

Quantitative Modeling Methods For Analyzing Clinical To Public Health Problems

by

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## ABSTRACT

Statistical Methods have been widely used in understanding factors for clinical and public health data. Statistical hypotheses are procedures for testing pre-stated hypotheses. The development and properties of these procedures as well as their performance are based upon certain assumptions. Desirable properties of statistical tests are to maintain validity and to perform well even if these assumptions are not met. A statistical test that maintains such desirable properties is called robust. Mathematical models are typically mechanistic framework, used to study dynamic interactions between components (mechanisms) of a system, and how these interactions give rise to the changes in behavior (patterns) of the system as a whole over time. In this thesis, I have developed a study that uses novel techniques to link robust statistical tests and mathematical modeling methods guided by limited data from developed and developing regions in order to address pressing clinical and epidemiological questions of interest. The procedure in this study consists of three primary steps, namely, data collection, uncertainty quantification in data, and linking dynamic model to collected data. The first part of the study focuses on designing, collecting, and summarizing empirical data from the only national survey of hospitals ever conducted regarding patient controlled analgesia (PCA) practices among 168 hospitals across 40 states, in order to assess risks before putting patients on PCA. I used statistical relational models and exploratory data analysis to address the question. Risk factors assessed indicate a great concern for the safety of patients from one healthcare institution to other. In the second part, I quantify uncertainty associated with data obtained from James A Lovell Federal Healthcare Center to primarily study the effect of Benign Prostatic Hypertrophy (BPH) on sleep architecture in patients with Obstructive Sleep Apnea (OSA). Patients with OSA and BPH demonstrated significant difference in their sleep architecture in comparison to patients without BPH. One of the ways

to validate these differences in sleep architecture between the two groups may be to carry out a similar study that evaluates the effect of some other chronic disease on sleep architecture in patients with OSA. Additionally, I also address theoretical statistical questions such as (1) how to estimate the distribution of a variable in order to retest null hypothesis when the sample size is limited, and (2) how changes on assumptions (like monotonicity and nonlinearity) translate into the effect of the independent variable on the outcome variable. To address these questions we use multiple techniques such as Partial Rank Correlation Coefficients (PRCC) based sensitivity analysis, Fractional Polynomials, and statistical relational models. In the third part, my goal was to identify socio-economic-environment-related risk factors for Visceral Leishmaniasis (VL) and use the identified critical factors to develop a mathematical model to understand VL transmission dynamics when data is highly underreported. I primarily studied the role of age-specific- susceptibility and epidemiological quantities on the dynamics of VL in the Indian state of Bihar. Statistical results provided ideas on the choice of the modeling framework and estimates of model parameters. In the conclusion, this study addressed three primary theoretical modeling-related questions (1) how to analyze collected data when sample size limited, and how modeling assumptions varies results of data analysis? (2) Is it possible to identify hidden associations and nonlinearity of these associations using such underpowered data and (3) how statistical models provide more reasonable structure to mathematical modeling framework that can be used in turn to understand dynamics of the system.

## DEDICATION

*This piece of work is dedicated to my beautiful daughter, Thalia Gordon, who has inspired me beyond belief, and has given meaning to my life. It is also dedicated to my family for being my source of strength. Lastly, to my God who never left me alone.*

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## Chapter 1

# INTRODUCTION TO CLINICAL PROBLEMS AND MATHEMATICAL MODELS

This dissertation, *Quantitative Modeling Methods For Analyzing Clinical To Public Health Problems*, focuses on the adaptation of techniques linking statistical and mathematical modeling methods. The novelty comes from the implementation of these methods using limited multinational clinical data. And so, the generated statistical hypotheses and the statistical and mathematical methods involved in analyzing the data, are used to quantify the degree of confidence in the existing experimental data and parameter estimates; in other words, to assess uncertainty, a process that, in general, demands the prior identification of as many sources of uncertainty in the data and the model inputs. The results are collected in the first four chapters of this dissertation. Three of them statistical in nature and a fourth assessing uncertainty in a dynamic setting.

Statistical Methods are systematically used to help, guide, improve and/or assess, for example, our clinical trial outcomes and public health data, often carried out via the acceptance or rejection of statistical hypotheses. The development and implementation of project- or question-tailored statistical hypotheses procedures, involve assessment of their performance. The process of assessing the validity of such procedures is invariably tied in to pre-determined sets of assumptions and such a discussion is the driver of Chapter one.

The applicability of statistical methodology depends, strictly speaking, on whether or not the assumptions of the procedures are met. Today, advances in computational statistics allow for testing whether or not the methodology performs well when

assumptions are not strictly met. A statistical test that maintains such desirable property is called robust. Testing for statistical robustness is naturally important in the context of nonlinear dynamics mathematical models, the kind used to study interactions between components of a system and the resulting system dynamics. The mathematical models that form part of this dissertation require input factors modeled by parameters and system's initial conditions linked to independent and dependent model variables. Inputs that are not known, in general, with a sufficient degree of certainty due natural variation, errors in measurements, and/or even a lack of techniques to measure them.

Chapter two involves the analysis of the only national survey of hospitals ever conducted regarding patient controlled analgesia (PCA) practices among 168 hospitals across 40 states, in order to assess risks before putting patients on PCA. The challenges in collecting sufficient data include lack of financial and human resources and difficulty in meeting ethical standards inherent to the process of data collection via surveys. And so, Chapter two revisits challenges in designing, implementing, collecting, cleaning, and summarizing available empirical data. We also used these data to describe the processes of gathering data from surveys and their analyses using simple statistical methods for generating relevant estimates from these data under *pre-specified* statistical distributions.

We had access to James A Lovell Federal Healthcare Center limited data collected from patients undergoing treatment. The survey's responses were used in evaluating the effect of Benign Prostatic Hypertrophy (BPH) on the sleep architecture of patients diagnosed, via polysomnography, with Obstructive Sleep Apnea (OSA). Uncertainty may come from fronts that include the collection of data by clinicians in a set up designed without consulting a statistician (underpowered data). The question whether or not we can guarantee reasonable power to detect an effect size significantly differ-

ent than zero, if one exists, needs to be addressed and, so, it is the driving force of Chapter 3. In this chapter, rather than generating simulated data from the survey data with replacement, I have simulated such data from my pre-specified distributions on the variables. The use of this approach increases precision, which allows finding associations that were considered null when tested under the ‘typical replacement approach. Yes, the results of this chapter identify relationships previously observed between OSA and BPH. However, the main point here is that these simple associations were not coming to light before my proposed method. This chapter identifies relationships between OSA and BPH using various approaches. The first determined the distribution of each of the variables in the under sampled data and resampling the variables assuming unique distributions in order to retest hypotheses. The second starts from the view that typically when studying associations, the natural starting point is to assume that the influence, the independent variable, has on the outcome variable is monotonic. And so, a straight-line model of the form  $\beta_0 + \beta_1 X$  would suffice. However, the relationship will not be monotonic for all-time and so, we introduce alternative models that address associations that bring possible improvements in fit when considering non-linearity via fractional polynomials.

Chapter four focused on the Influence of Under-Reporting in identifying Risk Factors for Kalaazar or Leishmaniasis, a vector-borne disease caused by a protozoan parasite and transmitted by the bite of a specific species of sandflies in Bihar, India. A problem that makes use of data collected in India, which due to the limitations imposed by multiple levels of data collection efforts, brings additional sources of uncertainty. It is believed that early diagnosis is now feasible with the increasing use of field-based rapid diagnostic tests (rK39) to detect antibodies to recombinant antigen rK39 which are highly sensitive (range 98% - 99%) and specific (range 96% - 97%) [65]. Amidst these advances, approximately one-third of physicians (especially

in the private sector) in India still rely on tests other than rK39 (despite availability) for VL diagnosis [41]. This continues to pose an under-reporting problem despite the advances via active case detection strategies. Chapter four aims to identify risk factors that are significant in predicting the true burden of Kala-azar in Bihar. And so, the first step is to estimate the true disease burden in Bihar using reported incidence and mortality data from 2003 to 2005. This was achieved by fitting a dynamical mathematical model to the temporal reported incidence and mortality data via a Bayesian parameter estimation procedure. Next, I identified and ranked risk factors using multivariate regression models on datasets that included socio-economic and climate factors and the true incidence and true mortality. Nonlinear models were used to make predictions on future Kala-azar burden in Bihar by connecting ranked risk factors and estimates of underreporting levels to compute the needed adjusted incidence rates to assess Kala-azars future transmission dynamics in a setting where control measures can be explored and assessed.

In conclusion, testing for statistical robustness, in the context of multiple settings of importance to clinical and public health settings, is the underlying methodological theme of my dissertation. The content of this dissertation collects my efforts to introduce methods that help identify associations that often go undetected when using standard statistical procedures for assessing uncertainty the only national survey of hospitals ever conducted regarding patient controlled analgesia (PCA) practices among 168 hospitals across 40 states. We used nonlinear dynamics mathematical models to estimate disease burden for Kala-azar burden in Bihar in order to improve the forecasting on disease prevalence in a setting where it is possible to introduce and test specific control methods. In short, this dissertation addressed three primary theoretical modeling-related questions: (1) How do we analyze collected data when sample size is limited and how do modeling assumptions impact the results of data



analysis? (2) Is it possible to identify hidden associations and quantify nonlinear associations using underpowered data? And (3) How can statistical models help inform mathematical modeling frameworks used to understand the nonlinear dynamics of a system?

## Chapter 2

# CLINICAL AND FINANCIAL IMPLICATIONS FOR HOSPITAL PRACTICE: RESULTS FROM FIRST NATIONAL HOSPITAL SURVEY REGARDING PATIENT-CONTROLLED ANALGESIA

### 2.1 Introduction

In the 21st century, with continuous increase in technological advancements, electronic healthcare monitoring has increased leaps and bounds. Although, current patient monitoring systems are now easier to use and can be rapidly deployed, there might be some challenges with its use if practitioners are not kept up-to-date with technology, if standard practices are not followed, or if there are other non-medical errors in the procedure.

A national survey of the United States hospitals regarding practices around patient-controlled analgesia (PCA) pump administration was carried out to begin to address some of the issues with electronic monitoring. Such survey analysis has never been conducted. Using PCA pumps to help manage patients' pain has become accepted medical practice and is generally considered safe and effective. In its Sentinel Event Alert, "Safe Use of Opioids in Hospitals" [18], the Joint Commission recommends the use of PCA to help avoid adverse events associated with the use of opioids. In the same Sentinel Event alert, the Joint Commission also warns against the possibility of opioid-induced respiratory depression (OIRD): *"While opioid use is generally safe for most patients, opioid analgesics may be associated with adverse effects. The most serious effect being respiratory depression, which is generally preceded by sedation"*.

Fifty percent of Code Blue events involve patients receiving opioid analgesia [19].

Unrecognized postoperative respiratory failure that results in cardiopulmonary arrest is a daily occurrence at healthcare facilities across the United States. Since cardiopulmonary arrest often results in death or anoxic brain injury, these events have been termed “failure to rescue”. Failure to rescue is the first and third most common cause of adverse events related to patient safety, accounting for 113 events per 1,000 at-risk patient admissions [20].

In his recent presentation at the Patient, Safety Science & Technology Summit [21], Robert Stoelting, MD (President, Anesthesia Patient Safety Foundation) stated that more than 13 million patients each year receive PCA in the United States. Estimates of respiratory depression range from 0.16 percent to 5.2 percent of all patients. This means that each year between 20,800 to 676,000 PCA patients could experience opioid-induced respiratory depression. As Dr. Stoelting explains, “Clinically significant drug-induced respiratory depression (oxygenation and/or ventilation) in the postoperative period remains a serious patient safety risk that continues to be associated with significant morbidity and mortality” [22].

The focus of this study is to identify risk factors for health care practices that may be critical to a large number of adverse events in patients on PCA after surgery.

## 2.2 Statistical Inference and Survey Design

The main idea of statistical inference is to take a random sample from a population and use this information from the sample to make inferences about particular population characteristics such as the mean (measure of central tendency), the standard deviation (measure of spread) or the proportion of units in the population that have a certain characteristic. Sampling saves time, money, and effort. Additionally, a sample can, in some cases provide as much information as a corresponding study that would attempt to investigate an entire population -careful collection of data from a sample

will often provide better information than a less careful study that tries to look at everything. The behavior of the mean of sample values from different specified populations must be specified. Because a sample examines only part of a population, the sample mean will not exactly equal the corresponding mean of the population. Thus, an important consideration for the planning and interpretation of sampling results, is the degree to which sample estimates, such as the sample mean, will agree with the corresponding population characteristic. In practice, only one sample is usually taken; however, there are instances in other survey data analysis, that a small pilot sample is used to test the data-gathering mechanisms and to get preliminary information for planning the main sampling scheme. For the purposes of understanding the degree to which sample means will agree with corresponding population mean, it is useful to consider what would happen if 10 or 50 or 100 separate sampling studies, of the same type, were conducted. If results from each of the samples show to be nearly the same, confidence is gained in the single sample that will actually be used. On the other hand, seeing that answers from the repeated samples are too variable for the needed accuracy, would suggest that a different sampling plan (perhaps one with a larger sample size) should be used.

In this study, a cross-sectional sampling technique was used to study the observation of a defined population (hospitals) at a single point in a time interval (March and April 2013). Both exposure and outcome were determined simultaneously.

## 2.3 Statistical Theory

### 2.3.1 *Linear Regression vs. Non-Linear Regression*

Linear Regression models or models that are linear in the parameters, are used to study the association independent variables have on a dependent variable. Linear

regression models include not only first-order models in  $p-1$  predictor variables but also more complex models. For example, a polynomial regression model in one or more predictor variables is linear in the parameters, such as the following model in two predictor variables with linear, quadratic, and interaction terms:

$$Y_i = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i1}^2 + \beta_3 X_{i2} + \beta_4 X_{i2}^2 + \beta_5 X_{i1} X_{i2} + \epsilon_i \quad (2.1)$$

Also, models with transformed variables that are linear in the parameters belong to the class of linear regression models, such as the following model:

$$\log_{10} Y_i = \beta_0 + \beta_1 \sqrt{X_{i1}} + \beta_2 \exp(X_{i2}) + \epsilon_i \quad (2.2)$$

In general, a linear regression model can be expressed in the following form:

$$Y_i = f(X_i, \beta) + \epsilon_i \quad (2.3)$$

where  $X_i$  is the vector of the observations on the predictor variables for the  $i$ th case:

$$X_i = \begin{bmatrix} 1 \\ X_{i1} \\ \cdot \\ \cdot \\ \cdot \\ X_{i,p-1} \end{bmatrix} \quad (2.4)$$

$\beta$  is the vector of the regression coefficients, and  $f(X_i, \beta)$  represents the expected value  $E(Y_i)$  which for linear regression models equals  $f(X_i, \beta) = X_i' \beta$ . Nonlinear regression models are of the same basic form as that for linear regression models:

$$Y_i = f(X_i, \gamma) + \epsilon_i \quad (2.5)$$

An observation  $Y_i$  is still the sum of a mean response  $Y_i = f(X_i, \gamma)$  given by the nonlinear response function  $f(X_i, \gamma)$  and the error term  $\epsilon_i$ . The error terms usually

are assumed to have expectation zero, constant variance, and to be uncorrelated, just as for linear regression models. Often, a normal error model is utilized which assumes that the error terms are independent normal random variables with constant variance. The parameter vector in the response function  $f(X_i, \gamma)$  is now denoted by  $\gamma$  rather than  $\beta$  to denote that the response function here is nonlinear in the parameters.

### 2.3.2 Logistic Regression

An important nonlinear regression model is the logistic regression model. This model with one predictor variable and normal error terms is:

$$Y_i = \frac{\gamma_0}{1 + \gamma_1 \exp(\gamma_2 X_i)} + \epsilon_i \quad (2.6)$$

where the error terms  $\epsilon_i$  are independent normal with constant variance  $\sigma^2$ , and the response function is not linear in the parameters. The response function is:

$$f(X, \gamma) = \frac{\gamma_0}{1 + \gamma_1 \exp(\gamma_2 X)} \quad (2.7)$$

A model like this is used in population studies to relate number of species  $Y$  to time  $X$ . However, when the response variable is qualitative, the error terms are not normally distributed with constant variance, and this poses constraints on the response function. If we consider the simple linear regression model:

$$Y_i = \beta_0 + \beta_1 X_i + \epsilon_i, \quad \text{for } Y_i = 0, 1 \quad (2.8)$$

where the outcome  $Y_i$  is binary, taking on the value of either 0 or 1. The expected response  $E(Y_i)$  has a special meaning in this case. Taking the  $E(\epsilon_i) = 0$  we end up with:

$$E(Y_i) = \beta_0 + \beta_1 X_i \quad (2.9)$$

Since  $Y_i$  takes on two values, we consider it to be a Bernoulli random variable for which  $\pi_i$  is the probability that  $Y_i = 1$  and  $1 - \pi_i$  is the probability that  $Y_i = 0$ . Using the

definition of expectation for a random variable, we obtain  $E(Y_i) = 1(\pi_i) + 0(1 - \pi_i) = \pi_i = P(Y_i = 1)$ . Thus,  $E(Y_i) = \beta_0 + \beta_1 X_i = \pi_i$ . The mean response, when the outcome variable is a 0, 1 indicator variable, always represents the probability that  $Y = 1$  for the given levels of the predictor variables.

### 2.3.3 Constraints with a Binary Response Variable

When the response variable is an indicator variable, special problems arise. The first is nonnormal error terms. For a binary 0,1 response variable, each error term  $\epsilon_i = Y_i - (\beta_0 + \beta_1 X_i)$  can only take on two values:

$$\begin{cases} \epsilon_i = 1 - \beta_0 - \beta_1 X_i, & \text{when } Y_i = 1 : \\ \epsilon_i = -\beta_0 - \beta_1 X_i, & \text{when } Y_i = 0 : \end{cases} \quad (2.10)$$

This is an indication that a normal error regression model, which assumes that  $\epsilon_i$  are normally distributed, is not appropriate.

The second is nonconstant error variance. The error terms  $\epsilon_i$  do not have equal variances when the response variable is an indicator variable. If we obtain the  $\sigma^2(Y_i)$  for the simple linear regression model:

$$\sigma^2(Y_i) = E[(Y_i - E(Y_i))^2] = (1 - \pi_i)^2 \pi_i + (0 - \pi_i)^2 (1 - \pi_i) = \pi_i(1 - \pi_i) = (E(Y_i))(1 - E(Y_i)) \quad (2.11)$$

which is equal to:

$$\sigma^2(Y_i) = (\beta_0 + \beta_1 X_i)(1 - \beta_0 - \beta_1 X_i) \quad (2.12)$$

This error depends on  $X_i$  which means that the error terms will differ at different levels of  $X$ , and ordinary least squares will not be optimal.

The third is the constraint on the response function. Since the mean response function represents probabilities when the outcome variable is a 0, 1 indicator variable,

the mean responses should be constrained as follows:

$$0 \leq E[Y] = \pi \leq 1 \tag{2.13}$$

Many response functions do not possess this constraint, and this is the most serious of the three. Using weighted least squares could be a potential solution to unequal error variances. Additionally, with large sample sizes the method of least squares provides estimators that are asymptotically normal under quite general conditions, even if the distribution of the error terms is far from normal. The constraint on the mean response to fall between 0 and 1, however, rules out a linear response function.

### 2.3.4 Response Functions for Binary Responses

There are several response functions used for modeling binary responses. These functions are bounded between 0 and 1, have a characteristic sigmoidal (S-shape), and approach 0 and 1 asymptotically. Some of these include the Probit Mean Response Function (which uses the standard normal cumulative distribution function to model  $\pi_i$ ), the Logistic Distribution (which uses the density of a logistic random variable  $\epsilon_L$  having mean zero and standard deviation  $\sigma = \frac{\pi}{\sqrt{3}}$  to model the  $P(Y_i = 1)$ ), and the Log-Log Response Function (used when the error distribution is not symmetric). For the survey analysis in this dissertation, some of the analyses required using Logistic Regression.

