Treatment-seeking behavior and delay in children with severe malaria in Uganda: results of a Markov analysis

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Abstract

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Background

Malaria is a treatable disease yet is a leading cause of death of children in Uganda. Children who experience ACT treatment delay of 24 hours or more are in danger of the progression of uncomplicated malaria to severe, life-threatening malaria. Previous research has examined populations that are more at risk of experiencing delay, and types of sources accessed by caregivers of children with malaria, but no quantitative model has been previous used to examine the relationship between treatment-seeking actions taken, delay, and disease progression.

Methods

Caregivers of children (n = 325) with severe malaria presenting to Jinja Children's Hospital were interviewed about their treatment-seeking itineraries from onset of fever up until hospital enrollment. The actions taken at each step and the exact time at which they occurred were used to create a continuous-time, multi-state Markov model. Frequency of each action, average time spent on each action, and probabilities of taking each action given the last action taken were calculated. Two hypothetical counterfactual scenarios, one in which visiting drug shops was not allowed (counterfactual 1), and another in which drug shop visits were considered perfectly effective (counterfactual 2), were simulated, and the proportion of delayed cases was calculated in each scenario.

Results

Of cases analyzed (314), 33.4% visited a drug shop at some point in their treatment-seeking itinerary. Almost half (48%) of all drug shop visitors went home to self-medicate as their next step. Staying home and staying home to self-medicate contributed the greatest amount of time (30 hours and 35 hours, respectively) of any action. Of the real itineraries analyzed, 86.0% of cases experienced treatment delay of greater than 24 hours. In counterfactual 1, this number dropped to 70.1% of cases experiencing delay, and in counterfactual 2, 65.3% of cases experienced delay.

Conclusions

Drug shops played a substantial role in the delay of appropriate treatment among cases with severe malaria eventually presenting to a regional referral hospital. Interventions that address both drug shop use and drug shop effectiveness have great potential to decrease delay and severe malaria progression on a population level.

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Introduction

Malaria is a treatable and preventable disease, yet is the leading cause of morbidity and mortality in Uganda and poses a major burden on the health care system (1). While the entirety of Uganda's population is at risk for malaria, children under the age of 5 are disproportionately burdened by severe, life-threatening malaria, due to a lack of partial immunity that is acquired through previous exposures (2). Severe malaria represents just a small proportion of all malaria cases, however this small proportion contributes substantially to childhood mortality in Uganda, with a case-fatality rate of up to 25% (3). *Plasmodium falciparum,* the most common malaria parasite in Uganda (1), is also the most common cause of severe complications of all four human malaria parasites species (3). The World Health Organization guidelines encourage prompt and effective treatment of malaria with artemisinin combination therapy (ACTs) within 24 hours of onset of fever (4). While the progression from uncomplicated to severe malaria is not well understood from a public health perspective, delayed treatment is a known cause (5). In line with international targets, the Uganda National Malaria Control Strategic Plan set a target for 2015 of 85% for children under-5 receiving a first-line antimalarial treatment within 24 hours (6), but currently only 44% of children with fevers received antimalarial medicines the same or next day following the onset of fever (7). Barriers to receiving prompt and effective treatment are multifaceted and occur to varying degrees at the caregiver, community, provider and health system levels.

Progression of malaria can happen rapidly, in a manner of hours, making even small delays to effective treatment very dangerous. Thus, the timing and choice of first step that a caregiver of a febrile child takes upon onset of fever often plays a critical role in the probability of disease progression from uncomplicated to severe malaria. In this sense, seeking a treatment-source that is ineffective is inherently harmful due to the fact this such an action contributes to delay in ultimately receiving proper antimalarial treatment. Previous research has been done to examine caregiver behavior among malarial children in Uganda (8–12). Analysis from the 2009 Uganda Malaria Indicator Survey showed that most (81.8%) caregivers of children with malaria seek some source of treatment, that private providers were the preferred option for treatment of children under five with malaria, and that medication and hospitalization are the costliest to caregivers, above consultation or transport (10). A number of studies examining types of treatment sources accessed in Uganda found that private drug vendors are preferred to public outlets due to close proximity, dependable/adequate drug supply, lower cost, opportunity to use credit to purchase drugs, and friendly service (8). While private drug vendors may be preferred, however, they are not necessarily the safest or most reliable option. A 2010 study from central Uganda found that only 34% of patients with malaria seeking drug shop care received appropriate ACT treatment, due to the practice of presumptive treatment and inadequate malaria management knowledge (13).

To date, to the best of our knowledge, no research has quantitatively examined the relationship between treatment-seeking actions taken, treatment delay, and disease progression. This analysis aims to better illustrate the delay attributable to various treatment-seeking actions presumed to be ineffective among children with severe malaria presenting to a regional referral hospital in Jinja, Uganda.

