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April 20, 2017
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Gooey Predictions: Utilizing a Graphical User Interface (GUI) to Increase Access to a Complex Predictive Statistics Model for Neglected Tropical Disease Management in Cameroon and Loiasis Endemic Regions

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Abstract

Gooey Predictions: Utilizing a Graphical User Interface (GUI) to Increase Access to a Complex Predictive Statistics Model for Neglected Tropical Disease Management in Cameroon and Loiasis Endemic Regions

By Mark (Marcel) W. Foster

The World Health Organization (WHO) treated at least 350 million persons with antiparasitic medicines globally, in an effort to control and eliminate onchocerciasis (oncho), lymphatic filariasis (LF), and other Neglected Tropical Diseases (NTDs). Unintended side effects, however, occurred for people in regions endemic with loiasis, with thousands of Serious Adverse Events (SAEs) that occurred solely as a result of the WHO's strategy, and 85% reported in Cameroon. To mitigate these undesired consequences, Schlüter, et al. (2016) developed a probability model to gauge a village's average intensity of loiasis by calculating the population's average microfilariae count within a milliliter of blood (mf/ml), and generating a recommendation output whether or not to administer antiparasitics. This project aims to reduce SAEs by making this statistical tool more accessible through a graphical user interface (GUI) and aid global policymakers in their decisions about dispersing the antiparasitic tablet, ivermectin. Data were collected in September 2016 in Cameroon and captured demographic information, as well as test results for oncho and LF prevalence, loiasis mf/ml intensity, and the Schlüter, et al., (2016) probabilities. 2,700 persons were tested within 27 villages. 93% of the villages were found to have loiasis with a mean of 4,009 mf/ml, as well as an 89% prevalence on oncho, and a 30% prevalence of LF. Approximately half of these villages, according the Schlüter, et al. (2016) test, were found to have too high of a loiasis intensity to merit mass treatment of ivermectin. These findings were then programmed into a GUI that depended on the RStudio Shiny application, which provides source code to make statistical tools accessible as a user interface. This application generated a successful GUI that allows anyone with a Microsoft Excel file (CSV) to upload a spreadsheet, and instantly view the statistical model's prediction with a useful graphic ('Thumbs up' for treating the village with ivermectin sans pre-testing; 'Thumbs Down' for not treating). With this innovation, steps towards approximating loiasis in Cameroon, and other African counties, can be made more accessible to a wider array of global health stakeholders.

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CHAPTER 1. INTRODUCTION

There is a need to create a user-friendly electronic tool to test the intensity of the parasitic disease loiasis at a community/village level so that public health policymakers, throughout the West Central African region, can minimize the potential of fatal side-effects among populations treated with medicines for other filarial diseases (e.g., lymphatic filariasis and onchocerciasis). This thesis outlines the history, etiology, and treatments related to loiasis, lymphatic filaraisis (LF), and onchocerciasis (oncho); and how the World Health Organization's (WHO) Mass Drug Administration (MDA) strategies of medicinal dissemination, sans pre-testing, unintentionally led to thousands (Boussinesq, et al., 2003) of life-threatening Serious Adverse Events (SAEs) for persons treated for LF/oncho, and unknowingly co-infected with loiasis. Additionally, a review of electronic tools in the context of global health interventions contextualizes the thesis' aim to develop a prototype that will increase access to a new biostatistics model that could aid in the effort to reduce serious adverse side effects for the control and elimination of these filarial infections.

CHAPTER 2. LITERATURE REVIEW

Literature Review Part I: NTD Elimination and Loiasis

LOIASIS

Loiasis (loa) was first documented in 1707 (Kean, et al., 1978) and was assumed to be a relatively innocuous filarial disease, with the exception of "calabar swelling," or irritation and swelling below the skin as well as its visible appearance in the outer surface of the eye (reviewed in Pion and Chesnais, 2016). The filarial parasite, *Loa,* is transmitted through forest-dwelling deer flies, primarily *Chrysops dimidiata* and *C. silacea* (Duke, et al., 1955), and is found in West Central Africa (Padgett & Jacobsen, 2008; Boussinesq & Gardon, 1997). Virtually 200 years later, in the 1990s, loa gained increased attention as a result of Serious Adverse Events (SAE) in response to treatment intended to prevent two major helminth parasitic diseases: onchocerciasis or lymphatic filariasis (Keating, et al., 2014; Bockarie, et al., 2009; Boussinesq, et al., 1998). An SAE is defined as a life-threatening side-effect, which in the context of LF/oncho and loiasis, resulted in life-threatening experiences encephalopathy, comas, seizures, and fatalities (Twum-Danso, 2003).

NEGLECTED TROPICAL DISEASES AND GLOBAL MANAGEMENT

Oncho, caused by the nematode *Onchocerca volvus* and spread through the hemotophagic black flies (*Simulium*), reportedly infects nearly 37 million people across 34 countries, 27 of which are in Africa (Basanez, et al., 2008), with estimations of 1.5 million related deaths annually (Remme, et al., 2006). LF, a disease caused by one of three round worms (*Wucheria bancrofti, Brugia malayi*, and *B. timori*) and transmitted through mosquitoes (*Culex, Anopheles, Mansonia*, and *Aedes* genera*)*, represents one of the highest global burdens among vector-borne diseases with 120 million infections worldwide across 83 countries. This ranks the disease as the second-most leading cause of lifelong disability across the globe (Taylor, et al., 2010).

LF and oncho are designated as Neglected Tropical Diseases (NTDs), which the WHO (2012) defined as seventeen diverse communicable diseases that impact over a billion people globally, with common assumptions that there is concentration in poor populations within equatorial regions (Houweling, et al., 2016). The WHO's definition is one of several, and it should be noted that the Public Library of Science (PLOS) include 27 diseases in its outline of NTDs (PLOS, 2017). Additionally, Médecins Sans Frontières (MSF) emphasized four as "the most neglected" (MSF, 2010). The institutional designation of NTDs is important since it has historically aided in prioritizing an epidemic as a major barrier to socioeconomic development

within an affected region (Molyneux & Malecela, 2011). Such a classification of a disease often brings increased access to pharmaceutical donations, as well as integrated approaches of control and elimination efforts (Allen & Parker, 2011; Baker, et al., 2010). As part of this ongoing work, innumerable stakeholders sustain a global web of Mass Drug Administration (MDA), or a coordinated system that disperses donated treatments to everyone in an endemic area, with no screening procedures performed before ingestion (reviewed in Hotez & Kamath, 2009). The medications, often referred to as Preventive Chemotherapies (PCs), reportedly resulted in mild side effects very rarely among patients across all ages (reviewed in Smits, 2009). MDA began in the 1980s, and has since emerged as an achievement of orchestrated communications across 56 countries, program coordination between hundreds of organizations, and billions of dollars' of gifted PCs from pharmaceutical companies (Hotez, et al., 2007), which treated over 350 million people globally (reviewed in Kamgno, et al., 2008). MDA's hallmark is its ability to treat communities without testing, and therefore, enable enormous financial and programmatic efficiencies (Linehan, et al., 2011; Ottesen, et al., 1990; Rothova, et al., 1989).

UNDESIRED CONSEQUENCES FOR NTD ELIMINATION

Oncho and LF were prioritized by the WHO for global elimination as a public health problem (WHO, 2016; WHO, 2011), and utilized MDA to disperse ivermectin, or diethylcarbamazine citrate (DEC), together with albendazole to treat LF; and ivermectin exclusively for oncho (Taylor, et al., 2010). Unlike the helminths associated with Oncho and LF, which filter through the lymphnodes following a nematocidal dosage—*loa* accumulates around the nervous system, and subsequently, clumps into the major organs and brain post-treatment of DEC or ivermectin (Gardon, et al., 1997). Albendazole demonstrates little to no SAEs among co-endemic patients (Bourguinat, et al., 2010), however, this PC has little to no effect to treat onchocerciasis (reviewed in Bradley, et al., 2005). Following ivermectin/DEC treatments, the *loa* carcasses infarct cerebral capillaries, and/or cause hemorrhages in vital tissues, which very often accelerates mortality (Mackenzie, et al., 2003). SAEs like this were identified to occur most commonly among individuals with at least 30,000 microfilariae per milliliter of blood (mf/ml) (Kouam, et al., 2013). One of the highest measurements recorded was 86,900 mf/ml (Gardon, et al., 1997), or approximately 434.5 million worms in a person's body (reviewed in Lee, 1998).

Studies have also found that there are adverse events that are not life-threatening and typically occur when someone has less than 30,000 mf/ml threshold (Kouam, et al., 2013). These side-effects included problems related to encephalopathy, inflammation, and kidney challenges and documented with intensities as low as 400 mf/ml (Cruel, et al., 1997) after ivermectin and/or DEC was ingested.

SAEs not only destroy lives, but present major ethical challenges that face LF and oncho MDA programs, which continue to receive support by myriad global partners (Keating, et al., 2014; Boussinesq, 2006). After approximately 40 years of succeeding to reduce the spread and impact of both pandemics, elimination goals are predicted as likely to occur by 2020 in areas with no loiasis cases, such as Bangladesh (Shamsuzzaman, et al., 2017) as well as Mali and Senegal (Diawara, et al., 2009). However, charging forward with MDA dispersal in areas with co-endemic loiasis would defy the primary principle of the Hippocratic Oath to "first, do no harm" (Edelstein, 1943).