Focusing on Logistic Regression, the method of maximum likelihood is used to estimate the parameters of the logistic response function. Since  $Y_i$  is a Bernoulli random variable where  $P(Y_i = 1) = \pi_i$  and  $P(Y_i = 0) = 1 - \pi_i$ , its likelihood function can be represented as:

$$L = \prod_{i=1}^n \pi_i^{Y_i} (1 - \pi_i)^{1-Y_i} \tag{2.14}$$

The maximum likelihood estimates of  $\beta_0$  and  $\beta_1$  in the simple logistic regression model



are those values of  $\beta_0$  and  $\beta_1$  that maximize the log-likelihood function. No closed-form solution exists for the values of  $\beta_0$  and  $\beta_1$  that maximizes the log-likelihood function, and as a result computer intensive numerical search procedures are required to find the maximum likelihood estimates  $\beta_0$  and  $\beta_1$ . Once the maximum likelihood estimates  $b_0$  and  $b_1$  are found, these values are substituted into the response function to obtain the fitted value which is equal to the estimated probability for the  $i^{th}$  case.

$$\hat{\pi}_i = \frac{\exp(b_0 + b_1 X_i)}{1 + \exp(b_0 + b_1 X_i)} \quad (2.15)$$

In the survey data analysis, most of the results are presented as Odds Ratios (OR), which after mathematical derivation equal  $\exp(b_1)$  in a simple linear regression. In the case of multiple logistic regression, the fitted values become:

$$\hat{\pi}_i = \frac{\exp(X' \beta)}{1 + \exp(X' \beta)} \quad (2.16)$$

The Odds Ratios can be derived the same way as in the case of simple linear regression, for example  $\exp(b_2)$  would be the odds ratio for the variable  $X_2$  provided that everything else in the model stays constant.

In order to address the specific questions of the survey and find associations, Logistic Linear Regression was used.

## 2.4 Methodology

During March and April 2013, this national survey of hospitals was conducted regarding practices related to PCA by *A Promise to Amanda Foundation and the Physician-Patient Alliance for Health & Safety*. The survey questions were prepared with the assistance and input from the individuals listed on Appendix A. The survey was distributed through The Institute for Healthcare Improvement Hospital Networks and Hospital Members of the Premier Safety Institute. Survey questions consisted

of demographic information (position, profession, location), risk factors considered before administration of PCA (obesity, low body weight, concomittant medications that potentiate sedative effects, advanced age, opioid naive, pre-existing conditions such as asthma, copd, sleep apnea) and PCA training and use (see Appendix B for the list of survey questions). Because all orders for PCA at any given institution must be processed by a pharmacist, hospital-based pharmacists were targeted to answer the survey. Consequently, most of the survey respondents identified themselves as hospital pharmacists (47%). Although this may lend itself to bias towards pharmacists, this likely means that the responses were representative of the hospital rather than an individual respondent's perspective. The remaining respondents identified themselves as either physicians (18%) or a non-physician healthcare provider, such as a nurse or respiratory therapist (35%). The 168 United States respondent hospitals represented the diversity of hospitals across the United States. Respondent hospitals were geographically dispersed and came from 40 of the 50 United States. Moreover, they varied in size, from as small as 14 beds to the largest having more than 1,500 beds, with the median hospital having 200 beds.

The respondent hospitals were more representative of teaching hospitals than non-teaching hospitals (55%) than non-teaching hospitals (45%). In the U.S., teaching hospitals represent 1,000 of the more than 5,000 hospitals in the U.S., or approximately 20%. [23]. However, this possible bias towards teaching hospital respondents may suggest that the survey results could be more reflective of future practice standards rather than current, as students leave these institutions to practice medicine at non-teaching hospitals. Teaching hospitals "provide clinical education and training to medical students, residents, and postgraduate fellows and are distinguished, in large part, by their clinical research programs, where drugs, medical devices and treatment methods are developed and tested" [23].

## 2.5 Statistical Analysis

The survey consisted of binary (Yes or No) responses, choice responses or open-ended responses. Binary responses were coded as 1 for Yes and 0 for No, while the questions that provided choices were coded as categorical numerical values. For the questions that were open-ended responses, these were clustered based on similarity of responses and were coded as categorical numerical responses.

Logistic regression was used to estimate the different associations involving PCA use, training, or monitoring. Odds ratios (OR) and 95% confidence intervals (CIs) were also estimated. Findings for statistical analyses were systematically recorded in Table 2.1 and implications from the study were collected. As well, we report two-sided p-values in support of finding associations in either direction. Statistical analyses were conducted using SAS release 9.3 (SAS institute, Cary, NC).

## 2.6 Key Clinical Insights

Survey responses provide key clinical insights into the following three processes or practice areas: (1) how the use of a standard risk factor assessment prior to initiating opioid administration could help reduce opioid-induced respiratory depression, (2) the role continuous electronic monitoring could play in decreasing hospital expenses and improving workflow, (3) the tools and training hospitals think they need to combat alarm fatigue. Each process area is discussed in the following sections.

### 2.6.1 Risk Factor Assessment

Many respected healthcare organizations have provided warnings that safe PCA use starts with selecting suitable patients. In discussing this issue of patient selection, the Pennsylvania Patient Safety Authority in its analysis of approximately 4,500

	Not Receiving Ongoing Training	Receiving Ongoing Training
Checks for Line Attachment to Patient and Tubing Insertion Into Pump Before Conducting PCA Pump Initiation, Refilling, or Programming Change: <b>OR</b> <b>95 % CI</b>	1.00 Reference	2.62 1.09 - 6.28
	Not Provided with Monitoring Purpose Pre-Operation	Provided with Monitoring Purpose Pre-Operation
For patients going on PCA, the extent of monitoring (post operation) involves: <i>All Pulse Oximetry:</i> <b>OR</b> <b>95 % CI</b>	1.00 Reference	3.33 1.24 - 8.92
For patients going on PCA, the odds that PCA pumps used post operation are more likely to be smart pumps:  <i>All Smart Pumps:</i> <b>OR</b> <b>95 % CI</b>  <i>All Smart Pumps With Integrated End Tidal Monitoring:</i> <b>OR</b> <b>95 % CI</b>	1.00 Reference 1.00 Reference	3.84 1.41 - 10.45 3.79 1.07 - 13.44
Consensus that PCA pumps used by Health Facility have safety software and have been in place and used between 3-5 years ago  <b>OR</b> <b>95 % CI</b>	1.00 Reference	6.44 1.44 - 28.89
	Not Investing on Returns	Investing on Returns
Health Care Facility's experience with continuous monitoring with Smart Pumps: <i>All or Some Integrated Pumps:</i> <b>OR</b> <b>95 % CI</b>	1.00 Reference	2.79 1.11 - 6.99
	No Concern Regarding Potential Alarm Fatigue	Concern Regarding Potential Alarm Fatigue
For those being continuously monitored in ventilation post operation, odds of concern regarding potential alarm fatigue:  <i>All or Some Integrated Pumps:</i> <b>OR</b> <b>95 % CI</b>	1.00 Reference	2.88 1.16 - 7.16

**Table 2.1:** Impact of PCA Training (Ongoing Training and Purpose of Monitoring Training) on Hospital Personnel Attitudes, First National Hospital Survey

Characteristics of Patients Who Are At Higher Risk for Oversedation and Respiratory Depression
Sleep apnea or sleep disorder diagnosis [22, 23, 36]
Morbid obesity with high risk of sleep apnea [22, 23]
Snoring [22, 23]
Older age: risk is
† 2.8 times higher for individuals aged 61-70
† 5.4 times higher for individuals aged 71-80
† 8.7 times higher for individuals over 80 [22, 29, 37]
No recent opioid use [23, 38]
Post-surgery, particularly if upper abdominal or thoracic surgery [22, 39]
Increased opioid dose requirement [23] or opioid habituation
Longer length of time receiving general anesthesia during surgery [22, 39]
Receiving other sedating drugs, such as benzodiazepines, antihistamines, diphenhydramine, sedatives, or other central nervous system depressants [21, 23, 25, 29]
Pre-existing pulmonary or cardiac disease or dysfunction or major organ failure [22, 23]
Thoracic or other surgical incisions that may impair breathing [22, 23]
Smoker [22, 23]

**Table 2.2:** Characteristics of Patients Who Are At Higher Risk for Oversedation and Respiratory Depression

event reports it received from June 2004 through May 2010 provides the following caution: “...*candidates for PCA should have the mental alertness and cognitive ability to manage their pain and communicate their pain level to their caregiver*”. Moreover, the Joint Commission in its Sentinel Event Alert #49 “Safe Use of Opioids in Hospitals” [18] provides the following chart showing characteristics of patients who are at higher risk of over-sedation and respiratory depression [see Table 2.2].

To determine which patient risk factors are assessed by hospitals prior to the initiation of PCA, the survey provided a short list of factors identified in the PCA Safety

Checklist. This recently developed checklist was accomplished with the assistance of a group of renowned health experts assembled by the Physician-Patient Alliance for Health & Safety. Respondents were asked whether before initiating patients on PCA, the following patient risk factors were considered: Obesity, Low Body Weight, Concomitant Medications that Potentiate Sedative Effects of Opiate PCA, Pre-existing Conditions (such as asthma, COPD, sleep apnea), Advanced Age, and Opioid Naive. The survey found that, although patient risk factors are considered, this is not being done by every hospital, with every patient, as indicated in the Figure 3 in Appendix C.

This suggests that there is a tremendous variation between the treatments being received by patients across the country with more than 60 percent of respondents considering five or less factors, and less than 40 percent indicating that they were considering all six patient risk factors. To illustrate the dangers of not considering a particular patient risk factor, an analysis was conducted against recommended practice. Three of these risk factors were chosen: opioid naive, obesity, and advanced age. These are discussed in the following sections.

### *2.6.2 Opioid Naive Patients*

The National Comprehensive Cancer Network defines opioid naive patients as those “who are not chronically receiving opioid analgesic on a daily basis” [26]. Consequently, because opioid naive patients are at greater risk for over-sedation and respiratory depression, the Joint Commission recommends taking “extra precautions with patients who are new to opioids or who are being restarted on opioids” [18]. Clinically significant to point out are the survey’s findings which indicated that almost one out of five hospitals are not assessing patients for being opioid naive. Additionally, pharmacists were four times more likely to consider opioid naive as a risk factors

versus other healthcare professionals (OR=4.07, 95 %CI: 1.59-10.43). Noteworthy to mention that physicians were approximately 70 percent less likely than the other types of respondents to say that they consider opioid naive as a patient risk factor (OR=0.32, 95 % CI: 0.13 - 0.79). This is indicative of a greater need for awareness among physicians to the heightened risk of the use of opioids in opioid naive patients.

The survey findings suggest that some opioid naive patients may be receiving PCA when they have not adequately and thoroughly been assessed and determined they are at too high of risk for adverse event occurrence.

### 2.6.3 Obesity

About three out of 10 hospitals do not consider obesity as a clinically significant patient risk factor, despite the indications of many studies that have shown the increased risk of using anesthesia with obese patients [27]. As researchers have stated:

One of the many problems in providing anaesthesia for morbidly obese patients is the influence of obesity on pharmacokinetics and pharmacodynamics. Drug administration in obese patients is difficult because recommended doses are based on pharmacokinetic data obtained from individuals with normal weights; therefore, mistakes in the determination of the appropriate dose are often made. Because of comorbidity in these patients, the function of organs involved in drug elimination (e.g., kidney, liver) can be affected making pharmacokinetics more difficult and complex [28].

The survey findings suggest that some obese patients may be receiving PCA when perhaps they should not be due to inadequate patient risk assessment.

#### 2.6.4 *Advanced Age*

The risk of respiratory depression increases substantially for patients over 60 years of age. The Joint Commission cautions against the use of opioids in older patients because of the heightened risk of over-sedation and respiratory depression with the risk being approximately 2.8 times higher for individuals aged 61-70, 5.4 times higher for individuals aged 71-80, and 8.7 times higher for individuals over age 80 [18]. Presently, not all healthcare facilities consider advanced age as a risk factor with about three out of every 20 hospitals not assessing their patients using PCA for advanced age.

Significantly, at those hospitals that provide on-going training in PCA administration, advanced age was more likely to be considered a patient risk factor that potentially poses greater risk of over-sedation and respiratory depression to the patient. This suggests that the clinical imperative is to have active on-going PCA administration training for all healthcare professionals using PCA as the pain modality treatment.

#### 2.6.5 *Continuous Monitoring*

Continuous electronic monitoring with pulse oximetry for oxygenation and capnography for adequacy of ventilation is recommended for greater patient safety. As Dr. Stoelting states in discussing patient safe measures to be used for patients using PCA:

APSF recommends that monitoring be continuous and not intermittent, and that continuous electronic monitoring with both pulse oximetry for oxygenation and capnography for the adequacy of ventilation be considered for all patients [28]

Despite these recommendations, patients are not monitored with either pulse oximetry or capnography at over three out of every 20 hospitals (16.07 %). How-



ever, of the hospitals that are not electronically monitoring any of their patients, almost nine out of 10 (86.7 %) say they are considering the use of monitoring. This suggests that continuous electronic monitoring may likely become a standard procedure. Though, time of adoption in some cases may be long and the assessment of use of additional electronic monitoring systems may be required. There is predominance of hospitals monitoring their patients using PCA with pulse oximetry with more than one out of every two using just oximetry (50.6 %) to monitor all or some of their patients. Two out of three hospitals (66.67 %) are using a mix of pulse oximetry and capnography.

In terms of greater patient safety significance and for hospitals that have identified cost and expense reduction, the clinical change that has occurred are in hospitals that are continuously electronically monitoring their patients with pulse oximetry and/or capnography. Of the respondent hospitals that continuously monitor their patients receiving PCA, 65 percent have experienced positive results—either in terms of a reduction of overall adverse events or a return on investment when measured against cost expenditures (including litigation costs). The other 35 percent of those that monitor say it is “too early to determine or have not determined” whether they have seen a reduction in adverse events, costs, or expenses.

While the merits or demerits of using pulse oximetry or capnography has been much debated, the survey results indicate the clinical value of patient surveillance monitoring, as has been suggested by research conducted by Andreas Taenzer, MD, and his colleagues at the Dartmouth-Hitchcock Medical Center [30]. Patient surveillance monitoring, where all patients are continuously electronically monitored, is distinct from condition monitoring where some patients are selected for monitoring without defined clinical criteria. As Frank Overdyk, MD, writes in describing this work at Dartmouth:

In their review of the approaches to address fail failure-to-rescue (FTR), Dr. Andreas Taenzer and his colleagues found that previous attempts [32] have largely focused, with limited success, on improving the response to an identified patient crisis. Such approaches have led to the development of rapid response teams (RRTs). However, the primary determinant for the success of RRTs have been found to be early recognition and this is where continuous electronic monitoring may provide an early detection solution [31].

Moreover, when we analyzed the type of smart pump being used at the facilities reporting a decline in adverse events or a return on investment, there was a significant correlation with those using smart pumps with integrated end tidal monitoring. Those using smart pumps with integrated end tidal monitoring were almost three times more likely to have had a reduction in adverse events or a return on investment when measured against costs and expenses (including litigation costs) that might have been incurred (OR=2.79; 95% CI: 1.11 - 6.99). The positive experience in terms of a reduction in adverse events and costs, and the use of integrated end tidal monitoring that was reported by survey respondents mirrors the experience of other hospitals that have instituted continuous monitoring of their patients, like St. Joseph/Candler Hospitals (SJ/C) in Savannah, Georgia. Harold Oglesby, RRT, manager of respiratory care at SJ/C [33]. He describes how his hospital has had more than eight years of event-free use of PCA using “smart” PCA pumps with integrated capnography monitoring:

A lot of the information comes from the research that we’ve done that has been focused on PCA patients monitored with capnography and the effectiveness gained in monitoring ventilation versus oxygenation. What

we found is that we have an earlier recognition of any patient deterioration using capnography versus using oximetry alone. We also have looked at several case studies of patients, and we noted that by the use of capnography, we've recognized deteriorating patients early; so it gives us the leeway to take actions before those patients get into any trouble.

Moreover, although a human life should never be measured in dollars and cents, St. Joseph's/Candler Hospitals calculated that their decision made great financial sense with \$4 million - estimated potential expenses averted (not including potential litigation costs) and \$2.5 million - 5-year return on investment [34]. From an engineering perspective, this "closed-loop" system of having the capnography monitor integrated with the PCA pump has been described as the ideal patient safety guard rail. A PCA pump with integrated end tidal monitoring allows the pump to automatically shut off when the monitor senses that the patient is becoming oversedated. Bryanne Patail, biomedical engineer at the U.S. Department of Veterans Affairs, National Center for Patient Safety, explains what the Veterans Health Administration has done to reduce errors related to PCA use and improve patient safety [35]:

Use of PCA pumps is a process, and improving that process is an area that involves many stakeholders. In looking at fixes, they can be categorized as strong, intermediate or weak fixes. The strongest fix for PCA pumps is a forcing function, such as an integrated end tidal CO<sub>2</sub> monitor that will pause the pump if a possible over infusion occurred. So, healthcare providers should first look at these strong fixes. There they will see the most impact on reducing errors and improving patient safety.

The survey results strongly suggest that using PCA pumps with integrated end tidal monitors will greatly improve patient safety.

### 2.6.6 Alarm Fatigue

According to The Joint Commission, alarm fatigue occurs when clinicians become de-sensitized or immune to the sound of an alarm [36]. Fatigued clinicians may turn down alarm volume, turn off alarms, or adjust alarm settings. Concern about alarm fatigue was extremely high, with only less than one in 20 hospitals (4.9 %) saying that they were “not concerned at all”. The vast majority (more than 95 %) are concerned about the issue of alarm fatigue, with 61.3 percent reporting that they are concerned but don’t believe alarm fatigue is an “unmanageable problem”. With almost two out of three hospitals seeing alarm fatigue as ”manageable”, this bodes well for the successful achievement of The Joint Commission’s national patient safety goal to manage alarms [37].

About one out of three hospitals (33.7 %) are either concerned that alarm fatigue will be a problem that is difficult to manage or the potential for alarm fatigue is preventing them from implementing continuous electronic monitoring. This indicates that for these hospitals, the issue of alarm fatigue is negatively impacting work processes and the safety of their patients. Almost nine out of ten hospitals (87.8 %) believe that a reduction of false alarms would increase the use of patient monitoring devices, such as oximeter or capnograph. Alarm fatigue and the need for improved alarm sound management is therefore preventing hospitals from implementing continuous electronic monitoring as a patient safety measure which would provide reduction in adverse events, costs and expenses. In the following analysis, three levels of concern with alarm fatigue have been used: Not concerned about alarm fatigue (4.9 % of hospitals), Concerned alarm fatigue is an unmanageable problem (33.73 % of hospitals), and Managing alarm fatigue (61.4 % of hospitals).

To help manage alarm fatigue, hospitals indicate that tools and training would

be of assistance. Seven out of 10 hospitals (70.7 %) would like “a single indicator that accurately incorporates key vital signs, such as pulse rate, SpO<sub>2</sub>, respiratory rate, and etCO<sub>2</sub>”. Additionally, almost half of the respondents (44.6 %) would like “recommendations on how best to easily make such assessments” of patients, and more than half (52.9 %) would like to see more clinical training. However, those concerned that alarm fatigue is an unmanageable problem were more than twice as likely to want a single-indicator assessment tool (OR=2.04; 95% CI: 1.07 - 4.84) and recommendations for ease of assessment for their nursing staff (OR=2.04; 95% CI: 0.99 - 4.19). This indicates that nursing staff may be having difficulty interpreting the data. This does not suggest a lack of knowledge (as there was not statistically significant correlation with a desire for more clinical training for nurses), but that the amount of data needing to be interpreted may be overwhelming. The volume of data about a patient together with the sheer number of alarms is a critical patient safety issue. The survey indicates that providing tools to address patient assessment, with both a technological aid to gather multiple parameters into a single indicator, as well as recommendations for easily assessing a patient, would assist with alarm management.

## 2.7 Conclusions

The survey results indicate three key areas where patient safety could be improved. First, the results demonstrate great variance in patient risk factors assessed which indicate great concern for the safety of patients from one institution to the next. Standardization of practices where every patient is assessed before initiating PCA would be of great assistance, according to Ana Pujols McKee, MD, executive vice president and chief medical officer, The Joint Commission:

The Joint Commission recognizes there is an opportunity to improve care

for patients by improving the safety of opioid use in acute care settings given that data show opioids are among the top three drugs in which medication-related adverse events are reported. Opioids are necessary to prevent suffering, but there are risks related to potency, route of administration, and patient history. By engaging in a comprehensive approach to assessment, monitoring, and patient education, opioid overuse and associated harm can be prevented [38].

The PCA Safety Checklist [39], which was developed with the help of a panel of health experts [25], contains one example of a risk factor assessment tool for evaluating patients. Second, the survey results also show that continuous electronic monitoring has reduced adverse events and hospital expenditures. Although continuous electronic monitoring is not universally applied for all patients receiving opioids, hospitals that do not monitor their patients should consider doing so, not only to improve patient safety, but to decrease their expenses. Lastly, although alarm fatigue is a concern of hospitals, clinical training and the use of a single assessment indicator have been indicated as two items that hospitals would like to better manage alarms.

