of higher socioeconomic status than households in the control group. However, households in this arm are actually somewhat younger on average than those in the control and were less likely to have heard of ACTs at baseline, a

knowledge indicator that would typically suggest lower socioeconomic status. In Appendix Table A3 we test the robustness of our main results to including controls for these variables in our regression.

Appendix Table A2 shows loss-to-follow-up across treatment arms. Attrition is fairly balanced across treatment arms, though the "Don't Save Pills..." group was 4.4 percentage points less likely to have a completed follow-up visit than the control group. Those who received the CAPSS pack were approximately 7 percentage points less likely to have their blisterpack available at the followup visit.[15][16]

5.2 Overall Adherence Behavior

We find an overall adherence rate of 65.4 percent, with no association between the age of the patient and the likelihood of adherence. This is somewhat surprising because infants and young children are much more at risk of serious consequences of sub-therapeutic malaria treatment than adults and because the total number of pills that adults must take is much larger. The mean number of doses left was 0.76 overall, and 2.2 among those who did not adhere. This means that non-adherent patients had on average about a day's worth of the three-day treatment left. We measured the percent of patients that took each dose at approximately the correct time of day and find that adherence was high for the first two doses (95 percent and 90 percent) and then fell steadily (between 8-11 percent percentage points) with each subsequent dose (data not shown).

[15] According to the survey team, the main reason that the CAPSS blister pack was slightly less likely to be available for inspection was because some households were using the CAPSS package insert to help start fires. We explore the robustness of our results to various assumptions about adherence among those who did not show their blister packs in Appendix Table A5

[16] We also checked for balance across characteristics of ACT purchasers who were assigned to a follow-up visit and those who were not. Only two variables were significantly different (patients and household heads of those assigned to receive a follow-up visit were likely to be younger than those not assigned to receive a follow-up visit) but the magnitude of the differences were on the order of 1-2 years (Results not shown).

5.3 Impact of Packaging and Messaging on Adherence

Graphical Evidence

We start by presenting a simple graphical analysis of the impact of packaging on adherence (Figures 4-7). For each treatment arm, we present two figures. The figure on the left plots the treatment coefficients (and 95 percent confidence intervals) from a regression in the form of Equation 1, but with a series of dummy variables for outcomes indicating "zero doses left" (i.e. full adherence), "one or fewer doses left", "two or fewer doses left", etc. The figure on the right shows the coefficient on tablets remaining instead. Graphical evidence of a positive treatment impact would be seen in the coefficients for a treatment arm lying above zero.

Figure 4 shows the impact of CAPSS packaging relative to the control for doses and tablets remaining. The figure suggests that there is no impact of CAPSS on medication taking, as the coefficients are close to zero, although the confidence intervals are very wide. We also do not see evidence that the "CAPSS Information Only" arm increases adherence (Figures 5). The point estimates are negative though quite noisy. Taken together, these results suggest that the current approach to promoting adherence through specialized packaging is not effective at improving medication taking.

The impact of the "Malaria is not gone until..." message on adherence is presented in Figure 6. While the difference in the probability of having five or fewer doses remaining is not affected by the message, the impact increases in magnitude and statistical significance as doses left decrease (and as tablets left decrease, see Figure 6B), suggesting that the message leads to improvements in medication taking at the later stages of the treatment course. Figure 7 shows the impact of the "Don't Save Pills" message on adherence. Although the point estimates on adherence by dose and tablet are positive–with a similar pattern of increasing impact as doses/tablets decline–the confidence intervals are wide and include a range of impact estimates.

Regression Estimates and Robustness

Regression estimates based on Equation 1 and Equation 2 are presented in Table 2. Column (1) presents coefficient estimates of the impact of each treatment arm on adherence. As seen in the figures, the CAPSS and CAPSS-Information Only arms have insignificantly negative impacts on adherence, while the "Malaria is not gone until..." message and "Don't save pills..." messages have positive effects on adherence, though only the "Malaria is not gone until..." message is statistically significant. The "Malaria is not gone until..." message increases adherence by 6 percentage points (9.1 percent), relative to the mean of 65.7 percent adherence in the control group. While the effect on overall adherence is modest, the magnitude of its effect on the number of pills remaining is more substantial. The "Malaria is not gone until..." sticker reduces the number of doses remaining by 0.23, a 31 percent decrease in remaining doses (Column 2), and reduces the number of tablets remaining by 0.71, a 36 percent reduction in remaining tablets (Column 3). The coefficient estimates on the "Don't save pills..." message are similar to the other sticker for all outcomes, but are not statistically significant, and the CAPSS and CAPSS-Information packages once again appear to, if anything, increase the number of doses/tablets remaining, though the results are not statistically significant.

Since the way the information is presented differs substantially between the short, targeted messages on the stickers ("Malaria is not gone until..." and "Dont' Save Pills...") and the CAPSS/CAPSS-Info Only packages, we also show regression results in Table 2 (Columns 4-6) where we compare adherence among patients receiving either of these two types of interventions. The sticker interventions increase adherence by 5.7 percentage points (8.7 percent) while the CAPSS/CAPSS Info Only packages reduce adherence by a statistically insiginficant 2.6 percentage points. An F-test confirms that the effects of these two types of messages are statistically different (p=0.002).

Appendix Table A3 presents several robustness checks. Since patients could buy ACTs multiple times throughout the study and might have been influenced by ACT packages that

they, or someone in their household, received previously through the study, in Columns 1 and 2 we limit the sample to the first ACT purchased by an individual and the first ACT purchased by a household, respectively. We also test the robustness of our estimates to our sample definition by including patients who were visited for a follow-up survey after 96 hours (Column 3) and by including patients who did not start taking their medication (Column 4). Finally, we show our main impact estimates with the sample limited to those who showed their blisterpack at the follow-up visit (Column 5), and with controls for variables that were not balanced at baseline (age of patient, household malaria episodes in the month prior to the baseline survey, and whether the female household head had heard of ACTs prior to the study) (Column 6).We find similar impacts as in the main analysis. The "Malaria is not gone until..." message increases adherence rates by 4.2-7.9 percentage points and is generally statistically significant, while the coefficients on the "Don't Save Pills..." message are always positive and similar to the other sticker, ranging from 4.6-8.1 percentage points, but not statistically significant. The CAPSS and CAPSS-Info Only packages seem to reduce adherence rates but the coefficients are not generally statistically significant. In Appendix Table A4, we examine the robustness of our results to limiting the sample to those who were not offered a free rapid diagnostic test for malaria. The results are very similar to our main results in Table 2.

Appendix Table A5 displays the robustness of our main results to three different assumptions about adherence rates among those who did not have their medication blisterpack available at the time of the follow-up survey. We assumed that everyone who did not show the blisterpack either all finished their medication (Column 1), or all did not finish the medication (Column 2), or that the adherence rates among those who did not show their blisterpack was the same as those who did show their blisterpack, separately by the type of package that they received (Column 3). As in our main results, the "Malaria is not gone until..." message increases adherence rates by 5.4-7.2 percentage points and is statistically significant. Under the assumptions that those who did not show their blisterpack did not

adhere, the CAPSS package reduces adherence rates by 10.7 percentage points.

6 Discussion

In this section, we use the theoretical framework outlined in Section 3 to explore how adherence varies across different sub-groups. We also examine some of the reasons why the sticker interventions might have led to increased adherence rates and consider why the CAPSS packages may not have had any effect on adherence.

6.1 Sympom Severity and Beliefs about Cure

The theoretical framework discusses ways in which symptom severity during the treatment course, and beliefs about being cured, could influence adherence. In the follow-up survey, we asked patients how sick they felt on each of the three or four days over which they were taking the medication. Specifically, they were shown a ladder with a scale of 0-10 (a visual analog scale) and asked to indicate how they felt on each day since medication purchase. The top of the scale (10) indicated the "worst feeling of illness", while the bottom of the scale (0) implied that they felt in perfect health (see Appendix Figure A3). We also asked patients what day during their treatment with ACTs they believed that their malaria went away (Day 0 is prior to starting the treatment).

The theoretical framework predicts that adherence rates will be lowest for patients who feel much better mid-course and for patients who still feel very sick, with adherence highest for those who have some symptom resolution. Figure 8 plots a local polynomial regression of adherence on illness severity on the second day of treatment. While symptoms on day two are, of course, partly themselves a function of adherence, nearly everyone adhered on the first day of treatment. The figure shows that adherence follows the predicted pattern in the control group, with adherence rates 25 percentage points higher for those who still felt somewhat "sick" than for those who still felt "very sick" and those who felt that they were

in "perfect health" on the second day of treatment. Figure 9 plots adherence rates (and confidence intervals) by the day patients said they believed their malaria went away. In the control group, patients who said they were cured earlier during treatment were much less likely to adhere compared to those who believed they were cured later during treatment.

Figures 8 and 9 also show that the sticker interventions increased adherence particularly among patients who felt relatively healthy on the second day of treatment and among patients who believed they were cured earlier during treatment. The stickers increased the probability of adherence by 50 percentage points relative to the control group among patients who believed they were cured after one day of treatment. Regression estimates of the interaction between the interventions and symptom severity on the second day (Table 3, Column 1) and between the interventions and the day patients believe they were cured (Table 3, Column 2) confirm the graphical results. The sticker interventions not only increase adherence, but reduce the association between adherence and symptom severity on the second day and the association between adherence and patients' beliefs about when they are cured of malaria.

These results suggest that the short messages emphasizing adherence encouraged patients to finish their medication even when they felt better mid-way through treatment and even when they believed they were cured of malaria. In addition, since the CAPSS and CAPSS-Info Only packs contain much of the same information about adherence that is on the stickers (albeit in smaller print), and had no effect on adherence, the results suggest that the way the information is presented may also be important for influencing behavior. While we cannot say precisely why the short messages were comparatively more effective in increasing adherence, perhaps having a single, easily visible message increased the salience of the information.

6.2 Perceptions of Drug Effectiveness

An important feature of the CAPSS package is the glossy, colorful packaging, which is intended to convey that the drugs are of high quality and are effective in treating the disease. Our theoretical framework predicts that adherence rates will be lower for patients who are

unfamiliar with the drugs, particularly for those who still feel quite sick mid-treatment, since they are more likely to conclude that the drug isn't very effective and stop taking the pills. Figure 10 plots a local polynomial regression of adherence on severity of symptoms on the second day, separately by patients who had heard of ACTs prior to the study and those who had not. The results suggest that familiarity with ACTs is strongly associated with adherence: among patients who hadn't heard of ACTs prior to the study (approximately 34 percent of ACT purchasers), both high and low levels of illness severity on the second day of treatment are associated with lower adherence rates. However, among patients who were already familiar with ACTs, there is no drop in adherence at high levels of illness severity on the second day of treatment.[17]

Regression estimates confirm the results in Figure 10: patients unfamiliar with ACTs were significantly less likely to adhere (by approximately 12 percentage points, p=0.043.) However, the CAPSS package did not differentially improve adherence for this group (coefficient on the interaction (CAPSS X "Hadn't Heard of ACTs")=0.021, p=0.827) (results not shown). It is possible that the CAPSS package was less effective at increasing adherence among those who were unfamiliar with ACTs because the experimental design, including the language on the purchase ID card and the study population's confidence in the study team, increased overall awareness and confidence in ACTs.