On top of this, recent evidence indicates that, irrespective of SAEs, loiasis does in fact increase mortality especially among men who are at least 25-years-old who have ≥ 8,000 mf/ml (Chesnais, et al., 2016). These findings echo other calls to the WHO to include loiasis as an additional NTD, so that it can receive increased funding prioritization (Metzger & Mordmüller, 2014). Finally, other research suggests that there is a dearth of financial support for clinical trials of alternative filaricides that could exterminate *O. volvulus* as well as *L. loa* nematodes at the same time without the potential of SAEs (Geary & Mackenzie, 2011).

Spatial Analysis of Loiasis and Onchocerciasis

Since the emergence of ivermectin-related SAEs in the 1990s, numerous studies were conducted that utilized spatial mapping to identify loa endemic regions (reviewed in Zouré, et al., 2011). Below, this thesis reviews the studies of LF/oncho interventions that sought to reduce SAEs by halting medicinal dispersion in areas that were found to contain high prevalence and/or intensities of loiasis.

The first documented method of spatially investigating the loiasis endemic involved drawing blood from research participants, freezing and examining the sample, microscopically identifying the presence of *L. loa* within the samples, and measuring the corresponding leukoconcentration (Touré, et al., 1997; Petithory, et al., 1997). These data were then cross-

referenced with the participants' homes with the satellite images of West Central African regions, and presented as a series of maps indicating the loiasis epidemic (Thomson, et al., 2004; Thomson, et al., 2000). Subsequently WHO took a stance in supporting the less invasive Rapid Assessment Procedure for Loa (RAPLOA), which approximated a community's prevalence of loiasis by counting the number of visible eye worms among individuals per community (Takougang, et al., 2002). This approach was the basis of many studies that located the epidemic (Zouré, et al., 2011; Crainiceanu, et al., 2008; MDP, 2004; TDR, 2002). Two studies validated this approach: the first (Tekle, et al. 2011) collected data from the same populations and two articles (Thomson, et al., 2004; Thomson, et al., 2000) that investigated and identified a number of inaccurate georeferences. Additionally, one study (Wanji, et al., 2012) sampled villages from the same areas as a previous study (Takougang, et al., 2002) and compared the RAPLOA results with parasitological examinations, which smeared and stained blood on a slide so that mf/ml could be counted. The validation (Wanji, et al., 2012) confirmed that using RAPLOA was indeed accurate.

Expanding from these methodologies, Schlüter, et al. (2016) created a model that generates a likelihood on whether or not less than 1% of a village population has a high intensity loa, or nearing 30,000 mf/ml (reviewed in Diggle, et al., 2007; Twum-Danso, 2003). The robust prediction, that incorporates the village's total population (N) as a finite population control,

provides one of the first endeavors to determine PC dispersal while approximating the potential for SAE risk. Ideally, the statistical tool will support the decision-making process for stakeholders who are responsible for LF/oncho and loa control within their regions. As part of this management strategy, this thesis aims to ameliorate policymakers' process of determining which villages can ethically receive MDA, as well as which villages might require "test and treat" procedures before PC dissemination. Should an administrator determine test and treat is required for a village, the usage of the Schlüter's, et al. (2016) model would assist in justifying the surplus funding needed for these methods (Rebollo, 2016).

Thesis proposal

In this thesis, I present new findings collected from Eastern Cameroon, contributing to the ongoing studies of loiasis and SAEs in this country loa (Thomson, et al., 2004; Boussinesq, et al., 2003; Boussinesq, et al., 1998; Boussinesq, et al., 2001; Garcia, et al., 1995; Kouam, et al., 2013;). The investigation analyzes loa intensity measurements from a projected sample of 3,000 individuals across 30 villages within the Garoua-Mboulaï province (Figure 1) and utilizes a probability model (Schlüter, et al., 2016) programmed in R to predict the likelihood of SAEs within each province. R is free, open-source, statistical computing program (reviewed in Braun & Murdoch, 2016). While it is a powerful program, it has also been dubbed as "hard to learn" by the prolific statistical programming author Robert Muenchen

(2014). Ultimately an instrument that is challenging to access is not useful, and therefore, this thesis proposes a Graphical User Interface (GUI) for end users to run and interpret the Schlüter, et al. (2016) model. This thesis' prototype not only draws upon decades of research related to loiasis and NTDs, but additionally, a theoretical framework that contextualizes the GUI as a health intervention.

Literature Review Part II: eHealth History and Implementation

Electronic Health (eHealth) Tools: Implementation & History within Global Health

There are ample accounts of public health interventions that fail to benefit their targeted populations (Haines & Borchert, 2004). One noted reason was associated with the ever-increasing demands of technology and computation, and a scarcity of opportunities to build systems that connect such innovations to the critical stakeholders (Berglund & Danielsson, 2015). As part of bridging this gap, it is essential to not only increase accessibility of an effectual statistical model, but pursue best practices in dispersing and implementing the system. This review discusses the five following topics intrinsic to this goal: (1) examples of

electronic health (eHealth) tools that invented GUIs for health practitioners, (2) definitions of eHealth, (3) conceptualizing eHealth as a formal intervention, (4) paradigms that ground eHealth implementation, and (5) the unique advantages that this tool could contribute to NTD management.

eHealth Examples

As catch phrases describing eHealth tools are ever changing, two concrete examples of GUIs that seek to broaden access to health informatics will clarify further discussion around this topic. Firstly, researchers rely on complex measurements of molecular interactions (Zauhar, 1985) as well as complicated formulae (e.g., Poisson-Boltzmann) for public health monitoring of prion diseases and other neurodegenerative disorders (Grant, et al., 2001). Recognizing the need to amalgamate these multiple processes, Callenberg, et al., (2010) developed software that allowed researchers to input data into a GUI and immediately observe visualizations of molecular structures based upon the information entered by the user.

Similar to this instrument, Oluwagbemi and Oladunni (2010) documented their process of programming an interactive tool that aided healthcare providers responsible for diagnosing NTDs. The mechanism invited clinicians to input the symptoms of a patient and the tool then

references a relational database (via Structured Query Language, or SQL) and outputs the most probable NTD afflicting the patient. Both GUIs provide strong examples that broaden the usability of complicated diagnostic procedures for public health actors, and aim to expedite processes for increased benefit among affected populations.

Definitions of "eHealth"

Oh, et al., (2005) reviewed 51 distinct definitions of the term "eHealth." The authors concluded that the concept is widespread, new, and therefore the lack of a specific definition allows for the coinage to be flexibly applied in its most appropriate context. Extending this approach, the two major themes included reference to health and technology, as well as emphasis on various stakeholders, attitudes embraced, the importance of place, and the anticipated benefits experienced by end-users. These various components of the broad term of eHealth pointed towards a "technology [that] was portrayed as a means to expand, to assist, or to enhance human activities" (page 9, para. 3) in achieving health-related goals (WHO, 1946). While it is tempting to source one of the 51 definitions for this thesis' prototype, several studies advise against prescribing definitions to a device before it has been tested among end-users, and the details on this process are discussed in the next section.

eHealth as a Health Intervention

In a meta-analysis of the related catchphrase Health Information Systems (HIS), Lau, et al., (2010) identified 136 studies, and within this sample, pointed out a dearth of benchmarking procedures among the hundreds of HIS models that were put into use. In a separate and related investigation, Black, et al., (2011), conducted a systematic review on systematic reviews on the effectiveness of eHealth. From 108 of findings, they discovered scarce empirical evidence that substantiated several eHealth programs' claims of effectively benefitting end-users. These cited authors uniformly encouraged readers to not merely invent devices, but incorporate ongoing monitoring and evaluation methodologies as part of distributing innovative technologies.

While these stances make sense, a separate study, which chronicles behavioral models in relation to 20th century technological innovation (Hamid & Sarmad, 2008), noted that the assessment process of eHealth programs are inherently tricky. The article argued that eHealth lies at the heart of three interdisciplinary and overlapping fields: information systems, public health, and evaluation methodologies. Moreover, multiple findings emphasize the potential landmines encountered when attempting to characterize the three respective fields (Friedman & Wyatt, 2000; Mingers & Stowell, 1997; Farbey, et al., 1995). Therefore, this thesis draws

upon the behavioral model proposed by Hamid and Sarwell (2008) in order to contextualize the proposed GUI in a framework that will ground future user evaluations.

