TITLE PAGE

MATHEMATICAL MODEL OF SNAKEBITE DYNAMICS IN TURKANA COUNTY AND OUTCOME BASED ON HOSPITAL SEEKING BEHAVIOR

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A REPORT SUBMITTED TO THE DEPT. OF PUBLIC & GLOBAL HEALTH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN MEDICAL STATISTICS OF THE UNIVERSITY OF NAIROBI

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Title of the work……………………………………. Mathematical model of snakebite dynamics in Turkana County and outcome based on hospital seeking behavior.

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DEDICATION

I dedicate this work to my parents and siblings for always believing in me, to my daughter for waking me at night and my loving wife for the encouragement and always looking forward to my graduation party.

LIST OF ABBREVIATIONS AND ACRONYMS

GoK Government of Kenya

DHIS District Health Information System

LMIC Low- and Middle-Income Countries

MOALF Ministry of Agriculture, Livestock and Fisheries

MOH Ministry of Health

NTD Neglected Tropical Disease

ODE Ordinary Differential Equation

PC Preventive chemotherapy

SB Snakebite

SBE Snakebite envenomation

SDGs Sustainable Development Goals

SSA sub-Saharan Africa

UHC Universal Health Coverage

WHA World Health Assembly

WHO World Health Organization

DEFINITION OF OPERATION TERMS

Envenomation - This is the injection of snake venom into the victim's body during snake bite.

Snake-bite envenoming (SBE) – Snake-bite envenoming results when venomous snakes introduce lethal toxins to victims either through a bite or spit in the eyes

Snakebite - Is an event that occurs when a snake bites a victim for purpose of protection or preying

Snake antivenom – The single recognized treatment for envenoming by snake-bites

Dry bite – Snakebite cases without successful deposition of venom into the victim's body.

ABSTRACT

Snakebite envenoming (SBE) is a public health concern of the poor tropical populations that results when venomous snakes introduce lethal toxins to victims either through a bite or spit in the eyes. Similar to other neglected tropical diseases (NTDs), snakebite programs in LMICs face challenges of inadequate data and statistics therefore making it difficult to make evidence based decisions towards public health interventions and resource mobilization/allocation. The currently available data from KHIS platform has greatly improved the situation by capturing snakebite cases reported at health facilities. However, the reported cases gravely under-estimates snakebite burden by failing to capture snakebite victims presenting to traditional healers and those seeking no treatment at all. This study investigate dynamics of snakebite disease and outcomes given access to treatment by incorporating both snake and human factors in a single model.

Applying a mathematical modeling approach, the study borrows from household surveys to obtain a non-reporting rates for adjusting the KHIS data. The adjusted data is used to calibrate a logistic growth model estimation population of snakes at the human-snake interface. Logistic growth model fitness is enhanced through trajectory matching using maximum likelihood estimates of simulated data. Simulated data on snake population is introduced into a SIRS model that simulates snakebite occurrence for a period of 365 days, estimates snakebite incidences and outcome given access to treatment. The effects of varying model parameters is investigated to understand dynamics of snakebite and advice on potential interventions. Finally, the study investigates the impact of hospital seeking behavior in averting snakebite-associated deaths.

Present study estimated 3,371 annual incidence of snakebite in Turkana County, amounting to 1,315 missed cases. The burden of snakebite from simulated data - 368/100,000 person-year (95% CI: 356-381) agrees with incidence rates from reported (adjusted) data - 364.99/100,000 person-year (95% CI: 353-378). Activities associated with increased exposure showed to half snakebite burden when the force of infection is reduced by 50%. The case fatality rate is estimated at 5.6 (4.2-7.4) deaths per 100,000 person-years with 52 deaths reported at the end of the simulation period ($t = 365$ days). There were 3.5% averted deaths for every 10% increase in the rate of hospital seeking amongst the snakebite victims. The model predicts 32.4% averted deaths if all victims were to present to health facility following snakebite, regardless of whether they receive antivenom or not.

It is important therefore that, public health awareness interventions be instituted in snakebite endemic communities to encourage victims to seek hospital treatment following snakebite. The model is transferrable in similar settings with limited data and no statistics on the burden of snakebite disease.

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1. CHAPTER ONE: BACKGROUND

1.1. INTRODUCTION

Snakebite envenoming (SBE) is a public health concern of the poor tropical populations that results when venomous snakes introduce lethal toxins to victims either through a bite or spit in the eyes (Yousefi et al., 2020; WHO, 2017). Globally, of the estimated 5 million annual snakebites, approximately 1.8 million victims are envenomed, yielding over 100,000 case fatalities and 400,000 permanent disabilities and physical disfigurements (WHO, 2017). South Asia region leads with the highest estimates of annual snakebite cases at 121,000 followed by Southeast Asia-111,000 and East Sub-Saharan Africa in third place reporting approximately 43,000 bites per year. Ochola in (Ochola et al., 2018) reported varied statistics in Kenya with the highest incidence rate being 67/100000 person-years in Baringo county.

Following treatment of snakebite envenoming, recovering patients tend to suffer associated physical and psychological disorders and socioeconomic losses arising from amputations, depression and work retrenchment respectively (Williams, 2015; Waikhom et al., 2012; Chippaux, 2008). These factors on burden and challenges associated with SBE led to the listing of snakebite as a priority NTD by the World Health Organization (WHO, 2019) and subsequent development of binding resolutions to aid in designing a road map for the control and management of snakebite envenoming (World Health Assembly, 2018). Citing the apparent lack of data and statistics on snakebite epidemiology as one of the major challenges, a global snakebite strategy was produced from the assembly with the aim of halving snakebite associated morbidities and mortalities by 2030 (De Silva et al., 2013).

The existing hospital-level data from previous studies are marked with poor recording and grave underestimations of incidences since majority of victims tend to seek traditional healers or no medication at all. A more realistic picture on snakebite epidemiology calls for well-structured survey capturing data at the community level and investigating distribution of venomous snakes (WHO, 2017). It is, however, unrealistic and financially hectic to undertake periodic surveys for up-to-date statistics and emphasis should therefore be made to developing a model to estimate incidences and outcomes of snakebite while integrating underlying factors (Goldstein et al., 2020; Bravo-Vega et al., 2019; Ediriweera et al., 2018; Kasturiratne et al., 2008)

To the best of our knowledge, only four studies have explored the use of mathematical modeling in explaining dynamics and variations of snakebite incidences at the human-snake interface. Bravo-Vega and co-workers developed a model using the law of mass action to estimate snakebite in Costa

Rica (Bravo-Vega et al., 2019). Kim successfully employed a conceptual epidemiological model to assess the risk factors associated with snakebite deaths in South Asia (Kim, 2020) while Goldstein and coworkers applied Agency Based Model to predict risk of snakebite in Sri Lanka while integrating both human and snake behavior (Goldstein et al., 2020). (Abdullahi et al., 2021) used compartmental SIRS model to evaluate the effectiveness of public health awareness and early treatment with antivenom on reducing snakebite incidences, deaths and disabilities.

Present study seeks to develop a mathematical model that simulates the dynamics of snakebite in Turkana County of Kenya incorporating snake and human factors. The model is further used to assess the impact of hospital seeking behavior on averting snakebite induced deaths by varying proportion of seeking hospital care in the population by 10% incremental rates.

1.2. Statement of the problem

Snakebite was listed as a priority Neglected Tropical Diseases by the WHO in 2017. In addition, the disease was acknowledged in the 71st World Health Assembly leading to the development and adoption of binding resolutions such as strengthening surveillance, control and management programs; transforming the knowledge, attitude and perception gaps at community level; and generating data that would improve on the understanding of SBE as a disease, among others.

Ochola and co-authors in (Ochola et al., 2018) reported varied statistics in Kenya with the highest incidence rate being 67/100000 person-years in Baringo county. Considering that hospital records were used, these statistics stand to be great underestimates since majority of snakebite victims tend to seek traditional healers (Ochola et al., 2018). Other existing surveys are equally marked with gross underestimates because of the weak surveillance systems that fail to capture snakebite incidences at the community level. Consequently, the available statistical models are unable to accurately capture the dynamics of snakebite and possible variations within the transmission system. As a result, there has been limited supply of the essential medical resources (such as snake antivenom) and relatively poor infrastructure required for treatment of snakebite in hospital facilities.

1.3. Justification of the study

Mathematical models are useful for analyzing diseases dynamics to predict/estimate the result of epidemics while integrating data to understand epidemiological patterns and creating quantitative evidence for health-care decision-making. The primary goal of this study was to develop a mathematical model that estimate the incidences and outcome of snakebite based on hospital seeking behavior. The model is applied in snakebite endemic setting has never been studied before.

Estimating true burden of snakebite in Turkana County will be important in guiding the mobilization and allocation of resources such as antivenom and other medications at both the County and national levels. The burden estimates will provide evidence for proper planning, design and implementation of public interventions associated with control and management of snakebite. Moreover, the model will act as a tool of estimating true burden of snakebite in Turkana County and other similar settings using data from health facility surveillance platform.

Outcome of this study will be important in guiding policies that advise resource mobilization and antivenom allocation. Above that, the disease requires other hospital resources like oxygen for assisted ventilation, adjunctive drugs and war space that require adequate prior planning for purposes of resource mobilization. Having knowledge on hospital seeking behavior and the associated outcomes will therefore advise on targeted interventions. The study offers a platform to derive evidence that will guide the mobilization and allocation of antivenom and other relevant resources, which has been a challenge facing the SBE space.

1.4. Research question

How does snake envenoming factor and human hospital seeking behavior the dynamics of snakebite envenomation in Turkana County, Kenya?

Does seeking hospital care following snakebite affect the outcome of snakebite?

1.5. Objectives

1.5.1. Broad objective

To mathematically model snakebite dynamics in Turkana County while integrating snake envenoming factor and human hospital seeking behavior.

1.5.2. Specific objectives

i. To formulate a mathematical model that represents the dynamic of snakebite in Turkana County, Kenya.

ii. To determine the effect of different model parameters on the number of snakebite cases

iii. To determine the level of hospital seeking that reduces snakebite induced deaths associated with hospital seeking behaviour

2. CHAPTER TWO: LITERATURE REVIEW

2.1. Epidemiology of snakebite

The global estimates of snakebite incidences range between 1.2 million and 5.5 million annually with 25% of these resulting in successful envenoming. South Asia, Southeast Asia and the east of sub-Saharan Africa are considered the most affected regions recording 121,000, 111,000 and 43,000 annual numbers respectively. India-81,000, Sri Lanka-33,000, Viet Nam-30,000, Brazil-30,000, Mexico-28,000 and Nepal-20,000 have the highest country-specific yearly incidences (Kasturiratne et al., 2008). On the flip side, Central Europe and Central Asia regions have been reported to experience lowest snakebite incidences.

SBE causes devastating losses to the already impoverished tropical populations effectuating over 400,000 physical and psychological morbidities and 20,000-94,000 case fatalities per year (World Health Assembly, 2018; Gutiérrez et al., 2013). South Asia-14,000, West sub-Saharan Africa-1,500 and East sub-Saharan Africa-1,400 carry the highest burden of snakebite associated mortalities per year with lowest numbers experienced in Australia, Europe and Southern Latin America regions. The East Africa region contributes approximately 6127 and 22,941 amputations and post-traumatic stress disorders (PTSD) respectively (Chippaux, 2011). Despite the availability of these statistics, scarcity of data on the epidemiology of SBE has been reported as a major contributor to its neglect stature in f the East Africa region including Kenya (Ochola et al., 2018; Kihiko, 2013).