6.3 Beliefs About Whether Illness is Malaria

Our theoretical framework suggests that patients with lower priors that they actually have malaria should be less likely to adhere, particularly if their symptoms are still quite bad partway through treatment. At the drug shop survey, patients (or their caregivers) were asked to indicate on a scale of 0-10 (a visual analog scale) the likelihood that the illness was

[17]We see a similar pattern if we look, instead, at patients who at baseline said that, if money were no object, they would prefer to take ACTs (compared to those who didn't), or at patients who said that they believed ACTs were the most effective drug for treating malaria in adults (compared to those who mentioned other drugs). While the latter is perhaps the most direct measure of beliefs about effectiveness, we don't have this variable for the entire sample–only for the sample who mentioned ACTs as a drug they have heard of. All of these measures yield similar results.

malaria where 0 indicated no chance of malaria and 10 implied that the illness was definitely malaria (see Appendix Figure A4). Figure 11 plots a local polynomial regression of adherence on severity of symptoms on the second day, separately by patients who had either low priors (a ranking of 0-4 on the scale) or high priors (7-10 on the scale) at the time of ACT purchase. Overall, patients who had low priors that they had malaria were 7 percentage points less likely to adhere than patients who had high priors, though the difference is not statistically significant (p=0.121), and does not appear to be larger among patients who were very sick on the second day of treatment.

6.4 Understanding Dosing Instructions

Another important characteristic of the CAPSS and the CAPSS-Information packs was that they both included pictorial instructions and visual cues to demarcate dosing (see Figure 3), which are designed to increase patients' understanding of how to correctly take the drugs, particularly for illiterate patients or caregivers. However, our evidence suggests that knowledge of dosing instructions was not the primary barrier to adherence in this context, since we find that 90 percent of patients (across all pack types) took the first two doses, with the correct number of pills per dose, at approximately the correct time (see Appendix Figure A4).[18] We also find no evidence that the CAPSS and CAPSS-Information packages significantly increased adherence rates among those who could not read English (Appendix Table A6) and no evidence that these packages increased patients' understanding of how to take the medication compared to the standard ACT control package (Appendix Table A7).

[18]While the instructions given at the shop may have been insufficient, it is likely that they were the best instructions patients would get in this context. This is because our shop attendants were provided with special training in ACT administration, were among the largest and most professional shops in these areas, and were working side by side with our study team throughout the project.

6.5 Saving Pills for a Future Malaria Episode

In a region where malaria is highly endemic, patients may be motivated to save some pills for a future episode of malaria. In particular, we would expect that patients who live further from a drug shop, who are poor, and who believe that there is a high incidence of malaria would have a greater incentive to save pills for future malaria episodes. However, we find no evidence that adherence is associated with distance, wealth or perceived incidence of malaria (results not shown). This suggests that the desire to save pills may not be a major driver of non-adherence, but this evidence is weak.

6.6 Perceived Private and Social Benefits of Adherence

The theoretical framework suggests that patients may gain utility not only from the benefits of adherence to themselves, but also from the benefits of adherence to the community. In our study, the "Malaria is not gone until..." sticker emphasized the private benefits of adherence while the "Don't Save Pills..." message emphasized that non-adherence is harmful to the community ("Finish ALL tablets. Saving tablets for later can be harmful for malaria control in your community.") Since both messages worked equally well, we do not have any evidence that patients respond more strongly to perceived private benefits of adherence compared to the social benefits of adherence. We do not have sufficient data, however, to determine whether patients read the entire message and which part of the message led to increased adherence.

7 Cost-Effectiveness of Sticker Interventions

In this section, we estimate the cost-effectiveness of the sticker interventions using published malaria cure rates from clinical trials of patients assigned to take 4 doses or 6 doses of Artemether-Lumefantrine, the ACT used in this study. We use cure rates from the published literature rather than endline malaria incidence or prevalence rates because, in a context of

very high malaria endemicity, extremely large sample sizes would have been required in order to have sufficient statistical power to detect differences in these outcomes.

The additional cost of adding a sticker, such as the one we used in this intervention, is approximately $0.015 per package. This includes the cost of the sticker itself which is approximately $0.013 and the cost of printing the message on the sticker which is $0.002 (assuming that printing a single page, which consists of 30 stickers, costs $0.06).

Appendix Figure A5 outlines the method used to calculate the number of averted infections using the targeted sticker messages. We assume that patients who do not finish the medication take four doses of the drug instead of the recommended six doses. This assumption seems conservative since we find that patients who did not finish the medication had, on average, 2.2 doses remaining at the time of the follow-up visit. In our main specification (Table 2, Column 4), the stickers increased adherence rates by 5.7 percentage points compared to the control group (which had an adherence rate of 65.7 percent). If we assume that everyone who buys the medication actually has malaria, and use cure rates from Vugt et al. (1999), this results in 5.7 averted infections per 1000 patients receiving the intervention, at a cost of $15. This implies that the cost of a single averted infection using this intervention is approximately $2.63. If we use alternative assumptions about the malaria positivity rates among the sample of ACT-buyers (for example in our sub-sample that was tested, 67 percent (74 percent among children under age five) tested positive for malaria) and about the differential cure rates for four versus six doses of ACTs (Makanga et al., 2006), we get costs per averted infection that range from $0.82 to $3.93 (see Table A8).

Unlike in randomized clinical trials, however, non-adherent patients in our study chose to take fewer than six doses of the drug, and did so particularly when they felt better midway through treatment. Non-adherent patients in our study may, therefore, have been more likely to have been cured of malaria than patients randomly assigned to take four doses of the drug. If so, we may have over-estimated the relative benefits of taking six doses of the drug (and, therefore, over-estimated the cost-effectiveness of the sticker interventions).

To our knowledge, there are no studies that provide evidence on concurrent symptoms and lingering parasite load for ACT-takers, but it is reasonable to assume that the resolution of symptoms is not a perfect indicator of parasite clearance. The artemisinin component of ACTs works quickly to bring down the parasite load and relieve symptoms (White, van Vugt and Ezzet, 1999), however patients may not yet be cured of the disease. For example, Makanga et al. (2011) find that the median time to fever clearance is approximately 28.5 hours from the first dose (95% CI = 22.3–34.0 hours) but that roughly 20 percent of adults and 10 percent of children still have parasites after 48 hours of treatment. We also find that patients with earlier symptom resolution are not more likely to have been malaria-negative to begin with. (see Appendix Figure A6).

8 Conclusion

The focus of most interventions to improve medication adherence is on chronic, long-term treatments (McDonald, Garg and Haynes, 2002; Haynes et al., 2008). However, sub-optimal adherence to short-course therapies such as antimalarial drugs and antibiotics not only makes it less likely that the disease is cured, but also encourages the development of pathogen resistance to the treatment. Currently, in many countries across Africa, the only large scale, patient-focused attempt to increase adherence to over-the-counter ACTs is to add pictorial instructions to enhance comprehension of dosing guidelines. Typically used in branded, "social marketing" campaigns distributing ACTs, the packaging is also glossy and colorful to convey the high quality of the drugs. We find that this common approach is not effective in increasing adherence. This is of particular importance because this type of package adds substantially to the cost of the drugs.[19] However simple stickers on the standard box of ACTs, with messages that emphasize the importance of completing the medication for curing the disease, are moderately succesful in increasing adherence rates. The messages appear to work

[19]It is important to note, however, that social marketing campaigns also have the objective of increasing uptake of products which we do not examine in this study.

a little better among patients and caregivers who can read basic English, but the difference is not statistically significant. This suggests that English literacy is not a barrier to the effectiveness of these types of short messages.

While the impact of the sticker messages on adherence may not be large enough to affect the probability of parasite resistance, this small addition to ACT packaging has a number of benefits. First, it has a more substantial impact on the number of doses taken which increases the probability of parasite clearance (and hence illness resolution for the patient). Further, adding a sticker with a message on the box of medications is very inexpensive, costing approximately 1.5 cents per package. We estimate that the messages cost between \$0.82-\$3.93 per averted malaria infection. Thus, these types of stickers are likely to be a very cost-effective way of increasing the number of patients cured of malaria through higher ACT adherence rates.

This study also presents some evidence on the reasons malaria patients fail to complete their medications. We find that patients who felt better mid-way through treatment, and patients who believed they were cured earlier during the treatment course, were more likely to stop taking their medication. Moreover, the sticker interventions increased adherence primarily among this group of patients, which suggests that the short messages convinced patients to not rely entirely on their own symptoms and beliefs about cure in determining whether to finish their medication. We also show that patients who were unfamiliar with ACTs prior to the study were less likely to complete the medication, particularly when they still felt very sick mid-treatment. This suggests that perceptions of drug effectiveness also influence ACT adherence rates in this context. However, the CAPSS package, which was designed to increase confidence in the effectiveness of ACTs, had no effect on adherence, not even among those who were unfamiliar with the drug prior to the study. Finally, we found that patients who had low priors that their illness was malaria were moderately (but not significantly) less likely to finish their medication than those with higher priors, and that the impact of priors did not vary with symptom resolution. This is consistent with evidence

we present in a companion paper (Saran et al., 2016) that positive diagnostic confirmation of malaria does not increase adherence rates to over-the-counter ACTs.

These results suggest that interventions succesful in increasing adherence rates will need to convince patients to continue taking the medication even once symptoms have resolved, while also increasing patients' confidence that the drug is effective in treating the disease. It is possible that the scale-up of malaria diagnostic testing could highlight for patients the imperfect connection between symptoms and malaria positivity. Higher rates of diagnostic testing could also enable patients to better learn about ACT effectiveness in treating the disease (Adhvaryu, 2014), though this will depend on the extent to which health workers comply with the results of the malaria diagnostic test in prescribing ACTs, which has varied considerably across different contexts (Odaga et al., 2014).

There are several limitations of this study. We cannot say precisely why the short messages were more effective in increasing adherence compared to the more detailed CAPSS/CAPSS-Info packages which contained much of the same information. The stickers may simply have been more visible or, because they only consisted of a single message, they may have highlighted for patients the importance of adherence. We also do not have sufficient data to determine how patients responded to different parts of the messages on the stickers: whether they were primarily influenced by the injunction to finish the medication or whether the reasons for finishing the medication were also important. More research is needed to understand how the content and design of messages affects patients' beliefs and behaviors. Finally, our study was not powered to determine the impact of the interventions on malaria transmission in this context.

While our interventions had moderate impacts on adherence, they do help shed light on why people may be stopping their medication and what types of interventions might be successful in increasing adherence rates. Further research to better understand how people's beliefs about malaria illness and treatment are formed may enhance our understanding of why they are so difficult to change.