Methods

Population

This analysis focused on the population of children aged 4 months to 10 years who presented to Jinja Regional Referral Hospital with severe malaria and their caregivers. Cases are defined as children in this specified age group that fulfill any of the criteria of either impaired consciousness, respiratory distress and/or severe anemia, with a *P. falciparum* parasitemeia count of over 2500/µl. Children with clinical evidence of other illness that could explain their symptoms, prior study participation or a history of chronically ill health were excluded.

Data collection

This analysis used a subset of data from a larger case control study, "Determinants of disease severity among children with severe malaria admitted to Jinja Children's Hospital, Uganda" conducted by Dr. Arthur Mpimbaza. The study took place at Jinja Regional Referral Hospital and Makerere University in Kampala, Uganda in collaboration with the University of California, San Francisco, funded by the National Institute of Health.

Itineraries were collected by in person interviews between clinical study staff and caregivers of the children enrolled the study. Itineraries detail each step taken by the caregiver from onset of fever to the point at which they arrived at Jinja Children's Hospital. Beginning with onset of fever, caregivers were asked to report symptoms, times of symptoms, actions taken, and times of actions taken up until hospital enrollment. Options for actions taken on the itinerary form were 1) stayed home, 2) stayed home (self-medicated) 3) stayed in the same health facility 4) went back home 5) sought care (private clinic) 6) sought care (private hospital) 7) sought care (herbalist) 8) sought care (traditional healer) 9) sought care (witchdoctor/Spiritual-healer) 10) sought care (church/pastor) 11) sought care (pharmacy/drug shop) 12) sought care (village health team) 13) sought care (HCII) 14) sought care (HC III) 15) sought care (HCIV) 16) sought care (hospital-government) and 17) other.

Analysis

Specific Aims

The specific aims of this analysis are as follows:

1. Identify common treatment-seeking actions taken among severe malaria case itineraries
2. Quantify the delay associated with common treatment-seeking actions
3. Examine patterns of treatment-seeking actions relative to previous and next actions
4. Simulate hypothetical treatment-seeking itinerary changes with regards to drug shop/pharmacy visits to determine how these changes could influence delay

Statistical Analysis

Analysis was performed using STATA 14 and R 3.3.0. Descriptive analysis on delay and actions taken were performed using frequency tables. Total time was measured starting time to end time: start time was, either defined as onset of fever or shortly before first action taken, whichever occurred first. If reporting onset of fever occurred after the first care seeking action (n = 25), the onset of symptoms was set to one hour before the first action was taken. Delay was defined as a binary variable indicating greater than 24 hours from onset of fever to reaching Jinja Children's Hospital. Intervals between each action taken were defined as the time interval between the time when the respondent said they took one action and the time the respondent said they took the next action. If time data was missing for any action between two time points, a time equidistant between each known time point was imputed. More details about handling of missing data can be found in Appendix 1.

Descriptive Analysis

Actions were collapsed, based on their prevalence in the dataset, into the following six categories: stayed home, stayed home (self-medicated), sought care (private clinic or hospital), sought care (pharmacy/drug shop), sought care (government facility), sought care (Jinja Children's Hospital). Government facilities were defined as health center II, health center III, health center IV or a government hospital other than Jinja Children's Hospital where they were recruited to the study. These 6 actions, plus an initial fever state, were entered as states into the Markov model for a total of 7 states.

Markov Model

Figure 2 illustrates the multi-state model in continuous time. At any time, *t,* an individual is in a state *S(t)*. Each arrow represents possible transitions between mutually exclusive states. In this model, an individual may move freely between any two states, with the exceptions being state 1, fever onset, which all individuals must start in and may not return to, and state 7, Jinja Children's, the absorbing state, in which all individuals eventually enter but may not leave. Given a certain state, the next state that an individual enters and the time at which they change states depends on a transition intensity matrix, q, which represents the instantaneous risk of moving from each state to each other state.

To perform this analysis, the Markov assumption, that the next step taken depends only on the current state, was made. Time-homogeneity, in which transition probabilities remain constant over time, was also assumed. The continuous-time multi-state Markov model (msm) was fitted using the R package msm version 0.8.1. Exact model specifications and detail on the modeling methods can be found in Appendix II. Sojourn times, defined as the average duration of stay in a state during a single period of occupancy, were calculated for each transient state, not including the absorbing state of Jinja Children's Hospital, which by definition has an infinite occupancy time. The probability that each state is next, given a current state, was calculated as well.

Simulation

Once the initial model was populated with real case data ("business-as-usual" model), two counterfactual scenarios were simulated. In counterfactual 1, the initial transition intensity matrix was altered such that visiting one state, drug shops, was no longer allowed. In counterfactual 2, drug shops were treated as a second absorbing state. This second counterfactual assumed that visiting drug shops would be perfectly effective in terms of proper ACT distribution and children would recover after the visit, thus ending their itinerary at that point. Proportion of children with treatment delay greater than 24 hours was calculated in each scenario and compared to the "business-as-usual" estimates.