Earliest evidence of SBE data in Kenya show the northern, eastern, coastal and western regions amongst the heaviest burden with the disease (Coombs et al., 1997; Snow et al., 1994). (Coombs et al., 1997) conducted a study on snakebite in Kenya and reported incidences in the former districts of Kakamega (1.9/100,000/year), Laikipia (4.5/100,000/year), Busia (25.3/100,000/year), Kilifi (44), Samburu (66/100,000/year) and Baringo (67.9/100,000/year). Additionally, (Snow et al., 1994) reported mortalities of as high as 6.7/100,000 persons in Kilifi which accounted for 0.7% of all case fatalities. (Kihiko, 2013) conducted a study on venomous snakebites in Kitui county and reported an incidence rate of 25.8 per 100,000 persons for a period of 8 months, translating to 38.7 cases per 100,000 person-year in 2012. Kitui county is believed to report the highest incidences (5.4/100,000 person-years) of snakebite in Kenya after Baringo county, higher than the reported national estimates of 2.4-6.7/100,000 person-years (Ochola et al., 2018).

2.2. Risk factors associated with Snakebite Envenomation

Globally, approximately 5.8 billion persons are at risk of snakebite (WHO, 2019). Different factors have been reported to predispose snakebite at different levels depending on environmental factors, socioeconomic and behavioral activities such as farming, livestock keeping, fishing, fetching drinking water, manual labor, housing design and also random attacks while walking e.g., to school (WHO, 2019; Ediriweera et al., 2016). The rural population is dis-proportionally (up to 10 times) predisposed owing to their high dependency on Agriculture, poor road infrastructure, unequipped hospitals, high poverty index, high illiteracy levels, reliance on traditional healers, and inadequate antivenom (Bravo-Vega et al., 2019; Chippaux, 2017b, 2008).

High incidences observed during rainy seasons and agriculture activities make the menace an occupational hazard (De Silva et al., 2013). In Kenya, factors associated with increased risk of snakebite include seasonal weather variations, agriculture and herding (Ochola et al., 2018). A study conducted on venomous snakebites in Kitui district hospital reported the following incidence rates with regards to activity at time of bite: herding-34%. Sleeping-21%, farming-19%, resting at home-13% and playing-4% (Kihiko, 2013). The findings are consistent with that of Ochola, where highest incidences were reported in the bush, among the manual laborers and in the evening (Ochola et al., 2018).

Variations in number of reported snakebite cases during rainy, wet and dry seasons point towards effect of weather variations in snakebite, potentially underpinning on climate change as an important factor to consider. The positive correlation with rainfall has been attributed to displacement of snakes from their predilection sites (holes and crevices) and increased livestock/agricultural activities hence increased human-snake interactions at their shared interface (Vaiyapuri et al., 2013). In dry seasons, snakes tend to frequent homesteads in search of feed and water hence increased human-snake interactions (Ediriweera et al., 2016).

The in between variations are partly defined by changes in humidity where low humidity levels is associated with increased bites and high levels with low number of bites through increased and decreased physiological activities of these reptiles in the respective seasons. This explains the geographical and seasonal variations in snakebite incidences (Rahman, Faiz, Selim, Rahman, Basher, Jones, Este, et al., 2010). However, with the current global changes and anticipated disease outbreaks, more focus on disaster management in the field of health has been put on food borne, water borne and vector borne diseases with little/no attention on SBE despite recording most deaths during floods in Bangladesh, second to drowning

Varied reporting has been observed in sex predisposition to snakebite. While some studies show higher incidences in males (Ediriweera et al., 2016), other have reported higher incidences in the females (Kenya Ministry of Health Neglected Tropical Diseases Program, 2019; Kihiko, 2013). This can be explained by the differences in community-specific cultural practices that aligns the socioeconomic activities handled by both males and females.

The devastating effects of SBE on the economy and it being viewed as both a disease of the poor and driver of poverty is due to its endemicity within the productive ages of 10-40 years-old that handles a lot of socioeconomic activities in the endemic settings (Williams, 2015; De Silva et al., 2013). The age exposure reports corroborate with findings from Kihiko in Kenya where higher exposures were recorded in the ages 15-40 in Kitui county (Kihiko, 2013) and (Ochola et al., 2018) reporting age-stratified incidences of 41.48% in age group 1-15 years, 31.82% in age group 16-30 years, 13.64% in age group 31-45 years, and 13.07% in those over 45 years old.

Cultural housing designs with holes and crevices has also been linked to increased exposure to snake bite. Traditional houses made from mud, grass-thatched, papyrus reeds and woods tend to have holes and crevices that act as points of entry when snakes seek for water and warmth in the during the hot and cold seasons respectively. Other practices like sleeping on the floor or sharing sleeping rooms with poultry raises the chances of attack because of the easy target. Kitui County, Kenya reported higher incidences of SBE in houses built using locally manufactured bricks and thatch/iron sheets-54.3%, followed by mud and thatched houses-38.6% then permanent structures with stone walls and iron sheet roofs-7.1% (Kihiko, 2013).

Approximately 75% of snakebite victims tend to be bitten on the lower limbs while working in the farm, walking, herding, or resting at home. The remaining 25% are bitten on the hands (9%), lower arm (7%), upper arm (6%) and 2% on other body parts (Ochola et al., 2018).

2.3. Previous select studies on mathematical modelling of snakebites

2.3.1. Control of snakebite envenoming: a mathematical modeling study

Applying a S-I-R-S model to investigate the dynamics and control of snakebite envenoming, Abdullahi and his team divide the susceptible, envenomed and recovery state variables into defined compartments showing alternative transitions (Abdullahi et al., 2021). The human susceptible at time t (S(t)) population is divided into susceptible aware ($S_A(t)$) and unaware ($S_U(t)$) populations based on whether the population had/not received public health awareness on snakebite prevention. The envenomed individuals I(t) treated with antivenom were divided into those receiving early ($T_E(t)$) and late ($T_L(t)$) treatments with antivenom with subsequent subdivision of the $T_E(t)$ and $T_L(t)$ compartments into individuals experiencing early and late adverse reactions – $V_E(t)$ and $V_L(t)$ respectively. The recovery compartment was divided into with/without ($R_D(t)/R_W(t)$) disabilities to give the total human population. Hence, the total human population was considered as a component of nine mutually exclusive compartments.

$$N(t) = S_A(t) + S_U(t) + I(t) + T_E(t) + T_L(t) + V_E(t) + V_L(t) + R_D(t) + R_W(t) \quad \textbf{(2.1)}$$

Interacting with susceptible humans in the S compartment, total population of snakes $N_S(t)$ was included in the deterministic compartmental model. The model calibration and numerical simulations were performed using retrospective data gathered from six states available in a hospital to define parameters on $I(t), T_E(t), T_L(t), V_E(t), V_L(t), R_D(t), R_W(t)$ and deaths. Initial conditions and additional parameters were estimated using Least Square Method (LSM) at 100,000 iterations and the LSM outcome this was set as the initial guess for the Markov Chain Monte Carlo (MCMC) method.

A Gelman-Rubin diagnostic test set at 80,000 iterations and 40,000 burn in of iterations was used to enhance the convergence of MCMC algorithm. The validation of the convergence was approved if the chains converged at posterior distribution with a Potential Scale Reduction Factor (PSRC) close to the value $R_c = 1$. The model performance was assessed by comparing the model estimated values to the real dataset on monthly incidences of snakebites.

The study findings show that a combination of both public health awareness on snakebite preventive measures and timely antivenom administration of antivenom averts considerable numbers of snakebite induced deaths and disability adjusted life years. A cost-effective analysis through incremental cost-effective ratio was done to identify the best strategy for resource limited snakebite endemic settings.

Despite the significant achievement of the model, the study did not investigate the impact of weather in snakebite variations and focused only data from one species of medically important snake (carpet viper). Using data collected in a hospital setting and failure to transition the recovery back to susceptible population increases the risks of underestimation in the model estimates. Moreover, failure to use data from the community-level led to a miss out on the estimates of non-venomous bites.

2.3.2. Introduction of a mathematical model to characterize relative risk of SBE

Here, Kim conceptualized a model based on sociodemographic factors associated with mortality from snakebite and further created a compartmental epidemiological model that integrates different hospital seeking behavior based on the sociodemographic groups to estimate the comparative risks of mortality from envenoming. The two distinct exposure groups defined in the study were rural/exposed and urban/unexposed populations (Kim, 2020). Mining of these parameters involved the review of published hospital records to determine the exposure rates of SBE to the different demographic categories.

Kim conceptualized S-I-R model fitted with parameters from published literature including human factors, snake factors, geo-location, seasonality and time to determine the rate of transitioning through the compartments. The aim was to represent the variations in dynamics and outcomes of snakebite envenoming based on exposure levels of the rural and urban populations. The transition from human susceptible to envenomed population was as a result of interaction between human-snake populations with the encounters proportional to the snake population. The ode15s function in MATLAB was used to solve the system of differential equations for the state variables.

The model did not take into account the demographic processes of births and deaths in the total human population despite SBE being endemic in the study area. The number of snake encounters were assumed to be constant and this could misrepresent the effect of seasonality of snakebite. The model also failed to include transitions from recovery back to the susceptible compartment hence failing to account for the reported repeated bites by accumulating recoveries on the R compartment after long period.

2.3.3. *Integrating human behavior and snake ecology with agent-based models to predict snakebite in high-risk landscapes.*

The study investigates the behavioral mechanisms of different snake species responsible for the spatiotemporal variations in snakebite risk dynamics by incorporating geographical and climatic factors in an agent-based model (ABM). The model is parameterized with real datasets from Sri Lanka. The study area provides adequate, good quality and reliable data on SBE. The different variables used for model fitting included snake distribution, snake behavior, landscape characteristics, and three farmer types (Goldstein et al., 2020).

The researcher's choice on ABM approach was based on its ability to reveal internal dynamics and identify emerging patterns of complex systems that cannot be easily represented as differential equations. Model development for this study was done using the NetLogo program where each unique landscape in a study location was represented by a 2*2km fitted with 10m*10m grid cells. This was done for a total of 17 landscapes. Pattern Oriented Modelling (POM) was then applied in both the design and analysis of the model. The approach allows for both the determination of overall dynamics of snakebite in the three farmer types for all the species as well as investigating the hidden roles of the model parameters that cannot be observed independently.

The four steps of POM used in this study are similar with the overall process of compartmental modeling from model conceptualization, parameter estimation, calibration and model analysis. The first step of POM involved data mining and developing a reproducible model capable of generating observed patterns. The second phase entailed defining model parameters. The third pattern was to compare model estimates to real observed datasets and refining the parameters until the model estimates best represents the real scenario. The final fourth step was predicting outcome of snakebite from the already validated model. Land association factor was used to calculate snake species' preference for the different landcover types from the data points generated to represent species distribution while the likelihood of a specific species inhabiting an area versus probability of it being found in that area was then determined using chi-square tests.

Despite the significant milestone by the study to develop a reliable methodology in understanding epidemiology of snakebite, few limitations that can be later improved were noted. Focusing only on the agricultural workers failed to give a nationwide perspective. Contrary to SSA, Sri Lanka has strong health surveillance system that provides good estimates on snakebite statistics from their collected data. Also, the model does not give the endemic and disease-free equilibrium points.

2.3.4. Using mathematical models to estimate snakebite incidence in Costa Rica.

Although referred as mathematical modeling, the study largely applied regression analysis that borrowed heavily from law of mass action, a mathematical modeling concept, to estimate incidence of snakebite based on human-snake interaction. Law of mass action estimates encounters between the susceptible human and venomous snakes as proportional to the product of the two populations. The distribution of *Bothrops asper*, as the venomous snake of choice for the study, was estimated using niche modeling and the relative abundance of *B. asper* identified using active field work, used to calibrate the spatial model (Bravo-Vega et al., 2019).

