ADAPTIVE INTERVENTIONS FOR GLOBAL HEALTH: A CASE STUDY OF MALARIA

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ABSTRACT

Malaria can be prevented, diagnosed, and treated; however, every year, there are more than 200 million cases and 200.000 preventable deaths. Malaria remains a pressing public health concern in low- and middle-income countries, especially in sub-Saharan Africa. We describe how by means of mobile health applications, machine-learning-based adaptive interventions can strengthen malaria surveillance and treatment adherence, increase testing, measure provider skills and quality of care, improve public health by supporting front-line workers and patients (e.g., by capacity building and encouraging behavioral changes, like using bed nets), reduce test stockouts in pharmacies and clinics and informing public health for policy intervention.

1 INTRODUCTION

Not everyone benefits equally from the same treatment, has the same environment, or can receive therapy at the same time. Adaptive interventions consider human differences as treatment begins and during its course to ensure each person gets the treatment that continuously works for them. Interventions are adaptive in that they adapt to the individual (providing personalization) and their evolving context and needs (i.e., adjusting dynamically).

Both clinical and patient actions are essential to high-quality, low-cost, effective healthcare. Human behavior constitutes the primary mode for activating health improvements, including decisions made by clinicians and their patients. In medical practice, clinicians can be gently nudged to improve decision-making by providing a decision architecture in which optimal default clinical actions are suggested. Outside controlled clinical environments (e.g., intensive care units), patient actions (e.g., lifestyle choices and treatment adherence) primarily determine health outcomes. Mobile health is key to promoting continuous and proactive healthcare monitoring. It can, for example, mitigate the lack of medication adherence, which can be low and challenging to address, as patient actions control healthcare delivery outside medical environments.

The data generated by the users of digital applications are instrumental in determining past and current behaviors and predicting future conduct. This information can be used to deliver personalized mobile-mediated interventions. Such interventions aim to provide the appropriate type or degree of support by adapting to an individual's changing internal and contextual states (Nahum-Shani et al., 2018; Menictas et al., 2019; Carpenter et al., 2020; Bidargaddi.N amd Schrader et al., 2020; Coppersmith et al., 2021).

Mobile health applications also serve as a direct channel of communication with their users, from front-line healthcare workers to patients and the general public. Interventions and incentives can be delivered directly to the users through their phones. Machine learning (ML) can help generate predictions regarding the behavior of app users, health outcomes, and their contexts. These predictions can be integrated with real-time information pertaining to the users' choices and circumstances to determine the individuals or groups needing additional support. Moreover, these predictions can be used to personalize the timing of the interventions delivered to each user. Similarly, reliable predictions regarding the evolution or variations in the demand for different medical supplies can help establish reminder and suggestion systems that can help ensure that all the supply chain actors (e.g., pharmacists) maintain adequate stocks of essential supplies at all times. Motivational prompts, personalized reminders, incentives, engaging elements (such as game-designed elements), and other nudges can be used to boost and reinforce good practices (Hrnjic & Tomczak, 2019).

Adaptive interventions in healthcare have primarily been deployed in resource-rich countries (Nahum-Shani et al., 2018; Hardeman et al., 2019). Given the immense disease burdens borne by low- and middle-income countries and the increasing smartphone penetration in these regions, the use of adaptive interventions to improve health outcomes may be highly beneficial to global health. In this research, we explore this potential based on a case study of malaria. A discussion of the ML methods can be found in the appendix A.

2 Malaria: A Case Study

Malaria, caused by the parasite *Plasmodium falciparum*, remains a deadly illness across much of the Global South.

Malaria in pregnancy and infancy is a major public health concern and a key driver of maternal and newborn mortality (Tarning, 2016). In 2020, nearly 630,000 deaths worldwide were caused by malaria, a disproportionate share of which (96%) occurred in Africa (Organization, 2022). In Sub-Saharan Africa, malaria is responsible for 12% of all child fatalities (Roser & Ritchie, 2019), and children under five account for approximately 80% of all malaria deaths (Organization, 2022).