In the influential theory of Diffusion of Innovation (DOI) (Rogers, 1962), the author advanced the notion that each new piece of technology has its own "rate of adoption" by populations, and in summary, the device's compatibility within a particular group of people is determined in part by how easy or difficult it is to use. More than twenty years later the Technology Acceptance Model (TAM) (Davis, 1989) stemmed from the DOI framework by offering a validated measurement scale that quantified users' perceptions of an innovation and assigned numbers to the various "rates of adoption." DOI and TAM both position the site of technological evaluation at the end-user and her/his reported experience. In placing the device's ultimate deduction at the site of the user — the interface, software, and other components become interconnected material on which an evaluation can be applied (Cronholm & Goldkuhl, 2003). DOI also argued that from this stance, a user is able to make comparisons about a technology's "relative advantage," or how it compares to a preceding mechanism (Rogers, 1962). These facets of the evaluation then allow a quantifiable framework to which notions of accessibility, quality, and savings in time/effort are self-evident and impact different user's time it takes to 'accept' the model into their regular life. In

positing a new technology as temporal, responsive, and dependent upon user's perceptions (Hamid & Sarmad, 2008), this behavioral framework aligns with other eHealth theorists who argue eHealth contributions are in fact interventions (Lucas, 2008; Catwell & Sheikh, 2009).

Health interventions are aptly described as an "action plan" that address health issues (DiClemente, et al., 2009), as well as the tertiary phase that follows: (1) empirical evidence as to why an epidemic is occurring, and (2) investigations related to how to address the epidemic. In this case, the technological innovation of this thesis' GUI could be inferred as the third step taken proceeding the subsequent empirical evidence that surrounds NTDs and the subsequent interventions put into place to address them (Schlüter, et al., 2016; Zoure, et al., 2011; Boussinesq, 2006)

eHealth and Implementation Processes

The Centre for eHealth Research (CehRes) produced a review (Gemert-Pijnen, et al., 2011), as well as a Wiki page (http://ehealthwiki.org), for the purposes of eHealth developers to incorporate behavioral theories, evaluation methods, and appropriate feedback loops as part of their proposed technology. Simultaneously, a separate group established a similar study (Van Dyk, et al., 2012) titled the Telemedicine Maturity Model (TMMM), which echoed these same needs, while focusing more on the importance of designing measurable indicators of

usage and satisfaction among end-users. Both studies recommend that tools begin with extensive feedback from as many known stakeholders as possible, and that this input be implemented not only in the making of the device but additionally as part of continuous evaluation. In addition to providing foundational structures for technological development, both reviews share the assertion that "the development of eHealth technology in itself can be considered as the creation of new processes and infrastructures for health care delivery" (Gemert-Pijnen, et al., 2011, pg 10, para. 3). Mars and Scott (2010) contributed a term that perhaps offers a synthesis between the subtle distinctions of the TMMM and the CehRes proposals—and that is quite simply coining the term "glocal" to emphasize that a prototype should have ongoing and constant feedback from "local users" as well as "global experts." TMMM, CehRes, and the "glocal" catch-phrase posit one common theme: ongoing and diverse feedback loops that should introduce a mechanism that meets WHO's criteria of a "strategic plan... [that] lay[s] the foundation of the development" (Kay, et al., 2006).

eHealth and NTD Management

This literature review contextualizes a biostatistical tool for SAEs in a larger setting of global health interventions and grounds the contribution in behavioral theory related to health technology (Davis, 1989). As the proposed tool will not only expand upon the statistical analysis established by Schlüter, et al. (2016), the intention to make this methodology more accessible through an eHealth interface will contribute a rare and sought-after combinatory approach for global health (Brinkel, et al., 2014; Nhavoto & Gronlund, 2014). Furthermore, the possibility for this tool to be utilized as part of a lower-cost coordinated threshold mapping program (Mathieu and Knipes, 2013; Brooker, et al., 2009; Finn, et al., 2009; Sturrock, et al., 2009), or simply integrated programs that incorporate diagnoses of several NTDs (e.g., schistosomiasis, leishmaniasis, soil-transmitted helminths, etc.), is also an attainable option. The development of an accessible graphical user interface, for an otherwise complex biostatistics model, aims to provide health policymakers with a robust tool that will increase their effectiveness in eliminating LF, oncho, and SAEs related to loiasis.

CHAPTER 3. PROJECT CONTENT

Methods

Data collection

This thesis examines a population from the Garoua-Mboulai province of Eastern Cameroon as part of the Defeating Filariases in Africa: District Filariases Elimination Action Tool (D-FEAT). This study, funded by the Bill and Melinda Gates Foundation through the NTD Support Center, sampled individuals from 30 villages within one ivermectin-naive district/village. Villages were first put in geographic order and then selected via probability proportionate to estimated population size sampling. Within each selected village, 100 people who were at least 10 years-old were randomly selected (by household) and tested for LF, oncho, and loa.

Data were collected in Garoua-Mboulai in September, 2016, which included skin snips for LF/oncho and blood samples for loa. The mf/ml of loa were measured using a mobile health tool (Cellscope) (D'Ambrosio, et al., 2015; Kelly-Hope, et al., 2014) and all measurements and demographic data were recorded in a separate smartphone survey app (LINKS: Pavluck, et al., 2014). Survey questionnaire captured information on the age, gender, household

latitude/longitude data (using the smartphones Geographic Positioning System), and additional epidemiological information relevant to the diseases.

Data analysis

Survey results automatically output into Microsoft Excel files and were merged and summarized in SAS. The data were uploaded into ArcGIS for geographic visualization and Voronoi polygons were drawn to represent the 30 sampled villages. The maps utilized "Roads," "Inland water," (both cited from the Digital Chart of the World) and 'Administrative areas' (cited from Global Administrative Areas, v. 01, www.gadm.org) using Diva GIS (diva-gis.org), and the map of Africa was sourced from the Map Library (maplibrary.org). The Projection used for all maps was the WGS.1984.UTM.Zone.33N.

System architecture

D. Schlüter provided the original code for probability tests, along with instructions on how to run the statistical test with R or RStudio. Through dialogue at the 2016 Coalition for Operational Research on NTDS (COR-NTD), the NTD Support Center of the Task Force for Global Health initiated the task to explore creating an interface for broadened usage of the biostatistical model (Schlüter, et al., 2016). As the code was conceived in R, the NTD Support Center proposed the GUI to be built in Shiny so that no adaptations would be required to the source code.

The GUI coding was based on RStudio's Shiny architecture, which is designed as a three-tier system, or in other words, the server and the user-interface are connected in the computing. The baseline code is open source (shiny.rstudio.com), with a wealth of instructional videos and templates, and allows anyone to copy existing language and reformulate using standard R coding to refine commands. The GUI featured in this thesis runs from RStudio, which defines the three-tiered system: (1) User Interface, (2) calculations/code, and (3) the RStudio server. User Interface code was sourced directly from the Shiny website, and the biostatistical formulae was inserted within Shiny's output module, which generated the same probabilities as the source code. This tertiary structure mimics the future implementation of Web browser, which would also depend on the RStudio Server (Figure 2).

System modeling

System modeling is a practice to illustrate the details of a system's architecture. The Unified Modeling Language (UML) is described as the "lingua franca" of communicating software systems (Evans & Selic, 2003) and utilized by others designing GUIs for NTD global management (Oluwagbemi & Oladunni, 2010). UML graphically displays how components of the system interact with one another and allow for clearer exchange for multifarious stakeholders. This thesis utilizes a Use Case diagram (Figure 3), which has been widely

referenced as one of the most effective tools to describe the actions that occur when using a device (Rosenberg & Stephens, 2007). Additionally, a Sequence Diagram (Figure 4) is included as this graphic relays valuable information regarding a computer program's chronological order of events (Pickin & Jézéquel, 2004). These UML graphics assist in displaying the code and mechanisms functioning beneath the gloss of the user-interface.

Probability model metrics

For tests related to the probability model (Schlüter, et al., 2016), this thesis depended on metrics defined by the Mectizan Expert Committee in 2016 as part of the NTD Support Center's annual meeting (COR-NTD), which determined that an acceptable risk for treatment with ivermectin was at least a 95% certainty that less than 1% of a village population had $\geq$ 20,000 mf/ml (MDP, 2016). In other words, this thesis defined a village that "passed" for ivermectin treatment (sans testing) as a village that generated an output of a $\geq$ 95% certainty that less than 1% of the village had 20,000 mf/ml, and "failed" if the certainty was below 95%.

Ethics

Ethical clearance to conduct the study was provided by the National Research Ethics Committee of Human Health under the Ministry of Public Health of Cameroon (0977/A/MINSANTE/SESP/SG/DROS). Ethical clearance was not required for Emory University's Institutional Review Board (IRB) because it was not considered human subjects research. This qualification was due to the fact that this special studies thesis did not engage in research as per IRB definition because the investigation did not contribute to generalizable knowledge. The IRB defines generalizability as "knowledge from which conclusions will be drawn that can be applied to populations outside of the specific study population" (Emory University IRB, 2017).