A maximum entropy algorithm was used to perform the environmental niche modeling to estimate the distribution of B. asper species. This is an imaging technique used to smoothen images with high level of pixilation. The method is important in obtaining prior distribution probability in Bayesian inference. To estimate the incidence of snakebites easily, the encounter frequency of human susceptible with snake was used, rather than the actual population of snakes which is difficult to estimate. This model intercept allowed the residual terms to equate to zero, so that predicted incidences could be equal to the actual incidences given by the dataset. Model calibration was performed using data on man-hour encounter frequency with snakes during fieldwork and yearly snakebite incidence data. Formulated using the 'desmo' package in R, the model validation performance measures were Area under the Receiver Operating Characteristic (AUROC) and proportion of truly predicted values from confusion matrix.

Linear regression was used to model the incidence of snakebite with the level of significance set at 1%. The comparison between residuals and predicted values was done using Pearson's product moment correlation test. The performance validation was conducted through hypothesis testing of four models. First, null model with intercept (overall mean incidence of snakebite) equated to zero, bivariate model fitted with rural population, bivariate model with mean district encounter frequency as predictor variable, and adjusted model fitted with both rural population and mean district encounter frequency. The Akaike Information Criterion (AIC) value was used to select best fitting model, with the best fitting model recording the lowest AIC value.

Despite providing a suitable methodology to estimate snakebite incidences using compartmental models, several points of improvement can be noted from this study. The use of linear regression limits the dynamics of snakebite recovery and hospital seeking behavior. Availability of accurate data on snakebite epidemiology and strong surveillance systems in Costa Rica that lack in the Kenya and the larger SSA context.

2.3.5. Snakes of medical importance in Kenya

Snakes belong to the carnivorous group of reptiles under the suborder *Serpentes*, majority of the population being non-venomous and the venomous ones believed to use the venom mainly for destabilizing their prey (Kenya Ministry of Health Neglected Tropical Diseases Program, 2019). It is approximated that more than 250 species of snakes considered medically important by the WHO exist worldwide (WHO, 2017). Kenya is believed to be a home of approximately 140 species of snakes, out of which 29 are considered venomous with 13 proven to be medically important i.e. causing significant health defects following envenomation. Three snakes of medical importance responsible for majority of the cases reported in health facilities in Kitui county are the black mamba (*Dendroapsis polylepis*), the puff adder (*Bitis arietans*) and the black necked cobra (*Naja nigricollis*) (Kihiko, 2013).

Table 1. Distribution of medically important snakes in Kenya

Species	**Distribution**
Black mamba (*Dendroaspis polylepsis*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mount Kenya, Lake Baringo, Mount Elgon, Kakuma, North-eastern province, Coastal regions, Lamu, Malindi, Mombasa, Ukambani (Makueni)
Eastern Green mamba (*Dendroaspis angusticeps*)	Aberdares, Lake Naivasha, Mount Kenya, Coastal region, Kibwezi/Chyulu, Nyambene/Meru area.
Jameson's mamba (*Dendroaspis jamesoni*)	Kakamega forest, Lake region, Mau Forest, Masai Mara.
Puff adder (*Bitis arietans*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mount Kenya, Lake Baringo, Mount Elgon, Kakuma, North-eastern province, Coastal regions, Lamu, Malindi, Mombasa, Ukambani (Makueni)
Gaboon viper (*Bitis gabonica*)	Kakamega forest, Lake region, Mau Forest, Masai Mara

Species	**Distribution**
Rhinoceros viper (*Bitis nasicornis*)	Kakamega forest, lake region, Mau Forest, Masai Mara
Kenya Horned Viper (*Bitis worthingtonii*)	Rift valley between Naivasha and Eldoret
Saw- scaled viper (*Echis carinatus*)	Lake Baringo, Kakuma, Mount Elgon, Makueni, Tsavo National Park, North-eastern Province.
Carpet Viper (*Echis pyramidum*)	North of the equator
Black-necked spitting cobra (*Naja nigricollis*)	Kakamega forest, Lake region, Mau Forest, Narok county, Lake Naivasha, Aberdares, Mount Kenya, Lake Baringo, Mount Elgon, Kakuma, North-eastern province, Coastal regions, Lamu, Malindi, Mombasa, Ukambani (Makueni)
Red spitting cobra (*Naja pallida*)	Lake Baringo, Mt. Elgon, Kakuma, North-eastern Province, Ukambani
Large brown spitting cobra (*Naja ashei*)	Kakamega forest, lake region, Maasai mara, Mau Forest, Kakuma, Mt. Elgon, Lake Baringo, Aberdares, Mt. Kenya, coastal parts of Kenya
Egyptian cobra (*Naja haje*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mount Kenya, Lake Baringo, Mount Elgon, Kakuma, North-eastern province, Ukambani (Makueni)
Forest cobra (*Naja melanoleuca*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mt. Kenya, Lake Baringo, Mt. Elgon, Kakuma, Nairobi, Makueni, Tsavo, Coastal region
Gold's Tree Cobra (*Pseudohaje goldi*)	Western Kenya

Species	**Distribution**
Boomslang (*Dispholidus typus*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mt. Kenya, Lake Baringo, Mt. Elgon, Kakuma, Nairobi, Makueni, Tsavo, Coastal region
Blanding's Tree Snake (*Toxicodryas blandingii*)	Western Kenya
Twig snake (*Thelotornis Kirtlandii*)	Coastal region
Mole Viper (*Atractaspis species*)	Distribution as for Black mamba
Night adders (*Causus defilippii*, *Causus lichtensteini*, *Causus resimus*, *Causus rhombeatus*)	Kakamega forest, Lake region, Mau Forest, Masai Mara, Lake Naivasha, Aberdares, Mount Kenya, Lake Baringo, Mount Elgon, Kakuma, Coastal regions, Lamu, Malindi, Mombasa, Ukambani (Makueni), Nairobi
Prickly Bush Viper (*Atheris hispida*)	Western Kenya
Green Bush viper (*Atheris squamigera*)	Western Kenya
Mount Kenya Bush viper (*Atheris desaixi*)	Mount Kenya and Nyambene
East African Garter Snake (*Elapsoidea loveridgei*)	Central Highlands and Nairobi
Usambara Garter Snake (*Elapsoidea nigra*)	Shimba Hills
Yellow-Bellied Sea Snake (*Pelamis platuru*)	East African Coast

2.4. Prevention, Control and Management strategies for SBE

Snake antivenom is the only proven therapy for SBE. However, this valuable remedy has, over the years, been characterized by limited production, ineffectiveness and even lack of production especially in sub Saharan Africa and South East Asia (Gutiérrez et al., 2014; Williams, 2015). Prevention of SBE is therefore, viewed as the best measure to reduce the burden associated with SBE. This involves majorly interventions geared towards health education and behaviour change communication (BCC) (Kenya Ministry of Health Neglected Tropical Diseases Program, 2019). Prevention measures focus on reducing snakebite incidences as well as minimizing the severity of envenomation.

3. CHAPTER THREE: METHODOLOGY

3.1. Introduction

This chapter highlights the technical approaches that will be used to meet study objectives. A detailed description of how the study will be implemented including data collection and analysis has been provided. The section highlights stepwise approach used through model formulation, obtaining model parameters, fitting model with real data, assessing dynamics of snakebite cases given different model parameters and determining optimal hospital seeking proportions that will avert maximum deaths. The method involving development of logistic growth model predicting population of snakes in the human-snake shared interface has been given including revising the values by adjusting for non-reporting rate.

3.2. Study design

Discrete-time, deterministic SIRS compartmental modeling. The study will model numbers of snakebite in days as the time events making it a discrete time model. Since the model will predict incidences based on average values of parameters, without considering randomness, deterministic approach will be used. Finally the model assumes susceptible class will go through the infected, recovered and back to susceptible, hence SIRS model.

3.3. Study area

Turkana County was purposively selected. Turkana County suffers the highest burden of snakebite disease according the Kenya Health Information System (KHIS) platform. Moreover, to the best of our knowledge, no research study on snakebite has been undertaken in the area hence having a wide knowledge gap on the burden and epidemiology of snakebites in the County.

3.4. Description of study area

Turkana County is one of the 47 counties of Kenya located in the North-west region bordering Uganda to the west, Sudan and Ethiopia to the North. Locally, Turkana County borders West Pokot, Marsabit, Baringo and Samburu Counties. The county covers and area 77,000 km2 approximately 13% of Kenya’s land mass, making it the second largest county in Kenya. Despite hosting Lake Turkana, the county experiences hot and dry climate with average temperatures of 30.70C, 50.35mm precipitation and 72 rainy days. The main economic activity is pastoralism characterized by nomadic lifestyle and cattle rustling that poses grave insecurity concerns especially with bordering communities like Pokot of W. Pokot County and Toposa of Sudan. The total population of Turkana

County as reported in the Kenya Population and Housing census report 2019 is 926,927 with an average household size of 5.6 (Kenya National Bureau of Statistics, 2019).

3.5. Sampling techniques

Study area was purposively selected due to the high number of snakebites reported in the County and lack of information on epidemiology and statistics of snakebite in Turkana County.

3.6. Sample size

Present study assumes a completely susceptible, naïve population hence the entire county population was regarded as susceptible to snakebite event. The total population of Turkana County based on the previous population and housing census report 2019 was 926,976 (Kenya National Bureau of Statistics, 2019).

3.7. Data sources

Model parameters for present study were sourced from published and grey literature using desk review as well as analysis of the KHIS data.

Sourcing of parameters for the model will exclusively rely on secondary data from different sources.

- Kenya Health Information System (KHIS) for the period January 2018 to December 2022. This was used to calibrate the logistic growth model.
- Desktop review of published literature. This will be used to determine model parameter values for the SIRS model and non-hospital reporting rate to improve the logistic growth model.

3.8. Mining for parameter values

Literature on snakebite was searched in PubMed journal to retrieve the most relevant papers using the syntax: (snakebite) AND ((mortalities) OR (fatalities) OR (envenomation outcomes)) AND ((health seeking) OR (hospital seeking)). The journal was last visited on the 11th August, 2023. A total of 26 papers were identified and screened through titles, abstract and full text. Duplicates were removed from the list of papers before commencing the screening process. Eight papers were omitted during title screening and twelve omitted at abstract screening phase. The remaining seven papers passed the full text screening and were included into the study. An addition of 11 papers were identified through references in the papers passed for data abstraction, totaling to 18 papers. Additional papers were identified through references in the papers that qualified for full text review. Excel worksheet was used for data abstraction of parameter values. The figure below highlights the process used in retrieving the most relevant papers used in data abstraction.

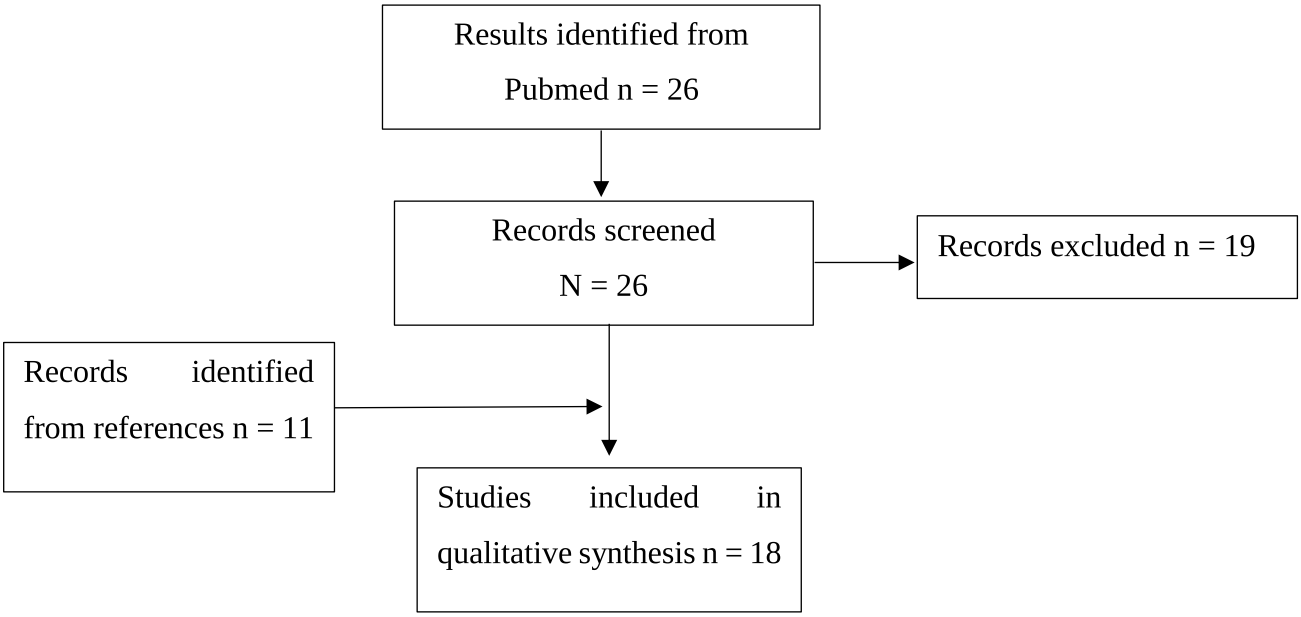


Table 2. The table below highlights the papers used in collecting snakebite envenoming determinant rates including the literature references.