Results

Treatment seeking itineraries were collected from 325 cases. Due to out-of-order time observations and time data that were incompatible with the Markov modeling technique, 11 observations were dropped from the preliminary analysis (see Appendix 1), leaving a sample size of 314 for the analysis.

Participating caregivers came from the area surrounding Jinja, with a large portion concentrated near Jinja Regional Referral Hospital and nearby districts but coming from as far away as far ends of the Kamuli, Kayunga, Kaliro, and Mayuge districts (see Figure 1).

Table 1 reports actions that were ever taken by caregivers during their treatment-seeking itineraries before hospital enrollment. Of the 314 itineraries used in the analysis, a majority (71.0%) of caregivers reported self-medicating at home, while over a third (n = 105) of caregivers reported visiting a drug shop at some point in their itinerary. About one fourth (n = 89) visited a government health facility (health center 2, 3, or 4) at some point in their itinerary. Only 1 caregiver reported a visit to a traditional healer.

Table 2 shows the average time spent in each state during a single stay, as reported by the multi-state model (msm). On average, caregivers took 3.48 hours, from onset of fever to taking their first treatment-seeking action. Staying at home accounted for the longest stays in any given state. On average, staying at home accounted for just under 30 hours, and self-medicating at home accounted for 34.7 hours of treatment-seeking time.

Table 3 shows probabilities that each state is next, given the individuals current state. The probability of returning home to self-medicate after visiting a drug shop was 0.48. The probabilities of going to Jinja Children's Hospital were highest after visiting another health facility of some type: 0.41 and 0.70 for private clinics and government facilities, respectively.

Lastly, table 4 summarizes delay among cases and the effect of two counterfactual scenarios on treatment delay, with delay defined as no treatment within 24 hours of fever onset. In the business-as-usual model, 86.0% of cases experienced treatment delay. Among simulated itineraries that were not allowed to visit drug shops, delay was reduced by 15.9 percentage points, with only 70.1% experiencing delay. In the second counterfactual scenario in which children were assumed to have received adequate treatment and recovered after visits to the drug shop, delay was reduced by over 20%, with 65.3% experiencing delay.

Discussion

Because all participants in the study ended up severely ill at Jinja Children's Hospital, where they were recruited as cases, it is plausible to assume that treatment-seeking steps before this point were to some extent ineffective. This analysis showed that over a third of participants reported seeking care at drug shops, and over 70% reported staying home to self-medicate somewhere in their treatment-seeking itinerary. The concept of ineffective self-medication and drug shop treatment is not unique to this analysis and has been documented in other literature examining antimalarial distribution from drug shops and pharmacies in Uganda (8,13).

Apart from being both a prevalent and ineffective source of antimalarial treatment among these cases, this analysis has also demonstrated that drug shops and pharmacies play an important role in next steps taken in the pathway to care, and in the overall delay of treatment among severe malaria cases. Results of the Markov model indicated that drug shops were more likely to send participants back home to self-medicate (Table 3), a state which an average occupancy time of greater than one day (Table 2), as opposed to government and private health facilities, which were more to likely to send participants directly to the hospital.

The modeling of two hypothetical counterfactual scenarios demonstrated the powerful impact that policy changes or interventions addressing drug shop use or policies could have on treatment delay and delay-associated disease progression on a population level. These results complement recent work on engaging Ugandan drug shops with the national health system and national strategies and guidelines (14–22). While presumptive treatment of all febrile children with antimalarial medication used to be the norm, in 2011 new WHO guidelines suggested universal diagnostic testing and parasitological confirmation of malaria before treatment with an antimalarial (23). In Uganda, this guideline is at odds with current treatment-seeking practices, as a large proportion of caregivers prefer drug shop vendors as their source of antimalarial treatment, and thus largely bypass any form of diagnostic testing before treatment. However, a number of studies conducted since the guideline shift towards test-and-treat have shown promising results. In an rapid diagnostic test (RDT) implementation study in 92 drug shops across 58 Uganda villages, RDTs were found to affect treatment decisions and RDT-positive patients were significantly more likely to buy ACTs (16). Qualitative analysis on similar implementations in Uganda has revealed that drug shop vendors enjoyed learning and practicing the new skill of blood drawing and testing, identifying as health workers, and feeling engaged with the health system. Patients also welcomed the local availability of RDTs (14). The current literature on RDT use in drug shops and drug shop engagement, combined with the results from this analysis shows promise that interventions engaging drug shop vendors with the health system via RDT implementation or other means has the potential to greatly reduce delay in treatment and ultimately decrease the number of child deaths due to the delay-induced progression of uncomplicated malaria to severe malaria.