This survey is a first national effort to gather data on PCA practices. Subsequent surveys could look further into the use of risk factor assessment tools in evaluating respiratory compromise, protocols for continuous monitoring, and how reducing alarm fatigue expends the use of continuous monitoring.

## Chapter 3

# EFFECT OF BENIGN PROSTATIC HYPERTROPHY ON SLEEP ARCHITECTURE AND SEVERITY OF SLEEP APNEA IN MEN WITH OBSTRUCTIVE SLEEP APNEA VIA A SIMPLE NOVEL STATISTICAL MODELING APPROACH

### 3.1 Introduction

Obstructive Sleep Apnea (OSA) is a common sleep disorder characterized by multiple cessations of breath during sleep, which cause intermittent hypoxia (IH) and sleep fragmentation. Each cessation of breath, referred to as an apnea, can last from 10 seconds to minutes. Sleep Apnea can be mild, moderate, or severe, according to the number of apneas per hour [2]. OSA is a common disorder that is often asymptomatic; the prevalence of patients with OSA who do not present clinical syndrome, might be as high as 20% to 30% in the middle-aged [3]. IH is one of the major pathological conditions to affect OSA patients, and chronic IH can activate inflammatory pathways [4]. A meta-analysis showed that systematic pro-inflammatory cytokines and inflammatory markers are elevated in OSA patients [5]; OSA may therefore be considered as a systematic inflammatory disease [6]. Benign Prostate Hyperplasia (BPH) is one of the most common chronic conditions in the male population with a histological prevalence at autopsy of 50% in men aged 50-60 years and 90% in men aged over 80 years [7]. Although the pathogenesis of BPH is unknown, data suggest a possible role of chronic inflammation in BPH [8] as suggested by inflammatory elements in surgically treated BPH [9]. A recent study indicates that patients with OSA are associated with increased longitudinal risk of BPH development, and that

the effects of OSA on BPH development are age-dependent. Treatment of OSA and BPH [10] improve sleep quality by subjective measurements and scales. We aim to objectively evaluate the effect of BPH on sleep architecture in patients with OSA diagnosed by polysomnography.

## 3.2 Materials and Methods

### 3.2.1 *Study Design and Population*

All adults ( $> 18$  years of age) male patients who were referred for polysomnography (PSG) first time for clinically suspected OSA by sleep clinic physicians at James A Lovell Federal Healthcare Center who were found to have OSA by sleep study during January 01, 2009, to December 31, 2011, were recruited for the study. BPH was clinically diagnosed by the primary care physician of the patient in some of these subjects. Data for both groups (OSA and OSA with BPH) was collected from computerized patients' record system (CPRS) for the demographic variables; age and body mass index (BMI). Each patient was diagnosed to have OSA by PSG (Somnostar-Pro 7-3A; Carefusion) and sleep stages were scored according to rules described by the Rechtschaffen and Kales (R & K) scoring manual [14] by the registered polysomnographic technologist. Data recorded from the sleep study included the following sleep characteristics: total sleep time (TST), sleep efficiency (SE), OSA severity (Apnea-Hypopnea index (AHI)) and Rapid Eye Movement Sleep AHI (REM-AHI), sleep stages (Percent of time spent in Stage 1, Stage 2, Stage 3 and 4, REM sleep), Arousal Index (AI), Sleep and REM Onset. Here, we develop statistical models using the clinical data to estimate model parameters. The simulated data from the model were used to study research questions and to derive robustness in implications. Throughout the paper, we will call "original data" to refer data obtained directly



from the patients, and “simulated data” to refer the sample data from models.

This OSA study was approved by the Institutional Review Board at Rosalind Franklin University for Medicine and Science located in North Chicago, Illinois. The Institutional Review Board approved conduct of the research without explicit consent from the participants and ethical guidelines were followed in the study.

### 3.3 Statistical Analysis

This retrospective study reviews 62 subjects with OSA diagnosed by PSG who had BPH (cases) and 62 patients with OSA diagnosed by PSG who did not have BPH (controls). In determining the effect of BPH on sleep architecture in patients with obstructive sleep apnea, we calculated and reported means of the sleep measure variables by case-controls status using a two-sample t-test using original data (Table 3.1). The total sample (62 cases + 62 controls) primarily consisted of obese (BMI  $32.6 \pm 5.11$ ), and older (Age  $63.06 \pm 11.11$ ) subjects. Subjects with BPH have higher age ( $67.11 \pm 9.81$  versus  $59.01 \pm 10.92$ ,  $p < 0.001$ ) but similar BMI ( $32.39 \pm 4.92$  versus  $32.8 \pm 5.33$ ,  $p < 0.65$ ).

Table 3.1 shows that time spent sleeping in stage 1 was found to be significantly different between both groups. Those patients with BPH demonstrated to have longer stage 1 (27.5 versus 21.1 % of total sleep time ,  $p=0.03$ ). This shows that those with BPH have additional reason for sleep interruption, which translates into more light stage (stage I) sleep and less stage 2 or 3 and 4. Although not statistically different, Table 3.1 also shows that controls have higher total sleep time, sleep efficiency, and time spent sleeping in REM stage, while stage 2, stage 3 and 4 were similar.

Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA)			
	OSA (Controls)	OSA w/BPH (Cases)	P-Value
N	62	62	
Mean Apnea and Hypopnea Index (AHI)	30.9	36.4	0.2
Mean Total Sleep Time (min)	284.5	268.7	0.2
Mean Sleep Efficiency (%)	76.7	71.2	0.07
Mean Sleep Onset (min)	27.8	22.0	0.3
Rapid Eye Movement Onset(min)	125.8	140.7	0.3
Time Spent Sleeping in Rapid Eye Movement Stage (%)	13.6	11.3	0.1
Mean Arousal Index	18.2	22.8	0.1
Mean Time Spent Sleeping in:			
Stage 1 (%)	21.1	27.5	<b>0.03</b>
Stage 2 (%)	57.4	55.5	0.6
Stage 3 (%)	1.4	0.8	0.3

**Table 3.1:** Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA)

### 3.4 Bootstrapping Approach

A specific bootstrapping sampling approach was developed to determine functional form of each of the variables in the original data. Since each of the subjects are different and their sleep measures were independently collected, we assumed that each sleep measure were independent and identically distributed. As a result, assumptions about the functional forms of probability distributions of the error terms were made for each of the sleep measures. The maximum likelihood estimation approach, which is significantly robust to deviations from model assumptions, was used to estimate the parametric distributions for each of the sleep apnea variables defined both under cases and controls. As such, all valid parametric distributions were fitted to each of the sleep measures under cases and under controls. The top five distributions were then sorted on a metric used to compare the goodness of fit- each derived from its own distribution. Goodness of fit criteria used in the selection process consisted of the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), the small sample size version of the Akaike Information Criterion (AICc), and the Negative Log Likelihood (NLogL) [1]:

$$AIC = -2 * \log(L(\mathbf{y}|\mathbf{x})) + 2p \quad (3.1)$$

where  $\log(L(\mathbf{y}|\mathbf{x}))$  represents the log likelihood as the product of the densities viewed as a function of the unknown parameters, and  $p$  represents the number of parameters.

$$BIC = \frac{RSS_p}{\sigma} + \log n * p \quad (3.2)$$

where RSS is the residual sum of squares.

$$AICc = n * \log(2\pi\hat{\sigma}^2) + \frac{n(n+p)}{n-p-2} \quad (3.3)$$

$$NLogL = -\log(L(\mathbf{y}|\mathbf{x})) \quad (3.4)$$

The list of parametric distributions for fitting original sleep measure data corresponding to continuous variables that were considered consisted of: Beta, Birnbaum-Saunders, Exponential, Extreme Value, Gamma, Generalized Extreme Value, Generalized Pareto, Inverse Gaussian, Logistic, Log-logistic, LogNormal, Nakagami, Rayleigh, Rician, T Location-Scale, and Weibull. Following are descriptions and applications of these distributions. The following distributions were derived from Casella and Berger [1].

The Beta family of distributions is a continuous family on the set (0,1) indexed by the two parameters  $\alpha$  and  $\beta$ . The *beta*( $\alpha, \beta$ ) pdf is:

$$f(\mathbf{x}|\alpha, \beta) = \frac{1}{B(\alpha, \beta)} x^{\alpha-1} (1-x)^{\beta-1}, \quad 0 < x < 1, \quad \alpha > 0, \quad \beta > 0, \quad (3.5)$$

where  $B(\alpha, \beta)$  denotes the beta function:

$$B(\alpha, \beta) = \int_0^1 x^{\alpha-1} (1-x)^{\beta-1} dx. \quad (3.6)$$

where the beta function is related to the gamma function through  $B(\alpha, \beta)$ . The beta function is one of the few distributions that give probability 1 to a finite interval, here taken to be (0,1).

The Birnbaum-Saunders distribution is also known as the fatigue life distribution used to model failure times. The pdf is:

$$f(\mathbf{x}|\mu, \beta, \gamma) = \frac{\frac{\sqrt{x-\mu}}{\beta} + \sqrt{\frac{\beta}{x-\mu}}}{2\gamma(x-\mu)} \phi\left(\frac{\frac{\sqrt{x-\mu}}{\beta} - \sqrt{\frac{\beta}{x-\mu}}}{\gamma}\right) \quad x > \mu; \quad \gamma, \beta > 0 \quad (3.7)$$

The Exponential distribution known to describe the time between events in a Poisson process (a process where events occur continuously and independently at a

constant average rate). The exponential distribution is also a special case of the gamma distribution, and has the key property of being memoryless.

$$f(\mathbf{x}|\beta) = \frac{1}{\beta} e^{-\frac{x}{\beta}}, \quad 0 \leq x < \infty, \quad \beta > 0 \quad (3.8)$$

The Extreme Value distribution is suitable for modeling the minimum value. To model the maximum value, use the negative of the original values. Its pdf:

$$f(\mathbf{x}|\mu, \sigma) = \sigma^{-1} \exp\left(\frac{x - \mu}{\sigma}\right) \exp\left(-\exp\left(\frac{x - \mu}{\sigma}\right)\right) \quad (3.9)$$

The Gamma distribution is also frequently used to model waiting times. Its pdf:

$$f(\mathbf{x}|\alpha, \beta) = \frac{1}{\Gamma(\alpha)\beta^\alpha} x^{\alpha-1} e^{-\frac{x}{\beta}}, \quad 0 < x < \infty, \quad \alpha > 0, \quad \beta > 0 \quad (3.10)$$

The Generalized Extreme Value distribution is the only possible limit distribution of properly normalized maxima of a sequence of independent and identically distributed random variables; It is often used as an approximation to model the maxima of long (finite) sequences of random variables.

$$f(\mathbf{x}|\mu, \sigma, \xi) = \frac{1}{\sigma} t(x)^{\xi+1} e^{-t(x)}, \quad \text{where } t(x) = \left(1 + \left(\frac{x - \mu}{\sigma}\right) \xi\right)^{-\frac{1}{\xi}} \quad \text{if } \xi \neq 0, \quad e^{-\frac{(x-\mu)}{\sigma}} \quad \text{if } \xi = 0 \quad (3.11)$$

The Generalized Pareto distribution is often used to model the tail of another distribution. Its pdf:

$$f(\mathbf{x}|\mu, \sigma, \xi) = \frac{1}{\sigma} \left(1 + \xi z\right)^{-\frac{1}{\xi}+1}, \quad \text{where } z = \frac{x - \mu}{\sigma} \quad (3.12)$$

The Inverse Gaussian distribution is used as a model for response times in psychology. Its pdf:

$$f(\mathbf{x}|\mu, \lambda) = \left(\frac{\lambda}{2\pi x^3}\right)^{\frac{1}{2}} \exp\left(\frac{-\lambda(x - \mu)^2}{2\mu^2 x}\right), \quad \text{where } x > 0, \quad \mu > 0, \quad \text{and } \lambda > 0. \quad (3.13)$$

The Logistic distribution is applicable to many areas. One of the most common applications is in logistic regression, which is used for modeling categorical dependent

variables. Its pdf

$$f(\mathbf{x}|\mu, \beta) = \frac{1}{\beta} \frac{e^{-\frac{(x-\mu)}{\beta}}}{\left(1 + e^{-\frac{(x-\mu)}{\beta}}\right)^2}, \quad -\infty < x < \infty, \quad -\infty < \mu < \infty, \quad \beta > 0 \quad (3.14)$$

The Log-Logistic distribution is a continuous probability distribution for a non-negative random variable. It is used in survival analysis to model events whose rate increases initially and decreases later, for example mortality rate from cancer following diagnosis or treatment. It is similar to a log-normal distribution but has heavier tails. Its pdf

$$f(\mathbf{x}|\alpha, \beta) = \frac{\left(\frac{\beta}{\alpha}\right)\left(\frac{x}{\alpha}\right)^{\beta-1}}{\left(1 + \left(\frac{x}{\alpha}\right)^\beta\right)^2}, \quad x > 0, \quad \alpha > 0, \quad \beta > 0 \quad (3.15)$$

The Lognormal distribution is a continuous probability distribution for a random variable whose logarithm is normally distributed. A random variable which is log-normally distributed takes only positive real values. It is important in the description of natural phenomena such as growth and used to analyze extreme values of such variables as monthly and annual maximum values of daily rainfall. Its pdf

$$f(\mathbf{x}|\mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma}} \frac{e^{-\frac{(\log x - \mu)^2}{2\sigma^2}}}{x}, \quad 0 \leq x < \infty, \quad -\infty < \mu < \infty, \quad \sigma > 0 \quad (3.16)$$

The Nakagami distribution is a probability distribution related to the gamma distribution. Being first proposed in 1960, it is relatively new and has been used to model attenuation of wireless signals traversing multiple paths. Its pdf

$$f(\mathbf{x}|\mathbf{m}, \Omega) = \frac{2m^m}{\Gamma(m)\Omega^m} x^{2m-1} \exp\left(-\frac{m}{\Omega}x^2\right), \quad m \geq 0.5, \quad \Omega > 0 \quad (3.17)$$

The Rayleigh distribution is a continuous probability distribution for positive-valued random variables and a form of the exponential distribution. Applications are found in magnetic resonance imaging (MRI) studies. As MRI images are recorded as complex images but viewed as magnitude images, the Rayleigh distribution is used to

model background data. Useful for estimating the noise variance in an MRI image from background data. Its pdf

$$f(\mathbf{x}|\sigma) = \frac{x}{\sigma^2} e^{-\frac{x^2}{2\sigma^2}}, \quad x \geq 0 \quad (3.18)$$

The Rician (or Rice) distribution is a probability distribution of the magnitude of a circular bivariate normal random variable with potentially non-zero mean.  $R \sim Rice(\nu, \sigma)$  if  $R = \sqrt{X^2 + Y^2}$  where  $X \sim N(\nu \cos \theta, \sigma^2)$  and  $Y \sim N(\nu \sin \theta, \sigma^2)$  are statistically independent normal random variables and  $\theta$  is any real number. The Rician distribution is related to the Poisson distribution, Chi-Square distribution, Rayleigh distribution, exponential distribution. Its pdf

$$f(\mathbf{x}|\nu, \sigma) = \frac{x}{\sigma^2} \exp\left(\frac{-(x^2 + \nu^2)}{2\sigma^2}\right) I_0\left(\frac{x\nu}{\sigma^2}\right), \quad \nu \geq 0, \quad \sigma \geq 0, \quad I_0 \text{ is the Bessel function.} \quad (3.19)$$

The t-Location Scale distribution is a non-standardized Student's t-distribution where  $\sigma$  does not correspond to a standard deviation. It is not the standard deviation of the scaled distribution nor standard deviation of the underlying normal distribution, it is simply the overall scale of the distribution. Useful in Bayesian Inference where the inverse gamma distribution is the conjugate prior distribution of the variance of a Gaussian distribution. Its pdf

$$f(\mathbf{x}|\nu, \mu, \sigma) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{\Gamma\left(\frac{\nu}{2}\right) \sqrt{\pi\nu\sigma}} \left(1 + \frac{1}{\nu} \left(\frac{x - \mu}{\sigma}\right)^2\right)^{-\frac{\nu+1}{2}} \quad (3.20)$$

The Weibull distribution, related to both the Exponential distribution and the Gamma distribution, plays an important role in the analysis of failure time data. Its pdf

$$f(\mathbf{x}|\gamma, \beta) = \frac{\gamma}{\beta} x^{\gamma-1} e^{-\frac{x^\gamma}{\beta}}, \quad 0 \leq x < \infty, \quad \gamma > 0, \quad \beta > 0 \quad (3.21)$$

The list of parametric distributions for fitting original sleep measure data corresponding to discrete variables that were considered consisted of: Binomial, Negative

Binomial, and Poisson. Following are descriptions and applications of these. The Binomial distribution is a discrete distribution of the possible number of successful outcomes in a given number of trials where each has the same probability of success. Its pmf

$$p(\mathbf{x}|\mathbf{n}, \mathbf{p}) = \binom{n}{x} p^x (1-p)^{n-x}; \quad x = 0, 1, 2, 3, \dots, n; \quad 0 \leq p \leq 1 \quad (3.22)$$

The Negative Binomial distribution is a discrete distribution similar to the Binomial distribution with the exception that we count the number of Bernoulli trials required to get a fixed number of successes before a specified number of failures (denoted  $r$ ) occur. It includes the Poisson distribution as a limiting case. Used in "contagious" discrete events such as modeling tornado outbreaks, the Negative Binomial can be used to give more accurate models than the Poisson distribution by allowing the mean and the variance to be different, unlike the Poisson. "Contagious" events have positively correlated occurrences causing a larger variance than if the occurrences were independent, due to a positive covariance term. Its pmf

$$p(\mathbf{x}|\mathbf{r}, \mathbf{p}) = \binom{r+x-1}{x} p^r (1-p)^x, \quad x = 0, 1, \dots; \quad 0 \leq p \leq 1 \quad (3.23)$$

The Poisson distribution is a discrete distribution used to model waiting times, and also used to model spatial distributions such as distribution of bomb hits in an area or distribution of fish in the lake. Its pmf

$$p(\mathbf{x}|\lambda) = \frac{e^{-\lambda} \lambda^x}{x!}, \quad x = 0, 1, \dots \quad (3.24)$$

The best, fitted distribution was chosen based on appropriate goodness of fit criteria. After the distributions were uniquely determined (see Appendix Figure A1), a sample of the same size as the original data (N=62 for each group) was generated for each of the sleep measure variables separately for cases and controls given their



derived distributions. As a result, we were able to obtain a sample equal in number of observations but with added information in the form of distributional assumptions made from probability distribution of the error terms for each sleep measure variable.

### 3.5 Results From A Simulated Sample

The sleep measures for the individuals deemed cases were sampled according to best fitting parametric distribution based on AIC criterion first, before considering the other goodness of fit criteria.

The apnea and hypopnea index (AHI) was distributed *Generalized Pareto*( $\mu_{location} = -0.34, \sigma_{scale} = 40.45, \xi_{shape} = 6.0$ ).

The total sleep time (TST) was distributed *Generalized Extreme Value*( $\mu_{location} = 300.94, \sigma_{scale} = 55.10, \xi_{shape} = 1.0$ ).

The sleep efficiency was distributed *Negative Binomial*( $r = 18.14, p = 0.20$ ).

The sleep onset was distributed *Exponential*( $\beta = 22.02$ ).

The rem onset was distributed *Rayleigh*( $\sigma = 112.63$ ).

The total sleep time in REM stage was distributed *Negative Binomial*( $r = 1.44, p = 0.11$ ).

The arousal index was distributed *Generalized Pareto*( $\mu_{location} = -0.46, \sigma_{scale} = 29.64, \xi_{shape} = 3.0$ ).

The stage I sleep measure was distributed *Negative Binomial*( $r = 2.98, p = 0.09$ ).

The stage II sleep measure was distributed *Negative Binomial*( $r = 5.95, p = 0.09$ ).

The stage III sleep measure was distributed *Negative Binomial*( $r = 0.05, p = 0.06$ ).

Age was distributed *Logistic*( $\mu = 67.16, \beta = 5.35$ ).

The sleep measures for the individuals deemed controls were sampled according to best fitting parametric distribution based on AIC criterion first, before considering the other goodness of fit criteria.

The apnea and hypopnea index (AHI) for this group was distributed *Generalized Pareto*( $\mu_{location} = -0.26, \sigma_{scale} = 32.97, \xi_{shape} = 5.1$ ).