Results and the GUI Prototype

27 villages were sampled (n=2700 individuals tested) and 89% (24/27 villages) included oncho cases with 138 oncho-infected persons (Table 1). 93% (25/27 villages) included loa cases with 304 loa-infected persons (Table 2). 30% (8/27 villages) included LF cases with only 10 LF-infected persons. Loa cases presented an average of 4,009 mf/ml, with the highest measurement at 48,391 mf/ml, and 10 cases that exceeded 20,000 mf/ml. Approximately half of the villages failed to pass the threshold of having a >95% likelihood that <1% of the

population has high intensity of loa according to the Schlüter, et al., (2016) model, and therefore, should not be administered ivermectin to treat oncho without prior test and treat programming. The 27 villages ranged in population from 400-10,000, and the associated data related to prevalence of oncho, loiasis intensity, and Schlüter, et al., (2016) probabilities were uploaded into ArcGIS and presented as a map (Figure 5). A high number of villages were clustered in the Northeast region of the Study Area sample (17/27), and a zoomed-in map is also presented for visual aid (Figure 6). The results of the GUI were cross-checked and validated with the original Schlüter, et al. (2016) algorithm by the NTD Support Center as well as D. Schlüter. Figure 7 features a screen shot of the GUI prior to testing. The original model required the user to input code and upload files onto an R console. The GUI features two inputs for the user: the village population (N) and a CSV file with loa intensity data. Depending on the input of the user, the GUI then generates either a "pass" output (Figure 8) that features a green "thumbs-up" image recommending MDA distribution of ivermectin; or a "fail" output (Figure 9), which features a red "thumbs-down" image that recommends test and treat prior to ivermectin dispersal.

CHAPTER 4. DISCUSSION

This first draft of an accessible user interface for Schlüter, et al., (2016) model has important considerations for future use in efforts to reduce SAEs related to MDA treatments as well as the potential for controlling loa as an epidemic. Below these implications for public health are discussed, as well as the GUI's limitations as a tool, and the remaining next steps before the interface can be put to actual use among stakeholders in West Central Africa responsible for the management of LF, oncho, and loa.

Loa intensity GUI contextualized

It is important to note that only two documented reports, which research the usage of GUIs to increase access to biostatics models, were found as part of this thesis (Callenberg, et al., 2010; Oluwagbemi & Oladunni, 2010). This is alarming given two major considerations: (1) extremely complex data (i.e., non-random samples, clustered designs, etc.) are quickly become the majority of quantitative social and behavioral science investigations (Heeringa, et al., 2010) and (2) complex data requires extensive training in program-specific computing (e.g., SAS, R, SPSS, etc.). As WHO, and several public health institutions, base their efforts in the Millennium Development Goals to eradicate pandemics that affect billions of people (Travis, et al., 2004) – the necessity for effective strategies that are both valid and accessible

to most public health professionals cannot be emphasized enough. Additionally, this thesis' GUI is distinctive from the two referenced studies (Callenberg, et al., 2010; Oluwagbemi & Oladunni, 2010) as the intended audiences are not necessarily working exclusively in clinical settings.

While the related studies documented extensive needs assessments and testing-trials as part of their innovations, neither mention a grounding in behavioral models in which their devices can be based. This is of potential concern given the copious number of devices and interventions that purportedly exacerbated negative conditions because of failing to frame the program in an evaluative model (Haines & Borchert, 2004). Substantiating this thesis' GUI within the TAM (Davis, 1989) framework and centering its evaluation in user-centered criteria (Hamid & Sarmad, 2008), the Schlüter, et al. (2016) model possesses increased capacity for wider reception, evaluation, and potential improvements. Furthermore, the vast majority of citations related to eHealth frameworks drew from clinical and formal healthcare settings – and this thesis contributes unique literature as is related to global health in resource-poor settings.

Next steps and limitations

As part of the sampling that took place in Cameroon in September 2016, it is the intention of this initiative to use these findings as a proposal to test and treat the villages that were predicted to fall beneath the 95% confidence level (Rebollo, 2016). This is a meaningful direction forward in the advancement of loa control and LF/oncho elimination, as up to this point, no alternatives existed for treating co-endemic regions. Additionally, research suggests that vector control of loa-spreading tabanids could also be a viable option for highly infected regions (Kamgno, et al., 2016; Chippaux, et al., 2000), and has been argued as effective for LF and oncho elimination (Bockarie, et al., 2009; Hougard, et al., 2001). Finally, there is increasing evidence that the antibiotic doxycycline has been effective in treating onchocerciasis with little to no reported SAEs in co-endemic regions (Wanji, et al., 2009; Turner, et al., 2010), and this is a third possibility for high loa intensity villages.

However, before these actions are implemented, there are three major limitations to consider before implementing test and treat programs in the region sampled. Firstly, the Schlüter, et al. (2016) model was developed using microscopy data techniques to detect loa parasitemia. This thesis relied on a separate collection methodology – a new smartphone test called Cellscope. Therefore, it is necessary to determine the relationship between microfilariae densities reported by the Cellscope, and those observed through microscopy, and to then calibrate the

Schlüter, et al. (2016) model with the Cellscope data. These validation measures might one day lead to future developments that would allow for automatic uploads of loa intensity directly from CellScope tools, which in turn would streamline data entry processes and remove the task of formatting a CSV file for end-users of the GUI.

An additional limitation of this thesis' GUI is that the process of coding and development did not involve a needs-assessment among the intended beneficiaries: health policymakers responsible for decision-making related to ivermectin dispersal. The other published article that developed a GUI for NTD diagnoses (Oluwagbemi & Oladunni, 2010) documented a lengthy survey before coding commenced, and this process would have enhanced the impact of this GUI. Due to time constraints, the coding was initiated with the approval of D. Schlüter and colleagues. Evaluations will build upon the framework described throughout the thesis (Davis, 1989) in emphasizing users' perceptions of the device's ease-of-use. The gold-standard of computational evaluation is argued to be the System Usability Scale, which formulated ten questions that comprehensively gauge the quality of a technology (Bangor, 2008) and has been used for other eHealth evaluations in Africa (Tilahun, et al., 2013). Future evaluations will invite stakeholders who are involved in decisions regarding ivermectin dispersal to use the tool and respond to a survey that draws from the System Usability Scale to infer how the GUI might best be improved.

Finally, this thesis depends on several behavioral models to ground the GUI as a formal health intervention (DiClemente, et al., 2009; Davis, 1989; Rogers, 1962). Davis (1989) and Rogers (1962) did not put forth their behavioral models for public health usage, and therefore, relating these theories to global health processes could raise potential issues in future evaluations of the GUI as solely a technological device. While this limitation is slightly mitigated by comparing these theories' similarities to influential public health models (DiClemente, et al., 2009), there remains a paucity of behavioral models that explicitly discuss global health interventions in resource poor settings (Howitt, et al., 2012).

Post-evaluation, and post-validation of the Cellscope and microscopy methods, the NTD Support Center as part of the Task Force for Global Health aims to advise pharmaceutical companies and the Bill and Melinda Gate Foundation on testing-and-treating the villages in this report that failed the Schlüter, et al. (2016) probability. These findings and procedures will be reported formally and it is the aim of the involved stakeholders to make the GUI available to other researchers and country programs in the ten loa co-endemic countries in Africa (Angola, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Equatorial Guinea, Nigeria, South Sudan, and Uganda).

As global health networks and intervention methods grow in complexity, it is vital to ensure that communication lines between the multifarious stakeholders remain transparent and accessible. Moreover, financial costs for NTD control will likely remain constricted, and this GUI will ideally lead toward more cost-effective decision-making and management for co-endemic regions of LF/oncho and loa by limiting treating to a minimum while preserving safety. The programming of this particular tool aims to provide health policymakers with a statistically rigorous method of providing certainty in their decision-making, and the assurance of usability will hopefully play an important role in the goal to eliminate LF, oncho, and SAEs related to loiasis.

CHAPTER 5. ADDITIONAL PAGES

Public Health Implications

- This technological innovation allows critical stakeholders to make prompt and rigorous decisions about ivermectin dispersal. The GUI will ideally save the lives of individuals living in loa endemic regions from receiving ivermectin, and avoiding SAEs.
- The GUI is a unique contribution to public health discourse, as only two publications were found that document similar efforts.
- The GUI will aid leaders involved with reducing SAEs related to MDA to validate existing models for a more unified approach to LF/Oncho and loa control efforts.
- Maps included in this report will enrich ongoing GIS literature related to loiasis.
- The findings will be immediately implemented as part of the Task Force for Global Health's current District Filariases Elimination Action Tool program.
- The GUI will be used immediately at the Task Force for Global Health to validate existing data and aid stakeholders who are engaged with loa/ivermectin management.
- The methodologies, processes, and approach described in this thesis can ideally aid future public health students and professionals access RStudio and related resources to increase the usability of other health tools.

Tables

Table 1.

Characteristics of population and oncho in villages in Garoua-Mboulaï, Cameroon, 2016

Villages	Population (N)	Tested (n)	Prevalence
Mbassi	586	88	18%
Yokosire	800	75	17%
Sabal Sud	735	73	14%
Komboul	400	61	13%
Gbagio	1,200	153	10%
Bethanie et captage	3,000	35	9%
Doforo	650	49	8%
Nandoungue	4,200	139	8%
Badan	1,085	82	7%
Sabal	2,560	155	6%
Goza 1 et 2	6,292	303	5%
Nagonda	1,192	154	3%
Gandong	675	67	3%
Gado Badzere	10,000	170	3%
Zoukounde	3,995	187	3%
Thiomo + Nyamdou	4,381	38	3%
Mombal	1,500	103	2%
Bindiki	2,500	63	2%
Frontière	3,347	127	2%
Sabongarie	1,915	195	2%
Gbaya	1,200	72	1%
Shell	3,588	182	1%
Ndanga Gbakobo	1,600	59	0%
Marche Central	2,423	23	0%
Foulbere	3,000	47	0%

Table 2.