Although global malaria incidence and mortality have substantially decreased in the recent two decades, progress stalled since 2015 (Noor & Alonso, 2022), and researchers worry that the COVID-19 pandemic has disrupted malaria intervention coverage, reversing these gains (Weiss et al., 2021).

2.1 Surveillance: Progress Towards Elimination

Even with the World Health Organization's (WHO) historic approval of a malaria vaccine (Li et al., 2022), senior leaders caution that a broader approach will be needed for malaria eradication, including improved collection and usage of high-quality data—from health-management information systems and electronic databases to geospatial models (Alonso, 2021)—and flexible evaluation and implementation of interventions by local decision-makers (Alonso & O'Brien, 2022). According to a global landscape review, malaria surveillance systems in 2015—2016 were "insufficient to support the planning and implementing of targeted interventions and measure progress toward malaria elimination" (Lourenço et al., 2019). Such elimination efforts require the accurate notification of individual cases within 24 h of diagnosis to provide timely and targeted responses, which essentially represent adaptive interventions (WHO, 2015).

Notably, such malaria surveillance frameworks must be integrated, data-driven, tailored, and based on mobile platforms. Mobile health for malaria surveillance, that uses a combination of message- and application-based reporting, can support health workers and clinicians in recording malaria case information (Githinji et al., 2014; Baliga et al., 2019; RTI, 2020; Oo et al., 2021; Bhowmick et al., 2021), decreasing delays in case reporting to health officials, and improving the quality of data collection. Data fragmentation remains a barrier to a cohesive malaria response, and previously siloed data from diverse sources (private/public healthcare providers, government agencies, etc.) must be integrated to create a real-time, case-based malaria surveillance system (Rahi & Sharma, 2020). Automation is essential, as analytics related to threat monitoring, requirement identification, and system performance must be readily available for decision-makers (Ohrt et al., 2015).

A comprehensive malaria surveillance system can inform policy interventions, e.g., the allocation of mosquito nets, tests, and antimalarials can be targeted to favor individuals and communities in need. By understanding the changes in people's mobility and clustering, the impact of non-pharmaceutical interventions can be evaluated, and geographic areas in which additional actions may be helpful can be identified (Grantz et al., 2020). Several studies revealed that the characterization of travel patterns through geolocation data and their combination with contextual information on malaria incidence can inform strategies to target travelers and reduce transmission (Milusheva, 2020).

2.2 Prevention

For pregnant women visiting institutions for antenatal care, the WHO recommends the administration of intermittent preventive treatment with sulfadoxine–pyrimethamine and distribution of long-lasting insecticide-treated mosquito nets (LLINs) (Salomão et al., 2017).

Unfortunately, many pregnant women in low- and middle-income countries do not receive either intervention owing to stock-outs in data-fragmented health systems (Salomão et al., 2017). Accurate demand forecasts that can integrate real-time contextual information are needed to ensure equitable and efficient allocation of important preventive goods. For example, by building geospatial models and combining data from net manufacturers, national programs, and cross-sectional household surveys, researchers can develop detailed maps of LLIN access and usage (Bertozzi-Villa et al., 2021). These analyses can also be automated to identify geographic areas in which additional supplies or different actions may be required.

Patient behavior also determines the efficacy of the interventions, as many pregnant women fail to take their pills (Mubyazi et al., 2005) or do not use bed nets for various practical reasons (Manu et al., 2017; Gultie et al., 2020). These aspects highlight the importance of communication to encourage behavioral changes (Ricotta et al., 2014).

For children aged 3—59 months, WHO recommends seasonal malaria chemoprevention (SMC) during the months of peak malaria transmission. Although SMC effectively controls malaria and reduces hospitalizations (Diawara et al., 2017; Baba et al., 2020; Issiaka et al., 2020; Cairns et al., 2021), clinical data and pharmacokinetic analyses reveal that complete adherence to treatment is observed in fewer than 20% of children outside the study setting (Ding et al., 2020). Targeted interventions for behavioral changes are required to improve the real-world effectiveness of SMC.