This analysis had some limitations. First of all, only health seeking itineraries among cases that eventually made it to Jinja Children's Hospital with severe illness were analyzed, meaning that these results may not be generalizable to all caregivers and their children in Uganda. More specifically, this analysis cannot account for behavior patterns of caregivers of children that recovered before seeking hospital care, or who did not make it to the hospital. Due to the large proportion of cases in the study population who experienced treatment delay of greater than or equal to 24 hours, this analysis also really cannot speak to the experiences and choices of caregivers who secure timely treatment for their children. Results should be interpreted as that from this particular population and not for all caregivers. For example, while a large proportion (33%) of caregivers in this analysis were found to visit drug shops at soe point, a 2009 study comparing febrile children who experienced delay to those who did not found that children *less* likely to delay were more likely to have visited drug shops or community medicine distributers (24). These results combined suggest that drug shops play an ever larger role in the general population than was revealed in the analysis of severe malaria cases. Future quantitative analysis of treatment-seeking itineraries using similar analytical methods but other populations and other study designs could help enhance the understanding of differing behaviors between groups that experience delay and/or severe malaria versus those that do not.

However, given these limitations, the goal of this analysis was to explore the nature of delays experienced by those who experienced severe illness and treatment delay, and the population studied is appropriate for this goal.

Another potential limitation is the possibility of reporting bias. It’s possible that caregivers may recall information about steps taken or times incorrectly, or intentionally leave some actions taken out of their itinerary. Only 1 participant reported the use of a traditional healer during their treatment-seeking itinerary, which could indicate low rates traditional healer, but could also indicate that participants may be more likely to report certain types of actions over others to the study team. Lastly, this analysis looks only at the bulk flow of all participants between various traditional states in the Markov model, and does not include covariates which may be important determinants of treatment-seeking behavior, including SES, child age, child gender, and education of parent. Further quantitative analysis should be done using these covariates to determine how these factors relate to delay and treatment-seeking behavior.

Conclusion

In conclusion, visits to drug shops and subsequent returning home to self-medicate account for a substantial number of treatment-seeking actions in the pathway from onset of fever to hospitalization, and a substantial portion of time delay in that pathway. While the prevalence of visits to health facilities was low, these states were most likely to refer to a government hospital. Treatment delay of greater than 24 hours among cases of severe malaria was high, but has the potential to be decreased through interventions and policy changes addressing drug shop use.

Tables and Figures

Table 1. Actions taken by caregivers throughout itinerary of events

Action	Frequency, n (%)
Stayed home	114 (36.3%)
Stayed home- self-medicated	223 (71.0%)
Sought care- traditional healer	1 (0.32%)
Sought care- private clinic	116 (36.9%)
Sought care- government facility	89 (28.3%)
Sought care- drug shop	105 (33.4%)
Sought care- Jinja Children's Hospital	314 (100.0%)

Table 2. Mean sojourn times in days from business-as-usual multi-state Markov model

State	Hours (SE)
Fever (before first action)	3.48 (0.19)
Stayed home	29.95 (2.62)
Stayed home- self-medicated	34.68 (2.14)
Sought care- private clinic	18.58 (1.63)
Sought care- government facility (excluding Jinja Children's Hospital)	23.16 (2.18)
Sought care- drug shop	13.54 (1.10)

Table 3. Probability of next action, given current state (95% CI)

	Fever	Home	Self-medicate	Private clinic	Drug shop	Government Facility	Hospital
Fever	0.00	0.17 (0.13, 0.21)	0.46 (0.40, 0.51)	0.10 (0.07, 0.14)	(0.22 (0.18, 0.27)	0.04 (0.02, 0.06)	0.01 (0.00, 0.02)
Home	0.00	0.00	0.22 (0.16, 0.29)	0.20 (0.14, 0.28)	0.13 (0.08, 0.20)	0.22 (0.15, 0.29)	0.24 (0.17, 0.31)
Self-medicate	0.00	0.15 (0.11, 0.20)	0.00	0.21 (0.17, 0.26)	0.09 (0.06, 0.13)	0.26 (0.21, 0.32)	0.28 (0.23, 0.34)
Private clinic	0.00	0.15 (0.10, 0.22)	0.18 (0.12, 0.26)	0.00	0.02 (0.00, 0.06)	0.25 (0.17, 0.32)	0.41 (0.32, 0.49)