Characteristics of population and loa in villages in Garoua-Mboulaï, Cameroon, 2016

Villages	Population (N)	Tested (n)	Prevalence	Average mf/ml	Shluter Probability*
Ndanga Gbakobo	1,600	89	1%	888	1
Shell	3,588	203	1%	312	1
Frontière	3,347	135	2%	780	1
Sabongarie	1,915	278	3%	1,058	1
Foulbere	3,000	57	0%	0	1
Bindiki	2,500	64	2%	263	0.99
Goza 1 et 2	6,292	387	5%	4,603	0.99
Zoukounde	3,995	220	5%	5,756	0.98
Doforo	650	100	5%	1,390	0.98
Marche Central	2,423	25	0%	0	0.98
Sabal	2,560	227	7%	3,146	0.98
Komboul	400	103	4%	1,971	0.97
Gbaya	1,200	73	3%	4,742	0.97
Bethanie et captage	3,000	41	2%	3,279	0.96
Nagonda	1,192	252	6%	8,542	0.85
Gado Badzere	10,000	173	8%	6,343	0.74
Gbagio	1,200	163	13%	3,529	0.7
Yokosire	800	91	13%	3,288	0.67
Gandong	675	77	6%	14,265	0.6
Thiomo + Nyamdou	4,381	73	12%	5,267	0.5
Sabal Sud	735	86	19%	6,311	0.21
Mbassi	586	92	18%	5,878	0.16
Mombal	1,500	113	35%	4,655	0.0093
Nandoungue	4,200	162	28%	7,177	0.0002
Badan	1,085	85	42%	6,775	0.0001

* *Schlüter, et al., (2016) probability that <1% of the village population has a loiasis intensity of ≥ 20,000 mf/ml. Green cells indicate that there is ≥95% confidence that <1% of the population is below the 20,000 (pass); red cells indicate <95% confidence (fail). Villages that failed would not be recommended to administer ivermectin.*

Figures

Figure 1.

Four maps that zoom-in on the locations of the 27 villages sampled. Country, Major Roads, and Province boundaries were accessed through Global Administrative Areas (www.gadm.org). Yellow village villages were drawn using the Voronoi polygons around geographic positioning system (GPS) points collected in September, 2016.

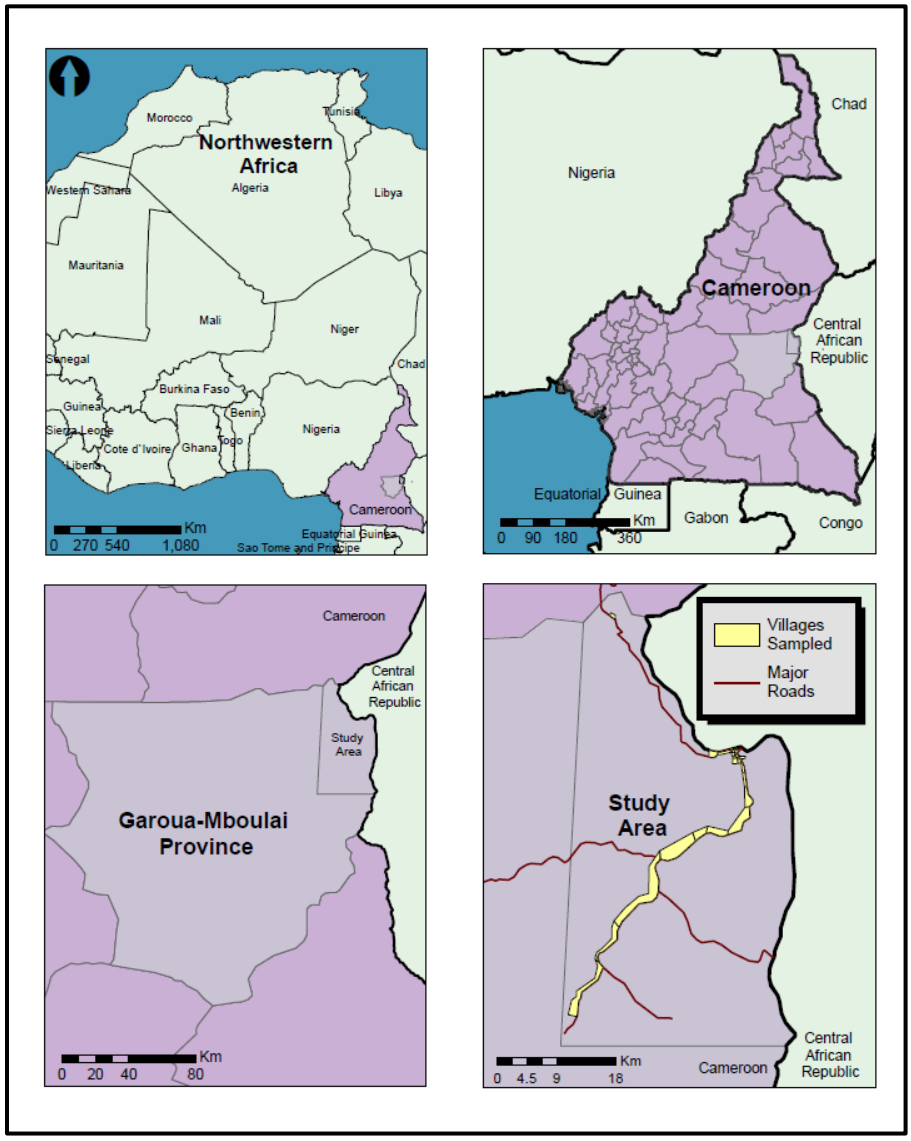


Figure 2.

Three-tiered structure of the RStudio Shiny system architecture flow chart. The 'Graphical User Interface (GUI)' indicates the first-tier of the GUI that the user will see. The second-tier is the existing code of the Schlüter, et al. (2016) model and open-sourced R code provided by RStudio Shiny product (https://shiny.rstudio.com, accessed April 10, 2017). The third-tier is the 'RStudio Shiny Server,' which transforms the R Coding into a GUI. The illustration utilized creately.com for flow chart diagram template (accessed April 10, 2017) that draws from software programming language (Evans & Selic, 2003) in distinguishing pink ellipsoids as 'Starting Points,' yellow cylinders as 'Direct Data,' and green rectangles as a 'Predefined Process.'

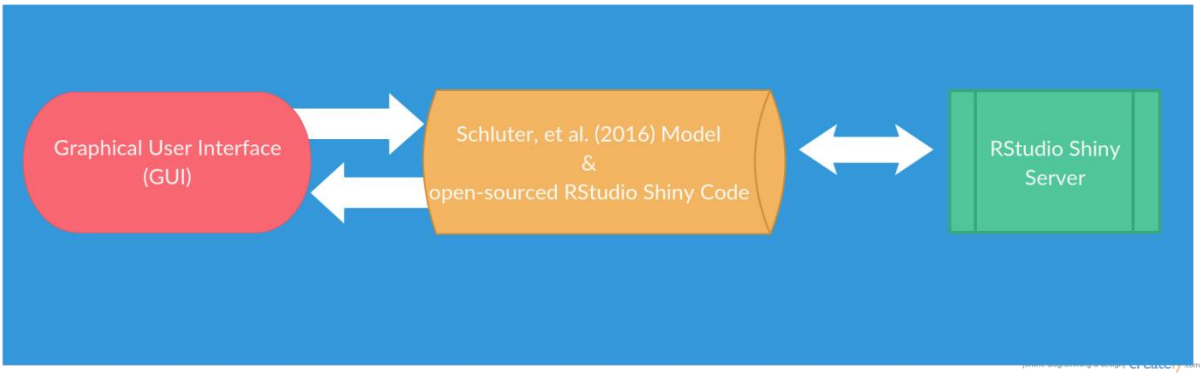


Figure 3.

Unified Modeling Language (UML): Use Case Diagram. Blue ellipses indicate visible content available on the GUI. Thick grey lines indicate immediately visible content, thick grey arrows with the caption "<<include>>" indicate required input and/or functions on behalf of the user whereas dotted-line arrows with the caption "<<extend>>" indicate optional functions. The illustration utilized creately.com for use case diagram template (accessed April 10, 2017).