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Figures and Tables

Table 1: Baseline Summary Statistics and Balance Tests

	ACT Purchases Randomly Assigned to Follow-Up Survey							
	Mean in Control Group	CAPSS	CAPSS-Information Only	"Malaria is NOT gone until..." Message	"Don't Save Pills…" Message	CAPSS/ CAPSS Info Only	Sticker Messages	Obs
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
A. Characteristics of Interviewed Household Head								
Age (Years)	32.729 (11.192)	-0.343 [0.801]	-0.292 [0.852]	-0.554 [1.139]	0.127 [1.285]	-0.392 [0.675]	-0.161 [1.076]	1695
Female	0.918 (0.274)	0.007 [0.030]	-0.013 [0.020]	0.013 [0.026]	-0.021 [0.019]	-0.001 [0.022]	-0.006 [0.017]	1702
Reads English	0.420 (0.494)	0.019 [0.044]	-0.059 [0.043]	-0.025 [0.061]	0.050 [0.040]	-0.017 [0.037]	0.014 [0.042]	1695
Years of Education (Among Those Who Reported Some Education)	7.362 (2.929)	-0.092 [0.255]	-0.291 [0.199]	-0.206 [0.346]	0.261 [0.228]	-0.167 [0.199]	0.033 [0.220]	1570
Years of Spouse/Partner Education (Among Those with Some Education)	8.603 (3.124)	-0.265 [0.269]	-0.221 [0.210]	-0.029 [0.403]	-0.583* [0.265]	-0.219 [0.193]	-0.345 [0.248]	1255
B. Household Characteristics								
Household Size	6.012 (2.737)	-0.059 [0.259]	0.291 [0.175]	0.294 [0.212]	0.004 [0.192]	0.128 [0.137]	0.139 [0.170]	1702
Has Electricity	0.170 (0.376)	-0.017 [0.031]	0.003 [0.045]	-0.016 [0.038]	-0.014 [0.035]	-0.010 [0.031]	-0.017 [0.032]	1689
Owns Mobile Phone	0.790 (0.408)	0.004 [0.026]	0.020 [0.028]	0.019 [0.049]	-0.098* [0.051]	0.011 [0.022]	-0.044 [0.046]	1691
C. Health Behaviors and Knowledge								
Member of Household had Malaria in the last 30 days	0.745 (0.436)	-0.071 [0.060]	-0.002 [0.050]	-0.068* [0.031]	-0.074 [0.059]	-0.037 [0.049]	-0.071* [0.031]	1702
Slept under Bednet Last Night	0.640 (0.480)	0.030 [0.045]	-0.008 [0.047]	0.032 [0.057]	0.012 [0.043]	0.013 [0.044]	0.021 [0.044]	1611
Heard of ACTs	0.663 (0.473)	-0.020 [0.029]	-0.028 [0.048]	-0.123** [0.052]	-0.006 [0.047]	-0.019 [0.033]	-0.061 [0.048]	1702
D. Treatment-Seeking Behavior for Previous Malaria Episode								
Sought Treatment at Drug Shop	0.304 (0.461)	0.056 [0.066]	0.022 [0.079]	0.044 [0.062]	-0.044 [0.046]	0.021 [0.061]	-0.011 [0.036]	612
Sought Treatment at Private Hospital Or Clinic	0.429 (0.496)	-0.132 [0.077]	-0.085 [0.104]	-0.055 [0.050]	-0.061 [0.081]	-0.088 [0.069]	-0.061 [0.049]	612

Table 1(Continued)

Received Confirmed Diagnosis (Microscopy or RDT)	0.153 (0.361)	0.106 [0.084]	0.006 [0.065]	-0.005 [0.052]	0.031 [0.043]	0.056 [0.065]	0.015 [0.033]	609
Used ACT (Among Those Taking Medicine)	0.527 (0.501)	-0.095 [0.074]	-0.060 [0.054]	-0.019 [0.081]	-0.103 [0.068]	-0.071 [0.051]	-0.063 [0.065]	472
E. ACT Purchases During Study								
Number of ACT Purchases per Individual	1.430 (0.652)	0.001 [0.060]	0.017 [0.048]	-0.060 [0.050]	0.018 [0.037]	0.012 [0.042]	-0.018 [0.038]	1702
Age (Years)	14.432 (17.004)	-1.390 [1.267]	-0.591 [1.375]	-2.699** [1.067]	0.611 [1.005]	-1.149 [1.318]	-0.970 [0.948]	1682
% of Adult Dose Purchases (Aged 12 years and above)	0.378 (0.485)	-0.002 [0.043]	0.011 [0.053]	-0.033 [0.045]	0.038 [0.037]	0.000 [0.043]	0.004 [0.037]	1696
Offered Free Rapid Diagnostic Test (RDT) for Malaria[a]	0.247 (0.432)	0.011 [0.030]	-0.001 [0.028]	-0.009 [0.033]	-0.065* [0.030]	-0.002 [0.028]	-0.037* [0.017]	1702
Tested Positive for Malaria on RDT[a]	0.658 (0.477)	-0.021 [0.132]	-0.047 [0.090]	-0.160* [0.083]	-0.105 [0.119]	-0.038 [0.087]	-0.134 [0.086]	362

Column 1 shows the mean and standard deviation (in parentheses) in the control group of the 'analysis sample': patients who purchased ACTs who were followed up within 96 hours and who started taking their medication. Columns 2-5 show the coefficients on dummies for each of the treatment groups with standard errors (clustered by shop) in square brackets. Columns 6 and 7 combine the CAPSS/CAPSS-Info treatments and the two sticker messages, respectively. The regression controls for shop, day, ACT purchase number, and previous pack type fixed effects. Regressions also control for whether a free rapid diagnostic test (RDT) was offered, and an interaction of each pack type with a dummy for whether an RDT was offered. *p<0.10, **p<0.05, ***p<0.01. . [a] Does not include controls for whether RDT was offered and interactions between each pack type and the RDT offer.

Table 2: Impact of Packaging Interventions on ACT Adherence

	By pack type			Pooled		
	Adhere	Doses	Tablets	Adhere	Doses	Tablets
Coefficient on:	(1)	(2)	(3)	(4)	(5)	(6)
A. CAPSS	-0.030	0.020	0.158			
	(0.038)	(0.106)	(0.360)			
	[0.443]	[0.851]	[0.673]			
	{0.430}	{0.846}	{0.760}			
B. CAPSS-Info Only	-0.033	0.181	0.535			
	(0.034)	(0.148)	(0.530)			
	[0.364]	[0.256]	[0.343]			
	{0.334}	{0.272}	{0.440}			
C. "Malaria is not gone until…" Sticker Message	0.060***	-0.232**	-0.707**			
	(0.014)	(0.094)	(0.301)			
	[0.003]	[0.039]	[0.047]			
	{0.000}	{0.040}	{0.026}			
D. "Don't save pills…" Sticker Message	0.055	-0.162	-0.603			
	(0.048)	(0.100)	(0.386)			
	[0.278]	[0.146]	[0.157]			
	{0.320}	{0.172}	{0.178}			
E. CAPSS/CAPSS-Info Only (A and B combined)				-0.026	0.089	0.314
				(0.026)	(0.107)	(0.388)
				[0.346]	[0.429]	[0.442]
				{0.316}	{0.428}	{0.488}
F. Sticker Messages (C and D combined)				0.057*	-0.196**	-0.650**
				(0.030)	(0.073)	(0.274)
				[0.088]	[0.028]	[0.045]
				{0.072}	{0.036}	{0.068}
Mean of Dependent Variable	0.657	0.752	1.960	0.657	0.752	1.960
P value: (C=D)	0.918	0.601	0.815			
P value (E=F)				0.002	0.002	0.002
R squared	0.139	0.142	0.194	0.132	0.135	0.189
Number of Obs	1702	1698	1698	1702	1698	1698

All regressions include shop, day, ACT purchase number and previous pack type fixed effects. Regressions also control for whether an RDT was offered and interactions of the RDT offer with each pack type. Regressions with tablets as an outcome also include dosage group fixed effects. Sample is limited to those who started taking the medication and who were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered at the shop level, p-values in square brackets. P-values using wild bootstrap clustered standard errors (at the shop level) are in curly braces. *p<0.10, **p<0.05, ***p<0.01.

Table 3: Interactions Between Packaging Interventions and Symptom Severity/Beliefs about Day Cured on Adherence

	Adhered (Completed Medication)	
Coefficient on:	(1)	(2)
CAPSS/CAPSS-Info Only	0.001	0.107
	(0.065)	(0.137)
	[0.986]	[0.454]
Sticker Messages	0.143**	0.426***
	(0.051)	(0.124)
	[0.022]	[0.009]
Symptom Severity on Second Day of Treatment (0-10 Scale)	0.030***	
	(0.009)	
	[0.007]	
CAPSS/CAPSS Info Only X Symptom Severity on Second Day	-0.007	
	(0.013)	
	[0.575]	
Stickers X Symptom Severity on Second Day	-0.024**	
	(0.010)	
	[0.042]	
Day Patient Believed They Were Cured		0.224***
		(0.036)
		[0.000]
CAPSS/CAPSS Info Only X Day Believe Cured		-0.016
		(0.047)
		[0.744]
Stickers X Day Believe Cured		-0.128***
		(0.037)
		[0.008]
Mean of Dependent Variable	0.658	0.705
P value: CAPSS/CAPSS-Info Only Interaction Term=Stickers Interaction Term	0.407	0.105
R squared	0.144	0.233
Number of Obs	1696	1097

All regressions include shop, day, ACT purchase number and previous pack type fixed effects. Regressions also control for whether an RDT was offered and interactions of the RDT offer with each pack type. Sample is limited to those who started taking the medication and were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered at the shop level, p-values in square brackets. *p<0.10, **p<0.05, ***p<0.01.

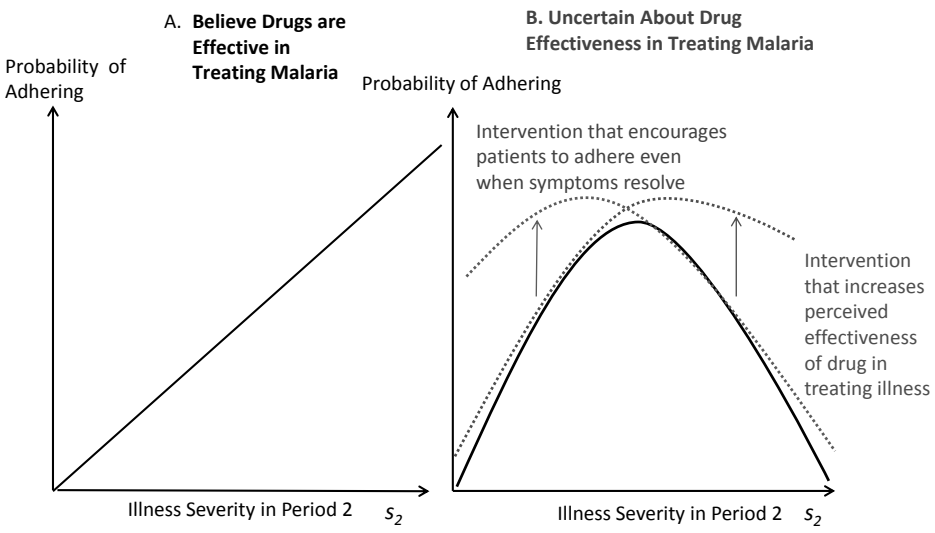


Figure 1: Theoretical Impact of Interventions to Increase ACT Adherence. s_2 is the severity of the illness experienced in period 2 (on the second day of treatment).