Determinant rates	References
probability of bite	(Farooq et al., 2022; Alcoba et al., 2020; Kenya Ministry of Health Neglected Tropical Diseases Program, 2019; Chippaux, 2017a, 2011)
Hospital seeking behavior	(Francis et al., 2023; Farooq et al., 2022; Alcoba et al., 2020; Dandona et al., 2018; Fox et al., 2006)
Outcomes from snakebite	(Abdullahi, S.A et al., 2022; Alcoba et al., 2020; Halilu et al., 2019; Gampini et al., 2016; Adiwinata & Nelwan, 2015; Kasturiratne et al., 2008; Fox et al., 2006; McGain et al., 2004)

3.9. Snake model - Logistic growth model

The snake model was first fitted to simulate density of snakes in the human-snake shared interface. A logistic model estimating change in density of snakes was generated in the form of

$$\frac{dP}{dt} = rP(1 - \frac{P}{K})$$

where:

P - Population of snakes; t - simulation time; r - rate of recruitment; K - carrying capacity

The model was calibrated with KHIS data on 2018-2022 monthly reported incidences of snakebites in Turkana County. Assuming that every bite comes from a single unique snake, the carrying capacity was capped at the maximum value of reported snakebites and the initial population set at the minimum possible value. The assumption takes account of the reported bites of more than once on an individual and multiple bites from a single snake.

Based on the monthly variation of reported snakebites, the rate of recruitment *(r)* was allowed to take multiple values and change over the 12 months of the year.

$$\frac{dP}{dt} = r_{(t)}*P(1 - \frac{P}{K})$$

Where t = 1, 2,… , 12

3.9.1. Obtaining rates of recruitment from KHIS data

The data on monthly incidences of snakebite 2016-2022 was accessed through Ministry of Health. Data cleaning and processing entailed filtering out all health facilities outside Turkana county, converting the data into long format by gathering the months into one column and reported cases in another column. The date object was converted to date class and the mean monthly incidences of reported snakebite cases obtained for the years 2018-2022.

3.9.2. Adjusting for under reporting and missed cases

The adjustment factor for the non-reporting rate was computed based on previous surveys identifying proportion of individuals who do not seek hospital care following snakebite. Present study assumed a constant non-reporting rate based on this value.

$$correctionfactor = \frac{Number\ snakebite\ victims\ seeking\ hospital\ treatment}{Numbersnakebite\ victims\ not\ seeking\ hospital\ treatment}$$

3.9.3. Improving fitness of the simulated data to adjusted observed data

Trajectory matching was used to improve the fitness of the simulated data to the observed (adjusted) data. This was done altering the recruitment rates in the logistic growth model of snake population. At first, the simulated model was plotted together with values from the observed (adjusted) data. Thereafter, differences in the points, trend and pattern of the plot was corrected by altering recruitment rates in the logistic model at points and observing as changes were effected in the plot in the plot. This was iteratively done for all the points until a better fit was achieved. The likelihood value for the simulated data was then obtained, given the observed data for the two logistic growth models (before and after trajectory matching) to determine model with maximum likelihood estimates.

3.10. SIRS deterministic model (Discrete-time)

Model formulation for this study followed individuals in the susceptible compartment through the infected, recovered and back to susceptible class using defined parameter values obtained from literature. Background characteristics like births and deaths were captured since snakebite is an endemic disease

3.10.1. Description of model diagram

A compartmental discrete-time SIRS model for endemic diseases was developed to simulate the dynamics of snakebite in Turkana County. The recruitment of susceptible (S) to the infected (I) when the human susceptible population interacted with snakes population occurred at a force of infection beta (β). The population of snakes in the human-snake shared interface was generated by logistic growth model from the snake compartment (P). The rate of transition from susceptible to infected was dependent on the population of snakes. Natural births and deaths were included into the susceptible compartment at rates b and mu (μ) respectively.

The infected (I) compartment was divided into two: hospital (H) and conservative (C) compartments representing snakebite victims who seek hospital and traditional/conservative treatments respectively. The rate of transition from S to H was defined by rate theta (θ) while the transition to C compartment was at rate sigma (σ). Recovered patients left the Hospital compartment at a rate psi (ψ) which represented inverse of the average duration of illness. Those in C compartment recovered at a rate phi (φ) representing the inverse for average duration of illness of snakebite victims that do not seek hospital treatment.

All the recovered individuals moved back to the susceptible compartment at rate gamma (γ). Snakebite induced mortality rates were defined using rates lambda (λ), rho (ρ) and omega (ω) for I, H and C compartments respectively. Natural deaths were also included in these compartments.

The model was simulated in a disease-free, fully susceptible population with initial conditions for S = 926,000 (obtained from 2019 census report), and I = 0. The population of snakes was kept constant, obtained as the median value of snake population from the simulated data.

3.10.2. Model assumptions

The following assumptions were used to define transition parameters and state variables

i. The population of snakes is constant throughout the simulation period
ii. No immigration and/or emigration of snakes into and out of the snake population.
iii. All species of snakes exhibit similar behavior during human-snake interaction

iv. The population is fixed. Birth/death and immigration/emigration rates are assumed to be equal
v. All the susceptible individuals are equally susceptible
vi. Envenomed individuals become susceptible again following recovery.
vii. There are no bites in snakebite victims undergoing treatment
viii. All cases of snakebites including multiple bites on an individual are from unique snakes.
ix. No immigration and/or emigration of susceptible and/or envenomed patients into and out of the human population.

3.10.3. Definition of state variables and model parameters

The following are the state variables and model parameters and their definition

i. **S** – Susceptible
ii. **I** – Infected (snakebite cases)
iii. **H -** Hospital treatment
iv. **C**- Conservative/traditional treatment
v. **R** – Recovery
vi. **P** - Population of snakes
vii. **b** - Birth rate
viii. **μ** - Natural deaths
ix. **β** - Force of infection
x. **λ –** Snakebite induced deaths (overall)
xi. **ϴ** - Proportion seeking hospital treatment
xii. **1- ϴ** - Proportion not seeking hospital treatment
xiii. **ρ** - Snakebite induced deaths in hospital compartment
xiv. **ω** - Snakebite induced deaths in conservative/traditional compartment
xv. **Ψ** - Rate of recovery in hospital
xvi. **Φ** - Rate of recovery in traditional

3.10.4. *Model conceptualization*

The initial conditions of the model were set at S (0) = S_0, I (0) = I_0 and R (0) = R_0 and total population N including the S, I and R.

$$N = S + I + R = N_o = S_0 + I_0 + R_0$$

The transition from human susceptible population (S) to infected (I) compartment was computed as a product of both the human and snake factors – human susceptible population, population of snakes in human-snake interface, encounter rate between snakes and susceptible human population, and the probability of bites given bite. The infected (I) compartment therefore referred all those who had experienced snakebite. The infected (snakebite victims) compartment was then stratified into two compartments: those seeking hospital treatment (H) and those not hospital treatment (C) compartments.

3.10.4.1. *The Susceptible (S) compartment*

The susceptible population at time t (S_t) represent the population at risk of experiencing snakebite at any given moment. In this study, we consider our human susceptible population as 'fixed' with rate of births (b) equal to the rate of natural deaths (μ).

$$b = \mu$$

The changes in numbers of susceptible was dependent on the rate of births (b) in the target population, rate of natural deaths (μ) and number of snakebites occurring in the population. The number of snakebites at a given time will be a product of the force of infection (β), human susceptible population at time t (S_t) and population of snakes at time t (P_t). The number of recoveries going back to the susceptible class were also factored in the equation.

$$\frac{dS}{dt} = bN - \beta SP + \gamma R$$

3.10.4.2. *The Infected (I) compartment*

Upon snakebite, the victims will move from the S to I compartment. The rate of change in number of individuals moving into I compartment was obtained as shown in the S to I transition equations. The infected individuals seeking hospital care at rate ϴ recovered at rate Ψ, died from disease induced deaths at rate ρ or died from natural deaths at rate μ

$$\frac{dI}{dt} = \beta SP - \Theta I - \sigma I - \mu I$$

Infected individuals who opted for other means of treatment other than hospital care (conservative) transitioned at rate σ, died from disease induced deaths at rate ω or died from natural deaths at rate μ

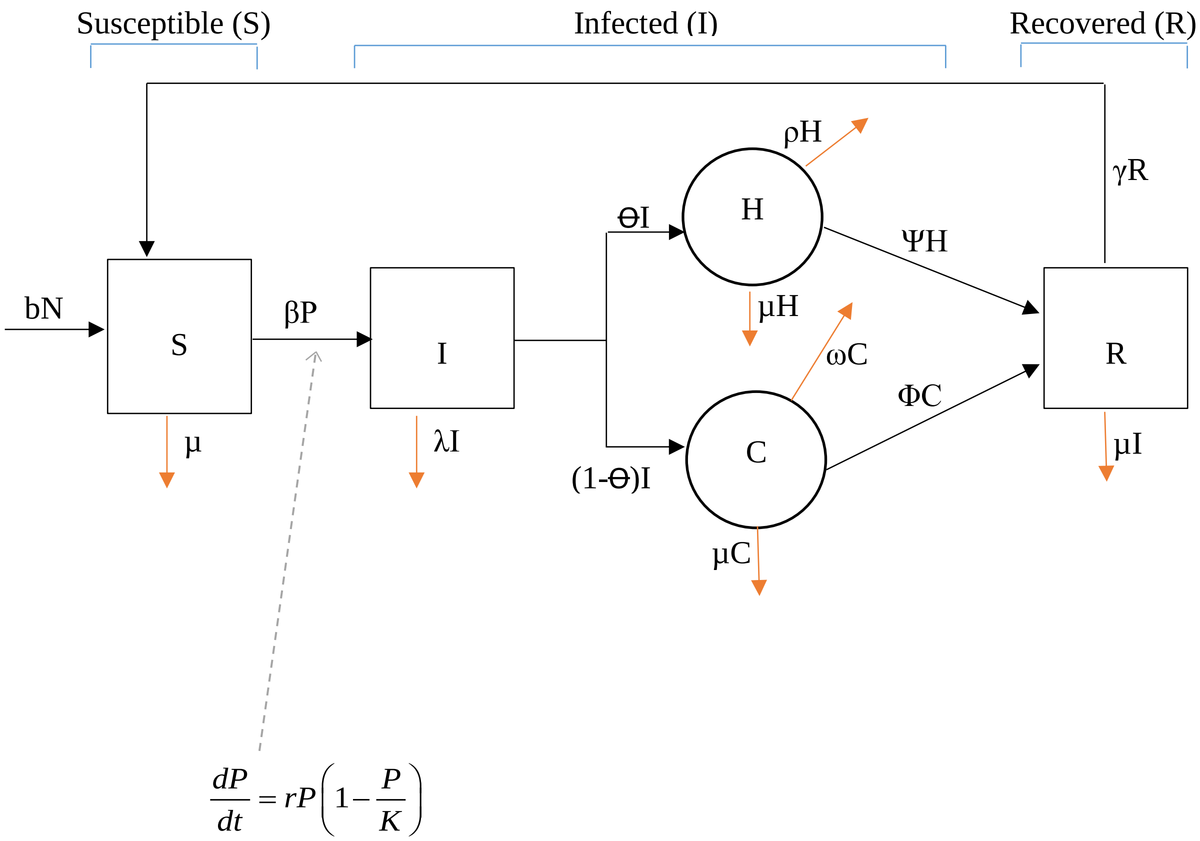
$$\frac{dH}{dt} = \square I - \Psi H - \rho H - \mu H$$