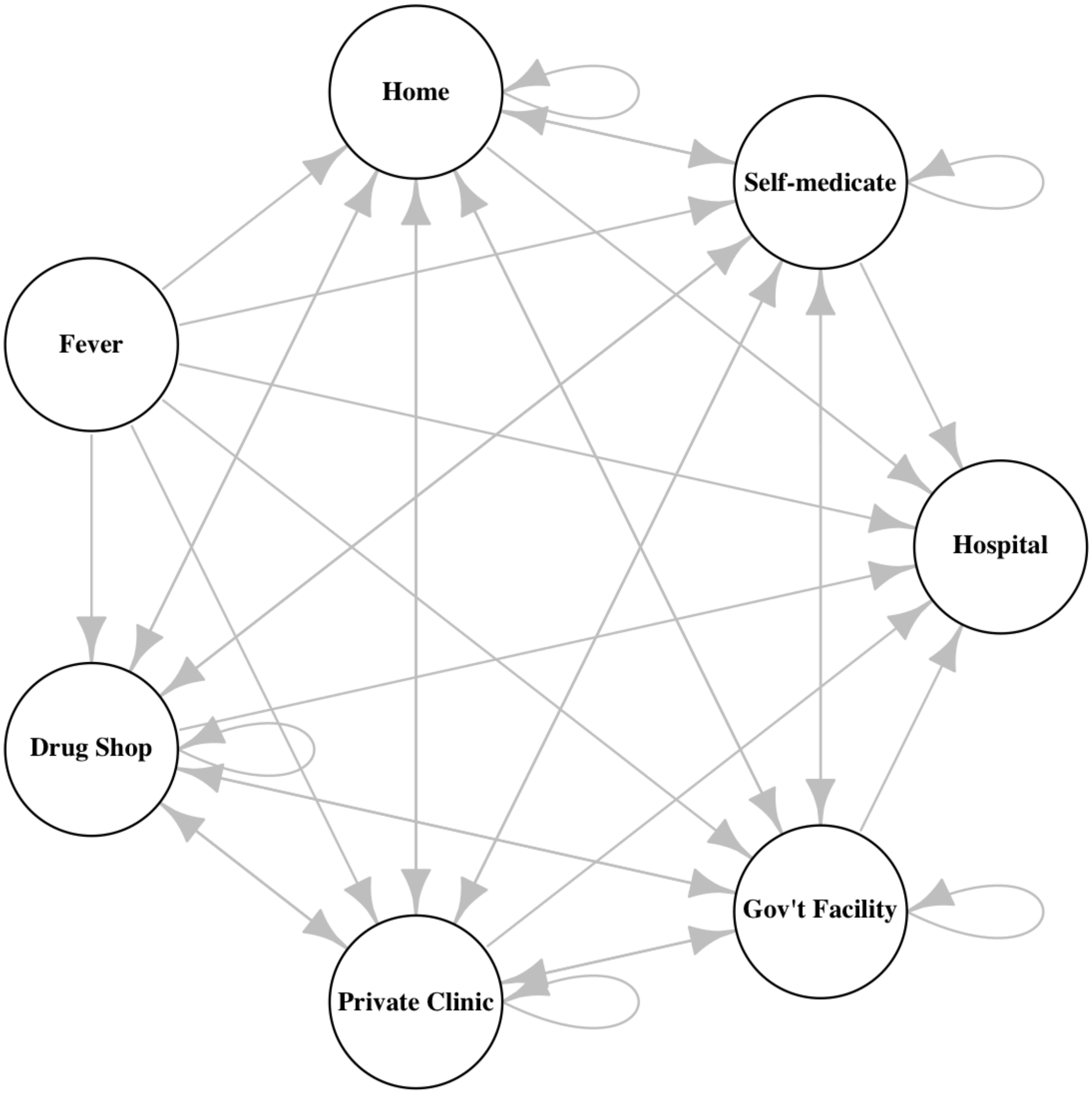
Drug shop	0.00	0.15 (0.10, 0.23)	0.48 (0.39, 0.57)	0.06 (0.03, 0.13)	0.00	0.15 (0.10, 0.23)	0.15 (0.09, 0.22)
Government Facility	0.00	0.09 (0.06, 0.15)	0.09 (0.05, 0.14)	0.12 (0.07, 0.18)	0.01 (0.00, 0.05)	0.00	0.70 (0.60, 0.76)
Hospital	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 4. Simulation results: percent of children experiencing delay > 24 hours from onset of fever to hospital arrival

	Business-as-usual	Counterfactual 1: No drug shops	Counterfactual 2: “Working” drug shops
Delay	270 (86.0%)	220 (70.1%)	205 (65.3%)
No delay	44 (14.0%)	94 (29.9%)	109 (34.7%)
Total	314 (100.0%)	314 (100.0%)	314 (100.0%)

Figure 1. Homes (red) of severe malaria cases presenting to Jinja Children's Hospital (green).

Figure 2. Markov state diagram representing the seven states used in the model and all possible transitions between states. Fever onset was the starting state for all cases, and hospital, representing specifically Jinja Children's Hospital where the cases were recruited from, was the absorbing state which all cases ended in.