The total sleep time (TST) for this group was distributed *Generalized Extreme Value*( $\mu_{location} = 313.68, \sigma_{scale} = 48.53, \xi_{shape} = 1.0$ ).

The sleep efficiency for this group was distributed *Negative Binomial*( $r = 21.38, p = 0.21$ ).

The sleep onset for this group was distributed *Exponential*( $\beta = 27.85$ ).

The rem onset for this group was distributed *Log - Logistic*( $\alpha = 4.65, \beta = 0.33$ ).

The total sleep time in REM stage for this group was distributed *Negative Binomial*( $r = 2.43, p = 0.15$ ).

The arousal index for this group was distributed *Lognormal*( $\mu = 2.54, \sigma = 0.87$ ).

The stage I sleep measure for this group was distributed *Negative Binomial*( $r = 3.93, p = 0.15$ ).

The stage II sleep measure for this group was distributed *Negative Binomial*( $r = 12.53, p = 0.17$ ).

The stage III sleep measure for this group was distributed *Negative Binomial*( $r = 0.12, p = 0.07$ ).

Age for this group was distributed *Logistic*( $\mu = 59.89, \beta = 5.88$ ).

With a same sized sample (N=62 for cases and N=62 for controls) obtained that now provide more information about the distribution of each of the variables, differences between the two groups using a two-sample t-test were again tested. Results are shown in Table 3.2.

While we see that stage I is still statistically significant (**p=0.01**), we are also able to detect other significant differences that might otherwise been undetectable due to under powered data. Using this new approach of adding more information via distributional assumptions, significant differences were also found for time spent

Characteristics of Patients Who Are At Higher Risk for Oversedation and Respiratory Depression
<ul style="list-style-type: none"> <li>• Sleep apnea or sleep disorder diagnosis [22, 23, 36]</li> <li>• Morbid obesity with high risk of sleep apnea [22, 23]</li> <li>• Snoring [22, 23]</li> <li>• Older age: risk is <ul style="list-style-type: none"> <li>† 2.8 times higher for individuals aged 61-70</li> <li>† 5.4 times higher for individuals aged 71-80</li> <li>† 8.7 times higher for individuals over 80 [22, 29, 37]</li> </ul> </li> <li>• No recent opioid use [23, 38]</li> <li>• Post-surgery, particularly if upper abdominal or thoracic surgery [22, 39]</li> <li>• Increased opioid dose requirement [23] or opioid habituation</li> <li>• Longer length of time receiving general anesthesia during surgery [22, 39]</li> <li>• Receiving other sedating drugs, such as benzodiazepines, antihistamines, diphenhydramine, sedatives, or other central nervous system depressants [21, 23, 25, 29]</li> <li>• Pre-existing pulmonary or cardiac disease or dysfunction or major organ failure [22, 23]</li> <li>• Thoracic or other surgical incisions that may impair breathing [22, 23]</li> <li>• Smoker [22, 23]</li> </ul>

**Table 3.2:** Characteristics of Patients Who Are At Higher Risk for Oversedation and Respiratory Depression

sleeping in REM stage (**p=0.04**) and sleep efficiency (**p=0.01**). Our analyses show that patients with OSA and BPH have low sleep efficiency, decreased time spent sleeping in REM stage, and spent more time sleeping in light stage (stage I). Although not statistically significant, analyses also show that patients with OSA and BPH demonstrate higher AHI.

### 3.6 Results From The Simulated Sample After Adjusting for Age

Our analyses also took into account testing and eliminating confounding information. Significant differences between the two groups were tested in the original sample while adjusting for age (Table 3.3) and also in sample with added distributional information (Table 3.4).

Results demonstrate that in the original dataset (Table 3.3), age is a confounder and significant associations found tend to go away with adjustment for age. In the sample generated from a variable's own parametric distribution (Table 3.4), the significant associations found still remain even after the age adjustment. An additional variable, sleep onset, was also found to be significant after adjusting for age.

Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA) After Adjusting for Age			
	OSA (Controls)	OSA w/BPH (Cases)	P-Value
N	62	62	
Mean Apnea and Hypopnea Index (AHI)	31.7	35.7	0.4
Mean Total Sleep Time (min)	279.5	273.7	0.7
Mean Sleep Efficiency (%)	75.2	72.7	0.4
Mean Sleep Onset (min)	29.9	20.0	0.08
Rapid Eye Movement Onset(min)	132.1	134.0	0.9
Time Spent Sleeping in Rapid Eye Movement Stage (%)	13.4	11.6	0.2
Mean Arousal Index	18.8	22.3	0.3
Mean Time Spent Sleeping in:			
Stage 1 (%)	22.1	26.6	0.2
Stage 2 (%)	56.1	56.9	0.8
Stage 3 (%)	1.3	0.9	0.4

**Table 3.3:** Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA) After Adjusting for Age

Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA) on Bootstrapped Sample After Adjusting for Age			
	OSA (Controls)	OSA w/BPH (Cases)	P-Value
N	62	62	
Mean Apnea and Hypopnea Index (AHI)	28.3	31.1	0.5
Mean Total Sleep Time (min)	281.8	278.3	0.8
Mean Sleep Efficiency (%)	76.1	67.0	<b>0.01</b>
Mean Sleep Onset (min)	28.7	20.7	<b>0.04</b>
Rapid Eye Movement Onset(min)	132.2	136.2	0.8
Time Spent Sleeping in Rapid Eye Movement Stage (%)	14.8	11.5	<b>0.04</b>
Mean Arousal Index	18.0	18.8	0.8
Mean Time Spent Sleeping in:			
Stage 1 (%)	20.4	25.8	<b>0.04</b>
Stage 2 (%)	55.5	58.5	0.4
Stage 3 (%)	1.8	1.1	0.4

**Table 3.4:** Effect of Presence of Benign Prostatic Hypertrophy (BPH) on Severity of Sleep Apnea and Sleep Architecture in Patients with Obstructive Sleep Apnea (OSA) on Bootstrapped Sample After Adjusting for Age

### 3.6.1 Bootstrapping Results From Many Random Samples

In order to address whether the associations seen in Table 3.4 were simply by chance or if there was valuable, additional information being added that was given rise to significant difference not otherwise seen, 5000 samples were drawn each of size 62 for cases and 62 for controls in where the specified distribution was considered for each. From Table 3.4 we are able to see whether there are significant differences between those that are controls and those that are cases on measures of central tendency. This is also an analogue for determining the odds that a participant will be a case( $Y = 1$ ) or control( $Y = 0$ ) given their measure on each of the variables separately. To address this question, a simple logistic regression model of the following form is be used:

$$\text{Logit } Y = \alpha + \beta X, \quad \text{for } Y = 0, 1 \quad (3.25)$$

What I am proposing when I sample each of the variables form specific distributions is that this method adds information. If it adds information, then running the logistic regression at each iteration would produce a different  $\alpha$  and a different  $\beta$ :

$$\text{Logit } Y = \alpha^* + \beta^* X, \quad \text{for } Y = 0, 1 \quad (3.26)$$

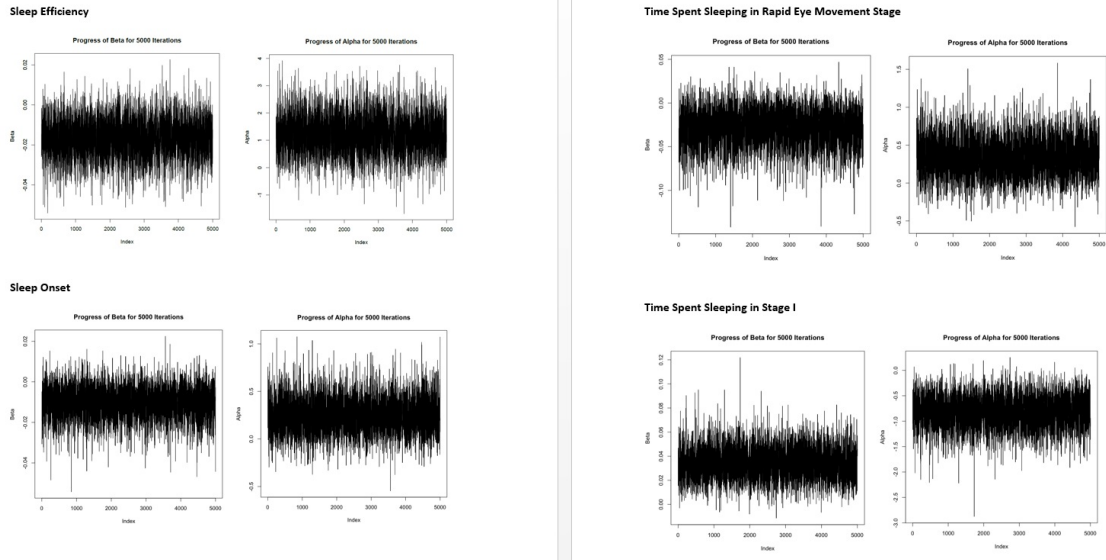
To determine this information, I sampled 5000 times each time obtaining 62 cases and drawing random samples for each of the variables with specific distributions 62 controls and drawing random samples for each of these variables with specific distributions. A confidence interval was obtained for both  $\alpha^*$  and  $\beta^*$  for the variables that showed a significant difference, and this was compared to the confidence interval for the same variables in the original raw data. Results are displayed below (Table 3.5).

Table 3.5 shows that the confidence interval for each of the parameters in where we assumed specific distributions for each of the variables is tighter with a smaller



Parameter Comparison for Simulated Data Assuming Specific Distributions and Original Raw Data				
Original Raw Data			Simulated Data	
Sleep Efficiency				
$\beta$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
-0.01904	0.01079	(-0.04019, 0.00209)	0.00014	(-0.04093, -0.00067)
$\alpha$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
1.41106	0.82213	(-0.200310, 3.02243)	0.01073	(0.07846, 3.03352)
Sleep Onset				
$\beta$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
-0.00670	0.00627	(-0.01899, 0.00558)	0.00011	(0.01821, 0.01426)
$\alpha$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
0.16564	0.23619	(-0.29730, 0.62859)	0.00280	(-0.32413, 0.44741)
TSS in REM				
$\beta$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
-0.03608	0.02280	(-0.08077, 0.00860)	0.00030	(-0.08340, 0.00255)
$\alpha$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
0.44979	0.33641	(-0.20956, 1.10916)	0.00368	(0.01765, 1.04012)
Stage I				
$\beta$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
0.02597	0.1268	(-0.22255, 0.27449)	0.00019	(-0.01057, 0.04302)
$\alpha$	<i>SE</i>	<i>95%CI</i>	<i>SE</i>	<i>95%CI</i>
-0.61949	0.34541	(-1.29650, 0.05750)	0.00471	(-1.03154, 0.25789)

**Table 3.5:** Parameter Comparison for Simulated Data Assuming Specific Distributions and Original Raw Data



**Figure 3.1:** Estimation of the Mean of Beta and Alpha for Each of the Variables

standard error, in comparison to the parameter confidence intervals derived from the original raw data. In each of the figures attached,  $\beta$  and  $\alpha$  do converge in the sense that the variability displayed stays within plus or minus 2. The proposed method adds more information in terms of precision and in turn allows us to find associations that were otherwise null.

### 3.7 Fractional Polynomials

Our outcome variable defined as whether an individual with OSA has BPH or not, is found to be related to various continuous sleep measure variables in the bootstrapped data using parametric distributional assumptions. Particularly, sleep efficiency, sleep onset, time spent sleeping in REM stage, and time spent sleeping in stage I were all significantly associated with the outcome variable. The natural starting point is to assume that the influence the independent sleep measures have on the outcome variable is monotonic; that the straight line model of the form  $b_0 + b_1x$  will suffice. However, not all the time will the relationship be monotonic. We propose investigating other models for possible improvements in fit by considering non-linearity. Splines is another way to handle non-linearity, however the results are often difficult to interpret given complicated equations at times. Here we fit a second-order fractional polynomial to the data which are easier to understand and tackles the non-linearity problem if it exists. In modeling a fractional polynomial, Royston and Sauerbrei (2008) recommend that a fractional polynomial of degree  $m$  for  $X$  with powers  $p_1, p_2, \dots, p_m$  is given by

$$\phi_m(X; \xi, p) = \xi_0 + \sum_{j=1}^m \xi_j X^{(p_j)} \quad (3.27)$$

where  $m$  is a positive integer,  $p = (p_1, p_2, \dots, p_m)$  is a real-valued vector of powers with  $p_1 < p_2 < \dots < p_m$  and  $\xi = (\xi_0, \xi_1, \dots, \xi_m)$  are real-valued coefficients. The Box-Tidwell transformation is specified by the round bracket,

$$X^{(p_j)} = \begin{cases} X^{p_j} & \text{if } p_j \neq 0, \\ \ln X & \text{if } p_j = 0 \end{cases} \quad (3.28)$$

In the cases of equal powers, the above formula may be extended, according to Royston and Altman (1994), for example for  $m > 1$  and  $p_i = p_j$  for at least one pair

of distinct indices  $(i, j)$ ,  $1 \leq i, j \leq m$ . For  $m = 2$ ,  $(i, j) = (1, 2)$  and  $p = (p_1, p_2)$ , we have

$$\phi_2(X; \xi, p) = \xi_0 + (\xi_1 + \xi_2)X^{(p_1)}, \quad (3.29)$$

a fractional polynomial of degree 1, not 2. However, the limit as  $p_2$  tends to  $p_1$  of

$$\xi_0 + \xi_1 X^{(p_1)} + \xi_2 X^{(p_1)} \frac{(X^{(p_2-p_1)} - 1)}{(p_2 - p_1)} \quad (3.30)$$

Royston and Altman proved it is equal to

$$\xi_0 + \xi_1 X^{(p_1)} + \xi_2 X^{(p_1)} \ln X, \quad (3.31)$$

a three parameter family of curves.

For  $m > 2$  and  $p_1 = p_2 = \dots = p_m$ , the previous expression generalizes to

$$\xi_0 + \xi_1 X^{(p_1)} + \sum_{j=2}^m \xi_j X^{(p_1)} (\ln X)^{j-1}. \quad (3.32)$$

For arbitrary powers  $p_1 \leq p_2 \leq \dots \leq p_m$ ,  $H_0(X)$  is set to 1,  $p_0 = 0$  and this extends to

$$\phi_m(X; \xi, p) = \sum_{j=0}^m \xi_j H_j(X), \quad (3.33)$$

where for  $j = 1, \dots, m$

$$H_j(X) = \begin{cases} X^{(p_j)} & \text{if } p_j \neq p_{j-1}, \\ H_{j-1}(X) \ln X & \text{if } p_j = p_{j-1} \end{cases} \quad (3.34)$$

For example, if 5 is the degree of the fractional polynomial and the powers consist of  $\phi_5(X; 0, 1, 2, 2, 2)$  then the component functions are  $H_0 = 1$ ,  $H_1 = \ln X$ ,  $H_2 = X$ ,  $H_3 = X^2$ ,  $H_4 = X^2 \ln X$  and  $H_5 = X^2 (\ln X)^2$ . In the case of non-positive values of  $X$ , a preliminary transformation of  $X$  to ensure positivity is needed.

The assumption is that all models will be fit by maximum likelihood. For given  $m$ , the best power vector  $\tilde{p} = (\tilde{p}_1, \dots, \tilde{p}_m)$  is associated with the model with the highest

likelihood or equivalently lowest deviance,  $D$ . Recall that  $D(x) = -2 \log f(y|x)$ . For convenience, we use the deviance  $D(1, 1)$  associated with the straight line model  $\phi_1(X; 1)$  (i.e.  $m = 1, p = 1$ ) as a baseline for reporting the deviances of other models. The gain  $G$  for a model on a given dataset is then the deviance for  $\phi_1(X; 1)$  minus that for the model in question,

$$G = G(m, p) = D(1, 1) - D(m, p) \tag{3.35}$$

Here it is important to note that since  $G$  moves in the opposite direction to  $D$ , a larger gain indicates a better fit. Recall that high values of  $D(x)$  indicate low values of the log likelihood and that the data deviates substantially from the model's assumptions. When looking at the deviance difference or gain, if this gain is high then it means  $D(1, 1)$  fit of straight line deviates by a lot from the model's assumptions.

### 3.8 Application to Logistic Regression Modeling for Predicting OSA w/BPH versus OSA

The simulated data (adjusted for age) based on each sleep measures unique parametric distribution as determined by the probability distribution of the errors will be used here to determine if linear representations of each of the variables result in the best fit or if non-linear representations via fractional polynomials are the best fit. Recall that the dataset comprises of  $N_1 = 62$  individuals with OSA and BPH and  $N_2$  with just OSA. Our outcome variable defined as whether an individual with OSA has BPH or not, is found to be related to various continuous sleep measure variables; particularly, sleep efficiency, sleep onset, time spent sleeping in REM stage, and time spent sleeping in stage I were all significantly associated with the outcome variable. In Table 3.5, we investigate whether fractional polynomials improves the fit.

Table 3.6 shows the Deviances for various fractional polynomial models with  $m \leq 2$ . For the sleep efficiency variable, the best model with  $m = 1$  has  $\tilde{p} = 3$  and deviance of 152.76. The best model with  $m = 2$  has  $\tilde{p} = (-2, 1)$  and deviance of 150.87. Between the two degrees ( $m = 1$  or  $m = 2$ ), the best model seems to be the one with the lowest deviance, or the model with  $m = 2$ . However, the variable was not significant when its fractional polynomial form  $\tilde{p} = (-2, 1)$  was put in the model for predicting OSA w/BPH vs OSA; this shows that the best functional form for sleep efficiency in predicting OSA w/BPH vs OSA is linearly. For the sleep onset variable, the best model with  $m = 1$  has  $\tilde{p} = 0$  and deviance of 152.44. The best model with  $m = 2$  has  $\tilde{p} = (1, 1)$  and deviance of 151.70. Between the two degrees ( $m = 1$  or  $m = 2$ ), the best model seems to be the one with the lowest deviance, or the model with  $m = 2$ . However, the variable was not significant when its fractional polynomial form  $\tilde{p} = (1, 1)$  was put in the model for predicting OSA w/BPH vs OSA; this shows that the best functional form for sleep onset in predicting OSA w/BPH vs OSA is linearly. For the time spent sleeping in REM stage variable, the best model with  $m = 1$  has  $\tilde{p} = 0.5$  and deviance of 169.08. The best model with  $m = 2$  has  $\tilde{p} = (0, 3)$  and deviance of 169.04. Between the two degrees ( $m = 1$  or  $m = 2$ ), the best model seems to be the one with the lowest deviance, or the model with  $m = 2$ . However, the variable was not significant when its fractional polynomial form  $\tilde{p} = (0, 3)$  was put in the model for predicting OSA w/BPH vs OSA; this shows that the best functional form for time spent sleeping in REM stage in predicting OSA w/BPH vs OSA is linearly. For the time spent sleeping in stage I variable, the best model with  $m = 1$  has  $\tilde{p} = 0.5$  and deviance of 151.55. The best model with  $m = 2$  has  $\tilde{p} = (-1, -.5)$  and deviance of 149.58. Between the two degrees ( $m = 1$  or  $m = 2$ ), the best model seems to be the one with the lowest deviance, or the model with  $m = 2$ . When put in the model with its functional form  $\tilde{p} = (-1, -.5)$ , this variable was significant for

Deviance Values for Fractional Polynomial Models for the Sleep Apnea Data						
Sleep Measure Variable	$m = 1$		$m = 2$		Deviance	Significant
	$p$	Deviance	$p_1$	$p_2$		
Sleep Efficiency	3	152.76	-2	1	150.87	No
Sleep Onset	2	152.44	1	1	151.70	No
Time Spent Sleeping in REM stage	.5	169.08	0	3	169.04	No
Stage I	0.5	151.55	-1	-.5	149.58	Yes

**Table 3.6:** Deviance Values for Fractional Polynomial Models for the Sleep Apnea Data

predicting OSA w/BPH vs OSA. This shows that the best functional form for time spent sleeping in stage I in predicting OSA w/BPH vs OSA is non-linearly or of the form  $stageI^{-1} + stageI^{-.5}$  ( $p - values = 0.06, 0.04$ ). Note here that significance is only for  $stageI^{-.5}$  in predicting OSA w/BPH vs OSA.

Our study shows that when data is under-powered, we might be able to find underlying associations by adding distributional assumptions from each variable's probability distribution of the error terms. Taking it a step further and using a technique developed by Royston and Altman, we propose that when we find the underlying associations via sampling from each variable's unique parametric distribution, we are also able to determine whether this association is best represented linearly or non-linearly.