3.10.4.3. The Recovered (C) compartment

The recovered compartment contained recovered individuals from hospital compartment (ΨH) and conservative compartment (ΦC) minus individuals going back to the susceptible class (γR).

$$\frac{dR}{dt} = \Psi H + \Phi C - \gamma R$$

3.11. Model diagram



The differential equations that define are the model are

i. $\frac{dS}{dt} = bN - \beta SP + \gamma R$

ii. $\frac{dI}{dt} = \beta SP - \square I - \sigma I - \mu I$

iii. $\frac{dH}{dt} = \square I - \Psi H - \rho H - \mu H$

iv. $\frac{dC}{dt} = \sigma I - \Phi C - \omega C - \mu C$

v. $\frac{dR}{dt} = \Psi H + \Phi C - \gamma R$

vi. $\frac{dP}{dt} = rP(1 - \frac{P}{K})$

3.12. Evaluating snakebite dynamics by varying parameter values

The dynamics of snakebite in the study population was assessed through variation of values for the parameters: force of infection (β) and disease induced death rate (λ). The numbers of snakebite cases were simulated for multiple parameter values as obtained from literature and a nested loop algorithm created to loop through the parameter values and predict snakebite incidences for the specific conditions.

3.13. Identifying rates of hospital-seeking behavior associated with lowest case-fatalities

The rates of hospital seeking behavior was varied from 0 to 100% at 10% intervals and cumulative number of deaths computed. Proportion of those seeking hospital care was obtained as number of those going to the hospital following snakebite (Hospital compartment), divided by the total number of bites (Incidence compartment)

$$\text{Proportion seeking hospital care after snakebite} = \frac{\boldsymbol{H}}{\boldsymbol{I}}$$

A total of ten (10) proportion estimates was calculated by varying the values of ϴ from 0% to 100% and the value of σ from 100% to 0% in 10% intervals such that when ϴ = 0%; σ = 100% and when ϴ = 10%; σ = 90%.

3.14. Numerical simulation of the ordinary differential equations

Model development and analysis was done in R software. An algorithm defining the system of ordinary differential equations for the transitions through state variables was developed and 'deSolve' package used for numerical simulation. The initial conditions and model parameters were all defined before running the simulation for a period of 366 days. The data output contained numbers of susceptible, infected, hospital, conservative and recovered individuals on a daily basis for the simulation period.

The cumulative number of infected was obtained by omitting the recovery part of the equation defining the infected compartment. 'ggplot2' package was used to generate graphs and plots using data predicted from the model. Numerical simulation of varying rates of hospital seeking behavior was done by generating a 'for loop' algorithm allowing the ODE equations to predict values of bite for hospital seeking rates of 0% to 100% at 10% intervals.

4. CHAPTER FOUR: RESULTS

4.1. Introduction

This chapter highlights findings from the model analysis, numerical simulation and optimal control for hospital seeking behavior associated with lowest numbers of snakebite induced deaths. The section starts by highlighting discrepancies between reported and expected number of monthly cases from KHIS after incorporating correction factor from literature. Subsequently the fitness of logistic growth model to the adjusted values is shown before and after trajectory matching using maximum likelihood estimates. The number of snakebite cases from SIRS model are given including deaths given the average hospital seeking behavior obtained from literature. Changes in snakebite numbers from varying model parameters is also shown. The chapter concludes by showing number of deaths from simulating different rates of hospital seeking behavior and further obtained optimal control that leads to highest number of averted deaths.

Table 2. Model parameter values

Interpretation	Parameter	Value	Units	Reference
human population	N	926000	persons	(KPHC, 2019)
Days per year	-	365	days	-
life expectancy	-	65	years	Please fill in the reference
birth rate	µb	4.21E-05	1/day	calculated
natural death rate	ud	4.21E-05	1/day	calculated
probability of bite 0.00003	β	0.000002	1/day	calculated
	β	0.0001	1/day	Farooq et al., 2022
	β	0.00002	1/day	Alcoba et al., 2020
	β	0.000001	1/day	Kenya Ministry of Health Neglected Tropical Diseases Program, 2019
	β	0.000002	1/day	J.-P. Chippaux, 2011
prop. Seeking hospital treatment 0.39	θ	0.16	1/day	Farooq et al., 2022
	θ	0.46	1/day	Dandona et al., 2018
	θ	0.375	1/day	Fox et al., 2006
	θ	0.47	1/day	Alcoba et al., 2020
	Θ	0.47	1/day	Francis et al., 2023

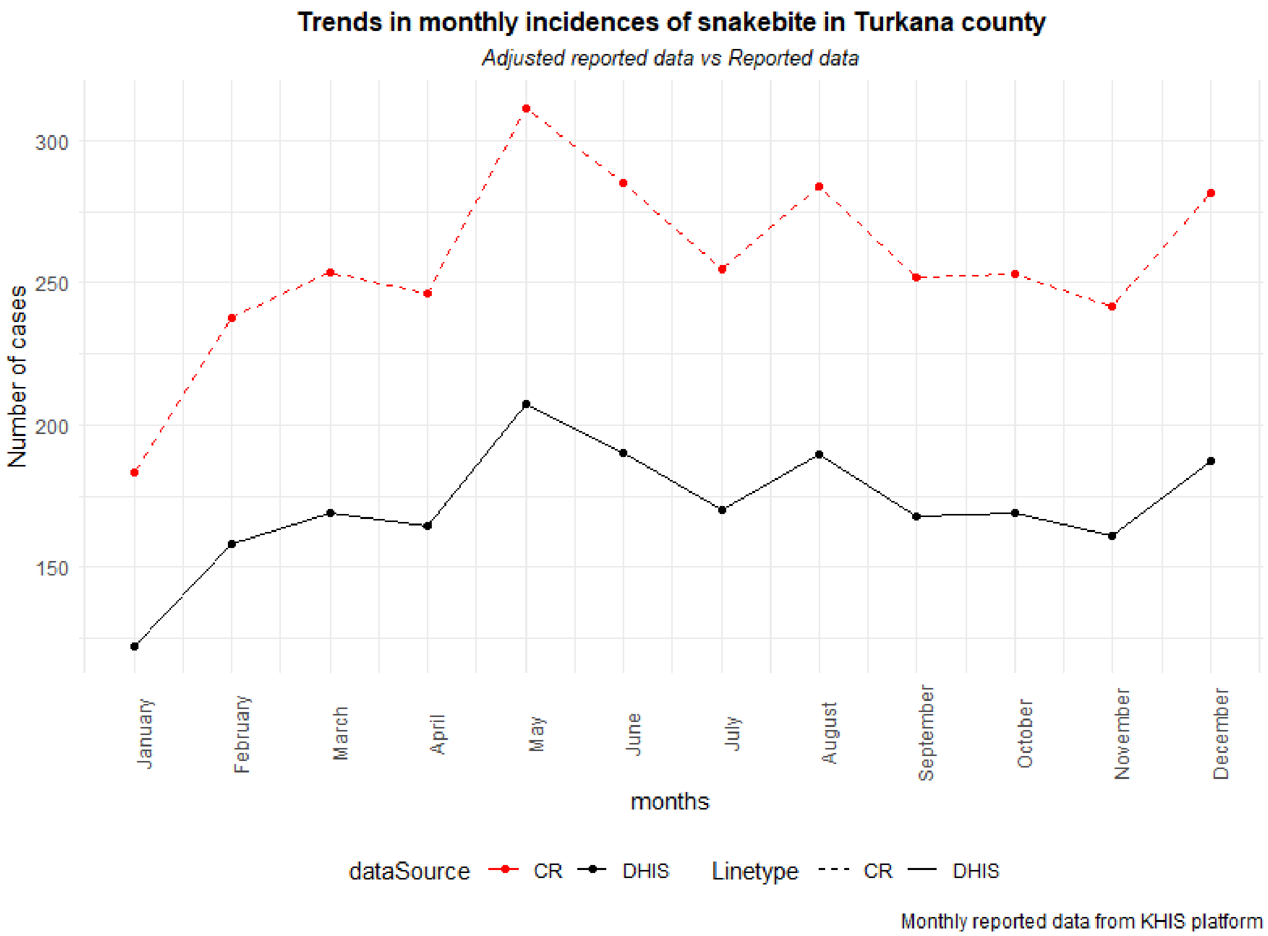
prop. Seeking traditional treatment	(1- θ)	0.59	1/day	Farooq et al., 2022
0.61	(1- θ)	0.625	1/day	Fox et al., 2006
Recovery rate for hospital treatment	ψ	0.142857143	1/day	Abdullahi, S.A et al., 2022
Recovery rate for traditional treatment	φ	0.047619048	1/day	Assumed
Overall recovery rate	γ	0.095238095	1/day	Assumed
disease induced death rate 0.04	λ	0.03	1/day	Alcoba et al., 2020;
	λ	0.03	1/day	Adiwinata & Nelwan, 2015
	λ	0.05	1/day	Halilu et al., 2019
	λ	0.02	1/day	Gampini et al., 2016
	λ	0.05	1/day	Gampini et al., 2016
	ρ	0.0064	1/day	McGain et al., 2004
	ρ	0.002	1/day	Fox et al., 2006
disease induced death rate (traditional)	ω	0.0358	1/day	Estimated

4.2. Snake model - Logistic growth model

The logistic model was fitted with 11 rates of recruitment that define values for subsequent months after January. Positive growth rates in the population of snakes were observed in the months of February, April, July, August, October and December.