Appendices

Appendix 1: Handling of missing data

Missing participants

Out of the 325 cases interviewed in the parent study, 314 were used in this analysis. The 11 observations (3.4% of data) that were dropped had times given that were out of order with respect to the step number that was reported for each action taken. This could be due to recall error from the caregiver, or transcription error from the interviewer. These participants are hypothesized to be missing at random, and also make up a small proportion of the data, and thus dropping them is not expected to have any large effect on the results of the analysis.

Missing time

Once the data was reshaped from long (each row representing a participant) to wide (each row representing an observation, or step, taken by participants), missing observations were examined. Of the 1,781 observations in the data set, 306 (17%) were missing times that a specific action occurred. Of these 306, 15 were also missing the action taken at that time point and thus not included in the Markov analysis. Of the 291 remaining actions with no time, or 231 or 79.4% of them were either staying home (n = 159) or staying home to self-medicate (n = 72). Missing times for these actions were reasonable as staying home represents more of a non-action than an action. Thus, assigning a specific time is in principle more difficult and doesn’t make sense in the same way that assigning a time to a concrete action, such as visiting a clinic does.

Although time was missing for these steps, the action data (the fact that they took that action at all, and the actions between which this action was taken) was still relevant and available.

In order to keep these observations in the model, time was imputed linearly for any action taken between actions with known times. For example, if action 1 occurred at time x, action 2 occurred at an unknown time, and action 3 occurred at time y, action 2 was assigned the time (x-y)/2. This was determined the best option due to it's simplicity and the lack of a clear best-practice imputation method for actual exact time data in panel datasets. Because the times of the previous and next action were known, and often not very far apart in terms of hours, this method is hypothesized to give a fairly accurate estimate and to not produce biases results.

Appendix 2: Guide to msm model

Markov modeling is a tool used to describe and quantify processes by which a group of individuals move between various states at various times. This framework can be useful in many medical and public health analyses, as many clinical and public health situations can be described using Markov chains. In clinical decision analysis, it is common to use Markov models to examine a cohort of patients who may transition through various disease states throughout the course of their illness, ultimately leading to recovery or death. However, the method is flexible and intuitive and can be applied to any dataset with a known group of individuals occupying known, mutually exclusive states, with known transition probabilities of moving from one state to another at any given time. In this analysis, the group of individuals was a population of severe malaria cases recruited from Jinja Children's Hospital, the known states were seven possible treatment-seeking actions in the path from child fever onset to hospital enrollment at the recruitment site. The times in each state were the times at which a caregiver reported taking a certain action.

While this method is flexible and has simple data requirements, Markov modeling rests on two important assumptions that should be taken into consideration before choosing this method for an analysis. The first is that the transition to each state and the probability of moving to any state depends only on the previous state, and not on any steps that occurred before that point. This is called the Markov assumption. The second important assumption is that the transition probabilities between states remain constant over time. For example, someone who moves from state 2 to state 3 as their first step has the exact same probability of moving from state 2 to state 3 as someone who moves from state 2 to state 3 much later in time. This is called the time-homogeneity assumption. In the case of the severe malaria caregiver analysis, these assumptions likely do not hold perfectly in reality. Initial actions that someone takes while seeking care may in fact have an effect later down the road and not just the subsequent step, and transition probabilities probability vary based on how long a caregiver has been seeking treating for their child (if it is their first step versus tenth step, for example). However, as long as we keep these assumptions in mind as a limitation and simplification of the behaviors observed in the dataset, the Markov model can still provide a plethora of interesting and relevant results.

The *msm* package for R allows for Markov analysis of longitudinal data sets. It requires minimal input and apart from a single log-likelihood summary measure (not used in this analysis), can provide valuable output via extractor functions, which are detailed later in this appendix. The inputs required are simple; *msm* just needs a long-form panel dataset, where each row represents an observation. For each observation, three variables are required: the participant identification number (if there are different participants, if not indicated, *msm* assumes all data is from the same participant), the time of the observation, and the state the participant is in during that observation. Additional covariates may be added but are not necessary. Covariates were not examined in this thesis so are not discussed in this appendix. For example, the Markov model in this analysis made use of three variables: *studyid* (participant identification), *action* (state), and *days* (time). The final input that *msm* needs for a simple Markov model is an initial transition intensity matrix. This represents the instantaneous risk of moving from any given state to any other given state. If this information is based on a real dataset and not available from another model, it can be estimated from observed transitions in the dataset. In the case of the severe malaria analysis, this input was a 7 x 7 matrix (due to there being 7 states in this model), with each transition intensity being roughly estimated by the proportion of individuals observed moving directly from one state to the next state (see Figure 1). The starting state (state 1, fever) was designated by setting the first column as entirely 0- indicating the risk of moving from any state *to* state 1 is 0 (i.e., these transitions are not allowed). The absorbing state (state 7, hospital) was designated by setting the last row as entirely 0- indicating that the risk of moving *from* state 7 to any other state if 0.