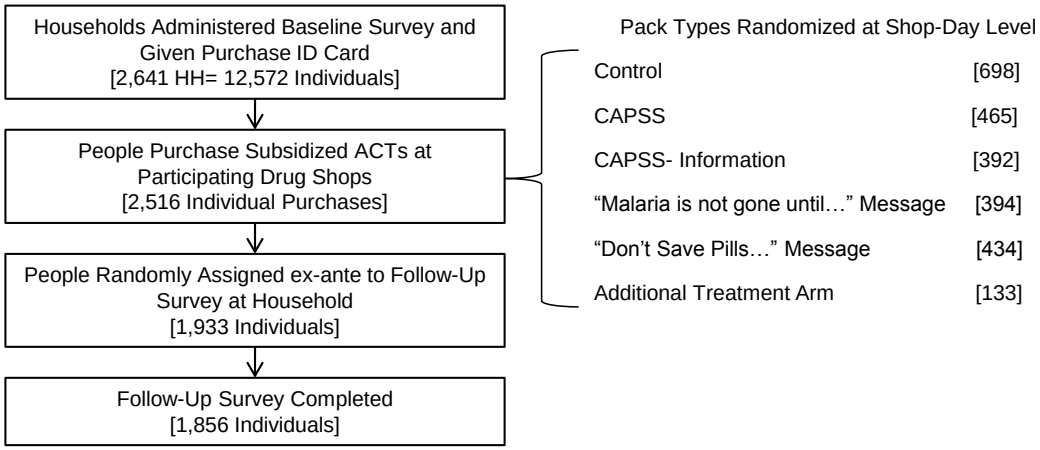
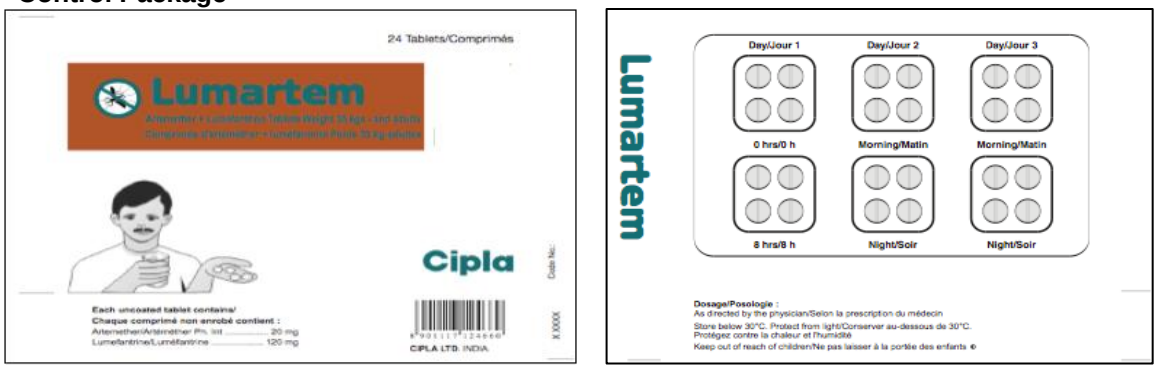
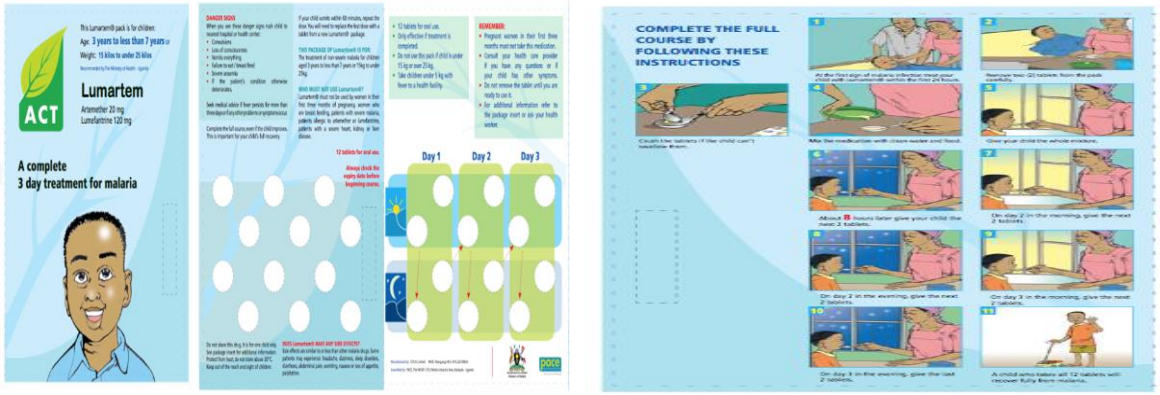


Figure 2: Experimental Design, Sample Size and Attrition. The 'Additional Treatment Arm' is not explored in this paper since it had to be dropped early in the study due to budgetary reasons. As a result, we do not have sufficient sample size to detect any treatment effects. People could buy ACTs multiple times over the study period.

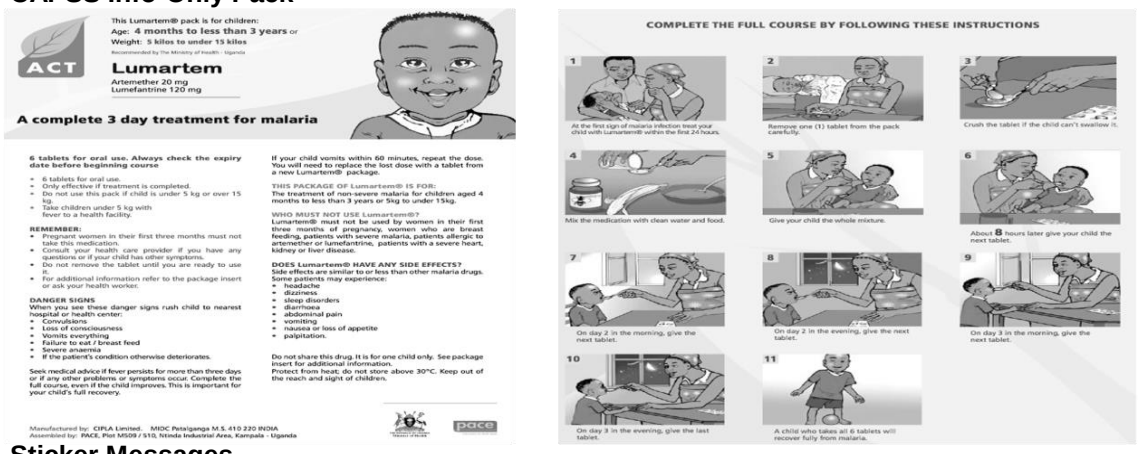
Control Package



CAPSS Pack



CAPSS Info-Only Pack



Sticker Messages

Figure 3: Control and Intervention Packages. The CAPSS pack shown here is for ages 3-7 years. The packages for the other dosage groups are very similar.

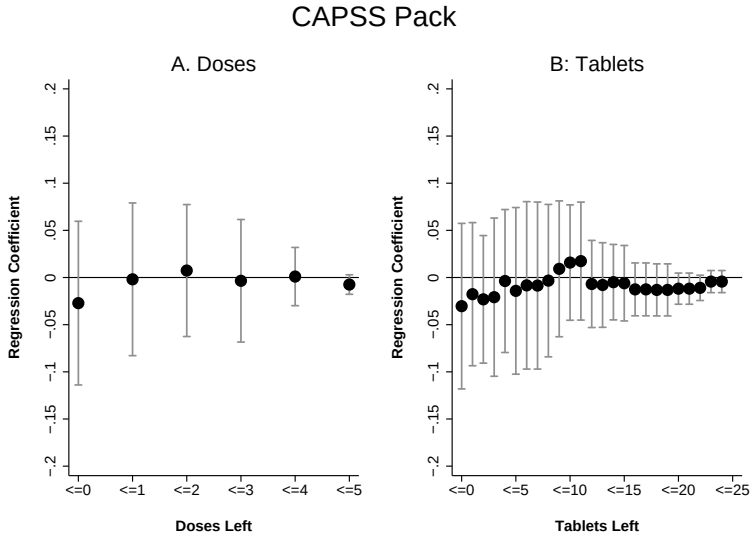


Figure 4: Impact of CAPSS Pack on Doses/Tablets Remaining

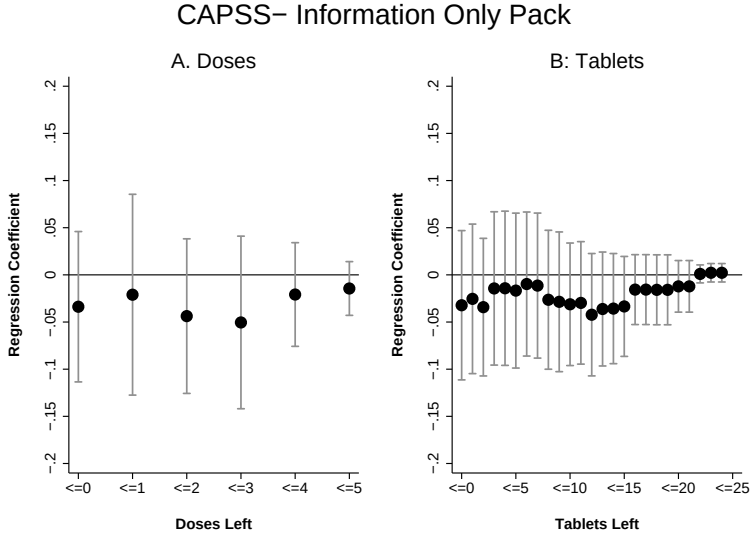


Figure 5: Impact of CAPSS Info Only Pack on Doses/Tablets Remaining. Figures plot regression coefficients of the impact of the treatment (compared to the control) on the cumulative probability of each dose (Panel A) or of each tablet (Panel B) remaining with 95% confidence intervals. The regressions control for shop, day, ACT purchase number and previous pack type fixed effects. Regressions also control for whether an RDT was offered, and interactions of each pack type with a dummy for the offer of an RDT. Regression with tablets remaining also include dosage fixed effects. Sample is limited to patients who were followed up within 96 hours of ACT purchase and who started taking the medication. Standard errors are clustered at the shop level.