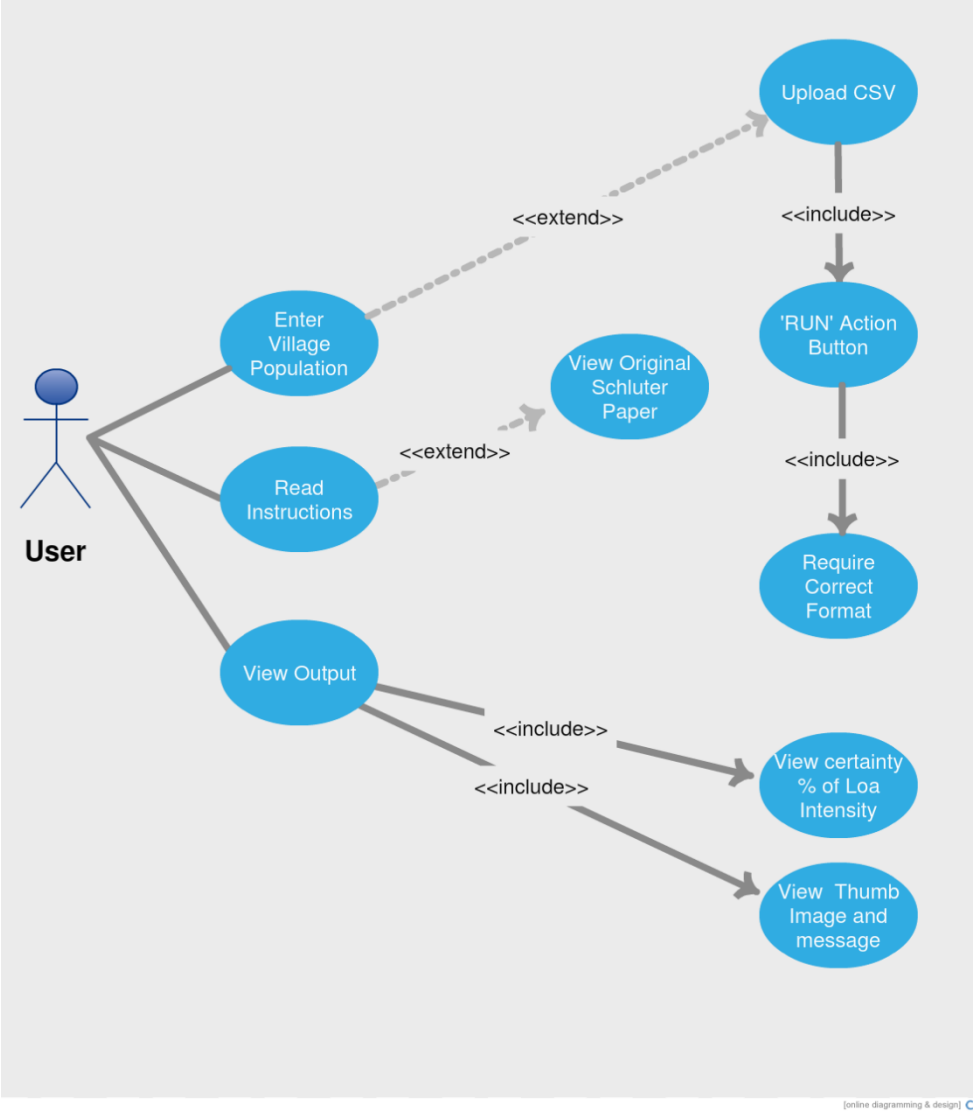


Figure 4.

Unified Modeling Language (UML): Sequence Diagram. Yellow titles indicate passage of time from left to right. Top layer (User Interface, Server, and Output) match three-tiered system as described in methods section. Second layer indicates phases of the device that the user accesses. The 'GUI' is the graphical user interface that displays data input fields, instructions, and a link to the original model. 'Data Validation' indicates step in sequence that screens for accurate formatting of data required to run in the formulae. 'Schlüter Model' indicates the copy/pasted code provided by D. Schlüter. 'Certainty %' is a calculation that indicates the percentage certainty that <1% of the population has loiasis at ≥ 20,000 mf/ml. 'Final Output' indicates with visual images whether the Schlüter model determined the village to be ≥ 95% certain that less than 1% of the village has loiasis (Green Thumbs up – or safe to treat ivermectin), or < 95 % (Red Thumbs Down – recommend to test and treat the village). Arrows and white blocks with text beneath yellow titles indicate logical sequence of events as experienced by the user. The illustration utilized creately.com for sequence diagram template (accessed April 10, 2017).

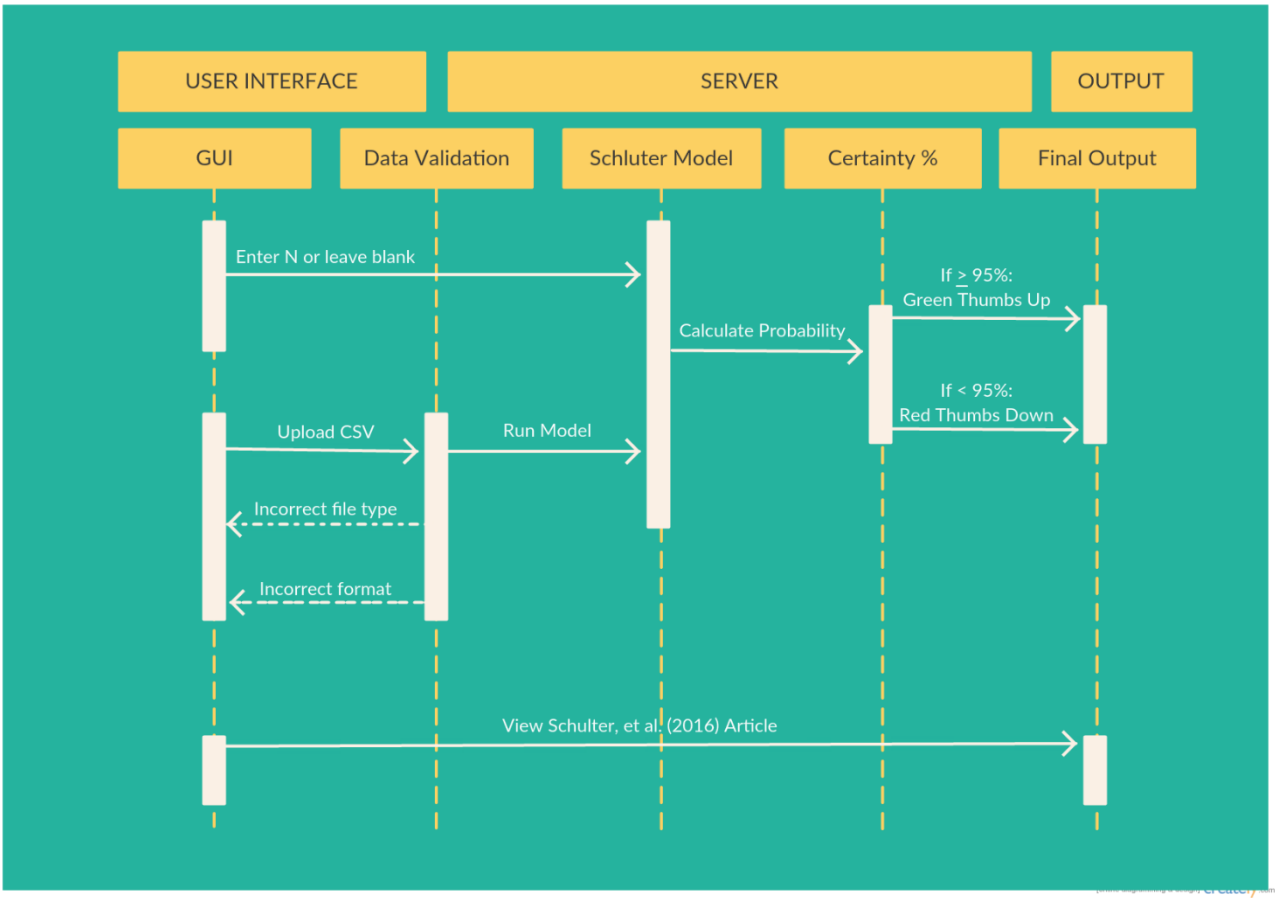


Figure 5.

Four maps that visualize the population, oncho prevalence, average loa intensities, and Schlüter, et al., (2016) probabilities. River shapefiles were accessed through Global Administrative Areas (www.gadm.org). These four maps feature data related to the population, oncho prevalence, loa intensity, and probabilities of the Schlüter, et al., (2016) model. Data were exported from original files collected using the LINKS (Pavluck, et al., 2014) smartphone system, then downloaded to Microsoft Excel files, and uploaded into ArcGIS. Voronoi polygons were drawn around Geographic Position Systems (GPS) points to aid visualization of the study area.