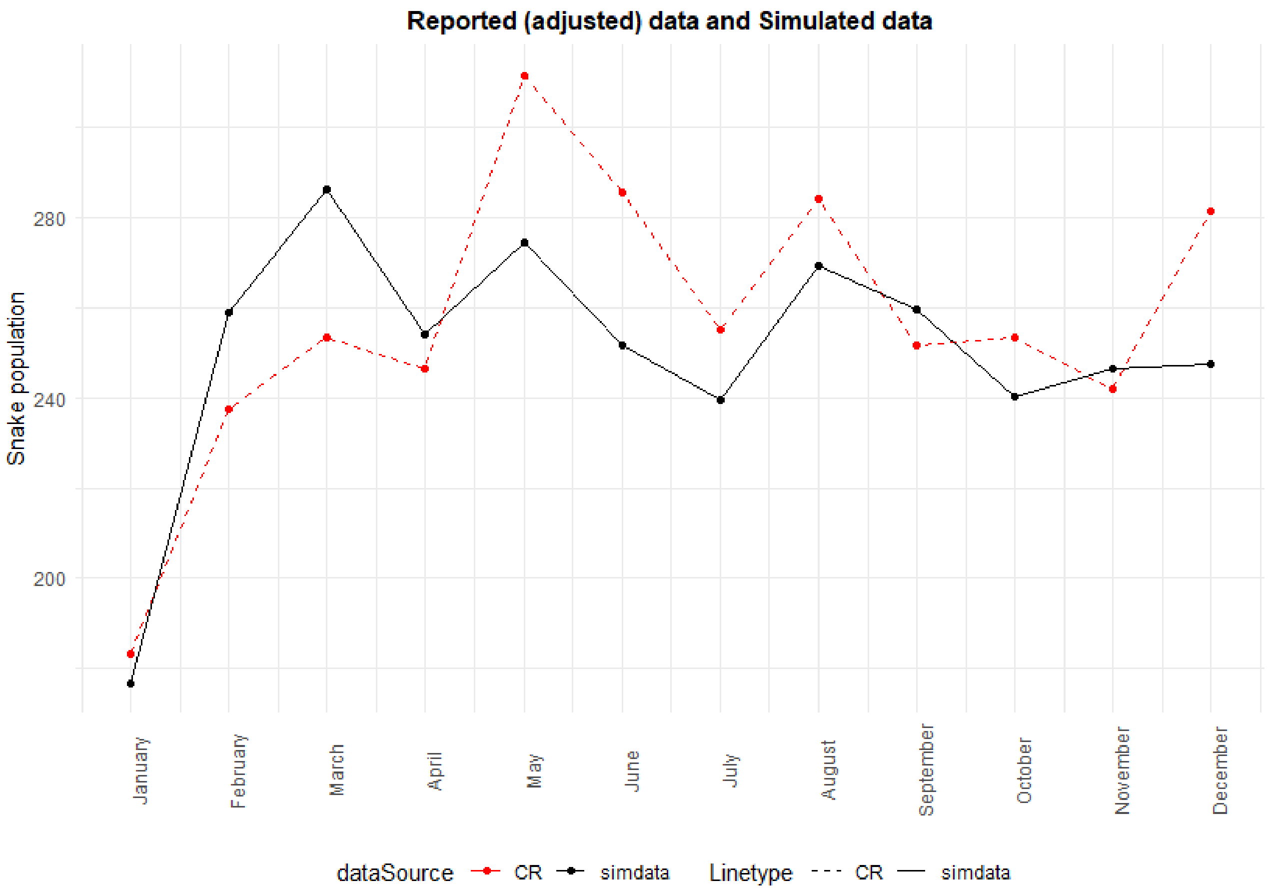
4.2.1. Comparison of KHIS reported and adjusted values

Despite showing the same trend, the line plot for adjusted reported data was shifted vertically along the values when compared to the plot for reported data from KHIS platform. While the maximum value for KHIS data was 207, the maximum value from reported data was 271. The minimum values were 122 and 159 for the KHIS and reported data respectively while the median and interquartile ranges were (observed: median - 168; IQR - 24) and (adjusted: median - 220; interquartile - 32)

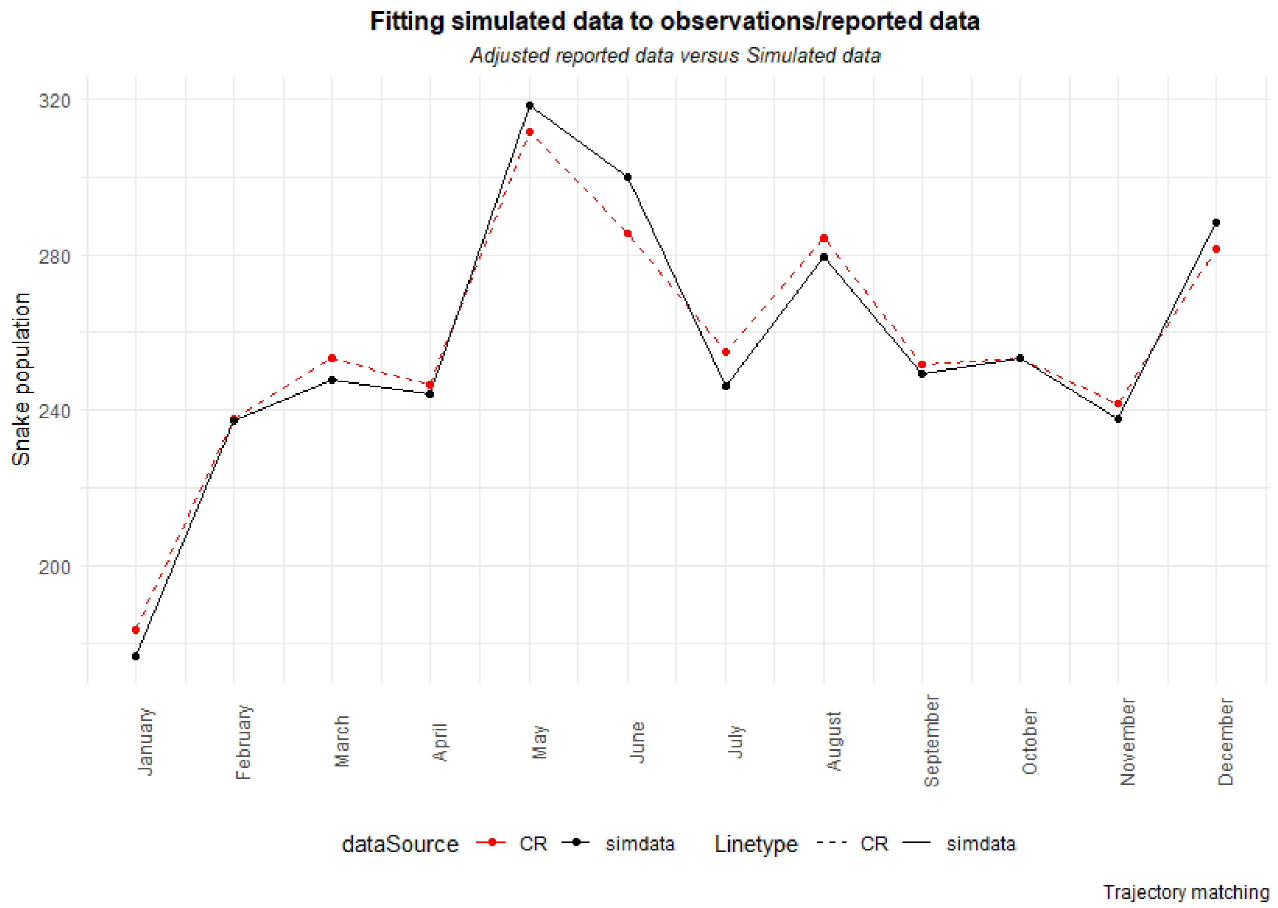


4.2.2. Fitting model with the observed data (adjusted)

Simulated data did not however, offer a good fitness to the adjusted data. Model simulated data predicted minimum value slightly below the observed (adjusted) data while the highest value was markedly lower than the highest point of the observed (adjusted) data. This was an indication of lower initial value and lower rates of recruitment for the simulated data. Furthermore, despite showing a similar pattern, simulated data did not align to the pattern of observed data hence giving wrong impressions on the seasonality associated with snake population. Simulated data predicted highest population of snakes in the month of March which was against the observed data (peak was in the month of May). The line graph below shows the values for each month and trends in number of snakes from both the observed data (adjusted) and simulated data



After adjusting the recruitment rates to match the adjusted observed data, simulated data of snake population showed improved fitness to the data. The pattern of simulated data showed to match that of the adjusted observed data with peak value reported in the month of May and lowest value in the month of January as was the case in the adjusted reported data. The covariance value between the adjusted observed data and the simulated data was higher (1160) than initially (631), an indication that there was a better correlation between observed and simulated data after trajectory matching.



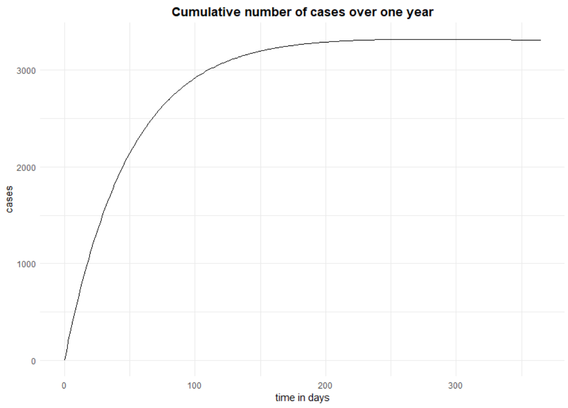
4.3. SIRS deterministic model (discrete-time)

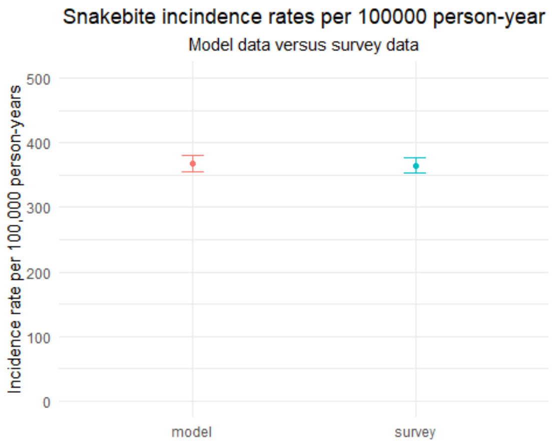
This section highlights the model results including the output on number of snakebite cases and deaths estimated by the model, variation in the snakebite incidences obtained by varying model parameter values and effect of hospital seeking on snakebite deaths.

4.3.1. Cumulative numbers of snakebite cases

When the median number of snakes from logistic growth model (220) was introduced into a naive human population of 926,000 completely susceptible individuals for a period of 360 days, a steady increase in recruitment of snakebite incidences was observed from day 0 to day 100. The rate of recruitment then increased at decreasing rate until day 200 where it stabilized into a steady state with no further increase in numbers of snakebite incidences with time. The maximum number of snakebite incidences was 3319.19.

A comparison between the annual incidence rates of snakebite between simulated and the survey data showed no marked difference. The incidence rate from simulated data as 368.15 cases per 100,000 person-year (95% confidence interval 355.73-380.89) while incidence rate from the adjusted data 364.99 cases per 100,000 person-year (95% confidence interval 352.79-377.51). The figures below highlight the changes in cumulative number of snakebites from model output in a completely susceptible disease-free population and comparison in incidence rates between the model output and survey data.





4.3.2. Change in number of Susceptible, Recoveries and Deaths

4.3.2.1. Susceptible (S) compartment

There was minimal change in the number of susceptible. The numbers of susceptible dropped from 926,000 to 920,023.3 at the end of the simulation period (365 days) with 5976.742 omissions. This is despite including deaths from natural causes in both the susceptible, infected and recovery compartments.