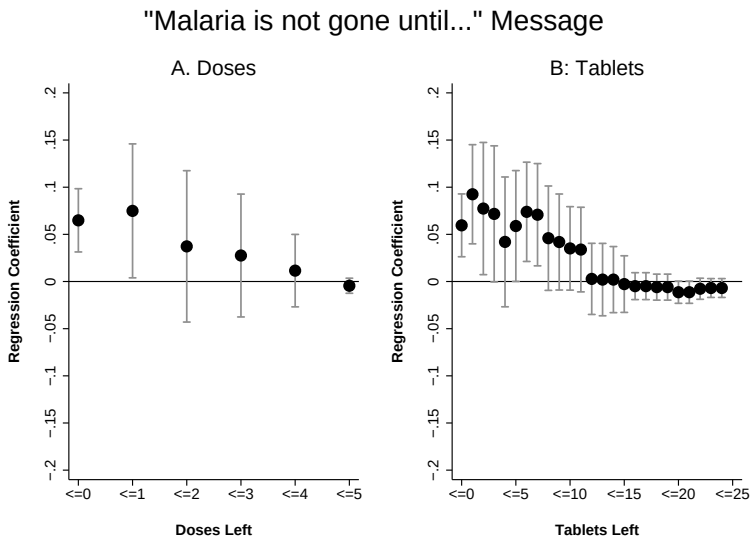


Figure 6: Impact of "Malaria is not gone until..." Message on Doses/Tablets Remaining

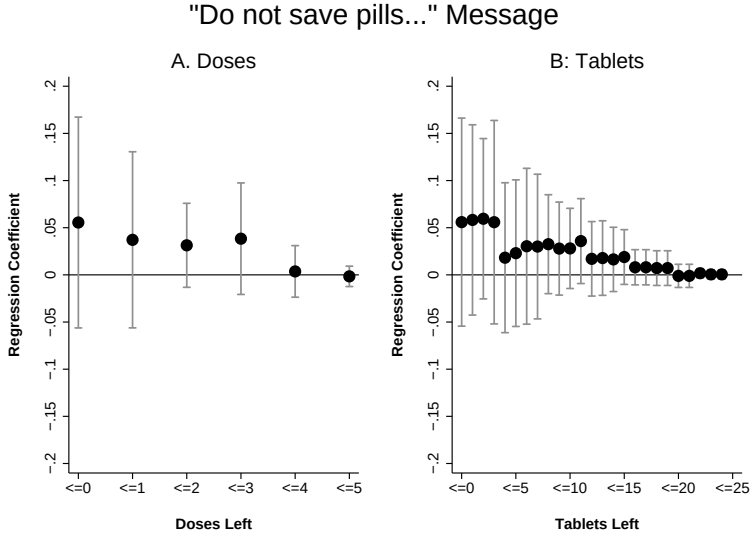


Figure 7: Impact of "Do Not Save Pills.." Message on Doses/Tablets Remaining. Figures plot regression coefficients of the impact of the treatment (compared to the control) on the cumulative probability of each dose (Panel A) or of each tablet (Panel B) remaining with 95% confidence intervals. The regressions control for shop, day, ACT purchase number and previous pack type fixed effects. Regressions also control for whether an RDT was offered, and interactions of each pack type with a dummy for the offer of an RDT. Regression with tablets remaining also include dosage fixed effects. Sample is limited to patients who were followed up within 96 hours of ACT purchase and who started taking the medication. Standard errors are clustered at the shop level.

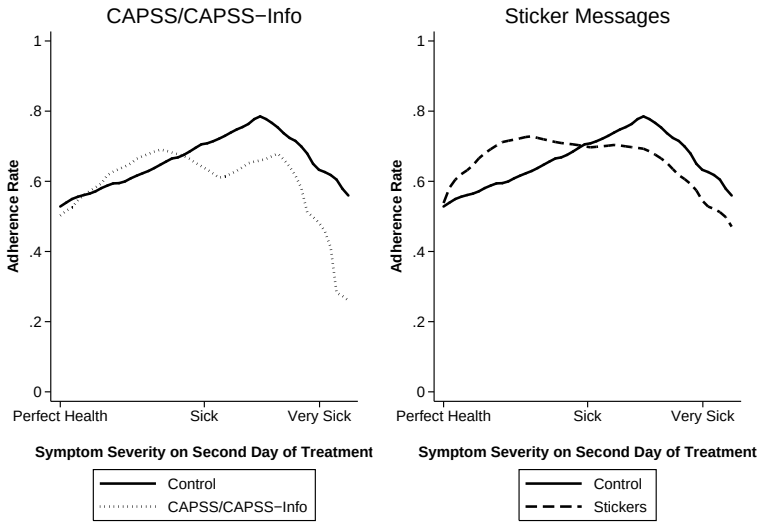


Figure 8: Mid-Treatment Symptom Severity and Adherence. Smoothed local polynomial kernel weight regression of adherence on symptom severity on the second day of treatment. Symptom severity was measured on a 10-point scale with larger numbers indicating increasing levels of sickness. Sample is limited to patients who started taking the medication and who were visited for a follow-up survey within 96 hours of ACT purchase.

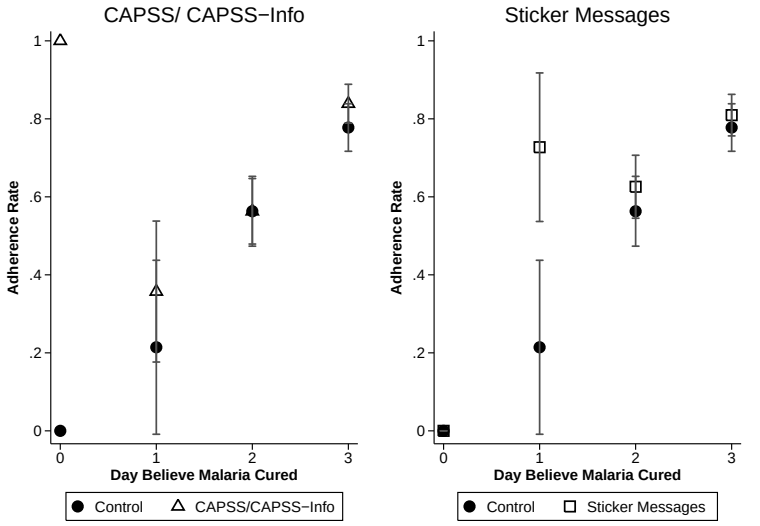


Figure 9: Beliefs about Day Cured and Adherence. Adherence Rates (and 95% confidence intervals) according to when patients said, at the follow-up survey, they believed their malaria went away (Day 0 is before beginning treatment). Sample is limited to those who started taking the medication and who were visited for a follow-up survey within 96 hours of ACT purchase.

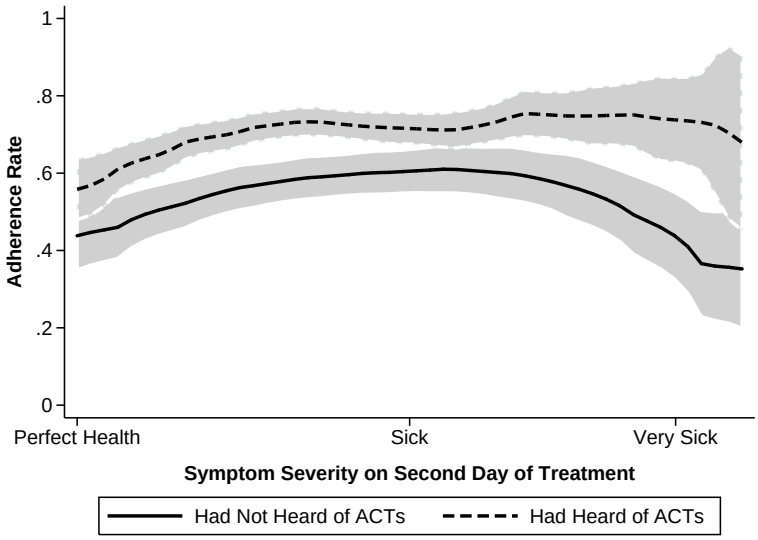


Figure 10: Adherence by Mid-Treatment Symptom Severity and Prior ACT Knowledge. Smoothed local polynomial kernel-weighted regression of adherence on symptom severity on the second day of treatment. Symptom severity was measured on a 10-point scale with larger numbers indicating increasing levels of sickness. Knowledge of ACTs is from the baseline survey (prior to the start of the intervention). Sample is limited to those who started taking their medication and who were visited for a follow-up survey within 96 hours of ACT purchase. Grey shaded areas indicate 95% confidence intervals.

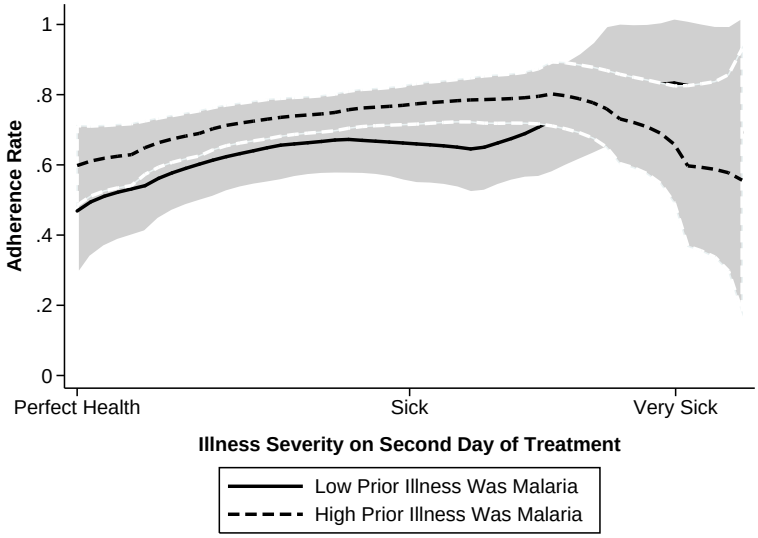


Figure 11: Smoothed local polynomial kernel-weighted regression of adherence on illness severity on the second day of treatment. Illness severity was measured on a 10-point scale with larger numbers indicating increasing levels of sickness. Priors about malaria are from the drug shop survey. Sample is limited to those who started taking their medication, were visited for a follow-up survey within 96 hours of ACT purchase, had heard of ACTs, and were not offered a rapid diagnostic test for malaria. Grey shaded areas indicate 95% confidence intervals.