$$\begin{pmatrix} 0 & 0.17 & 0.46 & 0.10 & 0.22 & 0.03 & 0.01 \\ 0 & 0.34 & 0.14 & 0.13 & 0.06 & 0.10 & 0.19 \\ 0 & 0.10 & 0.36 & 0.13 & 0.06 & 0.11 & 0.24 \\ 0 & 0.11 & 0.14 & 0.21 & 0.01 & 0.09 & 0.44 \\ 0 & 0.13 & 0.43 & 0.05 & 0.12 & 0.07 & 0.20 \\ 0 & 0.07 & 0.07 & 0.09 & 0.00 & 0.10 & 0.67 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Fig 1. Initial transition intensity matrix for the malaria case analysis. Transition probabilities were determined by the proportion of cases observed to move directly from each state to the next state at any time point.

Once the data has been cleaned and put into long-form format with the correct variables specified, the *msm* model can be created, using the following code with the malaria case analysis as an example:

```
install.packages(“msm”)
library(msm)

businessasusual <- read.csv(‘/location/datafile.csv’)

Q1 <- rbind( c(0, 0.1714, 0.4603, 0.1016, 0.2190, 0.0349, 0.0127),
   c(0, 0.3443, 0.1415, 0.1321, 0.0849, 0.1038, 0.1934),
   c(0, 0.0983, 0.3563, 0.1302, 0.0590, 0.1130, 0.2432),
   c(0, 0.1105, 0.1395, 0.2093, 0.0116, 0.0930, 0.4360),
   c(0, 0.1318, 0.4264, 0.0543, 0.1163, 0.0698, 0.2016),
   c(0, 0.0686, 0.0686, 0.0882, 0.0049, 0.1029, 0.6667),
            c(0, 0, 0, 0, 0, 0, 0) )

businessasusual.msm <- msm(action ~ days, subject = studyid, data
= businessasusual, qmatrix = Q1, exacttimes = TRUE)
```

Note that the *msm* function has a variety of options, the function of which is detailed in the *msm* manual. In the case of this initial, only the *exacttimes* option was specified, as in this dataset exact times of the transitions from one state to another were available.

Once the model is created as object, it can be called using a number of extractor functions, which can provide a variety of relevant information. Although there are many functions available in *msm,* the following information was extracted from msm and used in the severe malaria case analysis:

1. Transition intensity matrix. Called in R by the function qmatrix.msm(x). The transition intensity matrix call gives the instantaneous risks of moving from any given state to the next state, and their 95% confidence intervals. For example, in the malaria case analysis, with seven different states, gives a 7 x 7 matrix. This is not the most intuitive output, but can be useful as an input for microsimulations. The transition intensity matrix from the 'business-as-usual' model is shown below (Figure 2).

$$\begin{pmatrix}
-6.91\ (-7.72,\ -6.18) & 1.18\ (0.90,\ 1.55) & 3.17\ (2.69,\ 3.73) & 0.71\ (0.50,\ 1.01) & 1.54\ (1.21,\ 1.95) & 0.27\ (0.16,\ 0.47) & 0.04\ (0.01,\ 0.18) \\
0 & -0.78\ (-0.92,\ -0.66) & 0.17\ (0.12,\ 0.24) & 0.16\ (0.11,\ 0.23) & 0.10\ (0.06,\ 0.16) & 0.17\ (0.12,\ 0.47) & 0.18\ (0.13,\ 0.26) \\
0 & 0.11\ (0.08,\ 0.14) & -0.69\ (-0.78,\ -0.61) & 0.15\ (0.11,\ 0.19) & 0.06\ (0.04,\ 0.09) & 0.18\ (0.14,\ 0.23) & 0.20\ (0.16,\ 0.25) \\
0 & 0.19\ (0.12,\ 0.30) & 0.24\ (0.16,\ 0.36) & -1.29\ (-1.53,\ -1.09) & 0.02\ (0.01,\ 0.08) & 0.32\ (0.22,\ 0.45) & 0.53\ (0.40,\ 0.69) \\
0 & 0.16\ (0.10,\ 0.25) & 0.50\ (0.38,\ 0.65) & 0.06\ (0.03,\ 0.14) & -1.04\ (-1.25,\ -0.86) & 0.16\ (0.10,\ 0.25) & 0.16\ (0.10,\ 0.25) \\
0 & 0.16\ (0.10,\ 0.28) & 0.15\ (0.09,\ 0.26) & 0.21\ (0.13,\ 0.34) & 0.01\ (0.00,\ 0.08) & -1.77\ (-2.08,\ -1.51) & 1.23\ (1.02,\ 1.49) \\
0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}$$

Fig 2. Transition intensity matrix as outputted from the msm extractor function qmatrix.