Caregiver-targeted message-based interventions to increase preventive health behaviors (such as sleeping under a net) have been noted to be successful in decreasing the malaria prevalence in children under the age of five (Mohammed et al., 2019). Despite the vast potential of mobile health solutions, one-size-fits-all interventions are typically implemented in which a standard message is sent to all participants. There exists an enormous opportunity for the delivery of personalized interventions that can appropriately incentivize a given user and guide targeted public health campaigns, which may include gamification and leveraging of individual social networks (Ernst et al., 2017). As a potential example, researchers recently tested an ML model in conjunction with an accelerometer-based approach for measuring a range of LLIN use behaviors: Although these technologies represent a proof of concept at present, they can support the implementation of financial incentives based on granular LLIN-use monitoring over longer time periods (Koudou et al., 2022).

The only way to understand which interventions work best and which incentives drive behavioral change is by running experiments on the ground (Banerjee et al., 2010; Bates et al., 2012; Zhou et al., 2020a; 2021).

2.3 Quality of Care

2.3.1 Diagnosis

Malaria is one of the most under-diagnosed and over-treated diseases. The potential for severe outcomes means that any patient with a fever (especially a child) may be administered treatment for malaria, often without having received a diagnostic test (Amankwa et al., 2019; Ajibaye et al., 2019; Boadu et al., 2016; Beisel et al., 2016). The administration of drugs without a conclusive test may accelerate antimalarial resistance, an increasingly worrying problem according to WHO malaria experts (Rasmussen et al., 2022).

Although microscopy is the gold-standard for malaria diagnosis, its implementation remains infeasible in many resource-constrained settings (Beisel et al., 2016). Consequently, many stakeholders have turned to rapid diagnostic tests (RDTs). However, their access remains limited, with frequent stock-outs (Boadu et al., 2016; Blanas et al., 2013) that may be related to inaccurate record-keeping.

Digital tools and demand forecasting algorithms can alleviate this problem, as has been proved in India with an app that included a supply chain management component (Rajvanshi et al., 2021).

Furthermore, many lay community health workers struggle to appropriately perform RDTs (Boadu et al., 2016; Blanas et al., 2013; Beisel et al., 2016), and thus, capacity-building efforts to increase their skills are urgently required. Digital monitoring of the health workers' performance can serve as an effective quality control strategy and a mode of delivering feedback (Laktabai et al., 2018). Personalized digital nudges can direct the health workers who need additional support to specific online learning resources or encourage them to sign up for an in-person training session.

Patient-facing steering may also be required, as sick patients who receive a negative test may still expect treatment. Patient and provider education around antimicrobial resistance may help, in addition to increasing awareness and clinical decision support for the management of other febrile illnesses.

2.3.2 Artemisinin Combination Therapy (ACT)

ACT is the first-line malaria treatment throughout most of the malaria-endemic world. Notable issues include stock-outs (Blanas et al., 2013; Rowe et al., 2009; O'Connell et al., 2011) and the distribution of low-quality antimalarials, especially in urban areas Newton et al. (2017). Most antimalarials are distributed through the private sector, where non-artemisinin therapies are prevalent and 5–24 times less expensive than quality-assured ACT (O'Connell et al., 2011). In this context, it is important to strengthen the supply chain with a data-driven approach, potentially by using demand forecasting algorithms to send appropriately timed reminders to pharmacists to ensure that they restock necessary supplies.

The quality of care and clinical management of malaria remains widely varying and substandard. In Sub-Saharan Africa, less than one-third of the children diagnosed with malaria receive both a blood test diagnosis and appropriate antimalarial treatment (Cohen et al., 2020). Evidence for gaps in the community health workers' and drug dispensers' ability to appropriately manage malaria has been found in several countries (Rowe et al., 2009; Blanas et al., 2013; Chowdhury et al., 2020; Buabeng, 2010; Kamuhabwa & Silumbe, 2013). Capacity-building efforts are clearly necessary, and adaptive interventions can facilitate the assignment of appropriate content to each worker (Katsaris et al., 2021). AI-based user segmentation and behavioral phenotyping can yield highly granular cohorts to be focused on. For example, we research the capacity development of midwives by predicting their demand for specific contents (Guitart et al., 2021a) and building recommendation systems for an e-learning app by predicting the chance that a given user clicks on a certain item (Guitart et al., 2021b).