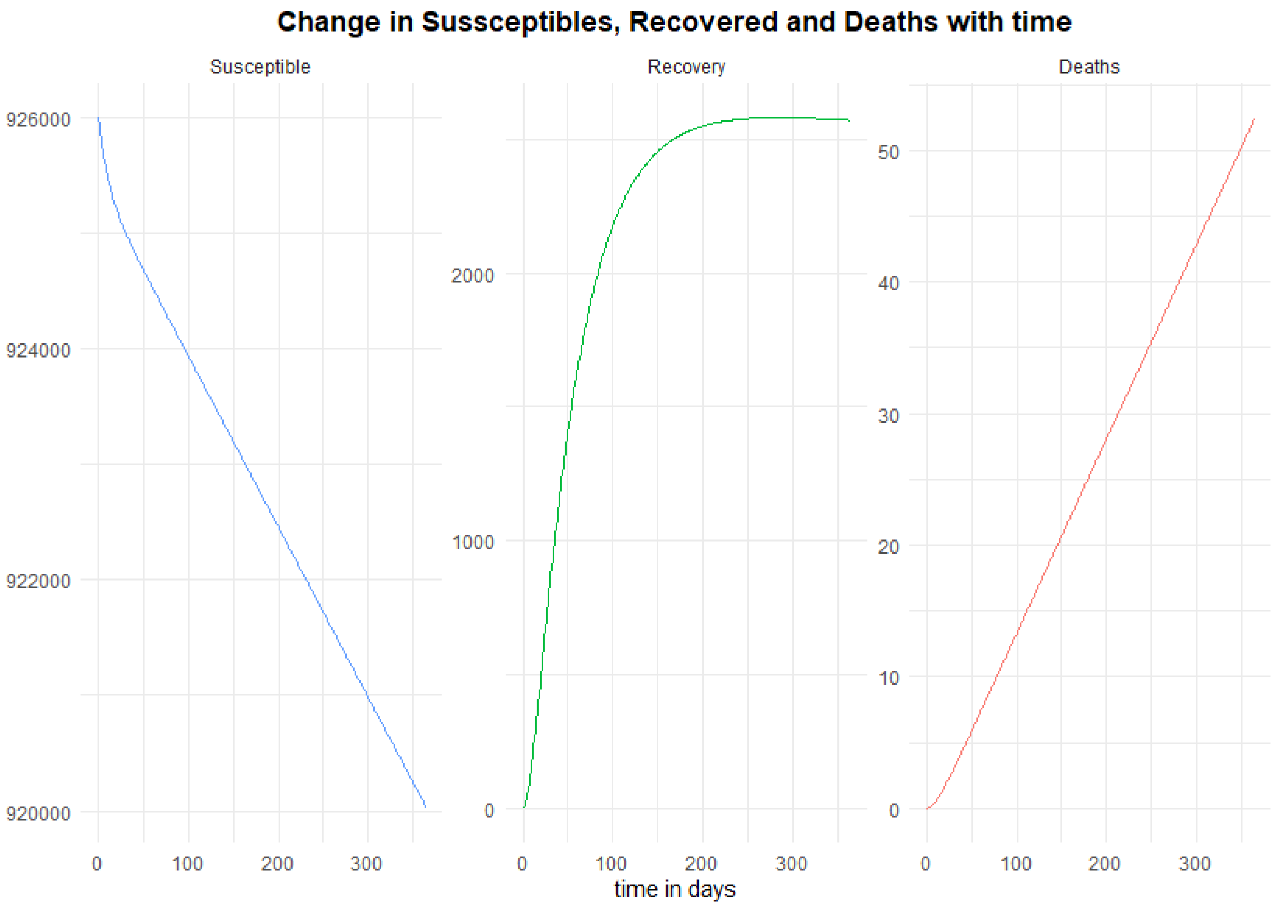
4.3.2.2. Recovery (R) compartment

There were total of 2580.49 recoveries recorded. The trend of recoveries over time assumed a sigmoid curve with rate of recruitment into the recovery compartment increasing at an increasing rate until around day 100 when the rate of recruitment into the recovery compartment begun to increase at a decreasing rate. The numbers stabilized at day 250 throughout the remaining simulation period.

4.3.2.3. Number of deaths

The numbers of snakebite induced deaths totaled to 52.46 at the end of the simulation period. Snakebite induced mortality rate was 0.016 (95% confidence interval 0.012 - 0.021; p-value < 0.001). The overall mortality rate was 5.7 deaths per 100,000 person-year (95% confidence interval 4.3 - 7.5; p-value < 0.001).

The following figure shows changes in the numbers of susceptible, recovered and deaths.

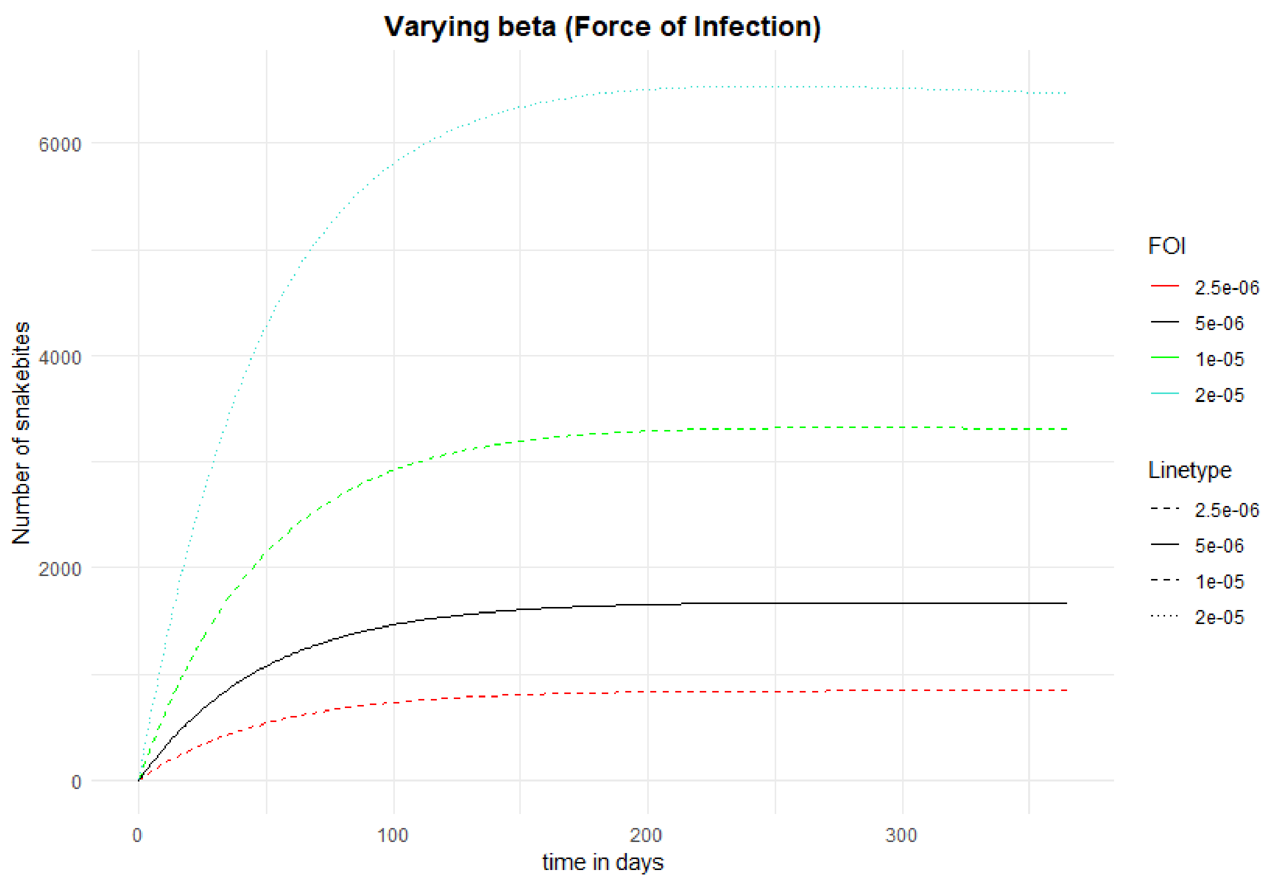


4.4. Snakebite dynamics from varying model parameters

4.4.1. Force of infection (beta)

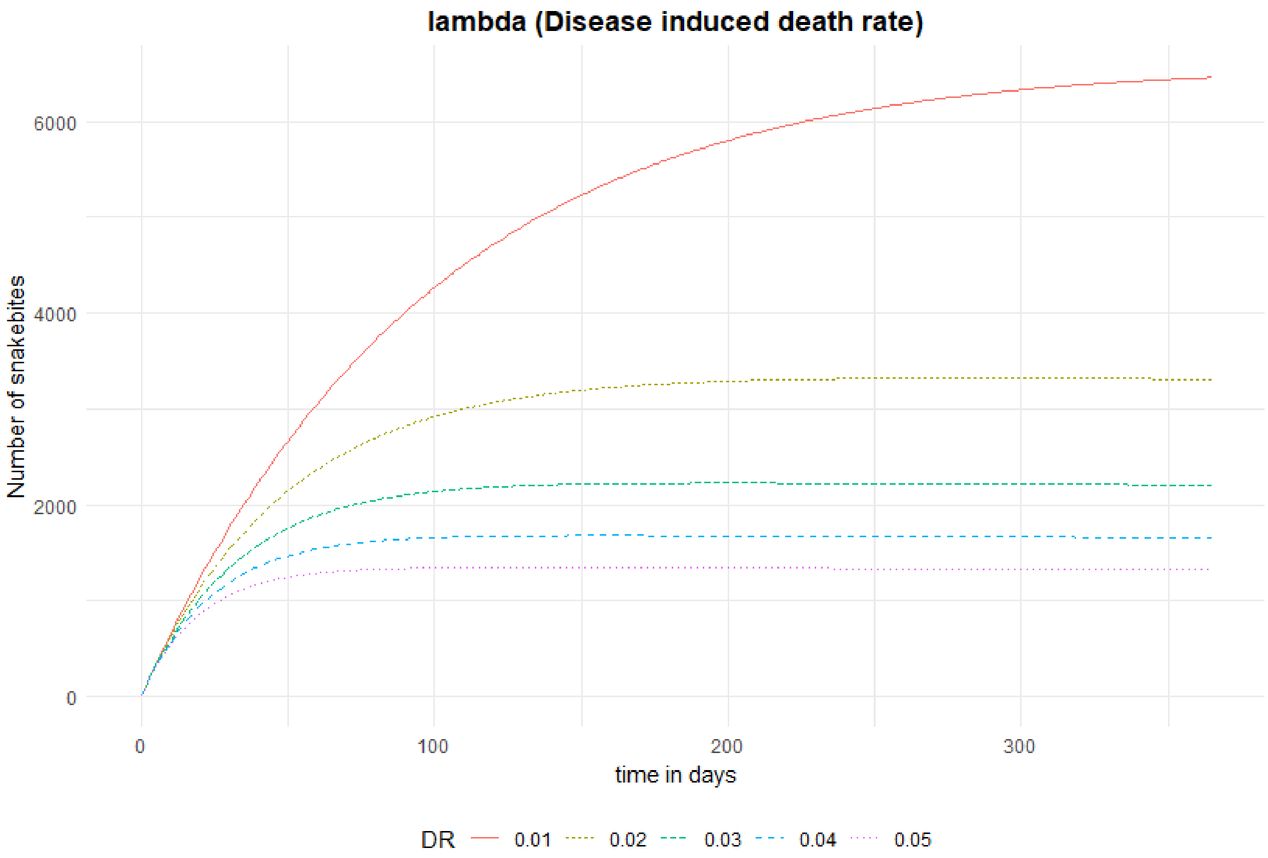
There was an increase in number of snakebites with increase in the force of infection. Doubling the value for force of infection resulted in double the peak number of estimated snakebite. For instance, at $\beta = 0.0000025$, the peak number of snakebites were 841.65. The peak number of snakebites at $\beta = 0.000005$, 0.00001 and 0.00002 were 1674.66, 3319.19 and 6536.44 respectively. When divided with subsequent, these values give a quotient of 1.97, 1.98 and 1.99 for 1674.66/841.65; 3319.19/1674.66 and 6536.44/3319.19 respectively.

A similar trend in number of snakebite cases over time was seen for all the values of beta, shown by an increasing trend and later of, flattening of the curve. There was however, delay in the flattening of the curve with increase in the values of beta an indication of lower parameter value. The figure below shows changes in the predicted number of snakebite cases with change in time for different values of force of infection.