### 3.9 Results and Discussion

This study shows that patients with OSA and BPH demonstrate a decrease in total sleep time, low sleep efficiency, delayed sleep onset, less REM sleep, and higher number of arousals. They also show higher Apnea-Hypopnea Index (AHI) and more time spent sleeping in stage I. We could not find any study documenting sleep architecture in patients with BPH and OSA. Other published articles show similar findings of poor sleep in patients with nocturia [3]. A higher proportion of light stage I sleep in subjects with BPH most likely affects sleep continuity owing to nocturia causing interruption in sleep which understandably causes delayed REM sleep and shorter REM sleep. It also suggests that older subjects with BPH may suffer from higher degree of OSA. Our study suggests subjects with BPH and OSA tend to show higher AHI. Chou et. al., also found interesting association between OSA and BPH in Taiwanese population [11]. While the mechanism for this finding is unknown, it could be related to androgens as Huggins et. al., showed the essential role of androgens in prostate pathology. They showed that castration was an effective treatment for metastatic prostate cancer, a discovery for which Huggins shared a Nobel Prize with Peyton Rous in 1966 [12]. Many clinical reports suggest that testosterone supplementation in hypogonadal men is associated with induction or worsening of OSA symptoms [13, 14]. It could also be from less continuity of sleep owing to higher number of arousals resulting in less stable upper airway resulting in more deranged lung mechanics leading to higher flow limitation and higher AHI. Younes et. al., showed that occurrence of unnecessary arousals at the time of opening airway accentuates the ventilatory overshoot, further destabilizing breathing [15, 16, 17] which increases risk for OSA. Our analysis have given new insights on predictors for severity of sleep apnea and have also generated some interesting questions worth exploring: (1) since

BPH causes a decrease in sleep efficiency, could this be the cause of poor compliance with CPAP in patients with OSA and BPH since patients are still suffering from less efficient sleep despite optimal treatment for OSA? (2) Would treatment of BPH increase compliance with CPAP? (3) Would treatment of BPH have an effect on OSA severity or compliance to CPAP treatment for OSA? (4) Could successful treatment of sleep apnea by CPAP improve BPH symptoms owing to improvement in sleep architecture? Nonetheless, as a starting point to all of these questions, this study objectively documents the effect of BPH on sleep architecture in patients with OSA. In summary, we found that average time spent sleeping in stage I is significantly different in those with only OSA and those with OSA with BPH in the original unadjusted for age sample, but the effect of BPH on sleep architecture appears to be blunted by an under-powered study. Additionally, our findings and proposed methods give rise to important clinical implications that might otherwise go undetected in light of a low sample size. With the high costs of conducting a clinical trial with enough patients to guarantee a power level of at least 80%, our methods propose to achieve finding associations that might otherwise go undetected by providing more information about each variable's probability distribution from its error terms, without the burden of high costs. Once this information is obtained via parametric assumptions, our goal is then to determine whether the associations found should be linear or non-linear.

As with any quantitative modeling study, our study has some limitations and its results are applicable under its assumptions. First, the cross-sectional design did not allow us to examine causal relationships. Second, our results may not generalize to studies in which participants might not represent independent and identical quantities. We have carried out simple validation of our approach by comparison of results from other well-known statistical methods; however, results could get further strengthened via a larger validation through patient data having a higher sample size.

Third, lack of data regarding stages and severity of BPH preclude any observation regarding severity of BPH with severity of sleep disruption. Likewise data details of surgical and medical treatment could allow assessment of effect of BPH treatment on sleep architecture. Nonetheless, this study systematically evaluates the effect of BPH on sleep architecture in patients with OSA.

## Chapter 4

### THE INFLUENCE OF UNDER-REPORTING ON IDENTIFYING RISK FACTORS FOR KALA-AZAR IN BIHAR, INDIA

#### 4.1 Introduction

Leishmaniasis is a vector-borne disease caused by a protozoan parasite and transmitted by the bite of certain species of sandfly (referred to as “vector”). Leishmaniasis is endemic in many tropical and sub-tropical countries. Because of the variation in type of host (animals and/or humans), species of sandfly and parasite as well as regional differences, the disease is found in many forms, collectively referred to as “family of diseases”. The most serious and potentially fatal, if left untreated, form of Leishmaniasis is the “Visceral” form. The Indian state of Bihar is one of the major foci of Visceral Leishmaniasis (VL) in the world. More than 30% of the worldwide VL cases are reported from Bihar. Poverty, overcrowding, malnutrition, polygamy, illiteracy, and poor domestic conditions facilitate the growth of this disease, which is a major public health problem in India [58].

The Health Information System (HIS) is a key component for any disease control program, and its accuracy is necessary for the assessment of actual disease burden. Unfortunately in India, Kala-azar surveillance is weak because of partial active surveillance and absence of public-private partnership for the disease containment in the affected areas. The surveillance data received to the National Agency (NVBDCP) by means of monthly, quarterly and annual reports, runs from the more peripheral facilities to the National level, through the districts and state health structures. The quality control of routinely collected data is performed by the staff of the National

and Provincial health structures. However, no formal assessment of data quality and its transmission has been carried out. Weak surveillance system and irregular active surveillance for Kala-azar leads to serious under-reporting of VL cases.

More recent pre- and post-intervention studies for 2009 and 2010, have shown that early VL detection have been accomplished via active case detection strategies which also reduce delays to diagnosis and treatment [41]. “In 2009 (pre-intervention phase), VL patients were identified thru active case detection strategies by researchers. Four active case detection strategies (camp approach, index case approach - focal house search around known VL case, incentive approach, and blanket approach –house to house search) were assessed for yield of new VL cases by researchers” [60]. In 2010, Kala-azar Elimination Program (KAEP) staff were trained in these strategies and in VL case management according to national guidelines accompanied by an increased procurement of diagnostics and drugs through the national program. It is believed that “early diagnosis is now feasible with the increasing use of field-based rapid diagnostic tests (rK39) to detect antibodies to recombinant antigen rK39 which are highly sensitive (range 98% - 99%) and specific (range 96% - 97%)” [65]. Amidst these advances, approximately one-third of physicians (especially in the private sector) in India still rely on tests other than rK39 (despite availability) for VL diagnosis [41]. This continues to pose an under-reporting problem despite the advances via active case detection strategies.

Previous research on diseases similar to Leishmaniasis has also shown how local climate variables such as rainfall and temperature can affect the incidence rate of the disease [45, 48]. These variables can be useful in predicting when outbreaks are at a higher risk of occurring. However, it is also important to consider the geographical difference in socio-economic variables such as literacy rates, types of houses, and distribution of individuals in different working environments, among others, because

VL is a disease that is heavily associated with third world countries [66].

The goal of this work is to identify risk factors that are significant in predicting the true burden of Kala-azar in Bihar, which involves first estimating the true disease burden in Bihar, to help inform mathematical modeling frameworks used to understand the nonlinear dynamics of Leishmaniasis. The process was carried out in two steps. The first step was to estimate underreporting levels in Bihar using reported incidence and mortality data from 2003 to 2005, and was achieved by fitting a dynamical mathematical model to the temporal reported incidence and mortality data via a Bayesian parameter estimation procedure. The second step was carried out by analyzing series of multivariate regression models on various datasets that included socio-economic and climate factors and the true incidence and true mortality. That is, the mathematical model captures the spread of Kala-azar in Bihar and estimates underreporting levels to compute adjusted incidence rates, and suggest mechanisms responsible for its control. Adjusted (for underreporting) and reported data are then used via statistical models to explore the relationships between socio-economic and climate variables, and incidence rates from 2003 to 2005.

In this analysis using data from years 2003 - 2005, we found younger age to be one of the most significant and consistent predictors of VL incidence and mortality at a high rate. Equivalently, even with active case detection strategies being developed in more recent years, VL patients continue to be significantly younger [41]. This adds validity to methods proposed in this paper for identifying the risk factors that truly predict the burden of Kala-azar in Bihar to this day. The third step was carried out by using age as a significant factor and developing an age structured model to not only study the Leishmaniasis dynamics but also to study the dynamic within each age compartment.

## 4.2 Data Collection and Preparation

We use cases and mortality data from 2003 to 2005 to study the dynamics of VL and evaluate the effects of the existing control program in Bihar during this time. The data obtained from Bihar State Health Society via Rajendra Memorial Institute of Medical Sciences contains monthly reported incidence rates (cases/deaths reported from government health institutions) (see Table 4.1).

	Incidence rate per 1 million individuals <sup>a</sup>			VL mortality rate per 1000 infected <sup>b</sup>		
	<i>2003</i>	<i>2004</i>	<i>2005</i>	<i>2003</i>	<i>2004</i>	<i>2005</i>
Mean	13.47	16.67	21.64	13.42	6.42	5.28
Median	13.71	16.19	22.56	13.49	6.87	4.48
Variance	12.52	61.70	42.90	41.97	7.88	6.82
1 <sup>st</sup> quartile	11.88	9.85	16.28	7.18	3.93	3.46
3 <sup>rd</sup> quartile	15.72	23.41	25.58	18.02	8.24	6.51

**Table 4.1:** Visceral Leishmaniasis Reported Data from Indian State of Bihar from 2003-2005.

<sup>a</sup>The rate is computed by dividing number of new cases reported in a particular month by the population of Bihar and then multiplying the resultant number by 1 million.

<sup>b</sup>The rate is computed by dividing number of deaths reported in a particular month by the number of new infections in that month and then multiplying the resultant number by 1000.

The State Health Society of Bihar is divided into 38 District Health Societies (DHS) which are further divided into Primary Health Centers (PHCs). The health systems vary substantially. The district hospitals and government medical colleges are the sources of the reported cases and reported deaths to the DHS. This, therefore, does not reflect the number of cases reported in privately owned health care facilities.

It is believed that more than 75% of the VL infected individuals will preferentially consult private practitioners or one of the not-for-profit private clinics [64]. Because private health providers are not part of the state public health surveillance system and continue to have limited knowledge on the innovative tools being developed for VL care, proper reporting is not undertaken [51]. Thus, the magnitude of the problem is difficult to assess.

Data from all 33 districts are obtained; however, because VL has been consistently shown in 21 districts which have high prevalence, the focus in this study is on the 21 districts. Additionally, socio-economic data are also collected. The data represent literacy rates, education level, worker types, house types, number of medical facilities, bus services, population density, and are taken from 2001 Census of India, through the Bihar state government website[43]. Rainfall related data are collected from a statistical survey carried out by the Directorate of Statistics and Evaluation, Patna, Bihar [43]. This data included district-wise annual numbers for the variables. These variables were especially considered due to their high association with third world living conditions and VL. Education levels were important factors to consider as better-educated individuals not only provide VL prevention benefits for themselves through greater disease awareness but can also lead their family and the group(s) for the uplifting of the community they live in [58]. Types of working population were also important to consider. Industrial environments may lead to close contacts among individuals for longer periods of time. Higher movements of marginal workers who may be infected can enhance the spread of the disease, whereas working in farm lands might lead to higher exposure of individuals to sandflies, as plants and trees serve as resting areas for the VL disease vector [58]. Data categorized into types of housing are also considered as housing conditions have been shown to have significant impact on disease trends [40]. Climate variables were also important to consider as climate



variables have long been linked to vector-borne diseases because of the evidence that the right humidity and temperature can drastically increase the number of sandflies, and thus incidence of VL [45, 48].

There are 35 factors/variables in the Bihar district data which could be used as predictor variables. Before any of the statistical or mathematical models are implemented, the raw data is prepared to facilitate further analysis. Because this analysis heavily relied on derived data, some variables of interest can not be measured directly but have to be calculated from other measured variables or from literature reviews. Some examples of derived data used in this study are incidence rates per million population and mortality rates per thousand individuals. However, before calculations for derived data are executed, the absence of some of the data is dealt with appropriately as follows.

Different sources of data are used and in the absence of detailed datasets, we apply 2 simple methods for estimating missing values: (1) least squares linear regression method or (2) mean substitution. In the least squares linear regression approach, the value of the dependent variable  $Y$  is predicted based on the value of an independent variable  $X$ . In this study, we have monthly reported data for cases and deaths for each of the 21 districts for each year from 2003 to 2005. If a particular month is missing data, using reported data from the remaining years for that same month we use least squares linear regression to predict the missing cases/deaths. As a result, missing values are dealt with via a higher-order polynomial used to fit the available data each time. The obtained polynomial is then used to obtain the missing value each time. If the fitted high-order polynomial predicts a negative value for either cases or deaths, then the mean substitution method is used instead. The mean of reported cases (deaths) for the same month from remaining years replaces the missing value.

The districts for which not all socio-economic or climatic data were not found

were not considered in the study. This data was only obtained for one year for each district. Our hope is that the socio-economic factors will capture well the health disparities seen in Bihar, one of the most illiterate and poor states of India.

Demographic Variables	Abbreviation	Description
Population Density	P	Represents the population per square kilometer area. This is an important variable to consider as high-density areas usually have high contact rates (ICDDR,B 2007).
Population	Pop-2001	Represents the population in 2001.
Decadal Growth Rate	Growth-rate10	Represents the population per 10 years growth rate.
Rural Population	Rural-pop	Represents percentage of rural population.
Female Male Ratio	Femal-mal-rat	Represents the sex ratio of females per 1000 males.
Total Population	Total-pop	Represents total number of individuals.
Age Group 1	Age-0-4	Represents individuals in age group 0 to 4 years of age.
Age Group 2	Age-5-14	Represents individuals in age group 5 to 14 years of age.
Age Group 3	Age-15-59	Represents individuals in age group 15 to 59 years of age.
Age Group 4	Age-gt60	Represents individuals in age group greater than 60 years of age.
<b>Social Variables</b>		
<b>Abbreviation</b>		
Education Level None	Pct-none	Represents percentage of total number of individuals without any level of education.
Education Level Below Primary	Pct-ltprimary	Represents percentage of total number of individuals with below primary education.
Education Level Primary	Pct-primary	Represents percentage of total number of individuals with only primary education.
Education Level Middle	Pct-middle	Represents percentage of total number of individuals with only middle school education.
Literacy Rate for Males	Lm	Represents the percentage of male population in a district that is literate. The male literacy rate is important to consider as the Indian societies are in general male dominated with the male head of the household usually making the final family decisions (Sinha et al. 2006).
Literacy Rate for Females	Lf	Represents the percentage of female population in a district that is literate. The female literacy rate is crucial for understanding the impact of VL as females come forward for treatment only at the last stage of the disease, which is mainly due to the social and economic stigma (Singh et al. 2006).
Percentage of Home Schooled Population	Pct-HS	Represents the percentage of home educated individuals in a district.
Percentage of population with Graduate Education	Pct-Grad	Represents the percentage of individuals in a district with a graduate degree.

**Table 4.2: Variables in Study (Socio-Economic Variables)**

Economic Variables		Abbreviation	Description
Medical Facilities/1 million inhabitants of district		Medical-facIM	Computed by first taking the ratio of number of villages that have health facilities (for VL treatment) and district-population and then multiplying the fraction by one million individuals. More than 70% of medical patients in Bihar consult unqualified practitioners, so the number of government regulated medical facilities could be an important factor in influencing disease trends (Sundar et al. 1994).
Percentage of population described as a Main (or Office) Worker		WT-Main	Represents the percentage of the workers who are employed in industry or factories.
Percentage of district population described as a Marginal Worker		WT-Marginal	the percentage of self-employed workers that sell goods in open markets in the cities, often traveling to new areas.
Percentage of district population described as a Non-Worker		WT-nonW	the percentage of farmers or other workers related to agriculture in some form.
Percentage of district houses classified as Permanent		HT-perm	Represents the percentage of homes constructed of brick.
Percentage of district houses classified as Semi-Permanent		HT-semi	Represents the percentage of homes constructed of mud.
Percentage of district houses classified as Temporary		HT-temp	Represents the percentage of homes constructed of bamboo and hay.
Percentage of villages within a district that have access to Bus Services		Bus-Service	This variable is essential to consider in the study since very few appropriate medical facilities are available for Kala-azar and hence people often have to travel long distances for the treatment. In addition, most of the individuals are poor and it is difficult for them to afford their own transportation.
Livestock		Livestock-Dist	Represents number of livestock per district.
Poultry		Poultry	Represents number of poultry per district.
Livestockp1k		Livestock-p1k	Represents livestock per 1000 individuals.
Poultryp1k		Poultry-p1k	Represents poultry per 1000 individuals.
Climate Variables		Abbreviation	Description
Rain Group 1		Rain-Ju-Sept	Represents average rainfall in mm from months of June to September.
Rain Group 2		Rain-Oct-Dec	Represents average rainfall in mm from months of October to December.
Rain Group 3		Rain-Mar-May	Represents average rainfall in mm from months of March to May.
Total annual rainfall		Total-Rain	Measured in millimeters per district.
Number of rainy days per year in each district		Rainy-Days	Count of rainy days.

**Table 4.3:** Variables in Study (Economic and Climate Variables)

### 4.3 Infection Dynamics Model to Capture Underreporting Parameter

We use a mathematical model (see Appendix D) that captures transmission dynamics and under-reporting levels of VL in a district. The same model framework is used for each district to estimate district specific incidence under-reporting, however, parameter estimates were different in each case. The model captures two interacting populations: humans and vector (sandfly) populations. The human population is divided into susceptibles (S), infected (I), under treatment (G or T) and permanently recovered (R) sub-populations. It incorporates the possibility that infected individuals seek treatment at private ( $T$ ) or public ( $G$ ) health facilities. The treatment of individuals at private health facilities results in *underreporting* of cases in the state as private practitioners are not required by law to report cases. Underreporting levels in incidence is captured by parameter  $(1 - p)$  and are unknown. The estimates of transmission coefficients ( $\lambda_h$  and  $\lambda_v$  in the Model) are also unknown for VL in Bihar. Even though we consider a systematic sub-representation of  $\lambda_h = CB_{hv}$  and  $\lambda_v = CB_{vh}$ , we do not estimate their sub-representation parameters. That is, we estimate transmission coefficients  $\lambda_h$  and  $\lambda_v$  as a lumped composite parameters and not estimate explicitly  $C$ ,  $\beta_{hv}$ , and  $\beta_{vh}$  separately.

Susceptible humans can be infected with the VL strain following contact with infected sandflies at an average rate  $F_h = mCB_{hv}\frac{Z}{N_h}S$ , where  $m$  is per-capita average number of sandflies (assumed constant),  $C$  is the average biting rate of a sandfly on humans in a unit time, and  $B_{hv}$  is the transmission probability of the parasite given a bite. Susceptible sandflies are infected with leishmania following contact with infected humans at an average rate  $F_v = CB_{vh}\frac{I}{N_h}X$ , where  $B_{vh}$  is the transmission probability of the parasite from an infected human to a susceptible sandfly given a bite. (See Appendix D).

Para.	Definition	Point estimate	Ref.
$p$	Proportion of infected using public health clinics	Estimated (with mean 0.24)	See Figure 1
$\eta$	Per capita treatment rate	Estimated (with mean 0.25 per month)	[61]
$\alpha_1$	Per capita recovery rate for G class individuals	1.32 per month	[54]
$\alpha_2$	Per capita recovery rate for T class individuals	0.65 per month	[54]
$b_h$	Per capita recruitment rate in human population	722.4 people per month	[54]
$b_v$	Per capita recruitment rate in vector population		
$\delta_1$ ( $\delta_2$ )	Disease related mortality in the I class (G and T classes)	38.5% (10%)(Estimated with mean)	[67] ([42])
$\mu_h$ ( $\mu_v$ )	Per capita natural mortality rate in humans (vectors)	0.0014 (2.13) per month	[54]
$\lambda_h$ ( $\lambda_v$ )	Transmission coefficients for humans (vectors)	Estimated (with mean of 2.1 (1.5) per month)	

**Table 4.4:** Model Parameters

## 4.4 Underreporting

### 4.4.1 Estimation Method

A Bayesian parameter estimation approach is used to estimate the underreporting parameter  $(1 - p)$  of the mathematical model (see Appendix B) to obtain estimates of adjusted incidence and mortality rates. We utilize the Metropolis-Hastings Monte Carlo Markov Chain (M-H MCMC) to fit the model to the observed data from Bihar. The M-H MCMC algorithm construct Markov Chain, which has limiting invariant distribution, as follows.