Appendix Figures and Tables

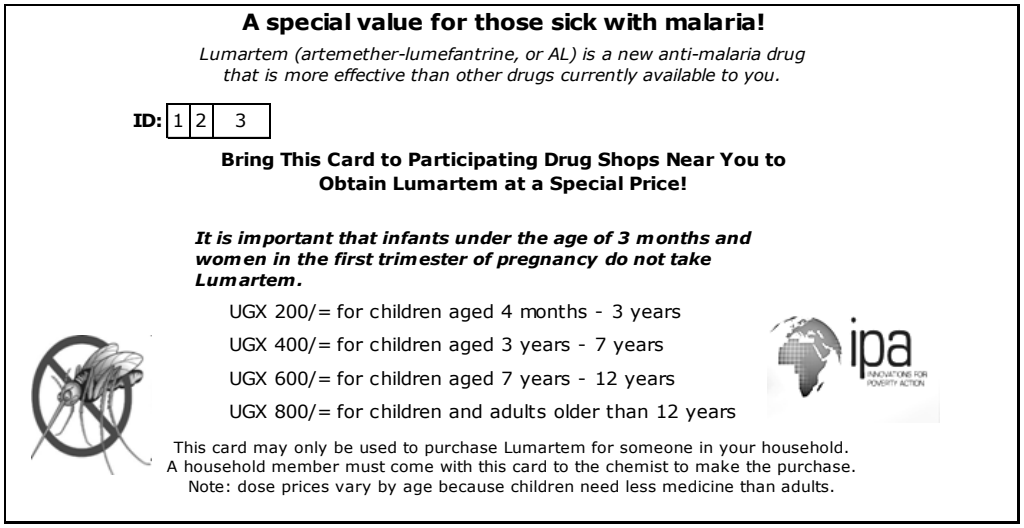


Figure A1: Example of Purchase ID card. Each household was given only one Purchase ID card that could be used by any member of the household as many times as they needed. The Purchase ID was used to link the drug shop and follow-up surveys for individuals to the baseline information for the household.

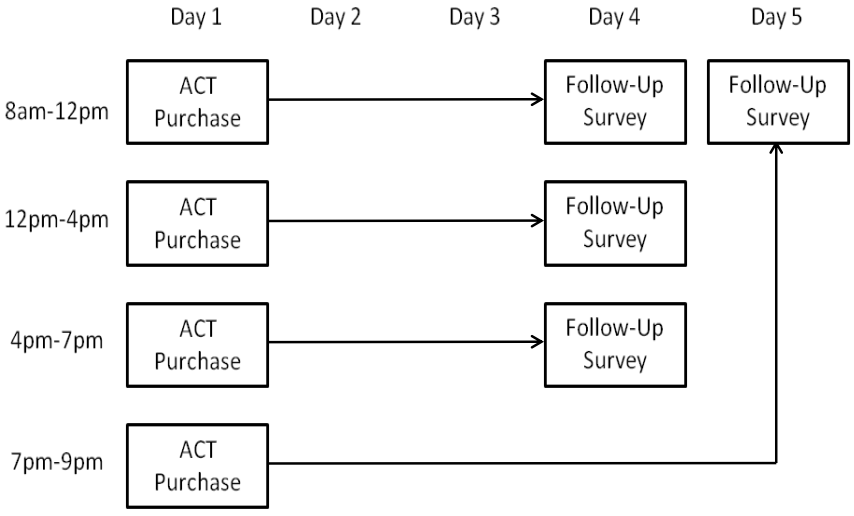


Figure A2: Timing of follow-up survey relative to time of ACT purchase. The follow-up survey was planned for 72 hours after the time of the ACT Purchase. If people purchased ACTs after 7pm in the evening, the follow-up was scheduled for approximately 85 hours later, that is the following day at 8am in the morning

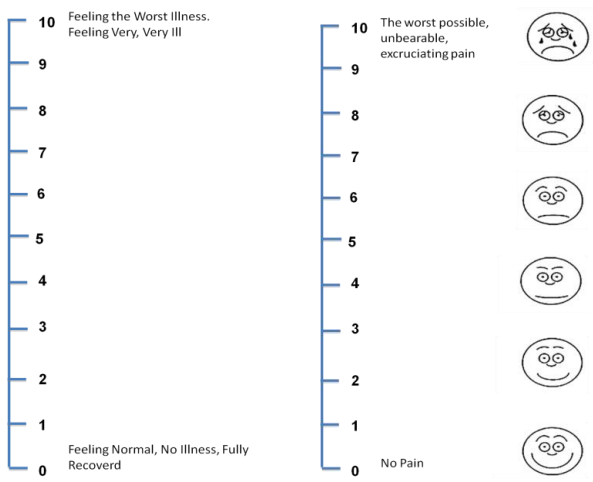


Figure A3: Ladder scales used to guage severity of symptoms.

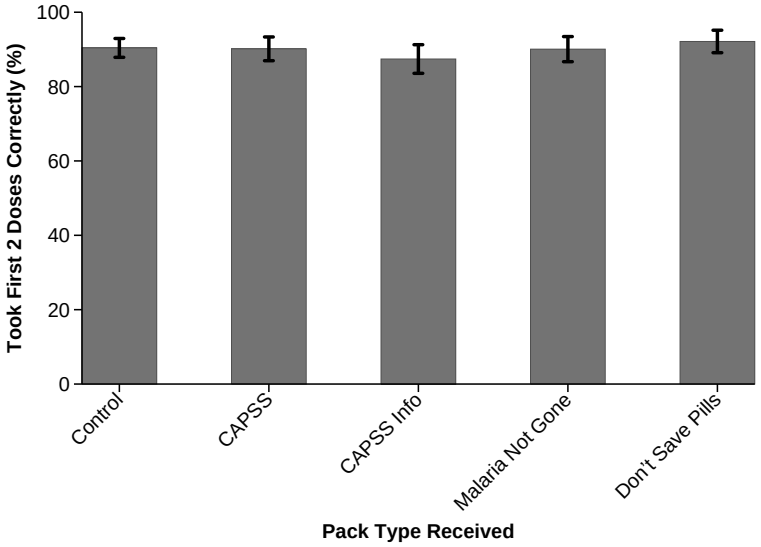


Figure A4: Timely adherence by dose. We use the time that people took their first dose to construct a variable for whether each subsequent dose was taken at the correct time, and using the correct number of pills. Timings are approximate (morning, afternoon, evening). Sample is limited to those who started taking the medication.

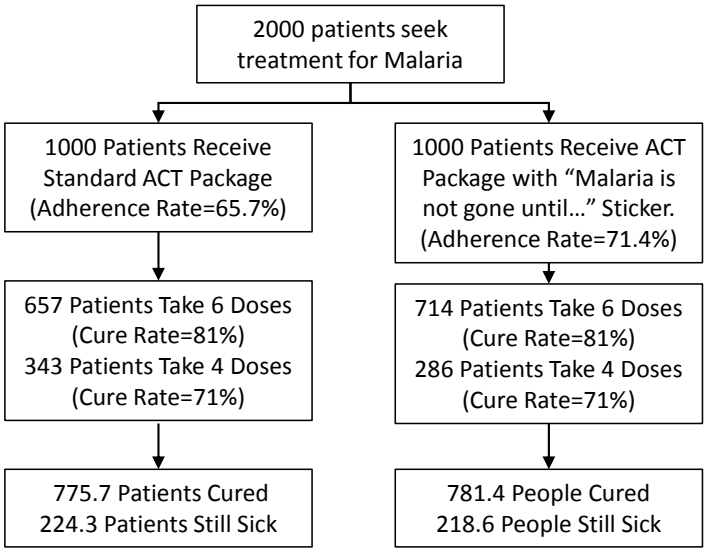


Figure A5: Estimates of number and cost of averted infections with the sticker interventions. We assume that patients who receive the targeted messages on the stickers have an adherence rate of 71.4% while patients who receive the standard ACT package have an adherence rate of 65.7% (see Table 2, Column 4). Patients who do not adhere are assumed to take 4 doses of the medication instead of the recommended 6 doses. Cure Rates are from Vugt et al (1999) and are not PCR-corrected to distinguish new from recurrent infection

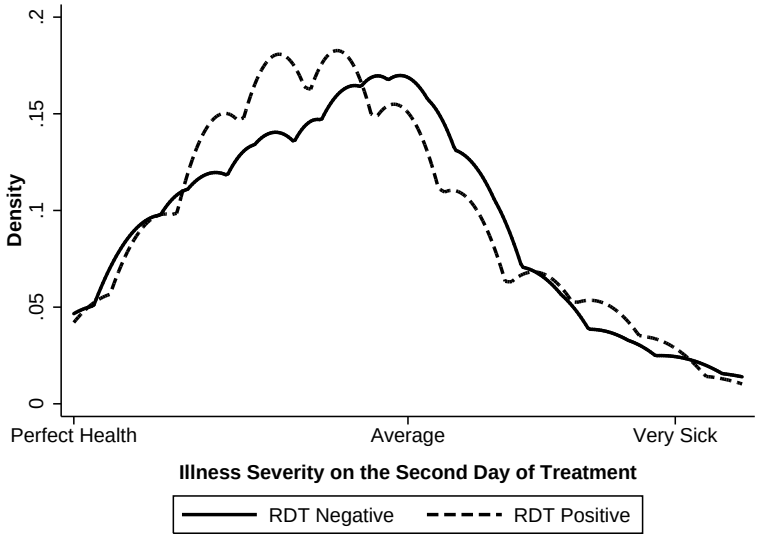


Figure A6: Distribution of Illness Severity on the Second Day of Treatment by Malaria Positivity. The distribution of people (using kernel density estimation) who tested positive for malaria on the RDT at time of ACT purchase and people who tested negative for malaria on the RDT across illness severities on the second day of treatment. Sample is limited to those who started taking the treatment.

Dosage Groups	Number of Pills Per Dose	Dosing Schedule	Number of Treatment Days	Subsidized Price USH (Ugandan Shillings)	Subsidized Price (USD)
4 months- <3 years	1	2 X Day (Morning and Evening)	3 Days	200	0.09
3 years-<7 years	2			400	0.17
7 years-<12 years	3			600	0.26
12 years and above	4			800	0.35

Table A1: Dosing regimen and prices of ACTs. The exchange rate in December 2010 was approximately 2250 USH to $1 USD

	Mean in Control Group	CAPSS	CAPSS-Info Only	"Malaria is NOT gone until..." message	"Don't Save Pills..." Message	CAPSS/ CAPSS Info Only	Sticker Messages	Obs
	(1)	(2)	(3)	(4)	(5)	(6)		(7)
Follow Up Completed	0.963	-0.008	0.014	0.004	-0.044*	0.004	-0.022	1850
	(0.189)	[0.019]	[0.020]	[0.021]	[0.020]	[0.018]	[0.018]	
Follow Up Completed in 96 hours or less	0.928	-0.013	0.000	-0.019	-0.039	-0.004	-0.030	1850
	(0.259)	[0.039]	[0.027]	[0.030]	[0.022]	[0.029]	[0.022]	
Blisterpack Available at Follow-Up Survey	0.864	-0.069**	0.052*	0.006	0.030	-0.012	0.018	1775
	(0.343)	[0.026]	[0.023]	[0.031]	[0.036]	[0.025]	[0.028]	

Table A2: Loss to follow-up across treatment groups. Column 1 shows the mean and standard deviation (in parentheses) in the control group for patients who started taking their medication. Columns 2-5 show the coefficients on dummies for each of the treatment groups with standard errors (clustered by shop) in square brackets. Columns 6 and 7 combine the CAPSS/CAPSS-Info treatments and the two sticker messages, respectively. The regression controls for shop, day, ACT purchase number, and previous pack type fixed effects. Regressions also control for whether a free rapid diagnostic test (RDT) was offered, and an interaction of each pack type with a dummy for whether an RDT was offered. *p<0.10, **p<0.05, ***p<0.01.