4.4.2. Death rate (lambda)

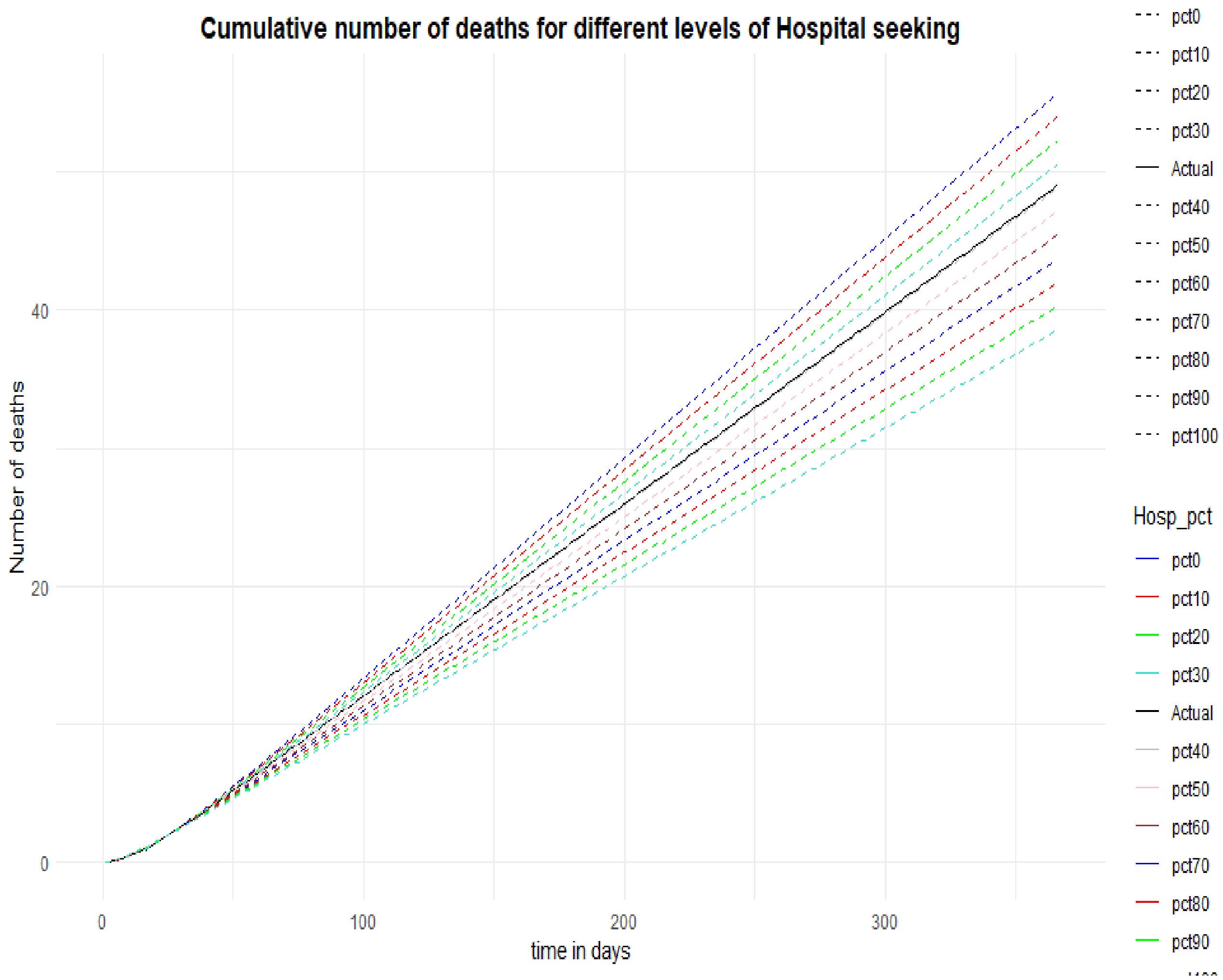
The relationship between the lambda and output in number of snakebite cases was inverse. Highest number of cases were reported for value of lambda = 0.01, followed by lambda = 0.02, 0.03, 0.04 and then lambda 0.05. All the values showed increase in number of snakebites with time with the graph flattening at some point with no increase in snakebite cases with increase in time thereafter. The flattening was however, delayed by 50 days with 0.01 increase in rate of death. At lambda = 0.05, maximum value was reported at around time day 50, after which the curve flattened. The maximum value when lambda = 0.04 was reported at around time 100 while flattening for time when lambda = 0.03 and lambda = 0.02 were recorded at time points 150 and 200 respectively. The figure below highlights trends in number of snakebite cases over time for the different parameter values of case fatality rate.



4.4.3. Assessing effect of hospital-seeking behavior on snakebite associated case-fatalities

The model predicted significant decrease in deaths with hospital seeking behavior. On overall, hospital seeking would reduce 32.14% of deaths (95% confidence interval: 20.6% - 46.1%; p-value: 0.01) if completely effected. Specifically, an average of 1.8 deaths were averted with every 10% increase in hospital seeking. The graph showed no significant differences (convergence) in number of deaths reported from H and C compartments when the percentage of snakebite victims seeking hospital treatment was set at 70%.

There was a decrease in the number of deaths from 56 to 54 (two averted deaths) when the proportion of those who seek hospital care was changed from 0 to 0.1 (10%). Increasing the proportion from 0.1 (10%) to 0.2 (20%) reduced the deaths from 54 to 52, with two averted deaths. The number of deaths averted from 0.2 (20%) to 0.3 (30%) proportion of hospital seeking was one (52 to 51); two deaths were averted from 0.3 (30%) to 0.4 (40%); two deaths averted at from 0.4 (40%) to 0.5 (50%); two deaths averted from 0.5 (50%) to 0.6 (60%); one death averted from 0.6 (60%) to 0.7 (70%); two deaths averted from 0.7 (70%) to 0.8 (80%); two deaths averted from 0.8 (80%) to 0.9 (90%) and two deaths averted from 0.9 (90%) to 1(100%). The figure below highlights reduction in number of deaths with increase in hospital seeking behavior.


Cumulative number of deaths for different levels of Hospital seeking
Number of deaths
0
20
40
0
100
200
300
time in days
pct0
pct10
pct20
pct30
Actual
pct40
pct50
pct60
pct70
pct80
pct90
pct100
Hosp_pct
pct0
pct10
pct20
pct30
Actual
pct40
pct50
pct60
pct70
pct80
pct90

5. CHAPTER FIVE: DISCUSSION

The use of mathematical modeling to improve understanding in the epidemiology and complex process involved in the pathophysiology of snakebite has been limitedly explored (Abdullahi, S.A et al., 2022; Abdullahi et al., 2021; Kim, 2020; Bravo-Vega et al., 2019). Kim in (Kim, 2020) applied SIR model to assess the risk of snakebite based on differential exposure between the rural and urban populations while integrating sociodemographic factors. Abdul and co-authors in (Abdullahi, S.A et al., 2022) assessed the optimal controls for snakebite and found out that combining public health awareness and early access to antivenom reduced deaths and disabilities associated with snakebite considerably. (Bravo-Vega et al., 2019) on the other hand was the first to experiment mathematical concept of law of mass action based on human-snake interaction combined with spatial model can be used in assessing how snakebite is associated with human demographics and snakes' distribution.

Present study predicts 3320 annual snakebite incidences in Turkana County, 60% above the average annual incidences reported in the KHIS platform for the period 2018 to 2022 (2057 cases per year). The incidence rate 368.15 cases per 100,000 person-year (95% CI 355.73-380.89) compared to that from the adjusted reported data 364.99 cases per 100,000 person-year (95% CI 352.79-377.51), an indication that the model performance was in agreement with the expected values. Other than the gross underestimation of snakebite incidences in Turkana County, the model shows clear difference in the burden of snakebite in Turkana County compared to other areas as reported in previous surveys. For instance, Coombs in (Coombs et al., 1997) reported incidence density of 67.8/100000 and 66/100000 person-year in the neighboring Baringo and Samburu Counties respectively. These values are even lower than the incidence density obtained from the KHIS data (212/100000 person year). When compared to hospital survey reports, Turkana County showed higher burden of snakebite, more than previously reported estimates in other counties of Kenya (Ochola et al., 2018). The burden of Turkana snakebite in Turkana County is comparable to other highly endemic regions like Tamil Nadu, India (Vaiyapuri et al., 2013) and still lower than other regions even within Africa (Farooq et al., 2022; Alcoba et al., 2020).

The model estimated 39% of snakebite victims seeking hospital care following snakebite. This estimate was lower than that recorded in other similar settings like Burkina Faso - 56% (Gampini et al., 2016). Poor hospital seeking behavior has been associated with detrimental outcomes following snakebite envenoming. Our study is the first to estimate mortality rate due to snakebite in the study. The snakebite induced mortality rate in the Turkana County 5.7 deaths per 100,000 person-year (95%

CI: 4.3 - 7.5; p-value < 0.001) was higher than that reported in (Coombs et al., 1997). Majority of deaths were however, associated with failure to seek hospital treatment with the risk of dying among the conservative compartment being 2.2 times more than risk of death in the hospital compartment. This trend corroborates with previously reported high numbers of snakebite induced deaths associated with poor health seeking behavior (Rahman, Faiz, Selim, Rahman, Basher, Jones, d'Este, et al., 2010). Snakebite prevention and control interventions should therefore put effort into public health advocacy, awareness creation and sensitization initiatives to reduce snakebite deaths and other devastating outcomes associated with snakebite event (Gutiérrez et al., 2013; Schurer et al., 2022). Present study failed to capture the effectiveness of early antivenom administration which has been to shown to further reduce snakebite case fatality rate among those who seek hospital treatment (Abdullahi et al., 2021). Since snakebite has an acute phase, the advocacy, sensitization and communication initiatives should also emphasize on prompt presentation to health facility to curb challenges associated with delayed presentation that reduces prognosis of patients (Aye et al., 2018).

The WHO aims at halve the deaths and disabilities associated with snakebite by 2030 (World Health Assembly, 2018). Owing to the complex nature of snakebite event, knowledge on the interplay between snakes, human and environmental factors will be key towards realizing this noble goal. Findings from varying model parameters offer insight into the direction to be taken and the key measurable indicators of performance for the global health goals. The model showed that the number of snakebite cases reduced by 50% when the force of infection, which is a product of human-snake contact and probability of bite, is decreased by 50%. This communicates to the need to involve a transdisciplinary One Health approach, involving different disciplines and the community itself, in controlling exposure factors such as clearing bushes and wearing protective gears among other (Francis et al., 2023; Schurer et al., 2022; Laing et al., 2021).

6. CONCLUSION AND RECOMMENDATIONS

Model shows that seeking hospital care after snakebite is important in improving outcome of snakebite envenomation.

It is important therefore that, public health awareness interventions be instituted in snakebite endemic communities to encourage victims to seek hospital treatment following snakebite.

The model showed that the number of snakebite cases reduced by 50% when the force of infection, which is a product of human-snake contact and probability of bite, is decreased by 50%.

Early treatment with antivenom should also be emphasized in treatment of snakebite envenomation to maximally improve the outcome.

7. STUDY LIMITATIONS

Despite improving on the understanding of snakebite dynamics and outcomes given hospital seeking behavior, present study failed to capture other key components considered essential in control of snakebite including differences in the capacity of hospital tiers. For instance, the model failed to capture heterogeneity associated with human behavior and snake species variation that varies the exposure to snakebite. Moreover, assuming equal susceptibility, the model may have failed to reveal the actual burden of the different population groups since reports have shown rural populations to be at higher risk compared to the urban populations (Chaves et al., 2015). Finally, the model failed to capture seasonality due to snakebite.

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9. APPENDIX

9.1. Turn it in report

Mathematical Modeling Of Snakebite Dynamics In Turkana County And Outcome Based On Hospital Seeking Behavior

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9.2. KNH-UoN Ethical Approval letter

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Ref: KNH-ERC/A/125

23rd March, 2023

Robert Ofwete
Dept. of Public & Global Health
Faculty of Health Sciences
University of Nairobi

Dear Robert,

RESEARCH PROPOSAL: MATHEMATICAL MODELING APPROACH TO INVESTIGATE DYNAMICS OF SNAKEBITE BASED ON WEATHER PATTERNS, SNAKE ENVENOMING FACTOR AND HOSPITAL SEEKING BEHAVIOR (P867/11/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P867/11/2022.**The approval period is 23rd March 2023 – 22nd March 2024.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

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