1. Choose *initial* values of parameters-set  $X_0$  (in our case, initial guess were given in Table 4.4).
2. Choose a *candidate* estimate value from the proposal distribution conditional on initial set, i.e., given  $X_n$ , generate a candidate  $Z_{n+1}$  from *proposal distribution*  $P(X_n, \cdot)$  (i.e., from  $P(\cdot|X_n)$ ). Perform *acceptance* criteria on the candidate, i.e., flip an independent coin, whose probability of heads equals  $\alpha(X_n, Z_{n+1})$ , where

$$\alpha(x, z) = \min[1, \text{ratio}] = \min \left[ 1, \frac{\pi(z) \cdot P(z, x)}{\pi(x) \cdot P(x, z)} \right] = (\text{more precisely}) \min \left[ 1, \frac{\pi(z) \cdot P(x|z)}{\pi(x) \cdot P(z|x)} \right]$$

where  $\pi(\cdot)$  is the distribution of the limiting invariant state (initially unknown) of the chain. If the coin is heads, “accept” the proposal by setting  $X_{n+1} = Z_{n+1}$ ; if the coin is tails then “reject” the proposal by setting  $X_{n+1} = X_n$ . (In our case, we considered symmetric normal distribution as our proposal distribution).

3. Go to step 2 above and repeat. (see Appendix B)

## 4.5 Statistical Analysis

### 4.5.1 Multicollinearity of Variables

There were 35 variables in the Bihar district data which could be used as predictor variables (Tables 4.2 and 4.3). Before using them in a regression analysis it was first

necessary to test them for independence from each other. First, the variables were each rescaled to a -1 to 1 range, in order to ensure that magnitude differences in the variable measures would not impact the results of the co-linearity testing. Rescaling consisted of standardizing the variables by subtracting the midrange and dividing by the range for each. Second, the rescaled variables were tested for co-linearity using variance inflation factors (VIF) and condition indices. The condition indices are the square roots of the ratio of the largest eigenvalue from design matrix to each individual eigenvalue. The largest condition index is the condition number of the scaled design matrix. When this number is small, weak dependencies might be starting to affect the regression estimates. The VIF provides a measure of how much the variance of an estimated regression coefficient is increased because of collinearity.

$$VIF_j = \frac{1}{1 - R_j^2} \quad (4.1)$$

where  $R_j^2$  is the coefficient of determination obtained from regressing the  $j$ th explanatory variable against all other explanatory variables.

If the  $j$ th explanatory variable is uncorrelated with all the others then  $VIF = 1$ ; however, VIF increases as the correlation increases. These factors measure how much the variances of the estimated regression coefficients are inflated as compared to when the predictor variables are not linearly related. The general rule of thumb is that VIFs exceeding 4 warrant further investigation, while VIFs exceeding 10 are signs of serious multicollinearity requiring correction. In this analysis, the minimum acceptance value for VIF and the condition indices was 10. All scaled variables were placed in the model and the variable corresponding to the largest condition index was removed and the model re-run. This procedure was repeated until a group of variables meeting the VIF and condition index criterion were identified.



#### 4.5.2 *Best Subsets Algorithm*

A best subsets algorithm approach applied to multiple linear regression analysis was performed to examine relationship between the variables meeting the variance inflation factor and the condition index. This approach was performed on both reported and adjusted (for underreporting) incidence and mortality rates for years 2003-2005. For these analyses, all ten variables (shown in Table 4.6) were entered as potential predictors into regression models with the incidence and mortality rates treated as the dependent measures.

The Akaike Information Criterion (AIC) was used to identify the best subsets in the algorithm. These algorithms searched for all the subsets of X variables with the smallest AIC values using much less computational effort than when all possible subsets are evaluated [44].

Not only do these algorithms provide the best subsets according to the specified criterion, but they often also identify several good subsets for each possible number of X variables in the model to give the investigator additional helpful information in making the final selection of the subset of X variables to be employed in the regression model. In each case, final linear regression models were selected by minimizing the AIC, which balances the regression model fit and its complexity. Increasing the number of parameters in the statistical models improves their fit to the data but at a cost of increased complexity. Thus, AIC balances the goodness of fit and the number of included covariates by penalizing the number of parameters in each model considered. The best model is the one with the lowest AIC. This method is considered more robust than the traditional stepwise selection procedures and produces parsimonious models balancing the goodness of fit and model complexity [44].

## 4.6 Insight from Statistical Results

By integrating mathematical and statistical models' analysis, we are able to identify relevant risk factors for VL in Bihar, India. In this section, we discuss findings from the Bayesian parameter estimation method, and compare results from the best statistical models for predicting reported and adjusted incidence, and reported and adjusted mortality rates as a way to identify risk factors for the VL. Our results also give insight to the importance of incorporating underreporting. Using age as the most consistent significant result from the statistical analyses, we proceed to develop a more precise mathematical model by developing an age structured model to study dynamics.

### 4.6.1 Bayesian Estimates from M-H MCMC

Parameter	Mean	Std.	MC error	2.50 %	Median	97.50%
$\delta_1$	2.395	1.036	0.01784	0.3358	2.514	3.925
$\delta_2$	0.501	0.2886	0.004041	0.02702	0.4986	0.9755
$\eta$	0.1428	0.08477	0.001472	0.01511	0.136	0.2912
$\lambda_h$	0.792	0.5681	0.01038	0.03014	0.6768	1.918
$\lambda_v$	1.266	0.8699	0.01611	0.04964	1.133	2.899
$p$	0.188	0.1142	0.002061	0.01525	0.1734	0.3871

**Table 4.5:** Results from MCMC Bayesian Estimation for the 2004 Data from State of Bihar

We estimated the 6 parameters ( $\delta_1, \delta_2, \eta, \lambda_h, \lambda_v, p$ ) for each of the 21 districts. As an example, we show results (in Table 4.5) for entire Bihar using 2004 data. The initial conditions were fixed according to the region of consideration; for example, for the whole state of Bihar the fixed initial conditions were ( $S(0)/N = 0.7, I(0)/N = 0.02, G(0)/N = 0.5E - 3, T(0)/N = 1.5E - 3$  and  $R(0)/N = 0.278$ ). The incidence-

underreporting level is computed by  $(1 - p) * 100\%$ .

Using the MH-MCMC Bayesian method, we have estimated the underreporting proportion and used it to adjust the reported incidence and reported mortality rates. The estimated districtwise underreporting proportions for the three years are given in the figure in Appendix E. For example, the underreporting proportion for the whole state in 2004 is 81.2% with credible interval of (69.7, 92.6), see last result of Table 4.5.

#### *4.6.2 Independent Variables Identified Via Statistical Method*

Descriptive statistics for independent variables that met VIF criteria are shown in Table 4.6. These ten independent variables were inputted in the best subsets algorithm as variables and used to identify the best models for predicting both reported incidence rates and adjusted incidence rates, and used to identify the best models for predicting reported mortality rates and adjusted mortality rates. This was done to identify risk factors for Leishmaniasis.

	Mean	Median	Std	Min.	Max.	1st Q	3rd Q
$Pop_{2001}$	2688369	2682720	909010	1280354	4718592	2158608	3295789
$Growth_{rate10}$	28.8	29.3	3.5	18.6	35.2	26.4	30.9
$P$	1033	1006	248	582	1471	853	1221
$Medical_{fac1M}$	79	81	24	28	140	65	92
$Femal - Mal_{rat}$	920	915	32	873	1031	910	920
$PCT_{tprimary}$	3362.4	3235.7	1468.0	1100.8	6149.0	2522.0	4167.7
$PCT_{primary}$	3469.8	3166.9	1510.7	1155.3	6557.3	2677.1	4177.0
$PCT_{middle}$	1757.1	1601.8	797.8	568.6	3726.0	1282.2	2093.6
$WT_{main}$	0.26	0.26	0.04	0.19	0.33	0.24	0.28
$Age_{5-14}$	0.29	0.29	0.01	0.27	0.30	0.28	0.29

**Table 4.6:** Descriptive Statistics

### 4.6.3 Impact on Reported and Adjusted Incidence Rates

Overall, there were several variables that were consistently found to be significantly associated with reported incidence rates between 2003 to 2005 (see Appendix F). Six variables were retained as significant predictors of reported incidence rates for 2003. Reduced incidence rates for 2003 were associated with increases in  $Pop_{2001}$  and decreases in variables  $Medical_{fac1M}$ ,  $PCT_{primary}$ ,  $WT_{main}$ ,  $Age_{5-14}$  and  $Growth_{rate10}$ . Four variables were retained as significant predictors of incidence rates for 2004. Increased incidence rates for 2004 were associated with increases in  $WT_{main}$ ,  $Age_{5-14}$ ,  $Medical_{fac1M}$ , and  $PCT_{ltprimary}$ . Increased incidence rates for 2005 were also marginally associated with  $WT_{main}$ . Overall,  $WT_{main}$  and  $Age_{5-14}$  were found to be consistently significant with the incidence rates for 2003, 2004, and 2005.

It seems that workers classified as main (WT-main) seem to consistently best predict incidence rates for the years 2003 to 2005 at an increasing rate. This might be a direct result from idea that industrial environments may lead to close contacts among individuals for longer periods of time; thus, those that might be infected can enhance the spread of disease. This is followed by the percentage of children whose age ranged from 5 to 14 years (Age-5-14). This age group seems to consistently significantly predict incidence rates for the years 2003 to 2004 at a very high rate. In a study done by Mueller, where age distribution of patients with VL in endemic areas in Ethiopia was analyzed via assessment of young and aged mice during the course of infection, it was concluded that macrophages from younger mice do not have an impaired capacity to kill parasites and tend to promote parasite growth more efficiently [56]. Another published study points to certain types of VL affecting certain pediatric age groups more than others [52]. Our results seem to support the high incidence rate among the younger group.

When the incidence rates were adjusted for underreporting, some results coincided with results for the reported incidence rates. Similar to the reported incidence rates for 2003,  $Growth_{rate10}$  was found to be a significant predictor for adjusted incidence rates in 2003. Increased adjusted incidence rates for 2003 were associated with increases in  $Growth_{rate10}$ . Similar to the reported incidence rates for 2004 and 2005, the age group between 5 and 14 years of age was the only significant predictor of adjusted incidence rates for 2004 and 2005. Increased adjusted incidence rates for 2004 and 2005 were associated with increases in  $Age_{5-14}$  for 2004 and 2005.(see Appendix F)

Results for the incidence rates adjusted for underreporting coincide with results from the reported incidence rates. Interestingly, the age group between 5 and 14 years of age was a consistent significant predictor for adjusted incidence rates for 2004 and 2005. There seems to be something about this particular age group that promotes the VL incidence.

In Table 4.7 we show the difference between results from adjusted and unadjusted incidence rates. When we do not adjust for underreporting, our statistical models correlate the incidence with more predictors compared to fewer predictors in the case of adjusted incidence. We are able to target what best predicts incidence when we incorporate underreporting. Additionally, the proportion of variability accounted for by each of the statistical models is higher for the models in which the cases were adjusted for underreporting. Thus, underreporting needs to be incorporated: otherwise we will get unreasonable results and implications.

Moreover, the total variability of incidence explained by the predictors for each model representing the different years is higher 66% of the time when the models

	Reported Results	Adjusted Results
$I_{2003}$	$Pop_{2001}$ $Medical_{fac1M}$ $PCT_{primary}$ $WT_{main}$ $Age_{5-14}$ $Growth_{rate10}$	$Femal - Mal_{rat}$      $Growth_{rate10}$
$I_{2004}$	$Medical_{fac1M}$ $PCT_{ltprimary}$ $WT_{main}$ $Age_{5-14}$	$Pop_{2001}$    $Age_{5-14}$
$I_{2005}$	$WT_{main}$ $Age_{5-14}$	$Age_{5-14}$

**Table 4.7:** Reported vs. Adjusted Incidence Rates Results

are adjusted for under-reporting. Variability for reported incidence in 2004 was 41% compared to 61% for adjusted incidence in 2004. Variability for reported incidence in 2005 was 25% compared to 27% for adjusted incidence in 2005. The variability was not higher for adjusted incidence in 2003. Because this total variation usually can be made larger by including a larger number of predictor variables, a modified measure (adjusted  $R^2$ ) was used to adjust for the number of predictor variables in each model. Even after adjusting for the number of predictor variables in each model, the variability of incidence explained by the predictors for each model is higher when the models are adjusted for under-reporting. Variability for reported incidence in 2004

was 25% compared to 57% for adjusted incidence in 2004. Variability for reported incidence in 2005 was 17% compared to 23% for adjusted incidence in 2005. The variability was not higher for adjusted incidence in 2003.



#### 4.6.4 Impact on Reported Mortality Rates

When analyzing the relation between the reported mortality rates and variables for each year, the rates for those regions that did not have any reported deaths were predicted using either regression analysis or mean substitution based on available data. There was one variable that was consistently found to be significantly associated with the reported mortality rates between 2003 - 2005 (Appendix G). Decreased reported mortality rates were associated with increases in  $Age_{5-14}$ .

One published study that consisted of “reviewing 546 records of patients younger than 15 years admitted with the diagnosis of VL at the Instituto de Medicina Integral Professor Fernando Figueira between May 1996 and June 2006” found that the presence of fast breathing, jaundice, mucosal bleeding and bacterial infections would increase the risk of death by 3 to 4-fold. The presence of very low counts of neutrophils and platelets would increase the risk of death by 3 and 12-fold respectively [59].

In Table 4.8 we again show the difference between results from adjusted and unadjusted mortality rates. When we do not adjust for underreporting, our statistical models correlate the mortality with the younger age group between 5 to 14 years of age.

The total variability of mortality explained by the predictors for each model representing the different years is higher 66% of the time when the models are adjusted for under-reporting. Variability for reported mortality in 2003 was 41% compared to 44% for adjusted incidence in 2003. Variability for reported incidence in 2005 was 66% compared to 67% for adjusted incidence in 2005. The variability was not higher for adjusted incidence in 2004. Because this total variation usually can be made larger by including a larger number of predictor variables, a modified measure (adjusted

	Unadjusted Results	Adjusted Results
$CFR_{2003}$	$Age_{5-14}$	$Age_{5-14}$ $Growth_{rate10}$
$CFR_{2004}$	$Age_{5-14}$ $Femal - Mal_{rat}$ $Growth_{rate10}$ $Pop_{2001}$	$Age_{5-14}$ $Growth_{rate10}$
$CFR_{2005}$	$Age_{5-14}$ $PCT_{ltprimary}$ $Medical_{fac1M}$	$Age_{5-14}$ $PCT_{ltprimary}$ $Medical_{fac1M}$

**Table 4.8:** Reported vs. Adjusted Mortality Rate Results

$R^2$ ) was used to adjust for the number of predictor variables in each model. Even after adjusting for the number of predictor variables in each model, the variability of mortality explained by the predictors for each model is higher when the models are adjusted for under-reporting. Variability for reported mortality in 2003 was 36% compared to 37% for adjusted incidence in 2003. Variability for reported mortality in 2005 was 52% compared to 53% for adjusted incidence in 2005. The variability was not higher for adjusted incidence in 2004.

#### 4.7 Motivation for Developing an Age Structured Model

Over the last few decades there has been a dramatic increase in the number of VL cases in India, due to a complexity of factors involved in the transmission of the parasite. Several studies have shown that malnutrition, environmental aspects,

and social and economic conditions are risk factors for VL. In general, risk factors may include factors related to hosts involved in life cycles of the parasites and their environments. However, data on socio-economic, and climatic risk factors for VL are comparatively scarce, and few studies have investigated the impact of such risk factors on the disease burden of VL in India. Changes in climate and land use patterns, economic developments, and increasing risk factors are growing concerns for public health departments in understanding VL outbreaks especially in developing countries like India. Moreover, current surveillance systems only capture reporting through public health institutions, while a significant number of VL patients undergo treatments at private medical facilities resulting in severe underreporting of cases and deaths in Bihar at that time. In recent years there has been some improvement in surveillance systems via the incorporation of some active reporting; however, there is still a long way to go before actual disease burden can be reported from the field. These issues may severely hinder the efforts to prevent and control the VL in Bihar. I used dynamical and statistical models to capture disease burden and to identify risk factors for KA in predicting incidence and mortality levels in India, respectively. The dynamical model was used to estimate underreporting levels via the reported data and Bayesian estimation method. The adjusted (for underreporting) incidences obtained from the model were taken in statistical models and were used to identify factors that may predict VL disease burden.

Using limited data from 2003 to 2005, we found that underreporting levels in Bihar ranges from 70% to 90%. The results from the study also provide some perspectives into socio-economic factors and their relationship to incidence and mortality of VL. We found that two particular variables were consistently retained as significant predictors of VL incidence.  $WT_{main}$ , which represented the percentage of the workers who were employed in industry or factories, was consistently retained as best pre-

dicator for the incidence of VL for all reported incidence years for the period 2003 to 2005. This might be a direct result from idea that industrial environments may lead to close contacts among individuals for longer periods of time; thus, those that might be infected can enhance the spread of disease. The percentage of children whose age ranged from 5 to 14 years (Age-5-14) also consistently predicted VL incidence at a high rate. Younger children experiencing malnutrition and extreme poverty environments tend to have an impaired immune system that could in these cases impair their capacity to kill parasites. This could then promote parasite growth more efficiently [56]. The age group represented by those less than 14 years of age was also the most consistent predictor of incidence when incidence was adjusted for underreporting and of reported and adjusted mortality.

Models developed for policy recommendations and implementation must be quite different than general math models used. In our case, the problem lies in recommending a specific age group to be the focus of attention in coping with VL outbreak; as a result, it is necessary that a model that separates the population into a sufficient number of age groups is used [69]. Since age structure is a critical risk factor in the transmission dynamics of Leishmaniasis, we conclude this chapter with a minimal age structured model and its preliminary analysis in order to highlight the nature of the modeling and technical challenges tied in to the study and parameter estimation of age structured models [73, 74, 75]. Our next step involved developing a more precise mathematical model using this information. An age structured mathematical model was developed to study the dynamics of Leishmaniasis.

#### 4.8 Age-Structured Epidemic Model

I developed an age-structured epidemic model. A typical Susceptible-Exposed-Infected-Recovered (SEIR) disease flow is assumed. Careful attention is paid to the

development of the infection rates as these recruitment rates drive the model. Age is discretized into age intervals or groups, e.g., infants, children, juveniles, adults, senior citizens, etc. Mild assumptions on the age-dependent parameters are imposed, namely that these values remain constant over each age group. By treating age as a discrete, rather than continuous variable and integrating each of the PDE's in each of the resulting age groups, it results in a system of ordinary differential equations. I locate the equilibrium point corresponding to an absence of infection and linearize about this point to determine under what conditions a small perturbation, in the form of the introduction of a small number of infections, will cause an epidemic. This threshold is determined by using the next generation operator. The goal is to examine the relative growth rates between the sizes of successive generations of infected individuals and arriving at the desired threshold [69].

#### 4.8.1 Discrete Age Groups

Using the approach described by Fred Brauer and Carlos Castillo-Chavez, the age axis was divided into four age groups  $[0, a_1)$ ,  $[a_1, a_2)$ ,  $[a_2, a_3)$ ,  $[a_3, a_4)$  [71]. All the age dependent parameters were assumed to be constant in each age group (for example,  $\mu_j$ ,  $\epsilon_j$ ,  $\lambda_j$ ,  $\beta_j$ ,  $\omega_j$ , and  $\gamma_j$ ).  $N(t) = \sum_{j=1}^n N_j(t)$  is the total human population as a function of time.  $S_j(t)$  is the number of susceptible humans in age-group  $j$ ,  $E_j(t)$  is the number of asymptomatic humans in age-group  $j$ ,  $I_j(t)$  is the number of infected humans in age-group  $j$ , and  $R_j(t)$  is the number of recovered humans in age-group  $j$ . Individuals progressing out of age group  $j - 1$  to group  $j$  at time  $t$  are represented by  $\eta_j$ . So the “aging” rate from group  $j$  is  $\eta_j$  and it was calculated as the mean time spent in group  $j$  as  $1/\eta_j$  [70]. We also assume that there is a constant inflow of human hosts  $\Lambda$ . Below a schematic diagram from the system is presented in Figure 2.