	Dependent Variable is Adhered (Completed All Medication)					
	(1)	(2)	(3)	(4)	(5)	(6)
A. CAPSS	-0.026	0.021	-0.027	-0.032	-0.070*	-0.018
	(0.040)	(0.073)	(0.035)	(0.039)	(0.032)	(0.032)
	[0.536]	[0.782]	[0.465]	[0.429]	[0.062]	[0.586]
B. CAPSS INFO ONLY	-0.051	-0.027	-0.030	-0.043	-0.040	-0.020
	(0.057)	(0.077)	(0.032)	(0.038)	(0.032)	(0.031)
	[0.403]	[0.737]	[0.384]	[0.287]	[0.250]	[0.529]
C. "MALARIA IS NOT GONE UNTIL..." MESSAGE	0.057*	0.078	0.042*	0.059***	0.079***	0.076***
	(0.026)	(0.078)	(0.019)	(0.014)	(0.018)	(0.011)
	[0.056]	[0.350]	[0.061]	[0.003]	[0.003]	[0.000]
D. "DON'T SAVE PILLS..." MESSAGE	0.046	0.072	0.049	0.053	0.081	0.068
	(0.057)	(0.089)	(0.046)	(0.049)	(0.045)	(0.043)
	[0.437]	[0.438]	[0.319]	[0.312]	[0.114]	[0.155]
Mean of Dep. Variable	0.643	0.612	0.662	0.645	0.628	0.658
P-value: C=D	0.787	0.942	0.888	0.899	0.974	0.840
R-squared	0.157	0.219	0.133	0.147	0.176	0.148
Number of Observations	1356	717	1755	1732	1480	1682
Only First Individual ACT Purchases	Yes	No	No	No	No	No
Only First Household ACT Purchases	No	Yes	No	No	No	No
Follow-Up Window	<=96hrs	<=96 hrs	All	<=96 hrs	<=96 hrs	<=96hrs
Includes Patients Who Didn't Start Medication	No	No	No	Yes	No	No
Only Those who Showed Blisterpack	No	No	No	No	Yes	No
Includes Additional Control Variables	No	No	No	No	No	Yes

Table A3: Robustness checks on the impact of packaging and messaging on adherence. All regressions include shop and day fixed effects. Except for those limited to first individual or first household purchases, regressions also include ACT purchase number and previous pack type fixed effects. Regressions control for whether an RDT was offered and interaction of the RDT offer with each pack type. The additional control variables in Column 6 are age of patient, probability of a malaria episode in the household in the month prior to the baseline survey and whether the female household head had heard of ACTs prior to the study. Except for where noted, sample is limited to those who started taking the medication and were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered at the shop level, p-values in square brackets. *p<0.10, **p<0.05, ***p<0.01.

	By pack type			Pooled		
	Adhere	Doses	Tablets	Adhere	Doses	Tablets
Coefficient on:	(1)	(2)	(3)	(4)	(5)	(6)
A. CAPSS	-0.030	0.034	0.185			
	(0.041)	(0.132)	(0.422)			
	[0.479]	[0.804]	[0.673]			
B. CAPSS Info Only	-0.040	0.176	0.458			
	(0.035)	(0.173)	(0.566)			
	[0.287]	[0.338]	[0.442]			
C. "Malaria is not gone until…" Message	0.054**	-0.198*	-0.699*			
	(0.016)	(0.105)	(0.309)			
	[0.010]	[0.097]	[0.053]			
D. "Don't save pills…" Message	0.032	-0.098	-0.442			
	(0.039)	(0.095)	(0.349)			
	[0.433]	[0.331]	[0.241]			
E. CAPSS/CAPSS Info Only (A and B combined)				-0.033	0.124	0.388
				(0.031)	(0.131)	(0.425)
				[0.317]	[0.372]	[0.388]
F. Sticker Messages (C and D combined)				0.046*	-0.124	-0.497
				(0.022)	(0.072)	(0.281)
				[0.071]	[0.124]	[0.115]
Mean of Dependent Variable	0.662	0.757	1.991	0.662	0.757	1.991
Test (C=D)	0.558	0.478	0.505			
Test (E=F)				0.006	0.039	0.035
R squared	0.174	0.178	0.227	0.170	0.172	0.222
Number of Obs	1297	1294	1294	1297	1294	1294

Table A4: Robustness of main results to limiting sample to those not offered a free RDT at the drug shop. All regressions include shop, day, ACT purchase number and previous pack type fixed effects. Regressions with tablets as an outcome also include dosage group fixed effects. Sample is limited to those who were not offered an RDT, who started taking the medication and were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered at the shop level, p-values in square brackets. *p<0.10, **p<0.05, ***p<0.01.

	Dependent Variable: Adhered		
	No Blisterpack = Adhered	No Blisterpack = Did Not Adhere	No Blisterpack = Blisterpack Adherence Rate
	(1)	(2)	(3)
A. CAPSS	-0.029	-0.107***	-0.066
	(0.037)	(0.031)	(0.040)
	[0.462]	[0.009]	[0.135]
B. CAPSS INFO ONLY	-0.056	-0.010	-0.038
	(0.034)	(0.036)	(0.029)
	[0.138]	[0.777]	[0.225]
C. "MALARIA IS NOT GONE UNTIL..." MESSAGE	0.054**	0.058*	0.072***
	(0.021)	(0.027)	(0.021)
	[0.034]	[0.059]	[0.008]
D. "DON'T SAVE PILLS..." MESSAGE	0.046	0.059	0.071**
	(0.038)	(0.037)	(0.030)
	[0.263]	[0.145]	[0.044]
Mean of Dependent Variable	0.680	0.537	0.625
P-value: C = D	0.849	0.970	0.967
R-squared	0.172	0.221	0.187
Number of Observations	1297	1297	1298

Table A5: Robustness of main results to assumptions about adherence rates among patients not showing medication blisterpack. We assume in Column 1 that everyone who did not show their blisterpack adhered, in Column 2 that people who did not show their blisterpack did not adhere, and in Column 3 that the adherence rate among those who did not show their blisterpack is the same as the adherence rate among those who did show their blisterpack (separately by each pack type). Regressions include shop, day, ACT purchase number, and previous pack type fixed effects. Sample is limited to those who were not offered a free rapid diagnostic test for malaria, who started taking their medication and who were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered by shop and p-values are in square brackets. *p<0.10, **p<0.05, ***p<0.01.

	Patient/Caregiver Can Read Simple Letter in English			Patient/Caregiver Cannot Read Simple Letter in English		
	Adhere	Doses Remaining	Tablets Remaining	Adhere	Doses Remaining	Tablets Remaining
A. CAPSS	-0.108	0.259	0.848*	0.023	-0.160	-0.284
	(0.069)	(0.178)	(0.440)	(0.054)	(0.169)	(0.392)
	[0.158]	[0.183]	[0.090]	[0.679]	[0.374]	[0.489]
B. CAPSS INFO ONLY	-0.045	0.115	0.203	-0.013	0.134	0.583
	(0.080)	(0.266)	(0.884)	(0.044)	(0.213)	(0.771)
	[0.587]	[0.676]	[0.824]	[0.782]	[0.549]	[0.472]
C. "MALARIA IS NOT GONE UNTIL..." MESSAGE	0.085	-0.258	-0.789	0.055	-0.191	-0.733
	(0.062)	(0.182)	(0.519)	(0.046)	(0.175)	(0.443)
	[0.208]	[0.194]	[0.167]	[0.261]	[0.309]	[0.137]
D. "DON'T SAVE PILLS..." MESSAGE	0.089	-0.307*	-0.980	0.024	-0.071	-0.366
	(0.064)	(0.161)	(0.553)	(0.045)	(0.129)	(0.403)
	[0.198]	[0.094]	[0.114]	[0.606]	[0.597]	[0.390]
Mean of Dependent Variable	0.679	0.706	1.925	0.638	0.791	1.982
P-value: C=D	0.959	0.816	0.778	0.546	0.513	0.492
R-squared	0.248	0.257	0.297	0.223	0.230	0.285
Number of Observations	791	788	788	908	907	907

Table A6: Impact of packaging and messaging on adherence and medication-taking by patient/caregiver English literacy. The ability to read English is defined at the patient level for those aged 12 and above. For patients below the age of 12, they are defined as being able to read English if either the patient or the caregiver can read English. All regressions include shop, day, ACT purchase number, and previous pack type fixed effects. Regressions also control for whether an RDT was offered and interactions of the RDT offer with each pack type. Sample is limited to those who started taking the medication and were visited for a follow-up survey within 96 hours of ACT purchase. Standard errors are in parentheses and clustered at the shop level, p-values in square brackets.*p<0.10, **p<0.05, ***p<0.01.

	A. Control Pack (Adult Dose)		
	Number of Days	Number of Pills Per Dose	Time of Day
Correct	33.6%	61.1%	46.1%
Wrong	19.1%	35.0%	35.3%
Didn't Mention It	44.3%	0.86%	15.7%
Don't Know	2.97%	2.97%	2.93%

	B. CAPSS Pack (Adult Dose)		
	Number of Days	Number of Pills Per Dose	Time of Day
Correct	33.4%	60.0%	46.3%
Wrong	18.1%	36.7%	35.8%
Didn't Mention It	46.0%	0.86%	15.5%
Don't Know	2.45%	2.50%	2.46%

Table A7: Understanding of dosing instructions on control pack and CAPSS pack. Respondents were the female head of household, if available. The surveyor showed the respondent each adult dose package (Control and CAPSS) separately and asked her to say how she would take the medication. Responses were not prompted. 'Didn't Mention It' is for people who didn't mention that particular aspect of the dosing regimen.