2. Sojourn times. Called in R by the function sojourn.msm(x). The sojourn times represent the mean time spent in each state during a single visit to that state. For each state *r*, this is calculated as $-1/q_{rr}$, where q_{rr} is the *r*th diagonal entry of the transition intensity matrix (see Fig 2). Sojourn times from this analysis are presented in table 2.

3. Probability that each state is next. Called in R by the function pnext.msm(x). Which presents the probabilities that each state is next given the state of the individual in current observation. This is a more intuitive than the transition intensity matrix. Each entry represents the probability of going to state *s* from state *r*, given that the current state is *r* and the next state is *s*. This is calculated as $–q_{rs}/q_{rr}$ where q_{rs} is the *s*th column

of the rth row of the transition intensity matrix, and q_{rr} is the rth diagonal entry of the transition intensity matrix

Simulations

The *msm* package for R contains a number of microsimulation functions. For this analysis, simmulti.msm was used to generate alternate datasets simulating the effects of hypothetical policy changes, input into the simulation as ‘rules’ via the transition intensity matrix.

The severe malaria case analysis simulated two counterfactual scenarios. The first eliminated drug shops as a possible option; individuals would go about their normal behavior except they were no longer ‘allowed’ to visit drug shops. Mathematically, this took the form of a change in the transition intensity matrix. The original transition intensity matrix, collected as output from the ‘business-as-usual’ model, was used except every entry involving state 5 (drug shops) i.e. row 5 and column 5, was set to zero, meaning that the simulation was being told the instantaneous risk of both going to drug shops and leaving drug shops was 0 (see Fig 3).

$$\begin{pmatrix} -6.91 & 1.18 & 3.17 & 0.71 & 0 & 0.27 & 0.04 \\ 0 & -0.78 & 0.17 & 0.16 & 0 & 0.17 & 0.18 \\ 0 & 0.11 & -0.69 & 0.15 & 0 & 0.18 & 0.20 \\ 0 & 0.19 & 0.24 & -1.29 & 0 & 0.32 & 0.53 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0.16 & 0.15 & 0.21 & 0 & -1.77 & 1.23 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Fig 3. Transition intensity matrix as input into the simulation function simmulti.msm. This matrix is identical to that in figure 3, but with row 5 and column 5 replaced with zero. This represents an alternate hypothetical reality in which individuals are no longer permitted to visit drug shops, but everything else is assumed to be the same.

A data frame with panel data for 314 individuals at 240 time points (allowing each individual enough time to eventually make it to an observed absorbing state, the hospital), was created to input alongside the new transition intensity matrix in the simulation. With this data frame and this matrix, along with a command specifying the presence of an absorbing state (death = TRUE), a new simulated dataset was created. Example code is below.

```
rm()
library(msm)

Q2 <- rbind( c(-6.91109, 1.18151, 3.16593, 0.71336, 0, 0.26750,
 0.04557),
    c(0, -0.77845, 0.16798, 0.15681, 0, 0.16798, 0.18476),
    c(0, 0.10602, -0.69180, 0.14578, 0, 0.18288, 0.19614),
    c(0, 0.18873, 0.23851, -1.29177, 0, 0.31795, 0.52664),
    c(0, 0, 0, 0, 0, 0, 0),
    c(0, 0.16442, 0.15260, 0.21138, 0, -1.77310, 1.23296),
    c(0, 0, 0, 0, 0, 0, 0) )

simpanel.df <- data.frame(subject = rep(1:314, rep(241, 314)),
 time = rep(seq(0, 240, 1), 314))

simmulti <- simmulti.msm(simpanel.df, Q2, death = TRUE)

library(foreign)
write.dta(simmulti, "location/simulated.dta")
```

Once this new dataset was exported as a .dta file, time was examined using STATA 14; a delay variable was created indicating whether the last observation (hospital) occurred > 24 hours after the first (fever onset), and then the proportion of cases experiencing delay was simply tabulated using a frequency table.

The second counterfactual, in which participants who visited drug shops and were assumed to receive proper antimalarial treatment and fully recover after that point, was created using STATA 14 and did not require the *msm* package, although it could have alternatively been performed in *msm.* In this case, all observations after a participant visited a drug shop were simply dropped, and the time of last observation for each participant was *either* a hospital visit or a drug shop visit. Again, the proportion of cases experiencing delay was tabulated using a frequency table.

Note: All information about *msm* written here comes directly from this analysis and the *msm* manual by the package's author, Christopher Jackson. The functions and options described in this appendix are limited to those that were used in this analysis. More functions, options and greater detail about each of these as well as the background behind *msm* can be found in the *msm* manual (25).

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