We have the following system of ordinary differential equations for the human

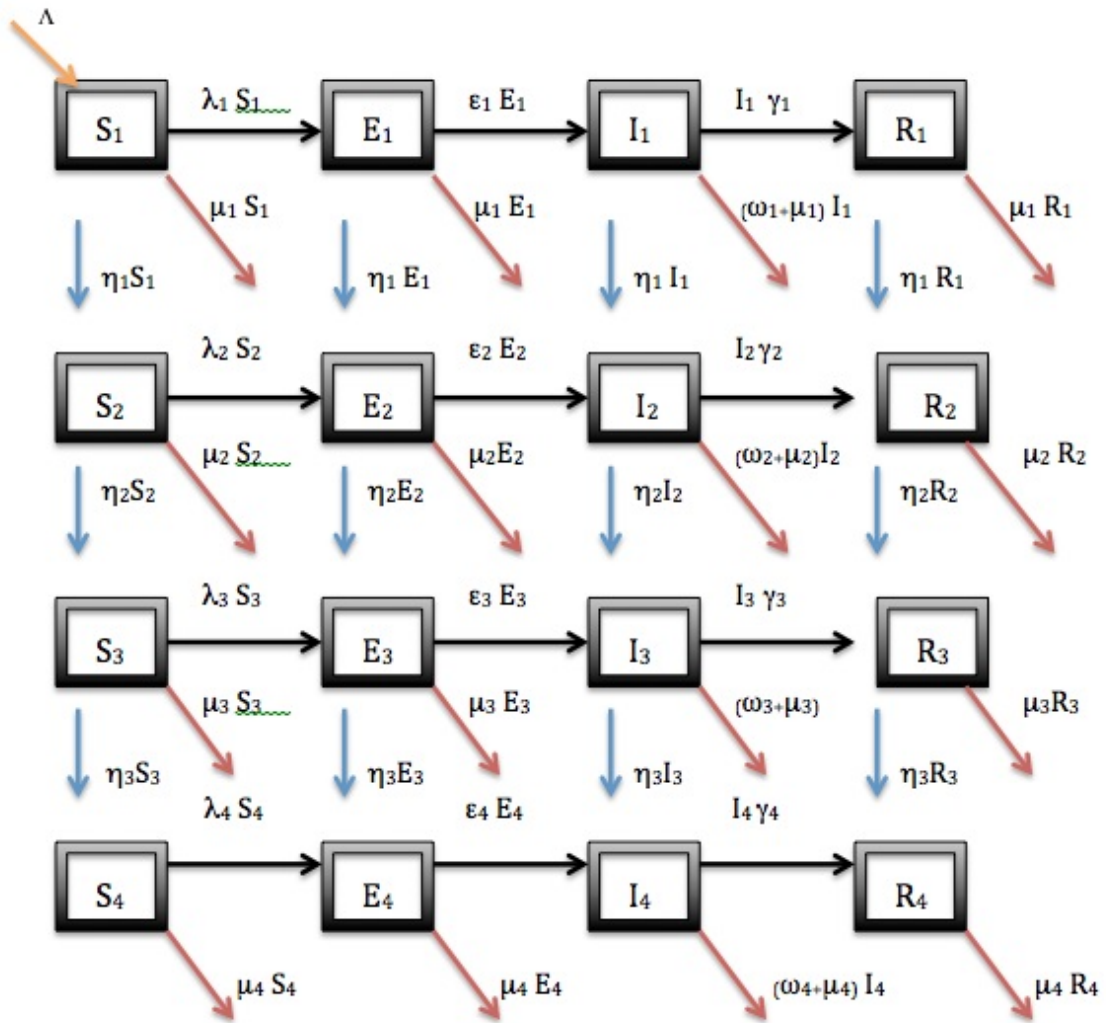
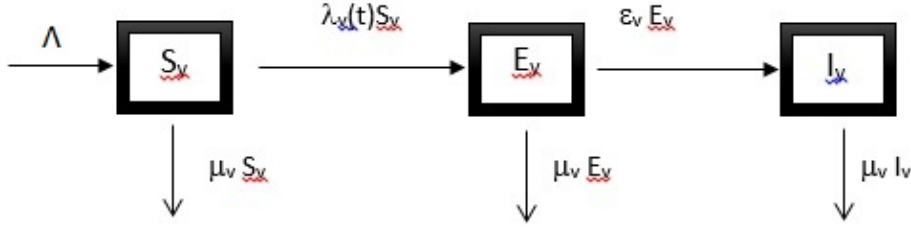


Figure 4.1: Compartmental diagram for the human population



**Figure 4.2:** Compartmental diagram for the vector

population once we have discretized the age axis into distinct age-groups.

$$\frac{\partial S_1}{\partial t} = \Lambda_h - (\eta_1 + \mu_1) - \lambda_1(t)S_1 \quad (4.2)$$

$$\frac{\partial S_2}{\partial t} = \eta_1 S_1 - (\eta_2 + \mu_2)S_2 - \lambda_2(t)S_2 \quad (4.3)$$

$$\frac{\partial S_3}{\partial t} = \eta_2 S_2 - (\eta_3 + \mu_3)S_3 - \lambda_3(t)S_3 \quad (4.4)$$

$$\frac{\partial S_4}{\partial t} = \eta_3 S_3 - \mu_4 S_4 - \lambda_4(t)S_4 \quad (4.5)$$

$$\frac{\partial E_1}{\partial t} = \lambda_1(t)S_1 - (\eta_1 + \mu_1 + \epsilon_1)E_1 \quad (4.6)$$

$$\frac{\partial E_2}{\partial t} = \lambda_2(t)S_2 - (\eta_2 + \mu_2 + \epsilon_2)E_2 + \eta_1 E_1 \quad (4.7)$$

$$\frac{\partial E_3}{\partial t} = \lambda_3(t)S_3 - (\eta_3 + \mu_3 + \epsilon_3)E_3 + \eta_2 E_2 \quad (4.8)$$

$$\frac{\partial E_4}{\partial t} = \lambda_4(t)S_4 - (\mu_4 + \epsilon_4)E_4 + \eta_3 E_3 \quad (4.9)$$

$$\frac{\partial I_1}{\partial t} = \epsilon_1 E_1 - \eta_1 I_1 - (\mu_1 + \omega_1) I_1 + \gamma_1 I_1 \quad (4.10)$$

$$\frac{\partial I_2}{\partial t} = \epsilon_2 E_2 - \eta_2 I_2 - (\mu_2 + \omega_2) I_2 + \gamma_2 I_2 + \eta_1 I_1 \quad (4.11)$$

$$\frac{\partial I_3}{\partial t} = \epsilon_3 E_3 - \eta_3 I_3 - (\mu_3 + \omega_3) I_3 + \gamma_3 I_3 + \eta_2 I_2 \quad (4.12)$$

$$\frac{\partial I_4}{\partial t} = \epsilon_4 E_4 - (\mu_4 + \omega_4) I_4 + \gamma_4 I_4 + \eta_3 I_3 \quad (4.13)$$

$$\frac{\partial R_1}{\partial t} = \gamma_1 I_1 - (\mu_1 + \eta_1) R_1 \quad (4.14)$$

$$\frac{\partial R_2}{\partial t} = \gamma_2 I_2 - (\mu_2 + \eta_2) R_2 + \eta_1 R_1 \quad (4.15)$$

$$\frac{\partial R_3}{\partial t} = \gamma_3 I_3 - (\mu_3 + \eta_3) R_3 + \eta_2 R_2 \quad (4.16)$$

$$\frac{\partial R_4}{\partial t} = \gamma_4 I_4 - \mu_4 R_4 + \eta_3 R_3 \quad (4.17)$$

where the last  $\eta$  ( $\eta_4$ ) will equal 0 because no one will age out of this class.

It is assumed that the vector population will have achieved a constant state for total population ( $N_v$ ).

$$\frac{\partial E_v}{\partial t} = \lambda_v(t)(N_v - E_v - I_v) - (\mu_v + \epsilon_v) E_v \quad (4.18)$$

$$\frac{\partial I_v}{\partial t} = \epsilon_v E_v - \mu_v I_v \quad (4.19)$$

$\lambda_i(t) = b\beta_1 \frac{I_v}{N_h}$  (for  $i = 1, 2, 3, 4$ ) and  $\lambda_v = b\beta_v \frac{\sum_{i=1}^4 P_i I_i}{N_h}$  (where  $P_i$  is the average infectivity level of an  $I_i$ ) represents per capita transmission rates of a vector and a human host, respectively.

#### 4.8.2 Analysis of the Age-Structure Model

##### Parameters Estimates of the Model

For example, using a paper on risk of VL based on age-groups, I was able to calculate the relative risk of developing VL given the age group by using the Odds Ratio



Parameter	Est. Value	Units	Comments	Ref.
$\Lambda, \Lambda_v$	.4491, 1.5	Constant/time	Constant inflow	[80, 70]
$\mu_j, \mu_v$	0.00004491, 0.0833	1/time	Natural mortality	[77]
$\omega_j$	0.385	1/time	Human excess mortality	[78]
$\gamma_j$	0.0006	1/time	Human recovery rates	[79]
$\epsilon_v$	0.25	1/time	Rate of becoming infectious (vector)	[78]
$\epsilon_j$	0.2	1/time	Rate of becoming infectious (humans)	[79]
$\eta_1$	0.000684	1/time	Human aging rate from Group 1 to Group 2	[70]
$\eta_2$	0.000304	1/time	Human aging rate from Group 2 to Group 3	[70]
$\eta_3$	0.0000622	1/time	Human aging rate from Group 3 to Group 4	[70]
$b$	0.25	bites/time/vector	Biting rate	[79]
$\beta_j$	$\beta_{j-1} = k\beta_j; \beta_j$	1/bite	Probability of infecting humans	[76]
$\beta_{v_j}$	1	1/time	Probability of infecting vectors	[79]
$\lambda_v(t)$	1.5	1/time	Infection rates for vectors	[78]
$\lambda_j(t)$	2.1	1/time	Infection rates for those in Age Group $j$	[78]

**Table 4.9:** Parameters for SEIR Model

information given. For the age group from 0 to 14 years of age, the odds ratio was 1.75, and 1.7 for those greater than 14 years of age. As a result, the relative risk of developing VL will be proportional to the next age group, where the proportionality constant can be defined as  $k = 1.75/1.7 = 1.029$  [76].

### Infection-Free Equilibrium

I determined the infection-free equilibrium; the steady state corresponding to the absence of infection in all populations. The goal is to determine the conditions under which an infection can “invade” a population. In other words, when will the infection spread by introducing a small number of infected individuals (humans or vectors) into the population. We can find this by calculating  $R_0$ , the number of secondary infections caused by the first infected in a completely susceptible population. Setting the equations equal to zero, we find the unique equilibrium point to satisfy  $I_j = I_v = 0$  for all  $j$ . We then see that  $E_j = R_j = E_v = 0$ . We find that the equilibrium susceptible states to be:

$$S_1^0 = \frac{\Lambda_h}{\mu_1 + \eta_1} \quad (4.20)$$

$$S_j^0 = \frac{\eta_{j-1}}{\mu_j + \eta_j} S_{j-1}^0 \quad \text{for } j = 2, \dots, n \quad (4.21)$$

$$S_v^0 = \frac{\Lambda_v}{\mu_v} \quad (4.22)$$

### Computation of Reproduction Number via The Next Generation Operator Method

I treat generations of infections rather than treating time in the usual sense. For example, the originally infected individuals are the first generation, those they infect are the second generation, those that second generation infects are the third generation,

etc. It describes the evolution of spread of the infection through these generations. Essentially, the rate of the sizes of the generations will be the threshold condition that determines the stability of the infection-free equilibrium.

F, the new infection matrix, is of the following form:

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & f1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & f2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & f3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & f4 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & g1 & 0 & g2 & 0 & g3 & 0 & g4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

where  $f1 = b\beta_1 \frac{S_1}{N_h}$ ,  $f2 = b\beta_2 \frac{S_2}{N_h}$ ,  $f3 = b\beta_3 \frac{S_3}{N_h}$ ,  $f4 = b\beta_4 \frac{S_4}{N_h}$ , and  $g1 = b\beta_v P_1 \frac{S_v}{N_h}$ ,  
 $g2 = b\beta_v P_2 \frac{S_v}{N_h}$ ,  $g3 = b\beta_v P_3 \frac{S_v}{N_h}$ ,  $g4 = b\beta_v P_4 \frac{S_v}{N_h}$

The  $V$  matrix is of the following form:

$$\begin{bmatrix} a & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ b & c & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ d & 0 & e & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & d & f & g & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & h & 0 & i & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & h & j & k & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & l & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & m & n & o & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & p & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & q & r \end{bmatrix}$$

where  $a = \eta_1 + \mu_1 + \epsilon_1$ ,  $b = -\eta_1$ ,  $c = \eta_1 + \mu_1 + \omega_1 + \gamma_1$ ,  $d = -\eta_1$ ,  $e = \eta_2 + \mu_2 + \epsilon_2$ ,  $f = -\epsilon_2$ ,  $g = \eta_2 + \mu_2 + \omega_2 + \gamma_2$ ,  $h = -\eta_2$ ,  $i = \eta_3 + \mu_3 + \eta_3$ ,  $j = -\epsilon_3$ ,  $k = \eta_3 + \mu_3 + \omega_3 + \gamma_3$ ,  $l = \mu_3 + \epsilon_4 - \eta_3$ ,  $m = -\eta_3$ ,  $n = -\epsilon_4$ ,  $o = \mu_4 + \omega_4 + \gamma_4$ ,  $p = \mu_v + \epsilon_v$ ,  $q = -\epsilon_v$ ,  $r = \mu_v$

The next generation operator is the matrix  $FV^{-1}$  and the reproduction number is the spectral radius and defined as:  $R_0 = \sigma(FV^{-1})$

It then follows that the  $R_0$  when there are no age groups considered is:

$$R_0 = \sqrt{\left(\frac{f_1 \epsilon_v}{\mu_v c_1}\right) \left(\frac{g_1 \epsilon_1}{a_1 b_1}\right)}$$

Here  $a_1 = a$ ,  $b_1 = c$ ,  $c_1 = p$ . Note,  $\frac{f_1 \epsilon_v}{\mu_v c_1}$  ( $= \frac{b \beta_1}{\mu_v} \frac{\epsilon_v}{(\mu_v + \epsilon_v)} \frac{S_h^0}{N_h^0}$ ) represents average number of new cases in human population generated by one infected vector and  $\frac{g_1 \epsilon_1}{a_1 b_1}$  ( $= \frac{b \beta_v P_1}{(\eta + \mu + \epsilon)} \frac{\epsilon_1}{(\eta + \mu + \omega + \gamma)} \frac{S_v^0}{N_h^0}$ ) represents average number of new cases in vector population generated by one infected individual. The  $R_0$  can be interpreted as a geometric mean of these two last quantities.

When there are two age groups,  $R_0$  is:

$$R_0 = \sqrt{\frac{\epsilon_v(f_1g_1a_2b_2\epsilon_1 + f_1g_2a_2\epsilon_1\eta_1 + f_1g_2b_1\epsilon_2\eta_1 + f_2g_2a_1b_1\epsilon_2)}{\mu_v c_1 b_1 b_2 a_1 a_2}}$$

When there are three age groups,  $R_0$  is:

$$R_0 = \left( \frac{f_1\epsilon_v}{\mu_v c_1} \left[ \left( \frac{g_1\epsilon_1}{b_1 a_1} \right) + \left( \frac{g_2\epsilon_1\eta_1}{b_2 a_1 b_1} \right) + \left( \frac{g_2\eta_1\epsilon_2}{b_2 a_1 a_2} \right) + \left( \frac{g_3\epsilon_1\eta_1\eta_2}{b_3 a_1 b_1 b_2} \right) + \left( \frac{g_3\eta_1\epsilon_2\eta_2}{b_3 a_1 a_2 b_2} \right) + \left( \frac{g_3\eta_1\eta_2\epsilon_3}{b_3 a_1 a_2 a_3} \right) \right] \right. \\ \left. + \left( \frac{f_2\epsilon_v}{\mu_v c_1} \right) \left[ \left( \frac{g_2\epsilon_2}{b_2 a_2} \right) + \left( \frac{g_3\epsilon_2\eta_2}{b_3 a_2 b_2} \right) + \left( \frac{g_3\eta_2\epsilon_3}{b_3 a_2 a_3} \right) \right] + \left( \frac{g_3\epsilon_3}{b_3 a_3} \right) \left( \frac{f_3\epsilon_v}{\mu_v c_1} \right) \right)^{1/2}$$

### 4.8.3 Results

The analysis of the model suggests existence of two equilibria, namely, disease-free and endemic equilibria. The results also provide condition on stability of the disease free equilibrium. Analytical calculations related to the computation of the endemic equilibrium is difficult, however, numerical simulations suggest its existence and local stability.

The analytical results can be interpreted as follows:

- If  $R_0$  can be reduced below 1, then VL can be controlled. Note, the  $R_0$  is a function of all age-dependent parameters as well as parameters that could be modified by interventions.
- If  $R_0 > 1$  then VL remains endemic and the level of endemicity depends on the estimate of  $R_0$  for the region.
- In VL naive region, introduction of an infected in the region may results in VL outbreak if  $R_0 > 1$ .
- Estimates of age-dependent parameters of the model can be used to study sensitivity and variability of VL endemic prevalence as a function of parameters.

## 4.9 Conclusions

In this chapter, we provided a procedure to link statistical models with mathematical models. The link was established via three different steps: (1) A mathematical model is used to estimate true incidence levels via fitting of the model to the underreported available data and bayesian MCMC statistical approach, (2) Regression-based statistical models were then developed to identify critical risk factors for the true incidence levels, and (3) The identified critical factor (age was identified as critical to the incidence) was finally used in the development of a mathematical model to understand the transmission dynamic of the Visceral Leishmaniasis in India.

In the third step, I considered age as a discrete variable by subdividing the population into age groups. I use SEIR type compartmental model for the disease flow in the human population and SEI type model in the vector populations. For  $n$  age groups, we have  $4n + 2$  nonlinear ordinary differential equations. I used the next generation operator to derive this threshold condition. Reproduction number ( $R_0$ ) is the expected number of secondary infections produced by a typically infectious individual in a wholly susceptible population. In the vector-borne disease case,  $R_0$  is a geometric mean of the two components: (1) average number of new infections in vector population generated by one infected individual and (2) average number of new infections in human population generated by one infected vector. It could be interpreted in a similar way as for a typical human disease, where vectors are not involved, that is, it represents average number of new infections in human (vector) population generated by one infectious human (vector). I also showed that  $R_0$  for our model is actually the geometric mean of both of these quantities.

This chapter ended with the demands for an age-structured model, the result of the identification of “age” as the critical risk factor associated with Leishmaniasis’

transmission. The task of parametrizing such a model in the context of Leishmaniasis would extend the time needed to complete this dissertation and hence is only carried out here in a simple sense and will be a part of the future work. Nevertheless, a minimal age-structured model is introduced to highlight the nature of the mathematical analysis and the challenges that we face in modeling neglected diseases such as Visceral Leishmaniasis. The challenges associated with parametrizing age structured models can be seen in similar studies conducted by Shim and also by Sutton [73, 74, 75]. However, the model used in these studies are applied to common diseases, which are non vector borne diseases.

## Chapter 5

### LIMITATIONS AND FUTURE WORK

#### 5.1 Limitations

The study addressed three primary theoretical modeling-related questions: (1) how to analyze collected data when sample size is limited, and how modeling assumptions varied results of data analysis. In the second chapter, we showed how to design, collect, and analyze the relevant data through survey. The data collected from the survey represented the first national survey of its kind understanding PCA administration across 48 states. While some of the associations seen in the analysis of the survey data were expected, by applying statistical methods that only work under certain assumptions, insights were drawn on the depth of the lack of standardization between hospitals, the implications of mistakes, and inferences made due to large number of research hospitals being part of the survey. In the fourth chapter, the differences in quality of health system and hospitals (public vs private) are evident; this highlights where the underreporting comes from. This type of underreporting was not so clear from the survey analyzing hospital practices until statistical analyses requiring specific assumptions were conducted and the magnitude of underreporting came to light. In the second chapter, the underreporting took the form of the magnitude of lack of standardization seen across different institutions. (2) How to identify hidden associations and nonlinearity of these associations using such under-powered data: In the third chapter, the association of men with BPH and OSA is compared with men that only have BPH on clinical and demographic variables. We expected certain differences to be seen that only came to light after assuming distributional



assumptions on the measures. This type of method gave insight into yet another type of underreporting: lack of information as it pertains to distributional information for each of the variables. (3)How statistical models provide more reasonable structure to mathematical modeling framework that can be used in turn to understand dynamics of the system: In the third chapter, we detect underreporting given the day to day operations in Bihar, India, estimate the underreporting via statistical methods, use the estimate to adjust incidence and mortality, and discover that children in between the ages of 5 and 14 are significant in all statistical models ran. This type of underreporting is two-fold: underrporting in terms of disease cases being reported by private health facilities, and underreporting in the sense that true associations are hidden due to lack of information being provided by health facilities. This dissertation very elegantly mixes the uses of statistics and mathematical modeling in order to address pressing issues by first appropriately dealing with lack of information from different sources.