Lastly, patient adherence to antimalarial regimes is a notable issue, with estimates suggesting that it ranges from 40% to 65% (Amponsah et al., 2015; Mace et al., 2011; Onyango et al., 2012). Trials of message-based-reminders to healthcare workers (Zurovac et al., 2011; Kaunda-Khangamwa et al., 2018) and patients (Macías Saint-Gerons et al., 2022) have shown promise while highlighting the necessity of personalized interventions involving relevant and actionable messages (Buabeng, 2010). In the case of tuberculosis, where adherence is also a problem, researchers have noted that an ML-driven approach to predict TB adherence risk in conjunction with adaptive interventions dynamically increases the odds ratio of next-day treatment adherence verification by 35% (Boutilier et al., 2021).

2.3.3 Pre-Referral Treatment

Another crucial area where malaria care delivery can be strengthened is pre-referral treatment, usually rectal artesunate (RAS), recommended by WHO for young children with suspected severe malaria when injections are not available (WHO, 2022). Although the effectiveness of RAS has been demonstrated in placebo-controlled trials (Gomes et al., 2009), more recent studies have indicated that its introduction in real-world conditions may increase the malaria case-fatality rates (WHO, 2022). This phenomenon is attributable to several reasons, such as low patient adherence to referral guidelines (Simba et al., 2010) and inadequate ability of health workers to deliver pre-referral care (Amboko et al., 2022) appropriately. Patient- and provider-facing steering and capacity building are needed to strengthen health systems and ensure that guidelines are followed.

3 CONCLUSIONS

Combating the devastating toll of malaria requires multifaceted and innovative strategies. Technology alone is not a panacea, and no simple solution exists. However, ensuring high-quality data collection from diverse sources, such as mobile phones, supply chains, public surveys, and electronic health records, can play a crucial step. These data can be integrated to obtain intrinsic and contextual information that can drive personalized and adaptive interventions.

The use cases are vast: Reminding antenatal care clinics to stock up on LLINs; providing capacity-building resources to struggling community health workers; supporting a district health officer in responding to a new malaria outbreak; incentivizing pharmacists to administer diagnostic tests before prescribing treatments; or encouraging patients to adhere to a treatment regime.

ACKNOWLEDGMENTS

This work was supported, in whole or in part, by the Bill & Melinda Gates Foundation INV-022480. Under the grant conditions of the Foundation, a Creative Commons Attribution 4.0 Generic License has been assigned to the Author Accepted Manuscript version that might arise from this submission.

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A Appendix: Tools and Methods

This appendix describes the proposed conceptual and methodological framework: a data-centric behavioral ML platform (Tang et al., 2021) that leverages logs from different types of mobile health solutions—together with contextual information—to deliver adaptive interventions to healthcare workers and their patients directly through their phones.

A.1 Data-Centric Platform

Our platform is data-centric in that data tracking, and labeling lies at its core. Integration with the different apps is achieved through our *Software Developer Kit* (HealthKit SDK), which provides specifications on what information should be logged (and how) and the messaging service that delivers the interventions. Integration through this SDK ensures that various user metrics and traits characterizing engagement and behavior are readily available, which can help clarify the individuals to be targeted by specific interventions and the time for delivering the interventions.

A.2 Machine Learning

The application of data science and ML methodologies to extract and predict valuable information to inform intervention design lies at the core of the software we build. As is generally the case, no single model is best across all datasets and use cases. Use-case-specific data pipelines transform incoming information through the HealthKit SDK into metrics ready to be consumed by the statistical and ML models, which in turn produce additional metrics that can be used in the intervention definition.