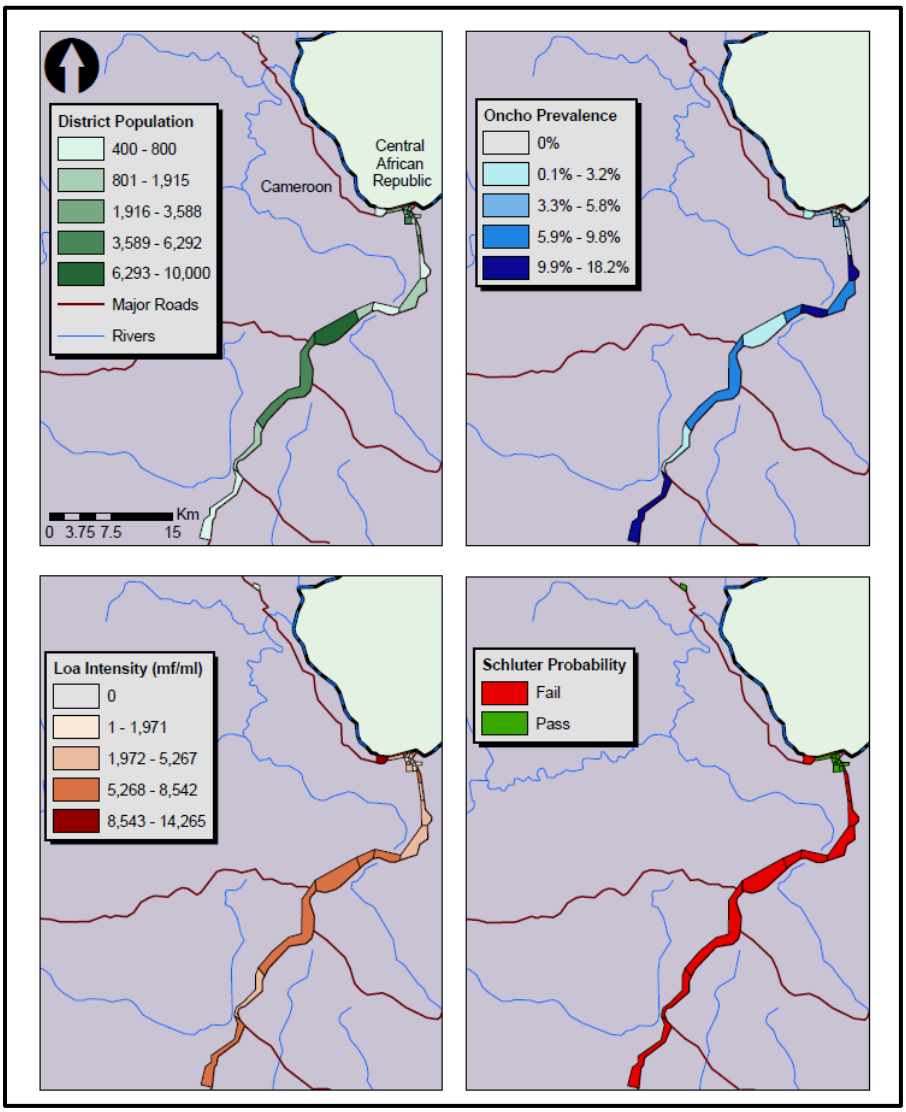


Figure 6.

Four maps that zoom-in on the dense cluster of villages in the Northeast corner of the study area, corresponding with Figure 2. These four maps replicate data featured in Figure 5, however, zoom-in on the Northeast region to aid in the geographic visualization. The majority of villages randomly sampled (17/27) were in this region of the study area.

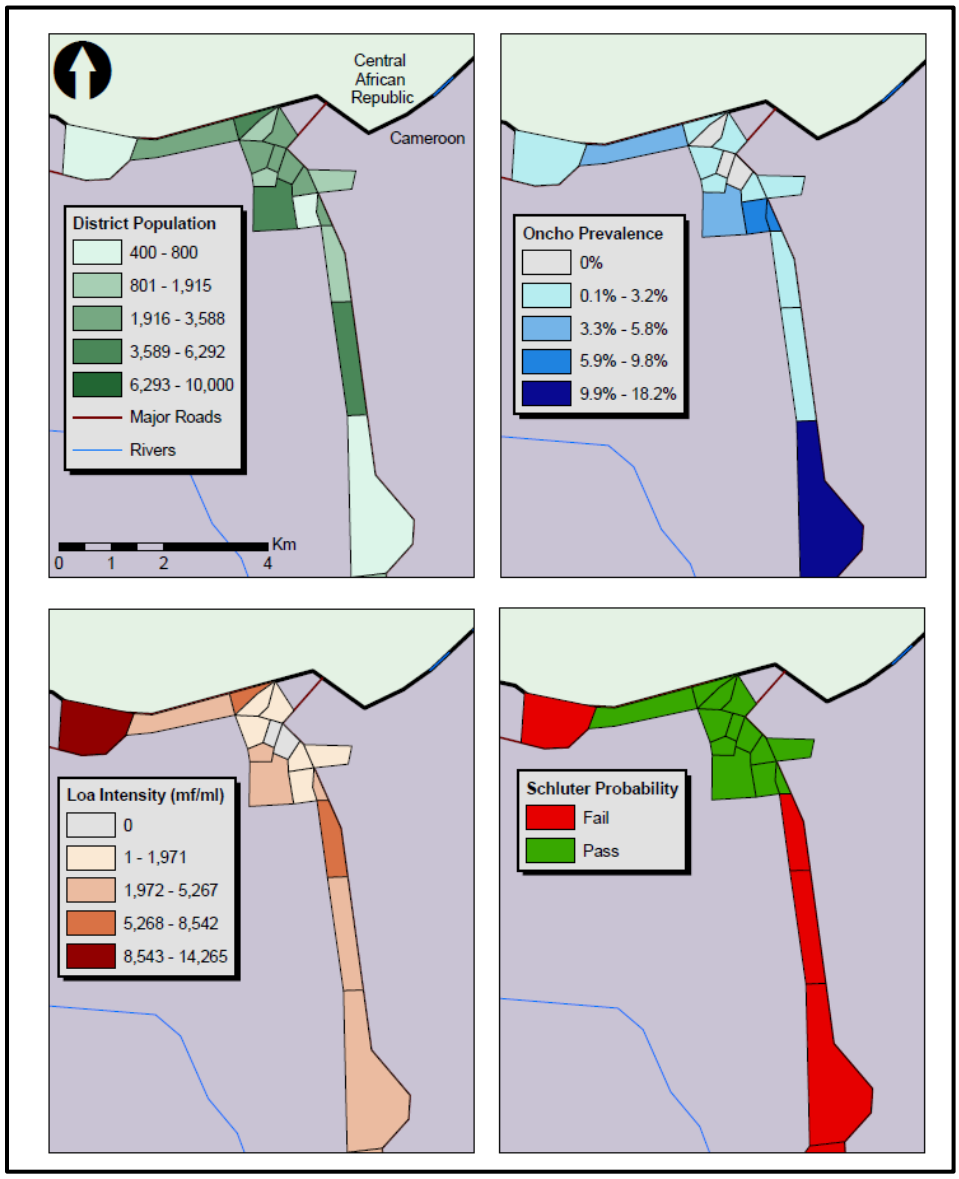


Figure 7.

Beginning screenshot of the GUI. This is the interface that users access to run the probability model (Schlüter, et al., 2016). The top of the model provides instructions and a link to users to access the original article. On the left is the window a user sees to enter the population (N) of the villages sampled as well as the opportunity to upload the CSV file that contains loa intensity information for the village.

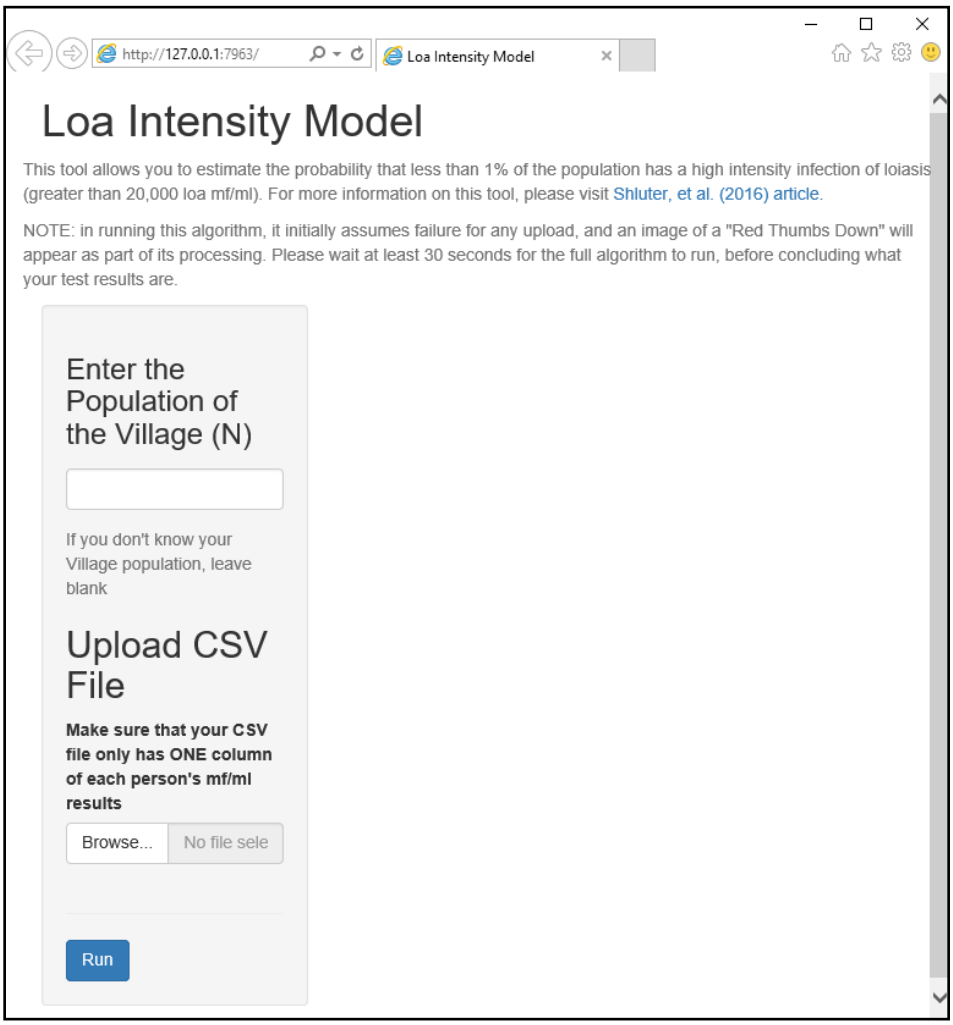


Figure 8.