## 5.2 Future Work

My future work will extend the methodology developed in this dissertation to throughly undertake understanding of transmission dynamics of a neglected disease, Visceral Leishmaniasis (VL) on the face of limited available data from the region and elimination goals.

VL is one of the most neglected diseases in the world, affecting the poorest segments of rural populations, causing significant morbidity and mortality. The campaign to eliminate VL (to reduce the annual incidence to less than one per 10,000 at the district level) has been underway since 2005 but has been unable to even reach intermediate targets of reducing burden. The Indian state of Bihar is one of the major foci of VL in the world. More than 30% of the worldwide VL cases are reported from

Bihar. Poverty, overcrowding, malnutrition, polygamy, illiteracy, and poor domestic conditions facilitate growth of this disease, which is a major public health problem in India. The Health Information System (HIS) continues to be a key component for any disease control program, and its accuracy is necessary for the assessment of actual disease burden. Unfortunately in India, Kala-azar surveillance is weak because of partial active surveillance and absence of public-private partnership for the disease containment in the affected areas. Different sources of data were used in the absence of detailed datasets. Monthly incidence and mortality data from the 21 most affected districts were obtained from Bihar State Health Society via Rajendra Memorial Institute of Medical Sciences, Patna. The additional data included demographic (such as population density, female to male ratio, age groups, decadal growth rate), social (such as literacy rates by gender, education level and percentage of home schooled and percentage with graduate education), and economic (such as worker types, house types, number of medical facilities, bus services, number of livestock, and number of poultry) variables and were taken from the 2001 Census of India, through the Bihar state government website [3]. Climatic data (such as rainfall related variables) was collected from a statistical survey carried out by the Directorate of Statistics and Evaluation, Patna, Bihar[3]. In my current research, I developed a novel quantitative technique, which handles the sparse data to estimate true burden, identify its risk factors, and understand VL transmission dynamics in one of the most vulnerable population of the region. The true VL burden was estimated using a mathematical model that used a least squares approach that derived the district-wise underreporting levels from available reported incidence data from Bihar during 2003 to 2005. The case-underreporting estimate was used to then adjust the incidence and mortality for under-reporting. After adjusting for under-reporting, biostatistical analysis was used to find the most significant predictors (risk factors among demographical,

social and economical variables) of mortality and incidence within this timeframe. In all of the statistical models developed, a specific age group (children between 5 and 14 years old) showed to be the most significant predictor of incidence and mortality both adjusted and not adjusted for under-reporting. This led to the idea that age related disparity may be relevant to understanding the dynamics of the VL in India, Hence, we developed and analyzed an age structured mathematical dynamic model to identify which age-related epidemiological quantities are critical to dynamics of VL. We found infection-susceptibility and disease-related mortality for children less than 14 years are more important parameter as compared to age-dependent incubation and infectious periods for same and other age-groups. My research objectives are to extend my current research by additionally collecting recent data (for example, incidence, and mortality from the past three years) so that we can evaluate practicality of VL elimination target, which is aimed to be achieved by 2020. Rather than collect data from different sources (Bihar state health society and census) like before, the goal for this project is to collect not only the same type of variables collected before but also collect additional information on a couple of new variables such as caste (lowest, lower, middle, upper classes), and religion (Buddhists, Muslims, Sikhs, Christians, Hindus), from the same patient data which would account for less variability in the measures. Using this newer information, I plan to carry out broadly the similar objectives: (1) estimate the underreporting by using Markov Chain Monte Carlo (MCMC) approach, which will give information in terms of the shape of the parameter's posterior distribution which is more informative (2) using statistical methods, I then plan to identify the risk factors (including a couple of new variables) most associated with incidence and mortality for the newer data, adjusting and not adjusting for underreporting, and compare the results and (3) with the aid of conclusion from objective two, develop a reasonable dynamic mathematical model in order to understand the

impact of identified risk factors after adjusting for underreporting on the transmission dynamics of VL in Bihar, India and VL elimination target. In particular, the secondary aims of the objective two will be to subset the data by age groups, gender, and religion and address following sub-questions critical for elimination: (2a) to identify which disparities and to what level are risk factors driving patient's symptoms at the initiation of treatment (thus, the quality of treatment received) (2b) to evaluate the factors that are delaying certain subset of groups from presenting to hospitals once they have the disease and (2c) to determine the likelihood of certain groups seeking a local healer vs professional practitioner given their first VL onset. All of these aims will be investigated and used collectively to study how these results will impact the transmission dynamics of VL in Bihar, India via mathematical models. A similar approach was conducted in a study looking at the epidemiological impact of rotavirus vaccination programs in the United States and Mexico [72].

Two Sample-Tests or One-Way ANOVA will be used to address Aim1, Aim 2 and 3, and test for univariate associations with both updated incidence and mortality (both adjusted and not adjusted for underreporting). Multivariate linear regression analyses will be used based on the results from the univariate analyses; a best subsets algorithm will be used to determine the best predictors of incidence and mortality for the more recent years. A logistic regression analysis will be used to address likelihood of patients to see a professional vs local healer on their first presentation. A random intercepts and random slopes repeated measures analysis will be used to assess risk change over time for the different factors considered. Using the results from all of the Aims, a Susceptible, Exposed, Infected, Recovered (SEIR) model will be developed to study how this new significant information alters the dynamics of the disease and its progression in the different age compartments now by gender via an age structure mathematical model.

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APPENDIX A  
SURVEY QUESTION DEVELOPMENT

1. Corey Angst, PhD, MBA (Assistant Professor, Department of Management, Mendoza College of Business, University of Notre Dame)
2. Richard Dutton, MD, MBA (Executive Director, Anesthesia Quality Institute)
3. Frank Federico, RPh (Executive Director, Institute for Healthcare Improvement; Patient Safety Advisory Group, The Joint Commission)
4. Matthew Grissinger (Director, Error Reporting Programs, ISMP)
5. Stephen Howell, MSN (Lead Nurse Practitioner, University of Alabama School of Medicine)
6. Ken Kelley, PhD, MA (Viola D. Hank Associate Professor of Management, Department of Management, Mendoza College of Business, University of Notre Dame)
7. Joe Kiani, MSEE (CEO, Masimo)
8. Carter King, MBA (Vice-President, Business Operations, AceIRx)
9. Mary Lynn McPherson (Professor, University of Maryland School of Pharmacy)
10. John Tucker, MBA (Chief Commercial Officer, Incline Therapeutics)
11. Rodney Tucker, MD, MMM (Associate Professor, University of Alabama)
12. Greg Spratt, RRT, CPFT (Director of Clinical Marketing, Covidien)
13. Tim Vanderveen, PharmD, MS (Vice President, Center for Safety and Clinical Excellence, CareFusion)
14. Michael Wong, JD (Executive Director, Physician-Patient Alliance for Health and Safety)



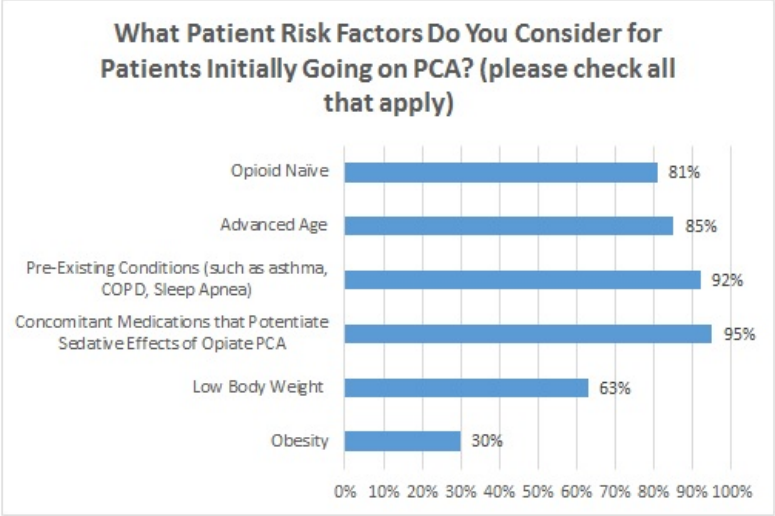
APPENDIX B  
LIST OF SURVEY QUESTIONS

1. What is your position (title)?
2. What is your profession?
3. What is your location (city)?
4. What is your location (state)?
5. Indicate number of beds?
6. Are you teaching?
  - Yes
  - No
7. Please indicate whether nurses, respiratory therapists, and pharmacists receive on-going training in PCA procedure and use?
8. What patient risk factors do you consider for patients initially going on PCA (please check all that apply):
  - Obesity
  - Low Body Weight
  - Concomitant Medications that Potentiate Sedative Effects of Opiate PCA
  - Pre-existing Conditions such as Asthma, COPD, Sleep Apnea
  - Advanced Age
  - Opioid Naive
9. Patients going on PCA are provided with information on (please check all that apply):
  - Proper Patient Use of PCA Pumps
  - Purpose of Monitoring
10. Before PCA pump initiation, refilling, or programming change, two healthcare providers double-check (please check all that apply):
  - Patient's Identification
  - Patient Allergies That Appear on Medication Administration Record
  - Drug Selection and Concentration Confirmed as That Which Has Been Prescribed
  - Any Necessary Dose Adjustments Completed
  - PCA Pump Settings
  - Line attachment to patient and tubing insertion into pump
11. For post-operative patients using PCA, my healthcare facility continuously electronically monitors (please check answers that apply):
  - All Patients for Oxygenation with Pulse Oximetry
  - Only Some Patients for Oxygenation with Pulse Oximetry
  - All Patients for Ventilation with Capnography
  - Only Some Patients for Ventilation with Capnography
  - Do Not Electronically Monitor

12. For these post-operative patients, please describe the PCA pumps used (please check all that apply):
- All of Our PCA Pumps are Smart Pumps that Contain Safety Software and Medication Libraries to Avoid IV Infusion Programming Errors
  - Some of Our PCA Pumps are Smart Pumps that Contain Safety Software and Medication Libraries to Avoid IV Infusion Programming Errors
  - All of Our PCA Pumps are Smart Pumps with Integrated End Tidal Monitoring
  - Some of Our PCA Pumps are Smart Pumps with Integrated End Tidal Monitoring
  - Our PCA Pumps are Not Smart Pumps
13. How Long Have You Been Using PCA Pumps That Contain Safety Software and Medication Libraries?
- 10 Years or More
  - 5-10 Years
  - 3-5 Years
  - 1-3 Years
  - Less Than a Year
  - Do Not Use Smart PCA Pumps That Contain Safety Software and Medication Libraries
14. How Would You Describe Your Healthcare Facility's Experience with Continuous Electronic Monitoring?
- Don't Monitor but are Considering Its Use
  - Too Early to Determine or Have Not Determined
  - We Monitor Continuously and We Have Seen Reductions in the Overall Incidence of Adverse Events Related to PCA Use
  - We Monitor Continuously and I Believe We Have Averted Adverse Events
  - We Monitor Continuously and We Have Seen a Return on Investment When Measured Against Costs and Expenses (including litigation costs) that We Might Have Incurred
15. What Do You Believe Would Help Improve The Ease of Assessing a Patient's Condition by Nursing Staff Faced With Interpreting Multiple Vital Sign Monitors? (please check all that apply):
- A Single Indicator That Accurately Incorporates Key Vital Signs, such as Pulse Rate, SpO2, Respiratory Rate, and etCO2
  - More Clinical Training for Caregivers
  - Recommendations on How Best to Easily Make Such Assessments
16. How Would You Rate Your Concern About Potential Alarm Fatigue About Continuous Electronic Monitoring? :
- Not Concerned At All
  - Concerned but Don't Believe It Will Be an Unmanageable Problem
  - Concerned That It Will Be a Problem That Is Difficult to Manage
  - Concern is Preventing Us From Implementing

17. Do You Believe That Reduction of False Alarms Would Increase The Use of Patient Monitoring Devices, Like an Oximeter or Capnograph? :
- Yes
  - No
18. Please Indicate Whether Your Facility's Identity and This Information Can Be Made Public in A Searchable Database Similar to HealthGrades :
- Yes
  - No

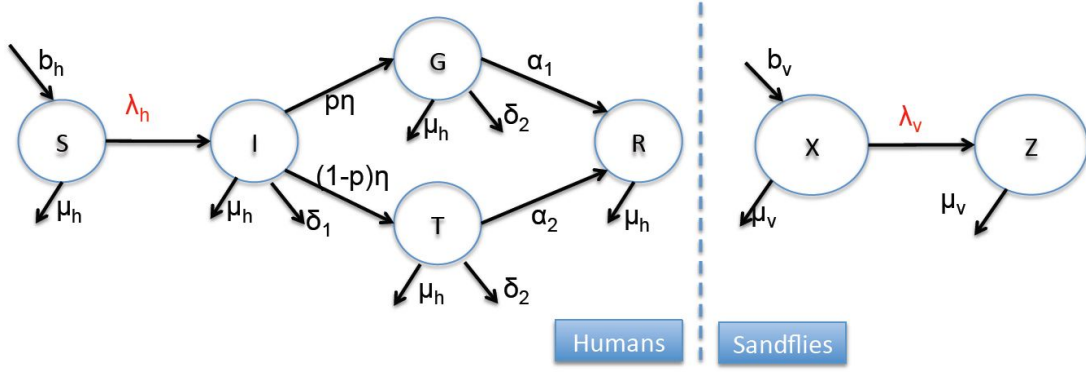
APPENDIX C  
PATIENT RISK FACTORS CONSIDERED



**Figure C.1:** Patient Risk Factors Considered

APPENDIX D  
INFECTION DYNAMICS MATHEMATICAL MODEL

Since human and sandfly populations approach demographic equilibrium after a sufficiently large time in our analysis, we consider the limiting system at the model where  $N_h$  and  $N_v$  are assumed to have reached equilibria. Using results from [62] and [63], the original system asymptotically approaches the limiting system given by the following scaled model:



**Figure D.1:** Transitions for FlowChartLast

**Table D.1:** Model Variables

Variable	Definition
$s$	Proportion of susceptible humans in the population where $s = \frac{S}{N}$
$i$	Proportion of infected humans in the population where $i = \frac{I}{N}$
$g$	Proportion of humans undergoing treatment at public health facilities where $g = \frac{G}{N}$
$\tau$	Proportion of humans undergoing treatment at private health facilities where $\tau = \frac{T}{N}$
$r$	Proportion of recovered individuals in the population where $r = \frac{R}{N}$
$N_h$	Total population of humans
$x$	Proportion of susceptible vectors where $x = \frac{X}{N}$
$z$	Proportion of infected vectors where $z = \frac{Z}{N}$
$N_v$	Total vector population size

$$\begin{aligned}
s'(t) &= b_h - \lambda_h s(t) z(t) - \mu_h s(t) \\
i'(t) &= \lambda_h s(t) z(t) - (\eta + \mu_h + \delta_1) i(t) \\
g'(t) &= p \eta i(t) - (\alpha_1 + \mu_h + \delta_2) g(t) \\
\tau'(t) &= (1 - p) \eta i(t) - (\alpha_2 + \mu_h + \delta_2) \tau(t) \\
r'(t) &= \alpha_1 g(t) + \alpha_2 \tau(t) - \mu_h r(t)
\end{aligned} \tag{D.1}$$

$$\begin{aligned}
x'(t) &= b_v - \lambda_v i(t) x(t) - \mu_v x(t) \\
z'(t) &= \lambda_v i(t) x(t) - \mu_v z(t)
\end{aligned}$$



The reproduction number for the Model is

$$R_c^2 = \left( \frac{\lambda_v}{\mu_h + \delta_1 + \eta} \right) \left( \frac{\lambda_h}{\mu_v} \right).$$

#### Acceptance Probability Computation

The acceptance probability is computed (using conditional probability formula) via

$$pratio = \frac{\pi(\mathbf{x}^{(*)}) \cdot P(\mathbf{x}^{(n)}|\mathbf{x}^{(*)})}{\pi(\mathbf{x}^{(n)}) \cdot P(\mathbf{x}^{(*)}|\mathbf{x}^{(n)})} = \frac{L(\mathbf{y}|\mathbf{x}^{(*)}) \cdot \prod_{k=1}^Q Pr(x_k^{(*)})}{L(\mathbf{y}|\mathbf{x}^{(n)}) \cdot \prod_{k=1}^Q Pr(x_k^{(n)})} \quad (\text{D.2})$$

where  $Pr(\cdot)$  represent prior probabilities. (In our case, uniform priors were assumed for the estimated parameters). The likelihood is given by

$$L(\mathbf{y}|\mathbf{x}) = \prod_{i=1}^T \left( \frac{1}{\sqrt{2\pi}} \right) \times \exp \left( -\frac{[\text{logit}(y_i) - \text{logit}(f_i(\mathbf{x}))]^2}{2} \right) \quad (\text{D.3})$$

where  $y_i$  represent observed data (in our case, it is reported monthly incidence and mortality rates), and proposal distribution is assumed to be multivariate normal distribution (a symmetric distribution). Note, conditional probability in equation (2) is:

$$P(\mathbf{x}^{(*)}|\mathbf{x}^{(n)}) = (2\pi)^{-Q/2} \det(\Sigma)^{-1/2} \exp \left( -\frac{1}{2} (\mathbf{x}^{(*)} - \mathbf{x}^{(n)})^T \Sigma^{-1} (\mathbf{x}^{(*)} - \mathbf{x}^{(n)}) \right) \quad (\text{D.4})$$

APPENDIX E  
UNDERREPORTING

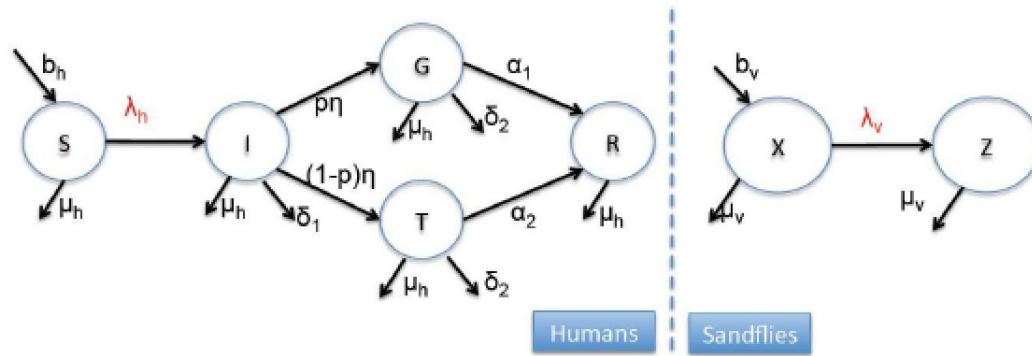


Figure E.1: Underreporting

## BIOGRAPHICAL SKETCH

Beverly Gonzalez was born in Chicago, Illinois, on December 20, 1980. She received her elementary education at Dr. Daniel Cameron School. Her secondary education was completed at Lane Technical High School in Chicago, Illinois. In 1999, Beverly entered the University of Illinois at Urbana-Champaign, majored in mathematics, and took part in numerous mathematical and statistical research opportunities. Beverly took part in the following summer programs as an undergraduate: The Mathematical, Theoretical, and Biological Institute (MTBI) at Cornell University; Rice Undergraduate Summer Institute of Statistics (RUSIS) at Rice University; The Vertical Integration of Research and Education in the Mathematical Sciences (VIGRE) at the University of Georgia. Beverly earned a Bachelor of Science in Mathematics in 2004 and joined the National Center for Supercomputing Applications in Urbana, Illinois, as Assistant Director for the Education, Training, and Outreach Division. In 2005 Beverly was accepted to the University of Illinois Statistics Graduate Program. Shortly after Beverly took a leave of absence from her studies to tend to motherhood and resumed her graduate studies in 2006. In 2011, Beverly earned a Master of Science in Biostatistics at Brown University. Upon completion of her Biostatistics degree, Beverly was accepted in the Simon A. Levin Mathematical, Computational and Modeling Sciences Center at Arizona State University as a doctoral candidate. While at Arizona State University, Beverly received a two-year fellowship from the Alfred P. Sloan Foundation to pursue her doctoral studies. After this, in order to support her daughter, Beverly moved to a Biostatistician role at Johns Hopkins University while pursuing her doctoral studies. Beverly was a member of the American Statistical Association (ASA) and the Society for the Advancement of Chicanos and Native Americans in the Sciences (SACNAS).