A.2.1 Reinforcement Learning

Reinforcement learning (RL) is the ideal paradigm for sequential decision-making in dynamically evolving contexts that respond to those decisions. It allows us to continually improve how we make choices for a patient at any given moment, maximizing the potential for positive outcomes while minimizing undesired side effects. A competition on policy learning for malaria control using RL was for example included as part of the KDD Cup Challenge 2019 (Zhou et al., 2020b; Nguyen et al., 2019; Zou, 2021).

Contextual are a formulation of the RL problem with limited state representation, and dynamics (Burtini et al., 2015; Yao et al., 2021; Dwivedi et al., 2022; Zhang et al., 2022). Similarly, restless bandits can be used for resource allocation (Mate et al., 2022). They are significantly less data-intensive than other RL approaches while being robust and tractable. This framework is instrumental in the context of adaptive intervention delivery. At their core lies the exploration-exploitation trade-off, i.e., the compromise between clinical research (to gather knowledge about treatments) and clinical practice (to benefit the patients) by assigning the best intervention possible based on all available information at that point.

A.2.2 Time-varying and Dynamic Prediction Modeling

Time series datasets such as clinical records represent valuable sources of information sometimes spanning a patient's entire lifetime of care. The approach to decision-making described in this paper is dynamic (i.e., sequential and adaptive). The analytic and predictive modeling to support this needs to be similarly dynamic, with the time-dependent evolution of the systems of interest and their characteristics at its core. Supervised and unsupervised ML with time-varying data (such as the survival analysis described in the next section), time series modeling, and longitudinal data processing should be part of the toolbox. We can use them to understand and predict how the systems of interest behave and evolve to inform our decision-making.

For behavioral nudging, besides the individual predictions generated using survival analysis described below, multivariate time series forecasting can be critical to optimizing specific interventions, such as reminders to prevent stockouts of medical supplies based on demand prediction. Furthermore, considering the time-varying nature of data and interventions within an RL framework allows us to understand and optimize a patient's treatment as different sequential interventions in time instead of as a single-point decision.

Predictive modeling can help define the target individuals for the intervention and appropriate delivery time. As discussed, accurate demand prediction is key to optimizing the supply chain and inventory. Forecasting methods that can learn simultaneously from multiple time series, often combining deep and state space modeling elements, have been noted to be effective (Seeger et al., 2017; Salinas et al., 2019; Lim et al., 2019; Salinas et al., 2020; Benidis et al., 2020).

A.2.3 Deep and Ensemble Survival Analysis

With time dependence at its core, survival analysis refers to a collection of algorithms used to predict time to an event of interest (which was traditionally death or organ failure) (Wright et al., 2017; Fu & Simonoff, 2016; Lee et al., 2020). These methodologies can be used to predict behavior and health outcomes at the individual level, as they are well suited to extract information from censored data (i.e., models that can learn from subjects who have yet to experience the event of interest besides those that have). Their output is a survival curve for each subject, indicating the probability of not having experienced the event of interest depending on the time. By carefully selecting the events we predict and how we measure time, we can profile individuals using multiple predictions and risk scores (of clinical complications or of lack of adherence to treatment, for example).

A.2.4 Recommendation Systems

Recommendation algorithms can be used to decide the techniques to target health workers, patients, and the general public. Different methodologies are expected to be suitable for different apps and use cases, from deep learning-based click-through-rate predictions (Qu et al., 2016; Guo et al., 2017; Lian et al., 2018; Lu et al., 2020; Guitart et al., 2021b) to collaborative, interactive recommendation systems Ie et al. (2019); Liu et al. (2019); Lillicrap et al. (2019); Chen et al. (2020). We foresee a growing shift toward reinforcement-learning-based methods beyond the (relatively widespread) use of contextual bandits (Barraza-Urbina & Glowacka, 2020). This approach is particularly useful for optimizing a *sequence of interventions* while reconciling short- and long-term goals in the desired outcome.