	Proportion of Patients Testing Malaria Positive		
	100%	74%	67%
4-Dose 28-day Cure Rate: 71%[a] 6-Dose 28-Day Cure Rate: 81%	\$2.63	\$3.56	\$3.93
4-Dose 28-day Cure Rate: 61%[b] 6-Dose 28-Day Cure Rate: 93%	\$0.82	\$1.11	\$1.23
4-Dose 28-day Cure Rate: 76%[c] 6-Dose 28-Day Cure Rate: 96%	\$1.32	\$1.78	\$1.96

Table A8: Cost of averted infection using sticker messages. We assume that patients who receive the targeted sticker messages have an adherence rate of 71.4% while patients who receive the standard ACT package have an adherence rate of 65.7% (see Table 2, Column 4). Patients who do not adhere are assumed to take 4 doses of the medication instead of the recommended 6 doses. The cost of adding a sticker to the package is \$0.015. Positivity rates are based on our measures of the sub-sample who were randomly tested (67%) and among the sub-sample under age five who were randomly tested (74%). [a]Cure Rates are from Vugt et al (1999) and are not PCR-corrected to distinguish new from recurrent infections. [b]PCR-corrected Cure Rates are from Makanga et al (2006) and based on ITT (all patients not available at 28-days were assumed as treatment failures). [c]PCR-corrected Cure Rates are from Makanga et al (2006) and based on evaluable population (patients available at 28-day follow-up)

A Appendix A: Theoretical Model

In this section we present a simple two period model of the adherence decision. In period one a patient is hit with an illness shock that he believes is malaria with some probabibility p_1, and begins taking malaria medication. In period two the patient decides whether to finish taking the pills or to stop treatment. The patient faces a tradeoff between the benefits of being cured of the disease and the costs of adhering to the medication. This tradeoff is mediated by the patient's perceived likelihood that he continues to suffer from the illness in the second period, the probability that the illness is actually malaria, and his belief in the effectiveness of the medication in treating malaria. We consider the predictions of the model under several simplified cases in order to provide intuition of how these different factors influence adherence in this framework.

A.1 Definitions

We begin by defining the following terms:

- s_2 denotes the severity of illness in period two after the patient has taken a few doses of the medication. We assume that illness severity in period two is independent of adherence behavior as 90% of patients in our sample took the first two doses of the medication on time.

- π_2 is the probability the patient assigns to continuing to have the illness (either malaria, or some other disease) in period two. We assume that beliefs about the probability of still having the illness are a function of illness severity in period two ($\pi_2 = f(s_2)$) and that the perceived probability increases with symptom severity in period two (i.e. $\pi_2^{'}(s_2) > 0$).

- λ_1 is the probability the patient assigns in period one to the effectiveness of the drug in treating malaria and λ_2 is the patient's updated probability in period two that the drug is effective in treating malaria .

- p_1 is the patient's perceived probability in period one (prior to beginning treatment) that the illness he is suffering from is malaria and p_2 is the patient's updated probability in period two that the illness he was suffering from (and potentially continuining to suffer from) is malaria.

- c is the cost of continuing to take the treatment in period two. The costs include possible side effects of the drugs, the effort to remember to take the drugs, and the opportunity cost of consuming pills that could otherwise be used to treat future malaria episodes. We assume that the cost of adhering to the treatment is the same regardless of whether the person is, in fact, still sick with the illness.

- U^H is the utility that a person gets from being healthy, while U^S is the utility that a person gets from being sick (which we normalize so that $U^S = 0$). The utility of being healthy includes factors such as increased productivity and wages as well as the intrinsic value of being healthy. We also include within U^H the patient's perceptions of the benefits to society of his being cured of malaria (less likelihood of malaria transmission, lower probability that the parasite will develop resistance to the drug). For simplicity, we assume the utility of being sick U^S is the same regardless of whether the patient is suffering from malaria or some other disease.

A.2 Patient Decision-Making

We first consider the case in which the patient has no uncertainty that the illness is malaria (i.e. p_1=p_2 = 1) and believes that the drugs are fully effective in treating the disease (i.e. λ_1=λ_2=1). In period one, the patient is hit with an illness shock he believes is malaria and begins taking ACTs. After having taken the first two or three doses of the medication in period one the patient has two possible actions in period two, $a \epsilon A, N$: (1) Continue to finish all the medications (i.e. adhere to treatment guidelines) $a = A$ or (2) Stop taking the medication (i.e., not adhere to treatment guidelines) $a = N$. The action decision in

period two is based partly on the perceived likelihood of still having malaria (π_2), which is a function of the severity of the symptoms (s_2) that the patient is experiencing in period two.

Then the expected utility of adhering $V^A(\pi)$ is as follows:

$$V^A(\pi_2) = \pi_2 * [U^H - c] + [1 - \pi_2] * [U^H - c] \tag{3}$$

$$V^A(\pi_2) = U^H - c \tag{4}$$

The expected utility of not adhering is:

$$V^N(\pi_2) = [1 - \pi_2] * U^H \tag{5}$$

By finishing the medication the patient pays the cost c in order to ensure that he will be healthy, regardless of whether or not he is still suffering from malaria in period two. If the patient chooses not to finish the medication he avoids the cost c, but assumes some risk that he is not fully cured of the disease and may continue to suffer from malaria (either from the current infection or a future recrudescence of the infection). The patient will adhere to the treatment if the expected value of adhering to the treatment exceeds the expected value of not adhering to the treatment:

$$V^A(\pi_2) - V^N(\pi_2) > 0 \tag{6}$$

$$U^H - c - [1 - \pi_2] * U^H > 0 \tag{7}$$

$$\pi_2(s_2) > \frac{c}{U^H} \tag{8}$$

This implies that a patient will adhere if the belief that he continues to suffer from malaria in period two exceeds some threshold value of c/U^H. Patients are thus more likely to adhere when symptom severity is relatively high in period two, when the costs of adhering are low (few side effects, low value of saved pills, etc.) and when the benefit to being healthy is high (see Figure 1A).

A.3 Uncertainty about Drug Effectiveness

We now turn to the case in which the patient still believes the illness is malaria (p_1=$p_2 = 1$) but is unsure whether the drugs he is taking are effective in treating malaria. The patient therefore updates the probability that the drugs are effective in period two based on his priors in period one that the drugs were effective and the severity of his symptoms in period two $\lambda_2 = f(\lambda_1, s_2)$. Since the patient is certain that the illness is malaria, holding constant his priors about the drug's effectiveness, the greater the severity of the illness in period two, the more likely he is to believe that the drug is not effective in treating malaria. Thus, we assume that $\lambda_2'(s_2) < 0$. The expected utility of adhering $V^A(\pi_2, \lambda_2)$ is as follows:

$$V^A(\pi_{2,}\lambda_2) = \pi_2 * \left[\lambda_2 U^H + [1-\lambda_2] * U^S - c\right] + [1-\pi_2] * \left[U^H - c\right] \tag{9}$$

$$V^A(\pi_2, \lambda_2) = \pi_2\lambda_2 U^H + [1-\pi_2] * U^H - c \tag{10}$$

The expected utility of not adhering is the same as in the previous section:

$$V^N(\pi_2) = [1-\pi_2] * U^H \tag{11}$$

Once again, the patient will adhere to the treatment if the expected value of adhering to the treatment exceeds the expected value of not adhering to the treatment:

$$V^A(\pi_2, \lambda_2) - V^N(\pi_2) > 0 \tag{12}$$

$$\pi_2\lambda_2 U^H + [1-\pi_2] * U^H - c - [1-\pi_2] * U^H > 0 \tag{13}$$

$$\pi_2\lambda_2 U^H - c > 0 \tag{14}$$

$$\pi_2(s_2)\lambda_2(\lambda_1, s_2) > \frac{c}{U^H} \tag{15}$$

As before, the likelihood of adhering increases with the utility of being healthy and decreases with the cost of adhering. However, since $\pi_2'(s_2) > 0$ and $\lambda_2'(s_2) < 0$, there is a

non-linear relationship between the probability of adhering and the severity of the disease in period two (see Figure 1B). At low symptom severities in period two, patients perceive the drug to be very effective in treating malaria, but are less likely likely to believe that they are still suffering from malaria and so the expected value of finishing the medication is low. At high symptom severities, patients are more likely to believe that they still have malaria, but the perceived probability that the drug is effective is low, so the expected utility of adhering is again low. The expected utility of adhering is therefore maximized at intermediate levels of illness severity in the second period.

A.4 Uncertainty About Malaria Diagnosis

Finally, we consider the case where the patient is uncertain about whether the illness he is suffering from is malaria in period one, but believes that the drugs are effective in treating malaria ($\lambda_1 = \lambda_2 = 1$). In this case, he updates his beliefs about the likelihood of the illness being malaria in period two (p_2) based on his beliefs that the illness was malaria in period one and the severity of his symptoms in period two ($p_2 = f(p_1, s_2)$). Since the patient is confident that the drug treats malaria, holding constant his priors about the likelihood that the illness was malaria, the greater the severity of the symptoms in period two, the more likely he is to believe that his illness was not malaria to begin with. Thus we assume that $p_2'(s_2) < 0$. The patient will continue taking the medication in period two if the utility of adhering exceeds the expected utility of not adhering to the treatment:

$$V^A(\pi_2, p_2) - V^N(\pi_2) > 0 \tag{16}$$

$$\pi_2 p_2 U^H + [1 - \pi_2] * U^H - c - [1 - \pi_2] * U^H > 0 \tag{17}$$

$$\pi_2 p_2 U^H - c > 0 \tag{18}$$

$$\pi_2(s_2) p_2(p_1, s_2) > \frac{c}{U^H} \tag{19}$$

Thus the likelihood of adhering increases with the patient's perceived probability that he is still suffering from the illness (π_2) and his perceived probability in period two that the illness is actually malaria (p_2). Since $\pi_2'(s_2) > 0$ and $p_2'(s_2) < 0$, as in Section A3, there is a non-linear relationship between the probability of adhering and the severity of the disease in period two. At low symptom severities, patients are more likely to believe that the illness is malaria (since the drug was effective in treating the disease), but are also more likely to believe that they are cured, so the expected value of finishing the medication is low. At very high symptom severities, while patients are more likely to believe that they still have the illness, the perceived probability that the illness is actually malaria is low, so the expected utility of adhering is again low. As in Section A3, the expected utility of adhering is therefore maximized at intermediate levels of illness severity in the second period.

A.5 Model Implications

The model assumes that adherence to ACTs is a function of patients' beliefs about the likelihood of the illness being malaria, their beliefs about the effectiveness of the drug in treating malaria, and also their beliefs about whether they are cured of the illness mid-way through the treatment course. In period one, patients have some prior beliefs about the likelihood of the illness being malaria and the likelihood that the drug is effective in treating malaria. In period two, the patient updates these beliefs based on the severity of his symptoms and decides whether to continue taking the drug.

If the patient feels relatively healthy in period two, he is likely to conclude that he is cured, regardless of whether he believes the illness was malaria or some other disease. In this case uncertainty about the diagnosis and about the effectiveness of the drug have less impact on adherence rates. If the patient feels very ill in period two, he is more likely to believe that he is not cured of the illness but is also likely to conclude that either the illness was not malaria to begin with (if in period one he believed that the drugs were quite effective in treating malaria), or that the drugs are not effective in treating malaria (if instead he was

confident, in period one, that the illness was malaria). Thus, uncertainty about the diagnosis and about the effectiveness of the drugs in treating malaria both result in lower adherence at high symptom severities.

The model suggests that interventions to increase confidence in the effectiveness of the medication, and reduce uncertainty about whether the illness is malaria should increase adherence for those who still feel unwell mid-way through treatment. On the other hand, interventions that target patients' beliefs that they are cured once they are feeling better should improve adherence primarily among patients whose symptoms have resolved mid-way through treatment.