'Pass' probability screenshot of the GUI. This image includes data entered from village 303 (Goza 1 et 2) from the study, which reportedly contained a total population (N) of 6,292 persons. The CSV containing the mf/ml for the sampled individuals within this village generated a .99 certainty that less than 1% of this village has loiasis above the threshold of 20,000 mf/ml. Given this certainty, a 'green thumb' image appears with the message that vindicates potential ivermectin usage for this particular village. The image was sourced from the following website on April 11, 2017: https://pixabay.com/en/good-hand-up-green-thumb-thumb-up-157436/

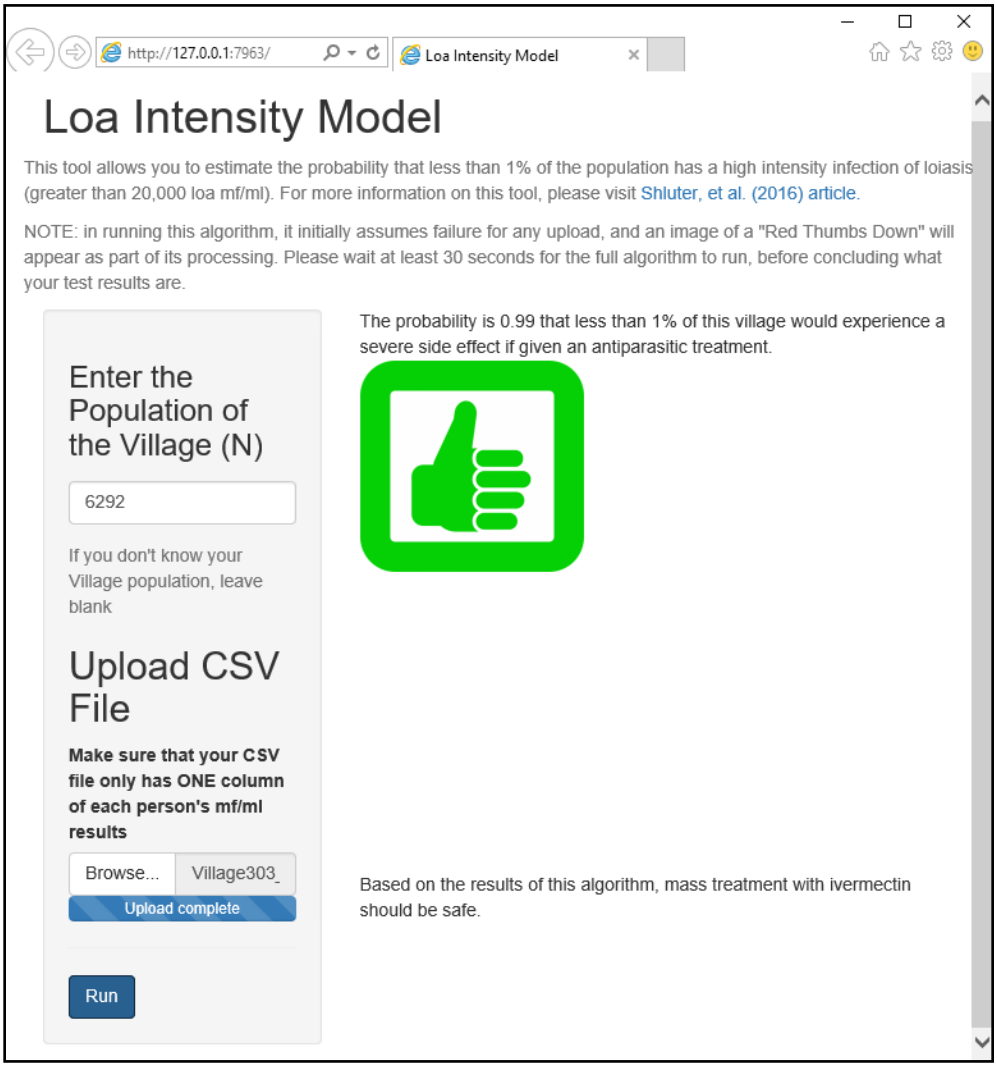
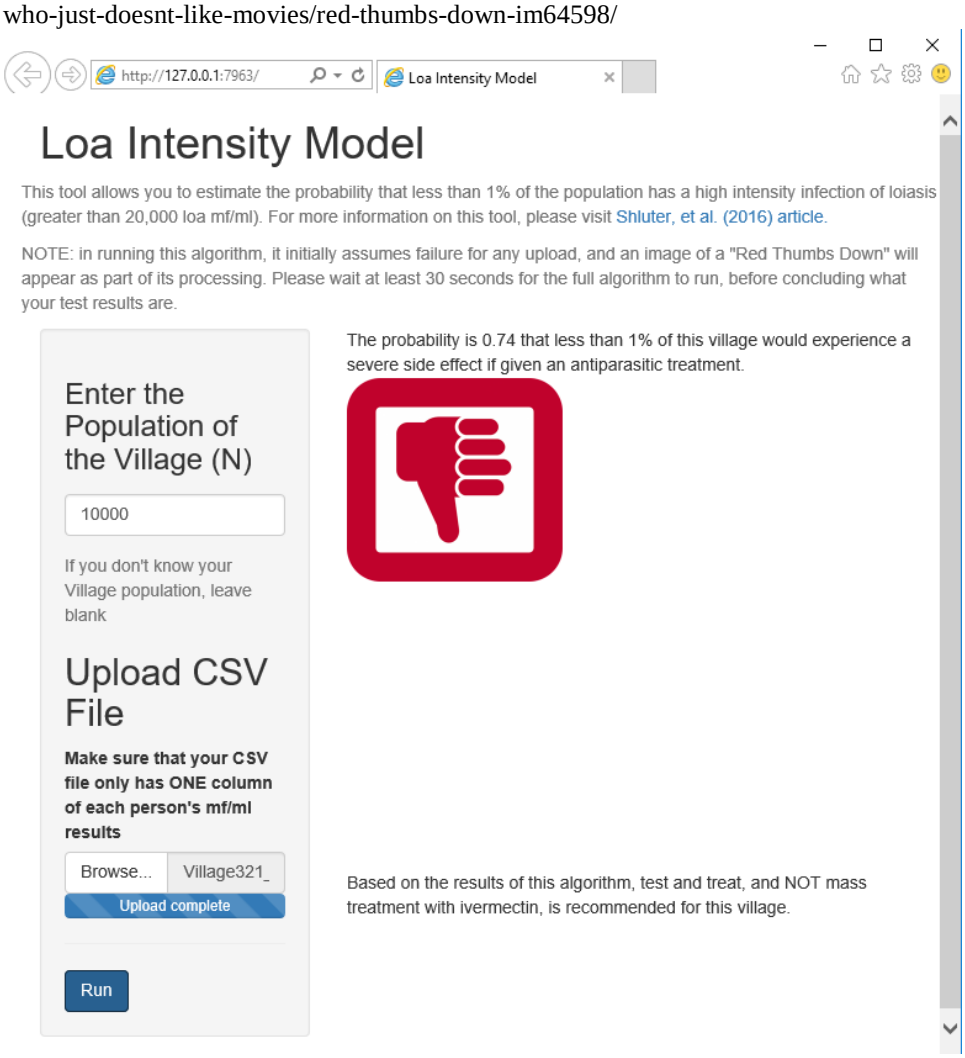


Figure 9.

'Fail' probability screenshot of the GUI. This image includes data entered from village 321 (Gado Badzere) from the study, which reportedly contained a total population (N) of 10,000 persons. The CSV containing the mf/ml for the sampled individuals within this village generated a .74 certainty that less than 1% of this village has loiasis above the threshold of 20,000 mf/ml. Given this certainty, a 'red thumbs down' image appears with the message that encourages test and treat practices for the village in place of ivermectin dispersal. The image was sourced from the following website on April 11, 2017: http://movieode.com/whats-a-good-movie-for-someone-who-just-doesnt-like-movies/red-thumbs-down-im64598/



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